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Aims and Scope

Neurospine provides spine clinicians and researchers with peer-reviewed articles on basic and clinical investigation of spine and spinal cord to enhance patient management, education, clinical or experimental research, and professionalism. The journal will consider submissions in areas on craniocervical to lumbosacral spine including the followings: neuroscience and pain research, bone and mineral research, disc and joint research, bio and industrial technology, pathophysiology, risk factors, symptomatology, imaging, treatment, rehabilitation of spine, spinal cord and peripheral nerve diseases. Specifically, basic and technology researches include the most influential research papers from all fields of science and technology, revolutionizing what physicians and researchers practicing the art of spinal neurosurgery worldwide know. Thus, we welcome valuable basic and translational technology research articles to introduce cutting-edge research of fundamental sciences and technology in clinical spinal neurosurgery. Clinical or basic research articles, review articles, case reports, technical notes, and letters to the editor written in English will be accepted.

About the Journal

Neurospine (ISO abbreviated journal name, *Neurospine*), the official journal of World federation of Neurosurgical Societies Spine Committee, is an international peer-reviewed open-access journal which published quarterly (last day of March, June, September, and December). It was first published in March 31, 2004 with Volume 1 and Number 1 with the name "*Korean Journal of Spine*," and renamed as "*Neurospine*" in March issue, 2018.

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Neurospine pISSN 2586-6583 • eISSN 2586-6591

Volume 19 No. 2 June 2022

Contents

Neurospine pISSN 2586-6583 • eISSN 2586-6591

Volume 19 No. 2 June 2022

Neurospine pISSN 2586-6583 • eISSN 2586-6591

Volume 19 No. 2 June 2022

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Review Article

Curcumin as a Promising Neuroprotective Agent for the Treatment of Spinal Cord Injury: A Review of the Literature

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Curcumin is a polyphenolic chemical derived from the rhizomes of *Curcuma longa*. It has been used throughout the Indian subcontinent for medicinal purposes, religious events, and regional cuisine. It has various pharmacological benefits owing to its anti-inflammatory and antioxidant properties. Its neuroprotective effects on the brain and peripheral nerves have been demonstrated in several *in vivo* neuronal tissue studies. Because of these functional properties of curcumin, it is considered to have great potential for use in the treatment of spinal cord injuries (SCIs). Numerous immunopathological and biochemical studies have reported that curcumin can help prevent and alleviate subsequent secondary injuries, such as inflammation, edema, free radical damage, fibrosis, and glial scarring, after a primary SCI. Furthermore, following SCI, curcumin administration resulted in better outcomes of neurological function recovery as per the Basso, Beattie, and Bresnahan locomotor rating scale. However, to date, its utility in treating SCIs has only been reported in laboratories. More studies on its clinical applications are needed in the future for ensuring its bioavailability across the blood-brain barrier and for verifying the safe dose for treating SCIs in humans.

Keywords: Antioxidant, Curcumin, Inflammation, Neuroprotective agent, Recovery of function, Spinal cord injury

INTRODUCTION

Spinal cord injuries (SCIs) have 2 phases—primary and secondary injuries.[1] A primary injury is caused by mechanical insult and structural damage, whereas a secondary injury is a sequence of systemic and local neurochemical and physiological alterations. Subsequent edema, ischemia, inflammation, cytokine production, free radical damage, glial scar formation, apoptosis, and necrosis contribute toward the development of secondary injuries.[2] A primary injury is immediate and irreversible; in contrast, a secondary injury worsens with time and necessitates therapeutic intervention. Thus, preventing or aggressively treating secondary injuries is the mainstay of care for acute SCIs.[3,4]

Curcumin is a promising therapeutic drug for SCI treatment because it reduces the incidence of secondary injuries. It is a yellow extract derived from *Curcuma longa* that is frequently used as a spice and food-coloring ingredient in India (Fig. 1). Curcumin has antioxidant and nonsteroidal anti-inflammatory pharmacological properties.[5,6] Preclinical and clinical trials have revealed its various pharmacological activities, including its anti-inflammatory, antibacterial, anticancer, and neuroprotective

effects on neurodegenerative disorders. Curcumin also has hepatoprotective, nephroprotective, cardioprotective, neuroprotective, hypoglycemic, and antirheumatic activities, and its neuroprotective activity against several neurodegenerative disorders is gaining researchers' attention.[7] As an anti-inflammatory agent, curcumin suppresses the production of many proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-8, and monocyte chemoattractant protein 1.[8,9] In a recent study, curcumin inhibited the hypoxia-induced upregulation of glial fibrillary acidic protein (GFAP) and neurofilament-H following hypoxia and downregulated the expression of proinflammatory cytokines, such as TNF-α and IL-1.[10] It also suppresses glial scar formation and GFAP expression, contributing toward the development of a more favorable environment for neurological recovery (Fig. 2).[11]

Fig. 1. *Curcuma longa* plant and powder. Curcumin is a yellow substance produced by *Curcuma longa*. Curcumin is the primary curcuminoid found in turmeric, a member of the ginger family. It is marketed as an herbal supplement, cosmetic ingredient, food-flavoring agent, and food colorant.

This study aimed to consolidate the knowledge essential for spine surgeons and related clinicians to understand how curcumin can alleviate secondary injuries observed in SCIs. Herein, we discuss the basics of neuroprotective effects and accumulate experimental evidence regarding the neuroscience of curcumin.

PHARMACOLOGY

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a complex pharmacophore that has the potential to serve as an antioxidant, chelate metals, and trigger the Michael reaction.[12] Additionally, it is a hydrophobic molecule with a strong affinity toward cellular membranes and consists of 2 ferulic acid residues connected by a methylene bridge.[13] The structure of the molecule is symmetrical. The 3 major components of curcumin molecules are the keto-enol tautomer in the

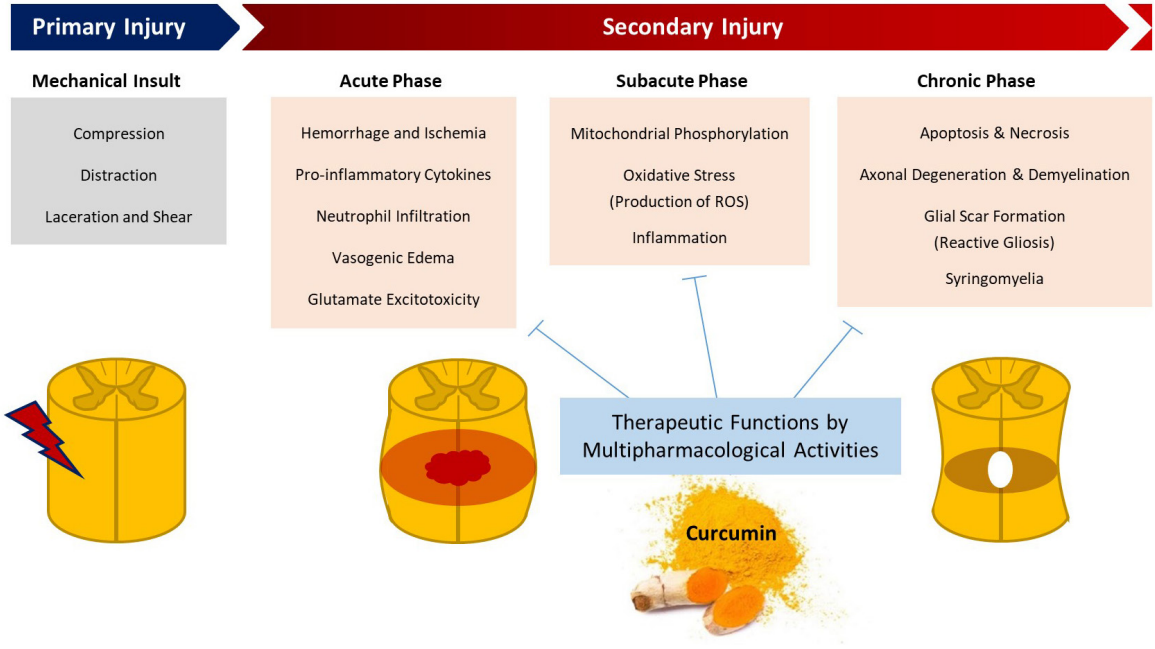

Fig. 2. Pathophysiological process following spinal cord injury and the targeted therapeutic function of curcumin. ROS, reactive oxygen species.

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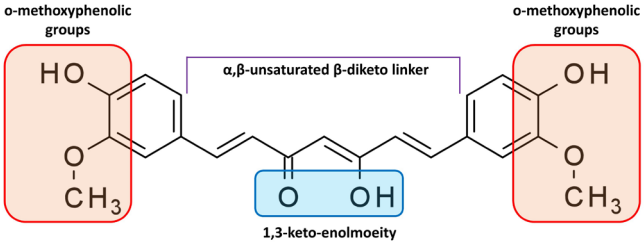

Fig. 3. Molecular structure of curcumin. The keto-enol tautomer in the center, flexible α,β-unsaturated β-diketo linker, and terminal o-methoxyphenolic groups make up the curcumin molecule, which has an asymmetric structure.

middle, flexible α,β-unsaturated β-diketo linker, and terminal o-methoxyphenolic groups (Fig. 3).

The structure of curcumin contains various functional groups (diketo group, carbon-carbon double bonds, and phenyl rings). Thus, curcumin is a unique and strong antioxidant. Structure-activity correlations have shown that the β-diketone (keto-enol) moiety acts as a chelator of cationic metals in protein-binding sites and as a Michael reaction acceptor for nucleophilic compounds that form covalent bonds with curcumin, such as reduced selenocysteine and sulfhydryl.[14] The antioxidant activity of curcumin is dependent on the phenolic hydroxyl group.[15] This group and methylene hydrogen are essential for curcumin's free radical scavenging activity, which involves electron transfer or H-atom abstraction from reactive oxygen species (ROS) and nitrogen species (Fig. 4).[16]

The wide range of interactions of curcumin might explain why it binds to various proteins. Curcumin affects the function of roughly 100 biological targets in various ways,[17] including the modification of the phosphorylation state of cellular proteins.[18] Curcumin has effects at doses above the micromolar level in general. This low binding affinity has aided various attempts to use a structure-based drug design to improve the efficacy of curcumin.

ANTI-INFLAMMATORY EFFECT

One of the most promising alternatives for primary SCI treatment is an anti-inflammatory multimodal neuroprotection strategy.[19] Spinal cord edema, which is accompanied by acute inflammation and precedes fibrosis, plays a critical role in neurological impairment. This provides a fundamental explanation for the clinical use of corticosteroids in patients with SCIs. Curcumin is an anti-inflammatory molecule that suppresses transcription factors including nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription (STAT) in the upstream signaling pathways of inflammatory mediators such as prostaglandins, cytokines, and chemokines, resulting in the global inhibition of the inflammation network.[20] Given the fundamental nature of NF-κB signaling pathway activation to neuroinflammation and SCI pathophysiology,[21] modulating NF-κB signaling could help minimize inflammation, lessen the severity of secondary injury, and maintain neuronal function.

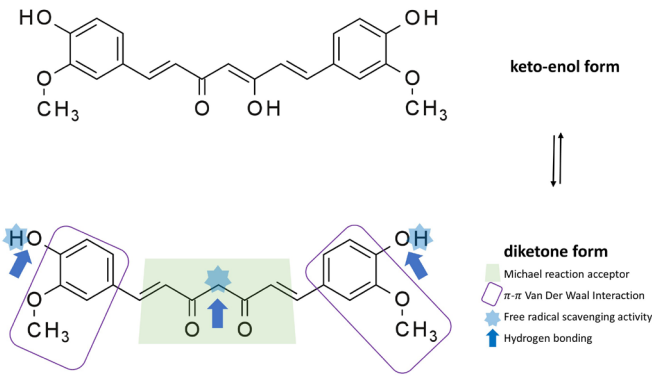

Fig. 4. Curcumin has a wide range of interactions. Curcumin contains a complex pharmacophore that can function as an antioxidant; chelate metals; and facilitate Michael reactions (used in the mild formation of C–C bonds), hydrogen-bonding interactions, π-π van der Waals interactions, and free radical scavenging.

Curcumin can also directly bind to inflammatory mediators and enzymes involved in downstream inflammatory pathways, such as IL-1 converting enzyme, TNF-α, TNF-α converting enzyme, p38 mitogen-activated protein kinase, myeloid differentiation protein-2, 1-acid glycoprotein, and glycogen synthase kinase-3 beta.[14,22] Additionally, curcumin suppresses the production of transforming growth factor-beta (TGF-β)1, TGF-β2, and sex-determining region Y-box transcription factor 9. It also facilitates the development of a microenvironment appropriate for nerve development.[23] Curcumin suppresses the upregulation of aquaporin 4 and GFAP and the atypical activation of the Janus kinase–STAT signaling pathway associated with SCI.[24] Recent *in vivo* studies on the anti-inflammatory function of curcumin are summarized in Table 1.

ANTIOXIDANT EFFECT

Numerous experiments have been conducted to determine the antioxidant capabilities of curcumin for SCI treatment. There is a strong correlation between SCI and inflammation-induced free radical formation.[25] Curcumin is a potent antioxidant that

Table 1. Anti-inflammatory properties of curcumin: list of recent evidentiary studies

Study	Specimen/sample size/ SCI method	Study design (experimental groups)	Curcumin treatment method	Summary of results
Zu et al.,[24] 2014	Male Sprague-Dawleyrats/N = 64/ Striking bar falling (diameter: 3 mm) 5-cm height (150 gcf) on T8 level	Sham/DMSO (n = 16) Sham/Curcumin (n = 16) SCI/DMSO (n = 16) SCI/Curcumin (n = 16)	40 mg/kg Single IP injection 30 min after SCI	Curcumin increased gray–white matter interface, tissue edema/ AQP-4 expression, and GFAP/pJAK-STAT expression Moderately improved BBB scores
Wang et al.,[59] 2014	Female BALB/c mice/N = No description/10-g force clip for 3 sec, extradural on T9 level	Sham SCI/DMSO SCI/Curcumin	50 mg/kg Single IP injection Immediately after SCI	Curcumin decreased tissue expression of GFAP and Iba-1 and increased NF-200 Decreased levels of IL-1β, NO, and NF-κB Increased neuromotor scores (Basso mouse scale)
Lin et al.,[60] 2015	Wild-type C57BL/6JNarl mice/ N = 18/Weight dropped Guide was lifted up to 4 mm to perform a hemitransection	Sham control (n = 6) SCI (n = 6) SCI+Curcumin (n = 6)	40 mg/kg Single IP injection 30 min after SCI	Curcumin attenuated the downregulation of CISD2 in SCI and LPS-treated astrocytes. (CISD2 exerts antiapoptotic and anti-inflammatory effects on neural cells)
Yuan et al.,[23] 2015	Female Sprague-Dawley rats/ N = No description/Aneurysm clip (fixed force of 50 g) for 60 secon T9 level	Sham SCI SCI+Curcumin 30 SCI+Curcumin 100 SCI+Curcumin 300 SCI+Methylprednisolone	Various dose of curcumin (300, 100, and 30 mg/kg) IP injection once per day for 7 days	Curcumin inhibited the expression of proinflammatory cytokines (TNF-α, IL-1β, and NF-κb) Reduced the expression of the intracellular components and GFAP through its anti-inflammatory effects. Suppressed reactive gliosis. Inhibited the generation of TGF-β1, TGF-β2, and SOX-9 Improved BBB scores
Ni et al.,[61] 2015	Male Sprague-Dawley rats/ N = 48/30-g force extradural compression with a clip for 30 sec on T8–9 level	Sham (n = 16) SCI (n = 16) SCI+Curcumin (n = 16)	100 mg/kg IP injections at 15 min after SCI	Curcumin modulated the TLR4/NF-κB inflammatory signaling pathway and significantly ameliorated SCI-induced spinal cord edema and apoptosis. BBB scores significantly increased
Yuan et al.,[9] 2017	Female Sprague-Dawley rats/ N = 280/50-g force clip compression for 60 sec on T9 level	Sham (n = 70) SCI (n = 70) SCI+Curcumin (n = 70) SCI+DMSO (n = 70)	100 mg/kg IP injections Immediately after surgery and once every 24 hr for 7 days	Curcumin regulated both the NF-κB and SOX-9 signaling pathways. Downregulated the expression of chemokines, MCP-1, RANTES, and CXCL10, released by astrocytes. Decreased macrophage and T-cell infiltration
Ruzicka et al.,[40] 2018	Wistar rats/N = 135/Balloon-induced compression using Fogarty catheter on T8 level	Saline (n = 34) Curcumin (n = 27) MSC (n = 28) Curcumin+MSC (n = 26)	High dose once a week (60 mg/kg diluted in olive oil) intrathecally 4 times (immediately after SCI followed up for 3subsequent weeks), low-dose IP injection daily (6 mg/kg diluted in olive oil) (immediately after SCI and on the 28th day)	The combined therapy facilitated axonal sprouting and modulated the expression of proregenerative factors and production of inflammatory responses. Both curcumin and curcumin combined with MSC therapy improved BBB score and the combined treatment group showed additional improvement in advanced locomotor performance.

(continued)

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Table 1. Anti-inflammatory properties of curcumin: list of recent evidentiary studies (continued)

Study	Specimen/sample size/ SCI method	Study design (experimental groups)	Curcumin treatment method	Summary of results
Ruzicka et al.,[62] 2018	Wistar rats/N = 131/Balloon-induced compression using Fogarty catheter for 5 min	Behavioral group study: Saline (n = 10) Curcumin (n = 13) EGCG (n = 19) Curcumin+EGCG (n = 9) Cytokine group study: Saline (n = 20) Curcumin (n = 20) EGCG (n = 20) Curcumin+EGCG (n = 20)	Curcumin 6 mg/kg, EGCG 17 mg/kg IP daily Curcumin 60 mg/kg EGCG 17 mg/kg IM weekly for 28 days	Curcumin and EGCG alone or in combination increased axonal sprouting, decreased glial scar formation, and altered the levels of macrophage inflammatory protein 1-alpha, interleukin-1β, interleukin-4, and interleukin-6. All treatments displayed significant behavioral recovery (BBB score) with no obvious synergistic effect after the administration of the combined therapy of curcumin and ECGC
Lee et al.,[4] 2019	Sprague-Dawley rats/N = 35/Clip with 30-g force for 2 min	Sham (n = 32) SCI only (n = 32) SCI+Hyperglycemia (n = 32) SCI+Hyperglycemia+ Curcumin (n = 32)	200 mg/kg/day for 8 weeks, IP	SCI+hyperglycemia+curcumin group: SOD activity increased, malondialdehyde and ED-1 macrophage marker levels decreased, IL-6, IL-8, TNF-α, phosphorylated extracellular signal-regulated kinase, phosphorylated JNK, and phosphorylated p38 levels decreased, Better BBB score
Yardım et al.,[63] 2021	Male Sprague-Dawley rats/N = 35/ PTX-induced SCI	Control (n = 7) Curcumin (n = 7) PTX (n = 7) PTX+Curcumin100 (n = 7) PTX+Curcumin200 (n = 7)	100 mg/kg or 200 mg/kg Oral daily for 10 days	Curcumin reduced mRNA expression levels of NF-κB, TNF-α, IL-6, iNOS, and GFAP and increased the levels of Nrf2, HO-1, and NQO1. Curcumin suppressed the activation of apoptotic and autophagic pathways by increasing Bcl-2 and Bcl-xL and decreasing p53, caspase-3, Apaf-1, LC3A, LC3B, and beclin-1 mRNA expression levels

SCI, spinal cord injury; DMSO, dimethyl sulfoxide; AQP-4, aquaporin 4; GFAP, glial fibrillary acidic protein; pJAK-STAT, phosphorylated Janus kinase-signal transducer and activator of transcription; BBB, Basso, Beattie, Bresnahan; BALB, Bagg albino; IP, intraperitoneal; NF-200, neurofilament-200; IL, interleukin; NO, nitric oxide; NF-κB, nuclear factor kappa B; LPS, lipopolysaccharide; TNF, tumor necrosis factor; TGF, transforming growth factor; SOX-9, sex-determining region Y-box transcription factor 9; MCP-1, monocyte chemoattractant protein-1; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; CXCL10, C-X-C motif chemokine ligand 10; MSC, mesenchymal stem cells; EGCG, epigallocatechin gallate; IM, intramuscular; iNOS, inducible nitric oxide synthase; Nrf2, nuclear erythroid 2-related factor 2; HO-1, hemeoxygenase 1; NQO1, NAD(P)H:quinone oxidoreductase 1; PTX, paclitaxel; LC3A, light chain 3 A; LC3B, light chain 3 B.

is reported to be superior to vitamin E, resveratrol, and other commonly used antioxidants.[26] Curcumin interacts with ROS directly and also acts as an activator of antioxidant signaling systems, making its effects more comprehensive and long lasting.[27] Curcumin can also neutralize free radicals via electron transfer and/or H-atom donation. The antioxidant ability of curcumin is influenced by 3 distinct functional dissociation groups and a β-diketone site.[28,29]

Curcumin binds to lipid radicals in cell membranes and converts them into phenoxyl radicals. Because phenoxy is more polar than curcumin, it diffuses to the membrane surface, where it can be repaired by any water-soluble antioxidant such as ascorbic acid. Thus, curcumin can protect cell membranes against oxidative damage by acting as a lipid radical scavenger.[30] It has the potential to enhance the activity of antioxidant enzymes, such as plasma catalase, erythrocyte superoxide dismutase (SOD), and plasma glutathione peroxidase.[31] Furthermore, malondialdehyde (MDA), which is the end product of lipid peroxidation, is a reliable marker of oxidative stress-mediated lipid peroxidation.[32] Curcumin decreased MDA based on a fixed-effects model (n = 56; pooled mean difference [MD] = -1.00; 95% confidence interval [CI], -1.59 to -0.42; p = 0.00008) in a meta-analysis of 4 studies on MDA levels.[8]

Additionally, curcumin could stimulate antioxidant protection genes via the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway.[33] It increases intracellular antioxidant defense responses by activating the Nrf2/antioxidant response element pathway, which results in the development of several antioxidants and detoxification and cytoprotective proteins.[34] Recently, Ni et al. showed that SCI caused a considerable increase in la-

Table 2. Antioxidant property of curcumin: list of recent evidentiary studies

Study	Specimen/sample size/SCI method	Study design (experimental groups)	Curcumin treatment method	Summary of results
Akar et al.,[64] 2017	Wistar rats/N = 40/ Spinal cord ischemia induced by clamping the aorta	Sham (n = 10) Ischemia–reperfusion (n = 10) Curcumin (n = 10) Solvent (n = 10)	100 mg/kg, IP at 30 min before ischemia Dissolved in 5 N NaOH	Decreased MDA levels in the spinal cord Increased SOD and GPx levels caused by curcumin Neurological outcome scores were significantly better when compared with those of the IR group.
Xi et al.,[65] 2019	Sprague-Dawley rats/ N = 24/A hammer was dropped on T8 level	Sham/control (n = 8) SCI (n = 8) Tetrahydrocurcumin treatment (n = 8)	80 mg/kg/day, IP Tetrahydrocurcumin for 2 weeks	Oxidative stress and apoptosis (caspase-3 activity and B cell lymphoma 2-associated X protein levels) were suppressed Tetrahydrocurcumin inhibits oxidative stress response by regulating FOXO4 in SCI model rats. Tetrahydrocurcumin increased the BBB scores
Daverey et al.,[10] 2020	Male Wistar rats/ N = 18/30-mm spinal cord section/ Hypoxia	Sham Hypoxia Hypoxia+Curcumin Sham Hypoxia Hypoxia+Curcumin Hypoxia+BAY11-7082	One hour incubation with 50 μM curcuminin 95% N2 and 5% CO_2	Curcumin inhibited hypoxia-induced HIF1-α expression and tissue damage by improving the morphology of astrocytes and remarkably reducting vacuolation. It inhibited the hypoxia-induced upregulation of GFAP and neurofilament-H (NF-H) after hypoxia and downregulated the expression of pro-inflammatory cytokines such as TNF-α and IL-1. Curcumin exerted its neuroprotective effect through cross-talk between the NF-κB and Nrf2 signaling pathways.
Daverey and Agrawal,[66] 2020	Human astrocytes Male Wistar rats/ N = 21/30-mm spinal cord section/ Hypoxia	Human astrocytes Sham Hypoxia Hypoxia+Curcumin Hypoxia+Riluzole Hypoxia+Riluzole+ Curcumin	Human astrocytes: Riluzole (1 μM) Curcumin (1 μM) Rat SCI model (white matter injury) Riluzole (10 μM) Curcumin (50 μM)	Riluzole protects white matter injury by the activation of Nrf2/HO-1 and caspase 9. Curcumin's neuroprotective effect is mediated through the inhibition of HIF-1α, GFAP, NF-H, and caspase 9. Curcumin is more effective than riluzole in reducing GFAP and NF-H injury.

SCI, spinal cord injury; IP, intraperitoneal; MDA, Malondialdehyde; SOD, serum superoxide dismutase; IR, ischemia–reperfusion; FOXO4, forkhead box protein O4; BBB, Basso, Beattie, Bresnahan; HIF1-α, Hypoxia inducible factor 1-α; GFAP, glial fibrillary acidic protein; TNF, tumor necrosis factor; IL, interleukin; Nrf2, nuclear erythroid 2-related factor 2; HO-1, hemeoxygenase 1; NF-H, neurofilament protein-H.

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bile Zn and inflammatory cytokines in an injured rat's spinal cord, and curcumin decreased the accumulation of labile Zn.[35] Zn is important in decreasing oxidative stress and generating inflammatory cytokines. Recent studies that demonstrate the antioxidant function of curcumin are summarized in Table 2.

STEM CELL PROLIFERATION

While research on stem cells for SCI treatment is ongoing, there still exist significant barriers in achieving excellent therapeutic results. It is critical to promote neural stem cell (NSC) proliferation for treating SCI, and several investigations have reported the contribution of curcumin to this process.[36-38] An improved therapeutic effect can be achieved by modifying stem cell proliferation and differentiation and reducing the inflammatory microenvironment in injured regions.[39]

Curcumin enhances the functional recovery of SCIs when combined with NSC or mesenchymal stem cell (MSC) therapy.[37,40] In a study by Ormond et al.[2] the combination of curcumin and NSC therapy led to a significant recovery of severe SCIs *in vivo*, which was evidenced by better functional locomotor recovery, body weight, and soleus muscle mass. Wanjiang et al.[41] confirmed that in combination with MSC therapy, curcumin suppressed human umbilical cord-derived MSC (hUC-MSC) apoptosis via the ERK1/2 signaling pathway, and the combined curcumin and hUC-MSC therapy improved the motor function of rats with SCIs. A study by Bonilla et al.[42] evaluated a combination therapy comprising human NSCs derived from induced pluripotent stem cells (iPSC-NSCs), human MSCs, and a pH-responsive polyacetal–curcumin nanoconjugate (PA–C) that allows the sustained release of curcumin. The combination of stem cell transplantation and PA–C therapy exerted higher neuroprotective effects compared with individual therapies. Representative studies showing that curcumin enhances stem cell proliferation are summarized in Table 3.

NEUROLOGICAL FUNCTIONAL IMPROVEMENT

Neurological function was found to be improved by curcumin in a random-effects model of a comprehensive meta-analysis.[8] The magnitude of the effect, as measured by the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale, was significantly increased when the curcumin dosage was elevated (4 trials; total, 132 rats; pooled MD = 3.09; 95% CI, 3.40–4.45; p = 0.04).[8] Several studies on functional recovery had the advantage of adopting a uniform scale (BBB score) for interstudy comparisons, making aggregated results reliable. In an animal trial, 60 Wistar rats were randomly assigned to receive either curcumin therapy (30 rats) or placebo (30 rats).[43] Curcumin therapy (immediately applied to the injured spinal cord surface and then administered intraperitoneally daily) resulted in behavioral recovery within the first week following SCI, as shown by better BBB and plantar scores for sensory function. This functional improvement was induced by the anti-inflammatory effects of curcumin. In another animal study investigating antioxidative characteristics and functional recovery, the curcumin-treated group demonstrated enhanced locomotor scores (BBB scores), increased SOD levels, reduced MDA levels, and reduced macrophage markers following SCI.[3]

One study found that curcumin was more effective than methylprednisolone, which is frequently used in clinical practice to treat secondary injury in patients with SCIs 2 weeks after primary injury based on BBB scores.[44] The study concluded that curcumin has a greater therapeutic potential than methylprednisolone, showing a longer duration of action in SCIs. Thus, *in vivo* studies on rats and their BBB scores offer substantial evidence of the efficacy of curcumin in causing functional recovery after SCIs. In many *in vivo* studies, neurological function was assessed using BBB scores (Tables 1–3). Other studies that evaluated functional recovery using BBB scores are summarized in Table 4.

OBSTACLES AND FUTURE DIRECTION

Although curcumin has been reported to be a promising neuroprotective agent, its practical applications are limited owing to a number of issues. Curcumin has limited bioavailability because of its low water solubility, poor absorption, rapid metabolism, and fast elimination. It cannot cross the blood-brain barrier, making it unsuitable for use in treating central nervous system injuries, including SCIs. Toxicity is also an issue. Curcumin induces damage to the DNA both *in vitro* and *in vivo*.[45] Curcumin acts as a dose-dependent antioxidant to inhibit ROS as well as a pro-oxidant to produce ROS.[46,47] Superoxide anion and hydrogen peroxide are the 2 types of ROS that may play an important role in carcinogenesis.[48] At high doses, curcumin can react with the thiol groups of cysteine residues,[49] causing DNA damage or p53 inactivation.[50,51]

However, these limitations are being addressed by encapsulating curcumin into nanoformulations. Encapsulation of curcumin into nanocarriers via various methods is an appropriate

Table 3. Recent studies showing proliferation enhancement through the combination of curcumin and stem cells

Study	Stem cell types and specimen/SCI method	Study design (experimental groups)	Curcumin treatment method	Summary of results
Son et al.,[36] 2014	Neural progenitor cell (NPC) from the spinal cord of Sprague-Dawley rats	Examine cellular proliferation (MTS assay) in control (no curcumin) and curcumin groups at 6 different dose levels	In culture medium at 0.1, 0.5, 1, 10, 20, and 50 μM	Lower dosage (0.1, 0.5, 1 μM) of curcumin increased SC-NPC proliferation. However, higher dosage decreased SC-NPC proliferation. Curcumin stimulates the proliferation of SC-NPCs via the MAP kinase signaling pathway, especially involving the p-ERK and p-38 proteins.
Requejo-Aguilar et al.,[39] 2017	Ependymal stem/progenitor cells of the spinal cord (EpSP-Ci) of Sprague-Dawley rats Contusion 250 kdyn Infinite Horizon Impactor	PA (as vehicle) (n = 12) PA–curcumin–Cy5.5 (n = 15)	Intrathecal administration PA–curcumin–Cy5.5 (10 μM) (combination treatment: epSPCs and a pH-responsive polymer–curcumin conjugate)	PA–C enhances neuroprotection, increases axonal growth PA–C can improve functional recovery in acute SCI Also enhances functional recovery in a rodent model of chronic SCI. *PA (polyacetal): enhances blood bioavailability and stability and provides a means for highly localized delivery.
Bang et al.,[37] 2018	Neural stem/progenitor cells derived from Sprague-Dawley rats N = 60/Clip with a closing force of 30 g & a 2-min compression	Sham (n = 20) SCI-Curcumin (n = 20) SCI-Vehicle (n = 20)	Implanting indwelling intrathecal catheters/ A concentration of 1 μmol/L for curcumin	SCI-Curcumin group: The co-immunoreactivity of nestin/BrdU was higher The GFAP immunoreactivity and lesion cavity was lower The BBB score was better (up to 14 days)
Wanjiang et al.,[41] 2020	hUC-MSC/Female Sprague-Dawley rats/N = 180/50-g aneurysm clip compression on for 60 sec on T9 level	Sham (n = 30) SCI+Veh (n = 30) SCI+cur (n = 30) SCI+hUC-MSC (n = 30) SCI+cur+hUC-MSC (n = 30) SCI+cur+hUC-MSC+U0126 (n = 30)	IP, 100 mg of curcumin, dissolved in 1 mL of DMSO and 0.5 mL of NS 1st injection: 30 min after the operation Once/day for 14 days.	Curcumin suppressed hUC-MSC apoptosis through the ERK1/2 signaling pathway The combination of curcumin and hUC-MSC therapies improved motor function after SCI in rats.
Bonilla et al.,[42] 2021	Induced pluripotent stem cells (iPSC-NSC) & Human MSC Female Sprague-Dawley rats/200 kdyne contusion on T8 level iPCS-NSC (n = 8)	Control (n = 16) MSC (n = 11) iPCS-NSC+MSC (n = 11) PA-C (n = 6) iPSC-NSC+MSC+PA-C (n = 7)	A pH-responsive polyacetal–curcumin nanoconjugate (PA–C) delivery into the intrathecal space in contusive SCI with stem cell transplantation.	PA–C-treated or PA–C and iPSC-NSC + MSC-treated groups: Smaller scars, whereas PA–C and iPSC-NSC + MSC therapy induced the preservation of β-III tubulin-positive axons. iPSC-NSC + MSC transplantation fostered the preservation of motoneurons and myelinated tracts, whereas PA–C therapy polarized microglia into an anti-inflammatory phenotype.
Elkhenany et al.,[67] 2021	Human induced neural progenitor cells (iNPC) Female Sprague-Dawley rats/200 kdyn Infinite Horizon Impactor on T8 level	HA_PM_iNPC (non SCI) (n = 3) HA_PPY_PM_iNPC (non SCI) (n = 3) HA_PM_CURC (n = 3) HA_PPY_PM_CURC (n = 3)HA_PM_iNPC (n = 3) HA_PPY_PM_iNPC (n = 3) HA_PM_CURC_iNPC (n = 3) HA_PPY_PM_CURC_iNPC (n = 3)	PM-embedded curcumin	PM-embedded iNPCs and CURC with PPY fibers supported a significant increase in neuropreservation (as measured by higher βIII tubulin staining of neuronal fibers) and decrease in the injured area (as measured by the lack of GFAP staining). *HA: hyaluronic acid *PM: Corning® PuraMatrix™ peptide hydrogel *PPY: polypyrrole-coated fibers

SCI, spinal cord injury; SC-NPC, spinal cord neural progenitor cell; MAP, mitogen-activated protein; p-ERK, phospho-extracellular signal-regulated kinase; PA, polyacetal; PA-C polyacetal-curcumin; epSPC, ependymal stem/progenitor cells of the spinal cord; GFAP, glial fibrillary acidic protein; BBB, Basso, Beattie, Bresnahan; hUC-MSC, umbilical cord mesenchymal stem cell; IP, intraperitoneal; DMSO, Dimethyl sulfoxide; ERK, extracellular signal-regulated kinase; CURC, curcumin.

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Table 4. Other studies showing the property of curcumin in promoting neurological functional recovery as evaluated by measuring the BBB score

Study	Specimen/sample size/ SCI method	Study design (experimental groups)	Curcumin treatment method	Summary of results
Kim et al.,[3] 2014	Male Sprague-Dawley rats/N = 36/ clipping 30-g force for 2 min on T9 level	Sham (n = 12) SCI/vehicle (n = 12) SCI/curcumin (n = 12)	200 mg/kg IP daily for 7 days	Curcumin group: Higher BBB scores 7–14 days after surgery (by anti-inflammatory and antioxidant action/ED-1, MDA, and SOD were measured)
Machova Urdzikova et al.,[43] 2015	Male Wistar rats/N = 60/or balloon compression using Fogarty catheter (2 Fr) on T8 level	Control (n = 30) Curcumin (n = 30)	60 mg/kg Epidural locally Immediately after injury and 6 mg/kg in olive oil IP daily for 1–28 days	Curcumin group: Improved behavioral recovery (BBB scores and plantar sensory performance scores) within the first week following SCI (by anti-inflammatory action/NF-κB, MIP1a,IL4, IL1b, IL2, IL6, IL12p70, TNF-α, and RANTES were measured)
Liu et al.,[44] 2018	Male Sprague-Dawley rats/ N = 60/10-g rod dropped, from 25-mm height on T9–10 level	SCI-Curcumin (n = 27) SCI-MP (n = 27) Sham group (n = 6)	200 mg/kg IP daily for 56 days	SCI-Curcumin group: Improvement in the BBB score MP-treated group better within the first 14 days Cur-treated group better from 21–49 days after SCI Paralleled BBB scores of the 2 treatment groups on 56 days after SCI (by anti-inflammatory action/Bax, Bcl-2, Caspase-3, and GFAP were measured)
Luo et al.,[68] 2021	Female Sprague-Dawley rats/ N = 24/2-mm segment of the spinal cord removed at T9 level	Control (n = 6). FC hydrogel (n = 6) FC/FI hydrogel (n = 6) FC/FI-Cur hydrogel (n = 6)	FC/FI-Cur hydrogel was implanted into the lesion area. FC: Fmoc-grafted chitosan FI: Fmoc peptide	FC/FI-Cur hydrogel group: Significantly promoted BBB walking score (by anti-inflammatory action/immunofluorescence staining of antibodies CD68, S100, neurofilament 200, GFAP, myelin basic protein, etc. were measured)

BBB, Basso, Beattie, Bresnahan; SCI, spinal cord injury; ED-1, CD68/SR-D1 antibody (marker for activated macrophages); MDA, malondialdehyde; SOD, superoxide dismutase; NF-kB, nuclear factor kappa B; MIP1a, macrophage inflammatory protein-1 alpha; IL, interleukin; TNF-α, tumor necrosis factor-alpha; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; MP, methylprednisolone; IP, intraperitoneal; GFAP, glial fibrillary acidic protein.

and effective strategy to increase its bioavailability because this method expands its solubility, promotes long-term circulation and retention in the body, and overcomes the physiological barriers of curcumin.[52,53] These nanoformulations can increase the half-life of curcumin in plasma and significantly reduce the administration dosage, resolving the toxicity issue associated with the use of high-dose curcumin.

Among the diverse nanocarriers developed for therapeutic applications, polymer therapeutics are the most successful polymeric nanomedicines.[54] For example, a combination therapy comprising ependymal stem/progenitor cells of the spinal cord and a pH-responsive polymer–curcumin conjugate for SCIs has been reported previously.[39] According to the study, conjugating curcumin with a pH-responsive polymeric carrier main chain, a polyacetal, improved its blood bioavailability and stability and facilitated a highly targeted curcumin distribution. PA–C also enhanced neuroprotection, axonal development, and functional recovery in acute SCIs. Recently, a new method that improves bioavailability by combining curcumin with extracellular vesicles was reported.[55] In the study, 120-nm engineered extracellular vesicles derived from primary M2 macrophages were used and nerve growth factors and curcumin were combined. The extracellular vesicles could effectively accumulate curcumin at the site of SCIs and inhibit uncontrollable inflammatory responses induced by secondary injury.

Further translational research is required to use curcumin in therapeutic settings. Oral intake of curcumin is insufficient for it to penetrate the blood-brain barrier; therefore, studies are needed to determine an effective administration method that would allow curcumin to act directly on injured neuronal tissues in the spinal cord. Furthermore, investigations on the safety of high-dose curcumin administration are required. In addition to nanotechnology, it is necessary to try various methods to enhance curcumin bioavailability. A strategy such as megadose administration might be crucial, and doses of previously commercialized curcumin products should be considered. Continuous or intermittent curcumin therapy has been administered in most animal investigations throughout the acute phase, which occurs within 24 hours of the primary injury, and the chronic phase, which occurs after the primary injury. Therefore, future research should focus on determining the most beneficial timing and duration of administration.

LIMITATIONS

The lack of information on certain aspects of curcumin is a

limitation of this paper. For example, we did not investigate the bioactivity of curcumin in astrocytes.[56] It also lacks detailed information on several signaling pathways that are regulated by curcumin, including the Nrf2/heme oxygenase 1 pathway,[30] the mammalian target of rapamycin,[57] and TGF-β–SOX9 pathway.[58] As a result, there are constraints in providing cutting-edge knowledge regarding curcumin therapy. However, the goal of this review paper is to provide clinicians with basic and comprehensive information regarding the role of curcumin in SCI treatment. The authors believe that this review paper would prove to be helpful to neurospinal clinicians.

CONCLUSION

Curcumin is a neuroprotective polyphenolic compound that has benefits such as pluripotency, oral safety, long usage history, and low cost. Several animal experiments have shown that curcumin can minimize secondary injury following primary SCIs through its anti-inflammatory, antioxidant, and stem cell mobilization properties. Curcumin is an influential therapeutic agent that can potentially treat catastrophic secondary injuries in the spinal cord, including inflammation, edema, free radical injury, fibrosis, and glial scar formation. It can enhance neurological function in rats, as measured using the BBB locomotor rating scale. Studies exploring ways to overcome its limited bioavailability have recently begun. More translational investigations on curcumin are necessary to facilitate its use in clinical settings.

NOTES

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REFERENCES

1. Lee YS, Kim KT, Kwon BK. Hemodynamic management of acute spinal cord injury: a literature review. Neurospine 2021;18:7-14.
2. Ormond DR, Shannon C, Oppenheim J, et al. Stem cell therapy and curcumin synergistically enhance recovery from spinal cord injury. PLoS One 2014;9:e88916.
3. Kim KT, Kim MJ, Cho DC, et al. The neuroprotective effect of treatment with curcumin in acute spinal cord injury: laboratory investigation. Neurol Med Chir (Tokyo) 2014;54:387-94.
4. Lee YS, Cho DC, Kim CH, et al. Effect of curcumin on the inflammatory reaction and functional recovery after spinal cord injury in a hyperglycemic rat model. Spine J 2019;19:2025-39.
5. Gautam SC, Gao X, Dulchavsky S. Immunomodulation by curcumin. In: Aggarwal BB, Surh YJ, Shishodia S, editors. The molecular targets and therapeutic uses of curcumin in health and disease. Boston (MA): Springer US; 2007:321-41.
6. Das L, Vinayak M. Long term effect of curcumin in restoration of tumour suppressor p53 and phase-II antioxidant enzymes via activation of Nrf2 signalling and modulation of inflammation in prevention of cancer. PLoS One 2015;10:e0124000.
7. Naqvi S, Panghal A, Flora SJS. Nanotechnology: a promising approach for delivery of neuroprotective drugs. Front Neurosci 2020;14:494.
8. Yao M, Yang L, Wang J, et al. Neurological recovery and antioxidant effects of curcumin for spinal cord injury in the rat: a network meta-analysis and systematic review. J Neurotrauma 2015;32:381-91.
9. Yuan J, Liu W, Zhu H, et al. Curcumin inhibits glial scar formation by suppressing astrocyte-induced inflammation and fibrosis in vitro and in vivo. Brain Res 2017;1655:90-103.
10. Daverey A, Agrawal SK. Curcumin protects against white matter injury through NF-κB and Nrf2 cross talk. J Neurotrauma 2020;37:1255-65.
11. Machova Urdzikova L, Karova K, Ruzicka J, et al. The anti-inflammatory compound curcumin enhances locomotor and sensory recovery after spinal cord injury in rats by immunomodulation. Int J Mol Sci 2015;17:49.
12. Minassi A, Sánchez-Duffhues G, Collado JA, et al. Dissecting the pharmacophore of curcumin. Which structural element is critical for which action? J Nat Prod 2013;76:1105-12.

 https://doi.org/10.14245/ns.2244148.074

13. Pérez-Lara A, Corbalán-García S, Gómez-Fernández JC. Curcumin modulates PKCα activity by a membrane-dependent effect. Arch Biochem Biophys 2011;513:36-41.
14. Gupta SC, Prasad S, Kim JH, et al. Multitargeting by curcumin as revealed by molecular interaction studies. Nat Prod Rep 2011;28:1937-55.
15. Selvam C, Jachak SM, Thilagavathi R, et al. Design, synthesis, biological evaluation and molecular docking of curcumin analogues as antioxidant, cyclooxygenase inhibitory and anti-inflammatory agents. Bioorg Med Chem Lett 2005;15:1793-7.
16. Priyadarsini KI, Maity DK, Naik GH, et al. Role of phenolic O-H and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. Free Radic Biol Med 2003;35:475-84.
17. Das J, Pany S, Panchal S, et al. Binding of isoxazole and pyrazole derivatives of curcumin with the activator binding domain of novel protein kinase C. Bioorg Med Chem 2011;19:6196-202.
18. Bill MA, Nicholas C, Mace TA, et al. Structurally modified curcumin analogs inhibit STAT3 phosphorylation and promote apoptosis of human renal cell carcinoma and melanoma cell lines. PLoS One 2012;7:e40724.
19. Song YH, Agrawal NK, Griffin JM, et al. Recent advances in nanotherapeutic strategies for spinal cord injury repair. Advanced Drug Delivery Reviews 2019;148:38-59.
20. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytother Res 2012;26:1719-25.
21. Xie XK, Xu ZK, Xu K, et al. DUSP19 mediates spinal cord injury-induced apoptosis and inflammation in mouse primary microglia cells via the NF-kB signaling pathway. Neurol Res 2020;42:31-8.
22. Elumalai M, Muthaiah R, Alf MA. Identification of curcumin targets in neuroinflammatory pathways: molecular docking scores with GSK-3β, p38 MAPK, COX, ICE and TACE enzymes. Acta Pol Pharm 2012;69:237-45.
23. Yuan J, Zou M, Xiang X, et al. Curcumin improves neural function after spinal cord injury by the joint inhibition of the intracellular and extracellular components of glial scar. J Surg Res 2015;195:235-45.
24. Zu J, Wang Y, Xu G, et al. Curcumin improves the recovery of motor function and reduces spinal cord edema in a rat acute spinal cord injury model by inhibiting the JAK/STAT signaling pathway. Acta Histochem 2014;116:1331-6.
25. Hausmann ON. Post-traumatic inflammation following spinal cord injury. Spinal Cord 2003;41:369-78.
26. Bengmark S. Curcumin, an atoxic antioxidant and natural NFkappaB, cyclooxygenase-2, lipooxygenase, and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases. JPEN J Parenter Enteral Nutr 2006;30:45-51.
27. Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. Adv Exp Med Biol 2007;595:105-25.
28. Yu T, Dohl J, Elenberg F, et al. Curcumin induces concentration-dependent alterations in mitochondrial function through ROS in C2C12 mouse myoblasts. J Cell Physiol 2019;234:6371-81.
29. Panahi Y, Ahmadi Y, Teymouri M, et al. Curcumin as a potential candidate for treating hyperlipidemia: a review of cellular and metabolic mechanisms. J Cell Physiol 2018;233:141-52.
30. Jin W, Botchway BOA, Liu X. Curcumin can activate the Nrf2/HO-1 signaling pathway and scavenge free radicals in spinal cord injury treatment. Neurorehabil Neural Repair 2021;35:576-84.
31. DiSilvestro RA, Joseph E, Zhao S, et al. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. Nutr J 2012;11:79.
32. Balci M, Namuslu M, Devrim E, et al. Effects of computer monitor-emitted radiation on oxidant/antioxidant balance in cornea and lens from rats. Mol Vis 2009;15:2521-5.
33. Daverey A, Agrawal SK. Pre and post treatment with curcumin and resveratrol protects astrocytes after oxidative stress. Brain Res 2018;1692:45-55.
34. Scapagnini G, Vasto S, Abraham NG, et al. Modulation of Nrf2/ARE pathway by food polyphenols: a nutritional neuroprotective strategy for cognitive and neurodegenerative disorders. Mol Neurobiol 2011;44:192-201.
35. Ni H, Jin W, Yuan B, et al. Curcumin inhibits the increase of labile zinc and the expression of inflammatory cytokines after traumatic spinal cord injury in rats. J Surg Res 2014;187:646-52.
36. Son S, Kim KT, Cho DC, et al. Curcumin stimulates proliferation of spinal cord neural progenitor cells via a mitogen-activated protein kinase signaling pathway. J Korean Neurosurg Soc 2014;56:1-4.
37. Bang WS, Kim KT, Seo YJ, et al. Curcumin increase the expression of neural stem/progenitor cells and improves functional recovery after spinal cord injury. J Korean Neurosurg Soc 2018;61:10-8.

38. Mujoo K, Nikonoff LE, Sharin VG, et al. Curcumin induces differentiation of embryonic stem cells through possible modulation of nitric oxide-cyclic GMP pathway. Protein Cell 2012;3:535-44.
39. Requejo-Aguilar R, Alastrue-Agudo A, Cases-Villar M, et al. Combined polymer-curcumin conjugate and ependymal progenitor/stem cell treatment enhances spinal cord injury functional recovery. Biomaterials 2017;113:18-30.
40. Ruzicka J, Urdzikova LM, Kloudova A, et al. Anti-inflammatory compound curcumin and mesenchymal stem cells in the treatment of spinal cord injury in rats. Acta Neurobiol Exp (Wars) 2018;78:358-74.
41. Wanjiang W, Xin C, Yaxing C, et al. Curcumin improves human umbilical cord-derived mesenchymal stem cell survival via ERK1/2 signaling and promotes motor outcomes after spinal cord injury. Cell Mol Neurobiol 2022;42:1241-52.
42. Bonilla P, Hernandez J, Giraldo E, et al. Human-induced neural and mesenchymal stem cell therapy combined with a curcumin nanoconjugate as a spinal cord injury treatment. Int J Mol Sci 2021;22:5966.
43. Machova Urdzikova L, Karova K, Ruzicka J, et al. The anti-inflammatory compound curcumin enhances locomotor and sensory recovery after spinal cord injury in rats by immunomodulation. Int J Mol Sci 2015;17:49.
44. Liu X, Zhang Y, Yang Y, et al. Therapeutic effect of curcumin and methylprednisolone in the rat spinal cord injury. Anat Rec (Hoboken) 2018;301:686-96.
45. Burgos-Morón E, Calderón-Montaño JM, Salvador J, et al. The dark side of curcumin. Int J Cancer 2010;126:1771-5.
46. Aggeli I-K, Koustas E, Gaitanaki C, et al. Curcumin acts as a pro-oxidant inducing apoptosis via JNKs in the isolated perfused rana ridibunda heart. J Exp Zool A Ecol Genet Physiol 2013;319:328-39.
47. Jantawong C, Priprem A, Intuyod K, et al. Curcumin-loaded nanocomplexes: acute and chronic toxicity studies in mice and hamsters. Toxicol Rep 2021;8:1346-57.
48. López-Lázaro M. Dual role of hydrogen peroxide in cancer: possible relevance to cancer chemoprevention and therapy. Cancer Lett 2007;252:1-8.
49. Ahsan H, Parveen N, Khan NU, et al. Pro-oxidant, anti-oxidant and cleavage activities on DNA of curcumin and its derivatives demethoxycurcumin and bisdemethoxycurcumin. Chem Biol Interact 1999;121:161-75.
50. Banerjee A, Kunwar A, Mishra B, et al. Concentration dependent antioxidant/pro-oxidant activity of curcumin: studies from AAPH induced hemolysis of RBCs. Chem Biol Interact 2008;174:134-9.
51. Moos PJ, Edes K, Mullally JE, et al. Curcumin impairs tumor suppressor p53 function in colon cancer cells. Carcinogenesis 2004;25:1611-7.
52. Yallapu MM, Jaggi M, Chauhan SC. Curcumin nanoformulations: a future nanomedicine for cancer. Drug Discov Today 2012;17:71-80.
53. Fonseca-Santos B, Dos Santos AM, Rodero CF, et al. Design, characterization, and biological evaluation of curcumin-loaded surfactant-based systems for topical drug delivery. Int J Nanomedicine 2016;11:4553-62.
54. Duncan R, Gaspar R. Nanomedicine(s) under the microscope. Mol Pharm 2011;8:2101-41.
55. Zhang C, Li D, Hu H, et al. Engineered extracellular vesicles derived from primary M2 macrophages with anti-inflammatory and neuroprotective properties for the treatment of spinal cord injury. J Nanobiotechnology 2021;19:373.
56. Eghbaliferiz S, Farhadi F, Barreto GE, et al. Effects of curcumin on neurological diseases: focus on astrocytes. Pharmacol Rep 2020;72:769-82.
57. Lin J, Huo X, Liu X. "mTOR signaling pathway": a potential target of curcumin in the treatment of spinal cord injury. BioMed Res Int 2017;2017:1634801.
58. Yuan J, Botchway BOA, Zhang Y, et al. Curcumin can improve spinal cord injury by inhibiting TGF-β-SOX9 signaling pathway. Cell Mol Neurobiol 2019;39:569-75.
59. Wang YF, Zu JN, Li J, et al. Curcumin promotes the spinal cord repair via inhibition of glial scar formation and inflammation. Neurosci Lett 2014;560:51-6.
60. Lin CC, Chiang TH, Chen WJ, et al. CISD2 serves a novel role as a suppressor of nitric oxide signalling and curcumin increases CISD2 expression in spinal cord injuries. Injury 2015;46:2341-50.
61. Ni H, Jin W, Zhu T, et al. Curcumin modulates TLR4/NF-κB inflammatory signaling pathway following traumatic spinal cord injury in rats. J Spinal Cord Med 2015;38:199-206.
62. Ruzicka J, Urdzikova LM, Svobodova B, et al. Does combined therapy of curcumin and epigallocatechin gallate have a synergistic neuroprotective effect against spinal cord injury? Neural Regen Res 2018;13:119-27.
63. Yardım A, Kandemir FM, Çomaklı S, et al. Protective effects of curcumin against paclitaxel-induced spinal cord and sciatic nerve injuries in rats. Neurochem Res 2021;46:379-95.
64. Akar İ, İnce İ, Arici A, et al. The protective effect of curcumin on a spinal cord ischemia-reperfusion injury model. Ann

 https://doi.org/10.14245/ns.2244148.074

Vasc Surg 2017;42:285-92.
65. Xi J, Luo X, Wang Y, et al. Tetrahydrocurcumin protects against spinal cord injury and inhibits the oxidative stress response by regulating FOXO4 in model rats. Exp Ther Med 2019;18:3681-7.
66. Daverey A, Agrawal SK. Neuroprotective effects of Riluzole and Curcumin in human astrocytes and spinal cord white matter hypoxia. Neurosci Lett 2020;738:135351.
67. Elkhenany H, Bonilla P, Giraldo E, et al. A hyaluronic acid demilune scaffold and polypyrrole-coated fibers carrying embedded human neural precursor cells and curcumin for surface capping of spinal cord injuries. Biomedicines 2021;9:1928.
68. Luo J, Shi X, Li L, et al. An injectable and self-healing hydrogel with controlled release of curcumin to repair spinal cord injury. Bioact Mater 2021;6:4816-29.

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Review Article

Recent Molecular and Genetic Findings in Intramedullary Spinal Cord Tumors

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The study of genetic alterations and molecular biology in central nervous system (CNS) tumors has improved the accuracy of estimations of patient prognosis and tumor categorization. Therefore, the updated 2021 World Health Organization (WHO) classification includes various diagnostic genes, molecules, and pathways for diagnosis, as well as histological findings. These findings are expected both to have diagnostic applications and to facilitate new targeted therapies that target tumor-specific genetic changes and molecular biology. Intramedullary spinal cord tumors (IMSCTs) are rare CNS tumors that are difficult to treat because they occur in eloquent areas. Although the genetic underpinnings of IMSCTs remain unclear compared to their intracranial counterparts, the genetic characteristics of these tumors are gradually being revealed. Here, we describe the major changes in the new 2021 WHO classification and review the major types of IMSCTs, with an emphasis on their clinical features and genetic alterations.

Keywords: Intramedullary spinal cord tumor, Astrocytoma, Ependymoma, Hemangioblastoma, Genomics, Genetics

INTRODUCTION

Central nervous system (CNS) tumors, which arise from the brain and spinal cord, are classified into over 120 entities. World Health Organization (WHO) Classification of Tumors of the Central Nervous System has been revised on several occasions since its first publication in 1979.[1] In the prior version of the WHO classification, CNS tumors were classified based on their histological findings with a diagnosis term and WHO grade (I–IV) embedded. However, recent comprehensive genomic studies revealed that an integrated diagnosis based on pathological and molecular findings more accurately predicted the prognosis than a diagnosis based on pathological findings alone. An integrated diagnosis with molecular information was first presented in the 2016 WHO classification,[2,3] and the latest version was published in 2021.[4]

Although intramedullary spinal cord tumors (IMSCTs) are included in the category of CNS tumors, they are much less common than intracranial tumors and their molecular and genetic studies considerably lag behind those of intracranial tumors. IMSCTs account for 5%–10% of all spinal cord tumors, with ependymomas and astrocytomas comprising 80%–90% of IMSCTs.[5-7] Hemangioblastomas are the third most common IMSCTs, after ependymomas and astrocytomas.[8] Recent advances in molecular and genetic research have revealed that some infratentorial tumors, including IMSCTs, have different genetic characteristics from supratentorial tumors.[9-11] In this article, we discuss the major changes in the 2021 WHO classification of CNS tumors and present a narrative review of the literature on recent molecular and genetic analyses that characterize the major types of IMSCTs.

Informed consent was obtained from all subjects involved in

the study. This study was approved by the Ethics Committee or Institutional Review Board of Nagoya University (2012-0067-19).

MAJOR CHANGES IN THE 2021 WHO CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMORS

CNS tumors were conventionally classified based on histological findings. Molecular parameters were incorporated into the classification of CNS tumors (i.e., an integrated diagnosis) in the 2016 WHO classification of CNS tumors and its update in 2021.[2,3] The process of an integrated diagnosis for CNS tumors is still developing in the 2021 WHO classification of CNS tumors, where various key diagnostic genes, molecules, pathways are applied to define entities, and the nomenclature was made more consistent and simpler by only including the location, age, or genetic modifiers of clinical utility. Modifier terms like "anaplastic" are not used because "grading within types" is applied. Thus, terms such as "diffuse astrocytoma, IDH-mutant," "anaplastic astrocytoma, IDH-mutant," and "glioblastoma, IDH-mutant" in the 2016 WHO classification of CNS tumors are now simply classified as "astrocytoma, IDH-mutant grade 2, 3, and 4." Adult-type diffuse gliomas, which were divided into 15 entities in 2016, have been classified into only 3 types in 2021. To standardize the 2021 WHO classification of CNS tumors with other non-CNS tumor classifications, the term "type" and "subtype" have been adopted instead of "entity" and "variant," respectively. For example, meningioma is considered a single type in the 2021 WHO classification of CNS tumors with 15 subtypes.

The WHO CNS tumor classification has adopted an original grading system in line with the non-CNS tumor classification to facilitate grading across different entities.[12] In the prior WHO classification of CNS tumors, a CNS was given one diagnosis name and automatically assigned to one WHO grade. In the 2021 classification, CNS tumors are graded within types and the grading is written using Arabic numerals, not Roman. For example, astrocytoma is assigned to grade 2, 3, or 4 based on its histological and genetic findings in 2021. Nonetheless, the 2021 WHO classification has generally retained the ranges of grades used for tumor types in prior editions (grade I: curable if surgically removed, grade IV: highly malignant, leading to death without effective therapy). Notably, although grading was based on histological findings in the prior version of the WHO classification of CNS tumors, molecular findings are applied as biomarkers to assign grades within the tumor type in the 2021 WHO classification of CNS tumors. The WHO grading of CNS tumors is no longer a histological system. For example, *CDKN2A/B* in IDH-mutant astrocytoma and the *TERT* promoter mutation, *EGFR* amplification, and +7/-10 copy number changes in IDH-wildtype astrocytoma are enough information to assign grade 4 even if the tumor is histologically low-grade.[13]

THE CLINICAL FEATURES AND GENETIC FINDINGS OF INTRAMEDULLARY SPINAL CORD TUMORS

1. Spinal Astrocytomas

Astrocytomas are the second most common IMSCTs observed in adults, but the most common in children.[9] Several recent studies have demonstrated a clear prognostic difference between high-grade (WHO grade 3, 4) and low-grade spinal astrocytomas (mainly pilocytic astrocytoma WHO grade 1 and diffuse astrocytoma WHO grade 2).[5-7] Therefore, we discuss spinal high-grade and low-grade astrocytomas separately, with descriptions of the important genetic mutations in each category.

1) High-grade astrocytomas

Gross total resection (GTR) is almost impossible for most high-grade astrocytomas, and subtotal resection or biopsy followed by radiation and chemotherapy is performed as the standard treatment in practical settings. Even with such treatment, the prognosis of these tumors is unfavorable (Fig. 1). There is a survival advantage with an excision extent of 78% or higher in intracranial glioblastoma, comparable to total excision.[14] Even in spinal high-grade astrocytomas, the extent of excision might be correlated with the prognosis, although the exact threshold of the extent of excision that improves the prognosis has yet to be clarified.[15,16] The benefits of adjuvant radiation and chemotherapy are controversial, although they are often performed for patients with residual tumors.[9,16-18]

(1) H3 K27M

The H3 K27M mutation of the *H3F3A* gene is the most important and well-established genetic mutation in high-grade astrocytomas (Table 1). Histones are major proteins that provide structural support for chromosomes. The histone tail (the N-terminal of the histone protein) plays an important role in the transcriptional regulation of DNA. Histone tail amino acids undergo various chemical modifications such as acetylation

and methylation. The major histone is H3.1 in humans, and the histone subtypes referred to as histone variants, such as H3.2 and H3.3, are functionally encoded by a different gene. The K27M mutation changes lysine 27 to methionine in the N-terminus of the histone tail of the *H3F3A* gene, which mainly encodes the histone variant H3.3. This mutation is frequently detected in pediatric glioblastomas, diffuse intrinsic pontine gliomas (DIPGs), thalamic gliomas, and spinal cord astrocytomas[19-21]; however, it is not found in other CNS tumors or normal nerve tissues. This indicates that H3 K27M is a driver gene abnormality in brain stem gliomas and could be a powerful diagnostic marker of spinal diffuse astrocytomas.[22]

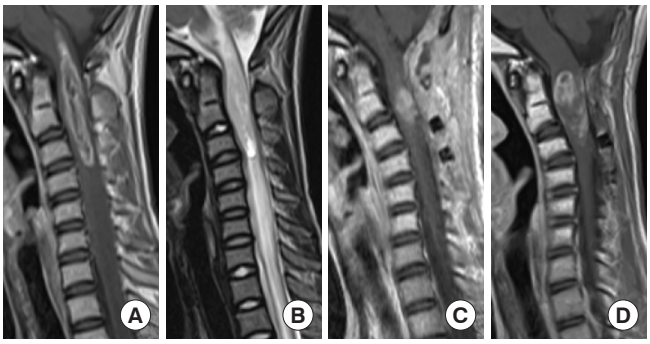

Fig. 1. Diffuse midline glioma, H3K27-altered. (A) A 15-year-old male patient with neck pain and limb weakness for 2 months presented with an intramedullary tumor with ring enhancement on gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) from the medulla oblongata to the C4 level on MRI. (B) T2-weighted MRI showed extensive edematous changes. (C) The tumor was surgically removed, although MRI one month later showed residual tumor. A histopathological examination showed anaplastic astrocytoma; however, the H3 K27M mutation was found, and the final diagnosis was diffuse midline glioma, H3K27-altered. After surgery, the patient underwent radiotherapy and chemotherapy. (D) Fifteen months after the first surgery, MRI showed tumor regrowth, and the patient died 21 months after surgery.

In the 2016 WHO classification of CNS tumors, diffuse midline gliomas with the H3 K27M mutation were categorized as having a poor prognosis following the results of molecular diagnosis. Diffuse midline gliomas, characterized by a specific site mutation of H3 K27M, usually occur in the midline of the CNS, and this entity was renamed "diffuse midline glioma, H3 K27-altered" to reflect the fact that other changes (e.g., EZHIP protein overexpression) can define this entity in addition to the previously recognized H3 K27 mutations in the fifth edition of the WHO Brain Tumor Classification (2021).[4]

According to recent studies of comprehensive molecular profiling of CNS tumors, approximately 50%–60% of high-grade spinal astrocytoma cases have the *H3F3A* K27M (H3 K27M) mutation, as do DIPGs and thalamic gliomas.[6,19,21-25]

H3 K27M-mutant spinal cord gliomas are highly malignant tumors according to the WHO classification; however, their clinical manifestations, imaging characteristics, chemotherapy,

Table 1. Summary of intramedullary spinal cord tumors

Tumor type	Gene mutation	Incidence	Clinical implications
High-grade astrocytomas	H3 K27M	About half of spinal high-grade astrocytomas were described to harbor the H3 K27M mutation.	H3 K27M mutation is associated with high malignancy, regardless of the histopathological findings.
Low-grade astrocytomas	*BRAF*	Although not restricted to spinal cord lesions, more than 75% of PA harbor the *KIAA1549-BRAF* mutation, and about 6% harbor the *BRAF* V600E mutation. The frequency of the mutation in DA is unknown.	*KIAA1549-BRAF* mutation is correlated with better prognosis. *BRAF* V600E is associated with more aggressive behavior in pediatric low-grade astrocytomas.
	IDH	Although common in intracranial counterparts, it seems to be quite rare in spinal cord lesions.	The relationship with the prognosis in spinal astrocytomas is controversial because of its rarity.
Spinal ependymomas	*NF2*	*NF2* mutation is not apparent in intracranial ependymomas.	Driver mutation for spinal cord ependymomas.
	MYCN amplification	Most likely present in a quite small number of patients in spinal ependymoma.	It has characteristic clinical features and correlates with poor prognosis.
Spinal hemangioblastomas	*VHL*	Most cases of VHL disease are associated with HB and some patients with sporadic HB carry the *VHL* mutation.	Benign vascular lesion.

PA, pilocytic astrocytoma; DA, diffuse astrocytoma; HB, hemangioma.

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and appropriate surgical treatment have not yet been well-elucidated due to their rarity. At present, there are few reports about the diagnosis and treatment of H3 K27M-mutant spinal cord gliomas.[24,26-28] Although H3 K27M-mutant diffuse midline gliomas have currently been classified as WHO grade IV, recent studies on high-grade gliomas of the spinal cord have not revealed a clear prognostic difference between the prognosis of H3 K27 wild-type cases and H3 K27M mutant cases.[6,24,28] However, high enhancer of zeste homolog 2 (EZH2) expression and H3 K27me3 loss may be associated with a poor prognosis.[22,29] The interaction between the H3 K27M mutation and polycomb repressive complex 2 is promoted by EZH2. This interaction results in an overall reduction of H3 K27me3, as observed in tumors other than spinal cord gliomas. Ishi et al.[22] found that the combination of H3 K27me3 status and EZH2 expression had prognostic value for WHO grade 2–4 diffuse spinal cord gliomas. Maeda et al.[30] reported that mutant allele-specific imbalance was associated with significantly higher Ki-67 index and poorer survival, and related to downregulation of H3 K27me3 modification.

2) Low-grade astrocytomas

The majority of spinal cord low-grade astrocytomas are grade 1 pilocytic astrocytomas and grade 2 astrocytomas. These tumors have been reported to have a better prognosis than high-grade astrocytomas.[6,31] Surgical resection is the mainstay of treatment for patients with low-grade spinal cord astrocytoma with the intention of maximizing resection and avoiding long-term neurological dysfunction. GTR may be possible in cases with a clear tumor-parenchyma interface (Fig. 2). It is difficult to achieve GTR with more invasive tumors, such as grade 2 astrocytoma, although a better prognosis is expected than with high-grade astrocytoma because of their slower growth pattern (Fig. 3).

(1) BRAF

Two major mutations have been noted in *BRAF*: a fusion oncogene between *BRAF* and *KIAA1549* (*KIAA1549-BRAF*), and the substitution of valine to glutamate at position 600 (*BRAF* V600E).[32] These genetic mutations have been reported to activate the mitogen-activated protein kinase (MAPK) pathway, which is associated with tumorigenesis.[33,34] Pilocytic astrocytomas harboring the *BRAF* V600E mutation account for about 5%–15% of all cases,[35] and the *KIAA1549-BRAF* fusion gene is more likely to be detected, especially in infratentorial lesions[32,36,37] (Table 1). In a study including 10 cases of grade 1 spinal cord pilocytic astrocytomas, there were 3 cases with *BRAF-KIAA1549* translocation and 5 cases with *BRAF* copy number gain.[38] Another study that included 26 grade 1 spinal cord pilocytic astrocytomas revealed that 10 patients harbored the *KIAA1549-BRAF* mutation and 1 patient harbored the *BRAF* V600E mutation.[31]

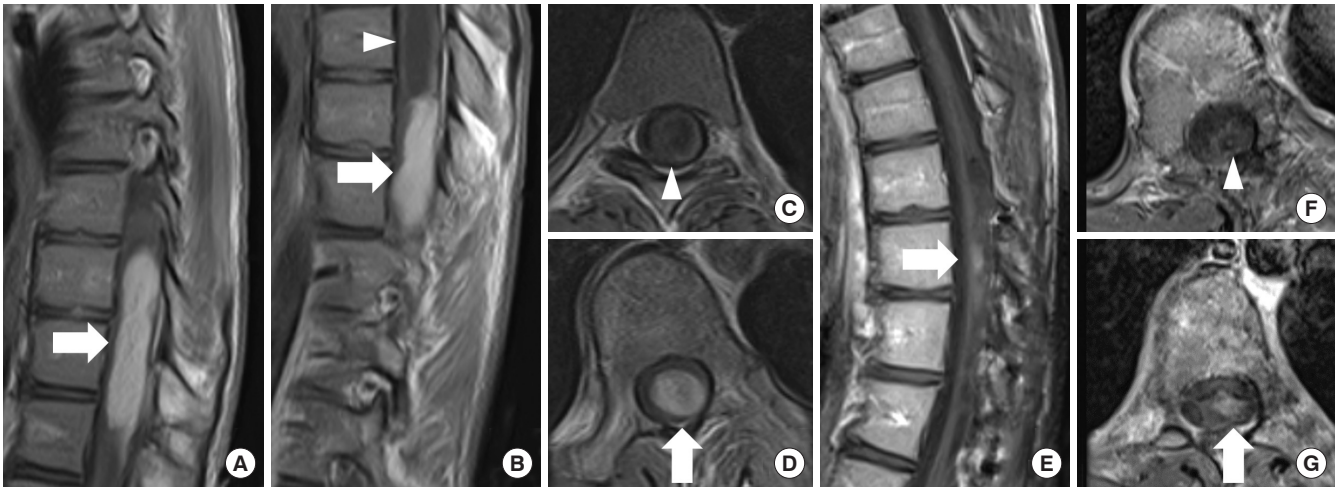

Fig. 2. Pilocytic astrocytoma, World Health Organization grade 1. (A–D) An 18-year-old man scheduled for surgery for scoliosis revealed a mass lesion at T8–12 with syrinx. The tumor was shown in contrast by gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) (arrow: tumor, arrowhead: syrinx). During the waiting period for surgery, the patient suffered from sudden onset of paralysis of the lower limbs and urinary retention, and emergency surgery was performed. The tumor had a relatively distinct surgical plane that separated it from the surrounding spinal cord parenchyma, and almost the entire tumor could be removed. Thirty-one months later, MRI showed that a tiny contrast-enhancing lesion was still present (E, G) and the syrinx resolution (F). At 40 months postoperatively, the patient's neurological symptoms were stable.

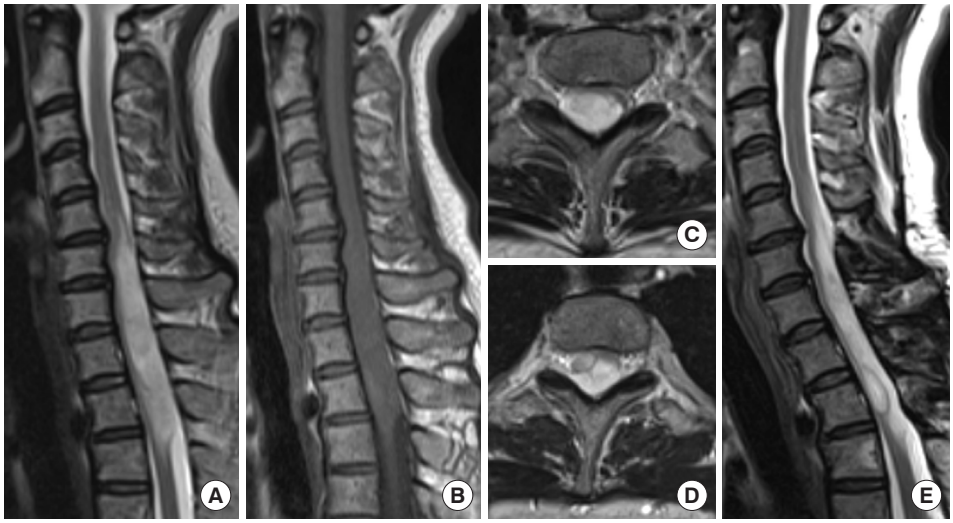

Fig. 3. Diffuse astrocytoma, World Health Organization grade 2, *IDH1* R132H mutant. A 42-year-old woman experienced numbness in both lower extremities for about 3 years and numbness in the right upper extremity and muscle weakness in the right lower extremity for 2 months. Magnetic resonance imaging (MRI) revealed an intramedullary spinal tumor at the C5–T3 levels. The tumor diffusely expanded with high signal intensity on T2-weighted MRI (A, C, D) and without any enhancements on gadolinium-enhanced T1-weighted MRI (B). It was difficult to identify a distinct surgical plane for the tumor, and partial removal was achieved. The tumor was diagnosed as diffuse astrocytoma, *IDH1* R132H mutant. Forty-two months later, MRI showed no evidence of tumor growth (E), and her symptoms were stable.

BRAF mutations have also been reported in grade 2 spinal cord astrocytomas. In a study including 10 cases of grade 2 spinal cord diffuse astrocytomas, 1 case had *BRAF-KIAA1549* translocation and 2 cases had *BRAF* amplification.[38] Another study that included 17 grade 1 spinal cord pilocytic astrocytomas revealed that 2 patients harbored the *BRAF* V600E mutation.[31] Low-grade gliomas with *BRAF* mutations can be classified into new tumor types according to the 2021 WHO classification. Reflecting the practical and conceptual importance of separating pediatric gliomas from other diffuse gliomas, 2 additional groups were added: pediatric diffuse low-grade gliomas and pediatric diffuse high-grade gliomas. "Diffuse low-grade glioma, MAPK pathway-altered" in the group of pediatric diffuse low-grade gliomas is defined as a pediatric glioma with broad histologic features, including astrocytic, oligodendroglial, or mixed morphology that shows activation of the MAPK pathway, such as *BRAF* mutations.[4]

The influence of *BRAF* mutations on the prognosis remains controversial. Some studies have shown that the *KIAA1549-BRAF* fusion is associated with improved prognosis in pediatric low-grade astrocytomas,[36,39,40] while another report revealed that the absence of the *KIAA1549-BRAF* fusion did not contribute significantly to the prognosis of spinal cord grade 1 pilocytic astrocytomas.[31] The *BRAF* V600E point mutation is thought to be associated with more aggressive behavior in pediatric low-grade astrocytomas.[40]

(2) IDH

Isocitrate dehydrogenase (IDH) mutations were first identified in 2008 in intracranial glioblastoma[41] and in >80% of WHO grade 2 and 3 cases.[42,43] Because IDH mutations are associated with the prognosis of intracranial gliomas,[43,44] IDH mutations are considered clinically significant, and the 2021 WHO classification classifies the common diffuse gliomas of adults into 3 types: "astrocytoma, IDH-mutant"; "oligodendroglioma, IDH-mutant and 1p/19q-codeleted"; and "glioblastoma, IDH-wild-type."[4] However, IDH mutations are extremely rare in spinal gliomas and their incidence in spinal cord gliomas is not well understood[32,45] (Table 1). According to the results of immunohistochemistry and Sanger sequencing for 120 midline gliomas, including 35 spinal gliomas, 61 patients tested positive for the H3 K27M mutation, while only 2 cases exhibited the *IDH1* R132H mutation.[46] In another study examining the molecular characteristics of 83 spinal gliomas, there were no *IDH1* mutations, although H3 K27M mutations were found in 35 cases.[6] Furthermore, the results of the genetic analysis of spinal cord gliomas by next-generation sequencing (NGS) have been recently reported. NGS for 61 intramedullary astrocytomas including 17

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grade 2 diffuse astrocytomas, revealed 2 cases of IDH mutations.[31] In another study of NGS for 26 spinal astrocytomas, there were 2 IDH mutation cases.[7] Thus, spinal cord gliomas are less likely to harbor the IDH mutation than intracranial gliomas.

In addition, the majority of IDH gene mutations in intracranial gliomas are *IDH1* R132H[43]; however, the IDH mutation variants found in spinal cord gliomas may be different from those found in intracranial gliomas. A recent retrospective study further supports this hypothesis. In this study of *IDH1* R132H mutant gliomas and noncanonical IDH-mutant (not *IDH1* R132H) gliomas, none of the 166 *IDH1* R132H mutant gliomas included an infratentorial region, while nine of 155 (5.5%) noncanonical IDH-mutant gliomas were infratentorial regions.[47] Intracranial gliomas and infratentorial gliomas including the spinal cord seem to have different genetic underpinnings. Even though IDH-mutant spinal gliomas are very rare, several spinal gliomas with variants other than *IDH1* R132H have been reported, and *IDH1* R132H mutations are probably not so prevalent in spinal gliomas. Konovalov et al.[48] reported 5 cases of spinal cord astrocytomas with IDH mutations: 2 had *IDH1* R132H mutations, while 1 had an *IDH1* R132G mutation. In addition, the remaining 2 cases had translocations at positions 82 (Arg → Lys, R82K) and 76 (Ile → Thr, I76T) of the *IDH1* gene, which had never been described in intracranial gliomas in the past. In another study, Takai et al.[49] reported one case of spinal astrocytoma with an *IDH1* R132S mutation, and we previously reported 2 cases with *IDH1* R132C and *IDH1* R132H mutations, respectively.[45] There is also a report of spinal cord glioma with *IDH2* R172.[31] Even though IDH-mutant spinal gliomas are very rare, several spinal gliomas with variants other than *IDH1* R132H have been reported, and *IDH1* R132H mutations are probably not very prevalent in spinal gliomas. Therefore, Immunohistochemistry using an anti-IDH1 R132H antibody, which is commonly used for intracranial gliomas, is not sufficient for spinal gliomas, and genetic testing is desirable.

The prognostic impact of IDH mutations in spinal cord gliomas is controversial.[7,31,45,49,50] Because IDH mutations are rare in spinal gliomas, the current knowledge of IDH mutations and the associated prognosis is inadequate. However, the prognosis of IDH-mutant spinal gliomas does not seem to be different depending on the IDH variant. A study of IDH variants and patients' prognosis found no significant difference in prognosis between *IDH1* R132H mutant glioma and noncanonical IDH-mutant glioma.[47] The clinical significance of IDH mutations in spine gliomas needs to be confirmed in a larger cohort.

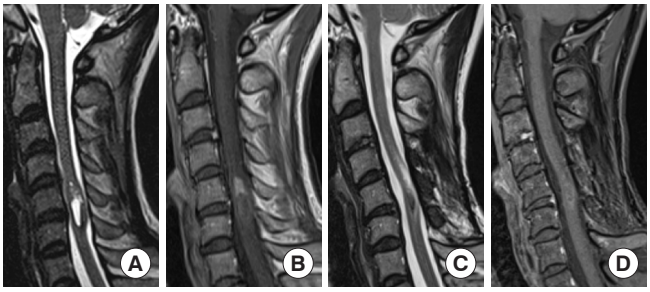

Fig. 4. Spinal ependymoma. A 44-year-old woman who had been treated for multiple intracranial meningiomas developed numbness in her right upper extremity. Magnetic resonance imaging (MRI) revealed an intramedullary tumor at the C5–6 level with an enlarged spinal cord. (A) T2-weighted MRI showed a hyperintense tumor with a syrinx and a partially hypointense lesion reflecting hemosiderin. (B) The tumor was shown in contrast by gadolinium-enhanced T1-weighted MRI. Tumor removal was performed via a posterior approach, and gross tumor resection was achieved because the surgical plane of the tumor was clear. (C, D) T2-weighted MRI 67 months after surgical removal showed low intensity that reflected hemosiderin, whereas there was no evident tumor recurrence and no enhancement on gadolinium-enhanced T1-weighted MRI.

2. Spinal Ependymomas

Spinal ependymomas are the most common IMSCTs.[9,51,52] Almost all ependymomas are benign tumors with clear tumor borders, and long-term survival can be expected by targeting GTR (Fig. 4).[8,53] Therefore, the long-term functional prognosis should also be considered in the treatment.[54-57]

1) NF2

Neurofibromin (*NF2*) gene mutations are driver mutations for spinal cord ependymomas and appear to be the most prevalent genetic mutations in spinal ependymomas[58] (Table 1). Pajtler et al.[10] analyzed about 500 ependymomas, including 47 spinal lesions and revealed that most spinal ependymomas had a loss of the 22q locus, which harbors the *NF2* gene, although *NF2* mutations were not seen in intracranial ependymomas. In another study, 47% (9 of 19) of spinal ependymomas had *NF2* mutations.[9,59] *NF2* is a tumor suppressor gene, and aberrations of the *NF2* gene make cells less responsive to contact inhibition, thereby promoting tumorigenesis.[58]

2) MYCN amplification

"Spinal ependymoma, *MYCN*-amplified" is a new category in the 2021 WHO classification.[4] Although *MYCN*-amplified ependymomas are very rare, they are associated with aggressive

behavior and unfavorable outcomes[60,61] (Table 1). Ghasemi et al.[62] investigated 13 *MYCN*-amplified ependymomas, of which 10 were WHO grade 3 and 3 were WHO grade 2 on histopathological examination. Compared to other subtypes of ependymomas, these groups had worse median progression-free survival (17 months) and median overall survival (87 months). These tumors were also characterized by a favored location of the cervical and thoracic spine, and were predominantly intradural and extramedullary.[63] The presence of diffuse leptomeningeal spread and dissemination has also been revealed as a distinctive feature of these tumors. Further study is required to develop new strategies to improve the prognosis of patients with *MYCN*-amplified spinal ependymoma.

3. Spinal Hemangioblastomas

Spinal cord hemangioblastomas are benign vascular lesions and constitute the third most common IMSCTs.[8] Surgical resection is recommended in cases of symptomatic lesions or lesions that appear to be growing on repeat imaging studies. Because hemangioblastoma generally shows a well-defined tumor border that allows GTR, radiotherapy has a limited role.[8,64] Although these are vascular-rich tumors, intraoperative hemorrhage is generally not a problem due to the availability of techniques such as temporary intraoperative arterial occlusion and preoperative embolization (Fig. 5).[8,65] Although hemangioblastoma regrowth is very rare once the tumor is completely removed, patients with von Hippel-Lindau (VHL) disease may show multiple hemangioblastomas with new lesions repeatedly arising.

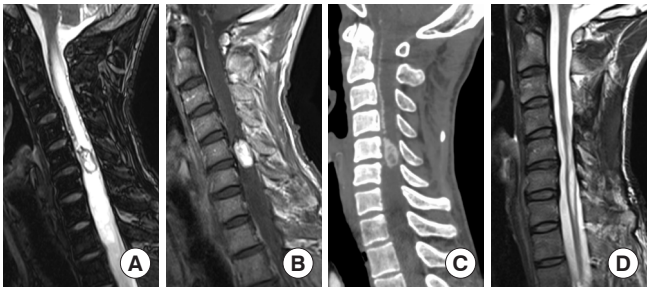

Fig. 5. Hemangioblastoma. A 44-year-old man presented with numbness in the right upper extremity and right paralysis. A radiological examination revealed a tumor at the C5 level. (A) T2-weighted MRI showed a well-defined tumor with a syrinx and flow void. (B) The tumor was strongly shown in contrast with gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI). (C) Dynamic computed tomography angiography also showed a strongly contrasted tumor with dilated feeder and drainer. Preoperative angiography and feeder occlusion were performed, and the tumor was totally resected microscopically via a posterior approach. Immediately after surgery, the patient's symptoms improved. (D) Thirty-six months later, MRI showed no recurrence of the tumor and the syrinx had collapsed.

1) VHL

Approximately 20% to 40% of patients who develop hemangioblastomas have VHL disease,[66] which is an inherited disorder that causes multiple tumors and cysts in various parts of the body (Table 1). Glasker et al.[67] reported that 94% of VHL disease-associated hemangioblastomas harbor *VHL* mutations and 62% exhibit loss of heterozygosity (LOH) at the VHL locus (3p25-56). By contrast, of 13 sporadic hemangioblastomas, 23% expressed germline mutations in *VHL* and 50% had LOH of the *VHL* locus.[67] The *VHL* gene encodes an E3 ubiquitin ligase that targets hypoxia-inducible factor-1a (HIF-α), which is known to be a regulator of vascular growth.[9] Mutations or deletions of the *VHL* gene cause cells to be unable to adequately degrade HIF-α, leading to vascular proliferation. Activated HIF-α and vascular endothelial growth factor were found to be correlated and increased in *VHL* mutant cells.[32,68]

CONCLUSION

The discovery of the genetic and molecular mechanisms of CNS tumors is beginning to impact the management of intracranial tumors, with improved predictions of prognosis and availability of targeted therapy. The 2021 WHO classification has been modified to reflect these facts. However, the genetic underpinnings of spinal cord tumors remain less well understood as those of their intracranial counterparts due to their rarity and difficulty in treatment because of their location in eloquent areas. Molecular and genetic differences exist between tumors located in the spinal cord and intracranial regions, even within the same pathological type. Therefore, further genetic studies on IMSCTs are warranted in order to develop novel therapies and improve the prognosis of patients suffering from these challenging tumors.

NOTES

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REFERENCES

1. Zulch K. Histological typing of tumours of the central nervous system. Vol no. 21. Geneva (Switzerland): World Health Organization; 1979.
2. Louis DN, Ohgaki H, Wiestler OD, et al. WHO classification of tumours of the central nervous system. Revised 4th ed. Lyon (France): International Agency for Research on Cancer; 2016.
3. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131: 803-20.
4. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol 2021;23:1231-51.
5. Zuchegna C, Di Zazzo E, Moncharmont B, et al. Dual-specificity phosphatase (DUSP6) in human glioblastoma: epithelial-to-mesenchymal transition (EMT) involvement. BMC Res Notes 2020;13:374.
6. Chai RC, Zhang YW, Liu YQ, et al. The molecular characteristics of spinal cord gliomas with or without H3 K27M mutation. Acta Neuropathol Commun 2020;8:40.
7. Biczok A, Strubing FL, Eder JM, et al. Molecular diagnostics helps to identify distinct subgroups of spinal astrocytomas. Acta Neuropathol Commun 2021;9:119.
8. Tobin MK, Geraghty JR, Engelhard HH, The molecular characteristics of spinal cord gliomas with or without H3 K27M mutation Intramedullary spinal cord tumors: a review of current and future treatment strategies. Neurosurg Focus 2015;39:E14.
9. Azad TD, Jiang B, Bettegowda C. Molecular foundations of primary spinal tumors-implications for surgical management. Ann Transl Med 2019;7:222.
10. Pajtler KW, Witt H, Sill M, et al. Molecular classification of ependymal tumors across All CNS compartments, histopathological grades, and age groups. Cancer Cell 2015;27:728-43.
11. Karsy M, Guan J, Sivakumar W, et al. The genetic basis of intradural spinal tumors and its impact on clinical treatment. Neurosurg Focus 2015;39:E3.
12. Louis DN, von Deimling A. Grading of diffuse astrocytic gliomas: Broders, Kernohan, Zulch, the WHO... and Shakespeare. Acta Neuropathol 2017;134:517-20.
13. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". Acta Neuropathol 2018;136:805-10.
14. Sanai N, Polley MY, McDermott MW, et al. An extent of resection threshold for newly diagnosed glioblastomas. J. Neurosurg 2011;115:3-8.
15. McGirt MJ, Goldstein IM, Chaichana KL, et al. Extent of surgical resection of malignant astrocytomas of the spinal cord: outcome analysis of 35 patients. Neurosurgery 2008; 63:55-60; discussion 60-1.
16. Nagoshi N, Tsuji O, Suzuki S, et al. Clinical outcomes and a therapeutic indication of intramedullary spinal cord astrocytoma. Spinal Cord 2022;60:216-22.
17. Zou Y, Sun J, Zhou Y, et al. Prognostic factors and treatment of spinal astrocytomas: a multi-institutional cohort analysis. Spine (Phila Pa 1976) 2018;43:E565-73.
18. Konar SK, Bir SC, Maiti TK, et al. A systematic review of overall survival in pediatric primary glioblastoma multiforme of the spinal cord. J Neurosurg Pediatr 2017;19:239-48.
19. Schwartzentruber J, Korshunov A, Liu XY, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature 2012;482:226-31.
20. Wu G, Broniscer A, McEachron TA, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet 2012;44:251-3.
21. Gessi M, Gielen GH, Dreschmann V, et al. High frequency of H3F3A (K27M) mutations characterizes pediatric and adult high-grade gliomas of the spinal cord. Acta Neuropathol 2015;130:435-7.
22. Ishi Y, Takamiya S, Seki T, et al. Prognostic role of H3K27M mutation, histone H3K27 methylation status, and EZH2 expression in diffuse spinal cord gliomas. Brain Tumor Pathol 2020;37:81-8.
23. Aihara K, Mukasa A, Gotoh K, et al. H3F3A K27M mutations in thalamic gliomas from young adult patients. Neuro Oncol 2014;16:140-6.
24. Yi S, Choi S, Shin DA, et al. Impact of H3.3 K27M mutation on prognosis and survival of grade IV spinal cord glioma on

the basis of new 2016 World Health Organization Classification of the central nervous system. Neurosurgery 2019;84:1072-81.
25. Alvi MA, Ida CM, Paolini MA, et al. Spinal cord high-grade infiltrating gliomas in adults: clinico-pathological and molecular evaluation. Mod Pathol 2019;32:1236-43.
26. Jung JS, Choi YS, Ahn SS, et al. Differentiation between spinal cord diffuse midline glioma with histone H3 K27M mutation and wild type: comparative magnetic resonance imaging. Neuroradiology 2019;61:313-22.
27. Cheng R, Li DP, Zhang N, et al. Spinal cord diffuse midline glioma with histone H3 K27M mutation in a pediatric patient. Front Surg 2021;8:616334.
28. Akinduro OO, Garcia DP, Higgins DMO, et al. A multicenter analysis of the prognostic value of histone H3 K27M mutation in adult high-grade spinal glioma. J Neurosurg Spine 2021;35:834-43.
29. Karlowee V, Amatya VJ, Takayasu T, et al. Immunostaining of increased expression of enhancer of zeste homolog 2 (EZH2) in diffuse midline glioma H3K27M-mutant patients with poor survival. Pathobiology 2019;86:152-61.
30. Maeda S, Ohka F, Okuno Y, et al. H3F3A mutant allele specific imbalance in an aggressive subtype of diffuse midline glioma, H3 K27M-mutant. Acta Neuropathol Commun 2020;8:8.
31. Lebrun L, Melendez B, Blanchard O, et al. Clinical, radiological and molecular characterization of intramedullary astrocytomas. Acta Neuropathol Commun 2020;8:128.
32. Abd-El-Barr MM, Huang KT, Moses ZB, et al. Recent advances in intradural spinal tumors. Neuro Oncol 2018;20:729-42.
33. Jones DT, Gronych J, Lichter P, et al. MAPK pathway activation in pilocytic astrocytoma. Cell Mol Life Sci 2012;69:1799-811.
34. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417:949-54.
35. Collins VP, Jones DT, Giannini C. Pilocytic astrocytoma: pathology, molecular mechanisms and markers. Acta Neuropathol 2015;129:775-88.
36. Grob ST, Nobre L, Campbell KR, et al. Clinical and molecular characterization of a multi-institutional cohort of pediatric spinal cord low-grade gliomas. Neurooncol Adv 2020;2:vdaa103.
37. Penman CL, Faulkner C, Lowis SP, et al. Current understanding of BRAF alterations in diagnosis, prognosis, and therapeutic targeting in pediatric low-grade gliomas. Front Oncol 2015;5:54.
38. Shankar GM, Lelic N, Gill CM, et al. BRAF alteration status and the histone H3F3A gene K27M mutation segregate spinal cord astrocytoma histology. Acta Neuropathol 2016;131:147-50.
39. Hawkins C, Walker E, Mohamed N, et al. BRAF-KIAA1549 fusion predicts better clinical outcome in pediatric low-grade astrocytoma. Clin Cancer Res 2011;17:4790-8.
40. Yang RR, Aibaidula A, Wang WW, et al. Pediatric low-grade gliomas can be molecularly stratified for risk. Acta Neuropathol 2018;136:641-55.
41. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. Science 2008;321:1807-12.
42. Han S, Liu Y, Cai SJ, et al. IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. Br J Cancer 2020;122:1580-9.
43. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360:765-73.
44. Ichimura K, Pearson DM, Kocialkowski S, et al. IDH1 mutations are present in the majority of common adult gliomas but rare in primary glioblastomas. Neuro Oncol 2009;11:341-7.
45. Nagashima Y, Nishimura Y, Ohka F, et al. Driver genetic mutations in spinal cord gliomas direct the degree of functional impairment in tumor-associated spinal cord injury. Cells 2021;10:2525.
46. Wang L, Li Z, Zhang M, et al. H3 K27M-mutant diffuse midline gliomas in different anatomical locations. Hum Pathol 2018;78:89-96.
47. Poetsch L, Bronnimann C, Loiseau H, et al. Characteristics of IDH-mutant gliomas with non-canonical IDH mutation. J Neurooncol 2021;151:279-86.
48. Konovalov NA, Asyutin DS, Shayhaev EG, et al. Rare cases of IDH1 mutations in spinal cord astrocytomas. Acta Naturae 2020;12:70-3.
49. Takai K, Tanaka S, Sota T, et al. Spinal cord astrocytoma with isocitrate dehydrogenase 1 gene mutation. World Neurosurg 2017;108:991.e13- 6.
50. Sun M, Wang L, Lu D, et al. Concomitant KIAA1549-BRAF fusion and IDH mutation in pediatric spinal cord astrocytoma: a case report and literature review. Brain Tumor Pathol 2021;38:132-7.
51. Milano MT, Johnson MD, Sul J, et al. Primary spinal cord glioma: a Surveillance, Epidemiology, and End Results database study. J Neurooncol 2010;98:83-92.

 https://doi.org/10.14245/ns.2244168.084

52. Samartzis D, Gillis CC, Shih P, et al. Intramedullary spinal cord tumors: part I-epidemiology, pathophysiology, and diagnosis. Global Spine J 2015;5:425-35.
53. Constantini S, Miller DC, Allen JC, et al. Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. J Neurosurg 2000;93:183-93.
54. Ahmed R, Menezes AH, Awe OO, et al. Long-term disease and neurological outcomes in patients with pediatric intramedullary spinal cord tumors. J Neurosurg Pediatr 2014;13:600-12.
55. Gonda T, Nagashima Y, Nishimura Y, et al. Postoperative cervicothoracic kyphosis following infantile intramedullary tumor resection accelerates neurological deterioration. NMC Case Rep J 2021;8:705-11.
56. Behmanesh B, Gessler F, Quick-Weller J, et al. Regional spinal cord atrophy is associated with poor outcome after surgery on intramedullary spinal cord ependymoma: a new aspect of delayed neurological deterioration. World Neurosurg 2017;100:250-5.
57. Lundar T, Due-Tonnessen BJ, Fric R, et al. Outcome after treatment of spinal ependymoma in children and adolescents: long-term follow-up of a single consecutive institutional series of 33 patients treated over eight decades. World Neurosurg. 2021;150:e228-e35.
58. Connolly ID, Ali R, Li Y, Gephart MH. Genetic and molecular distinctions in spinal ependymomas: a review. Clin Neurol Neurosurg 2015;139:210-5.
59. Bettegowda C, Agrawal N, Jiao Y, et al. Exomic sequencing of four rare central nervous system tumor types. Oncotarget 2013;4:572-83.
60. Shatara M, Schieffer KM, Klawinski D, et al. Clinically aggressive pediatric spinal ependymoma with novel MYC amplification demonstrates molecular and histopathologic similarity to newly described MYCN-amplified spinal ependymomas. Acta Neuropathol Commun 2021;9:192.
61. Raffeld M, Abdullaev Z, Pack SD, et al. High level MYCN amplification and distinct methylation signature define an aggressive subtype of spinal cord ependymoma. Acta Neuropathol Commun 2020;8:101.
62. Ghasemi DR, Sill M, Okonechnikov K, et al. MYCN amplification drives an aggressive form of spinal ependymoma. Acta Neuropathol 2019;138:1075-89.
63. Larrew T, Saway BF, Lowe SR, et al. Molecular classification and therapeutic targets in ependymoma. Cancers (Basel) 2021;13:6218.
64. Chamberlain MC, Tredway TL. Adult primary intradural spinal cord tumors: a review. Curr Neurol Neurosci Rep 2011;11:320-8.
65. Saliou G, Giammattei L, Ozanne A, et al. Role of preoperative embolization of intramedullary hemangioblastoma. Neurochirurgie 2017;63:372-5.
66. Augtein J, Green SM, Monro AM, et al. Adrenergic neurone blocking agents derived from 1,4-benzodioxan. J Med Chem 1965;8:446-56.
67. Glasker S, Bender BU, Apel TW, et al. Reconsideration of biallelic inactivation of the VHL tumour suppressor gene in hemangioblastomas of the central nervous system. J Neurol Neurosurg Psychiatry 2001;70:644-8.
68. Bader HL, Hsu T. Systemic VHL gene functions and the VHL disease. FEBS Lett 2012;586:1562-9.

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Review Article

The Role of Alginate Hydrogels as a Potential Treatment Modality for Spinal Cord Injury: A Comprehensive Review of the Literature

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Objective: To comprehensively characterize the utilization of alginate hydrogels as an alternative treatment modality for spinal cord injury (SCI).
Methods: An extensive review of the published literature on studies using alginate hydrogels to treat SCI was performed. The review of the literature was performed using electronic databases such as PubMed, EMBASE, and OVID MEDLINE electronic databases. The keywords used were "alginate," "spinal cord injury," "biomaterial," and "hydrogel."
Results: In the literature, we identified a total of 555 rat models that were treated with alginate scaffolds for regenerative biomarkers. Alginate hydrogels were found to be efficient and promising substrates for tissue engineering, drug delivery, neural regeneration, and cell-based therapies for SCI repair. With its ability to act as a pro-regenerative and antidegenerative agent, the alginate hydrogel has the potential to improve clinical outcomes.
Conclusion: The emerging developments of alginate hydrogels as treatment modalities may support current and future tissue regenerative strategies for SCI.

Keywords: Spinal cord injury, Alginate hydrogel, Biomaterial, Tissue regeneration

INTRODUCTION

Biomaterial engineers and physician-scientists have come together to create innovative solutions as the burden of chronic diseases rises worldwide.[1] While the application of injectables and enhanced medical device systems of synthetic materials has led to breakthrough outcomes, the biomaterial's reactivity with the biological system can lead to cytotoxic immunological effects.[1] This has created a bottleneck in the development of biomaterial-based treatments that can promote optimal physiological functions while remaining chemically inert.[2] Recently, biomolecular and cell-based approaches have taken the spotlight in treating a wide variety of pathologies, with spinal conditions now at the forefront of biomedical research.[3]

Spinal cord injury (SCI) is a traumatic life-changing pathology with substantial physical, emotional, and socioeconomic implications on the patient.[3] SCI outcomes often include partial or complete loss of sensory and motor function below the injury level. The therapeutic role of biomaterials, such as hydrogels, has previously been evaluated extensively as a regenerative modality. In general, hydrogels are separated into naturally derived and synthetic forms. The natural forms may be derived from chitosan, hyaluronan, collagen, agarose, or alginates.[4] Synthetic forms may be derived from polyethylene glycol, polyurethane, and poly(-ε-caprolactone) which have been U.S. Food and Drug Administration approved for use in humans subjects.[5-7] Hydrogel materials have also been found to occupy the injury site and take on a variety of shapes for *in situ* gelations. Once incorpo-

rated, their soft, highly porous, and 3-dimensional (3D) structure can mimic the extracellular matrix (ECM) environment to support damaged spine tissue.[8]

The introduction of alginate hydrogels into clinical spine research may drive the application of biomaterials in mainstream spinal care.[9] Alginates in their basic forms are a family of naturally occurring polysaccharides that are purified from brown algae.[10,11] Historically, alginates have been utilized in several industries. For example, in the food industry, it is used as an additive for food stabilization or as a binding agent.[12] When alginates are hydrated, they form into a viscous, hydrophilic, and biocompatible hydrogel.[2,13] This key feature is valuable due to the broad range of its applicability, particularly in tissue engineering in regenerative medicine, where it can be designed to mimic the mechanical integrity of natural-human tissue.[2,14] Herein, we describe alginate hydrogels' properties while presenting their functional outcomes in SCI. We also aim to provide an overview of the current advances in spinal care related to this biomaterial and depict its value in future treatment considerations.

METHODOLOGY

A comprehensive search of the literature was performed using electronic databases such as PubMed, EMBASE, and OVID MEDLINE electronic databases. The keywords used were "alginate," "spinal cord injury," "biomaterial," and "hydrogel." Studies that did not discuss alginate hydrogels, conference abstracts, or non-English articles were omitted. Our search yielded 180 articles, of which 81 were selected for inclusion in our review.

GENERAL PROPERTIES

1. Composition

Alginates are polysaccharides extracted from brown algae; these include Laminaria hyperborea, *Laminaria digitata, Laminaria japonica, Ascophyllum nodosum,* and *Macrocystis pyrifera.*[15] D-mannuronic acid constitutes the primary component in alginate hydrolysate, which is made of guluronic acid.[16] Further characterization has shown that alginate is composed of homopolymeric blocks of (1, 4)-linked beta-D-mannuronic acid (M-residues) and alpha-L-guluronic acid (G-residues) arranged in diaxial links (Fig. 1).[17] The ratio of the 2 polymers depends on the algae of origin.[17,18] Alginate readily forms a hydrogel in the presence of crosslinking agents such as divalent cations.[2] Crosslinking occurs through carbodiimide coupling or Schiff base reactions. Gelation could also occur as a result of a physical network stabilized from hydrophobic interactions within the alginate backbone.[19] This composition allows for a high water retention capacity that ranges between 20%–90% of its original mass, a characteristic that improves its biocompatibility for biomedical applications.[20] Alginate hydrogels can also be easily modified in their chemical composition; thus their molecular weights can vary. The molecular weights of alginate range from 32,000 and 400,000 g/mol.[1,21] Increasing the molecular

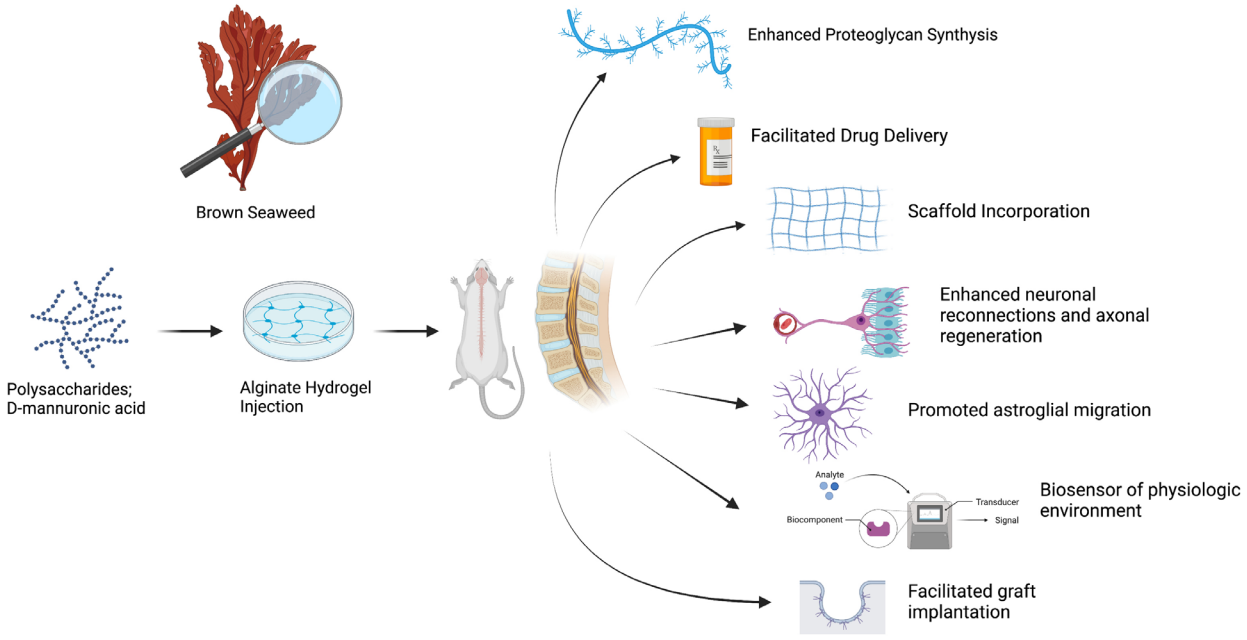

Fig. 1. Overview of alginates use in spinal cord injury.

weight of alginate can modify the hydrogel's physical properties, however, it can also elevate the viscosity level, which is undesirable for biomedical applications.[2,22] By manipulating the molecular weight, the hydrogel's chemical and physical properties can be directed toward various biomedical applications.[23]

Alginate-derivatives such as cell-interactive alginate and amphiphilic-alginate create specific drug delivery vehicles while influencing cell-based behaviors.[24] For example, covalent coupling with biomolecules such as gelatin or tripeptides like arginyl glycyl aspartic acid can provide cell-specific binding sites, making them more suitable in drug delivery.[25,26] Krebs et al.[27] in 2010 demonstrated the use of an injectable system for localized gene delivery of calcium phosphate-DNA nanoparticles using alginate hydrogels containing proteo-blastic cells for *in vivo* osteogenesis. Another study by Lawson et al.[28] demonstrated the ability of alginate gels containing collagen type 1 and beta-tricalcium phosphate to enhance human cell growth and differentiation *in vitro* before implantation. The role alginate hydrogels may play in drug delivery has also previously been demonstrated. In a study by Gao et al.[29] in 2020, modified pH-responsive alginate hydrogel beads were demonstrated to effectively increase the concentration of berberine hydrochloride delivery within the gastrointestinal tract, thus showcasing their potential role in sustained drug delivery via oral administration.

Finally, synthetic polymers can be structurally altered to influence different degradation, mechanical or chemical properties. In comparison, however, natural hydrogels, such as alginates, display structural similarities like that of the human ECM. Alginates share structural similarity with hyaluronic acid which is a major component of the brain and spinal cord ECM. This biomechanical similarity allows natural-derived alginates to be incorporated within live tissues and reduce the inflammatory processes or immunological reactions often associated with synthetically derived hydrogels.[30-33] Alginate hydrogels can be delivered *in vivo* through minimally-invasive techniques, including direct injection, emphasizing the ease of clinical applications.[34]

2. Hybrid Hydrogels

Hydrogels may be composed of a mixture of several biomaterials. These mixtures allow for specialized properties, depending on the desired characteristics. Alginates have been combined with polyacrylamide to achieve increased stiffness.[35] Hydrogels made of alginate and chitosan are also used in combination as biomaterials to generate a hybrid hydrogel. Chitosans are cationic polysaccharides produced by the deacetylation of chitin; this makes them favorable in combination with alginates for the delivery of anionic compounds such as nucleic acids.[36-38] When combined, the alginate-chitosan hybrid forms polyelectrolyte complexes with increased stability.[39,40] Hybrid hydrogels [NNM1] are being tested in the field of regenerative medicine for wound healing, bone healing, and tissue engineering.[36,41-45] Recently, Steinle et al.[46] explored the role of chitosan-alginate hybrid hydrogels for the continuous delivery of synthetic mRNA to obtain a sustained release of exogenous protein (humanized gaussia Luciferase). Results demonstrated the drug delivery potential of the hybrid hydrogel for the sustained release of synthetic mRNA into cells.

3. Regenerative Potential

The possibility of modifying the molecular weight and degree of crosslinking makes hydrogels, including alginate hydrogels, novel option for treating spinal pathologies.[10,47,48] Slight modifications to the polymeric chain structure, such as ionic, covalent and thermal crosslinking of the gels during the manufacturing process, have extended the hydrogels' versatility as a bulking agent in rat models.[2] Alginates have been described as "antidegenerative" and "pro-regenerative" agents, making them a good candidates to be studied in spinal pathologies such as SCI.[49] Several studies have demonstrated the use of alginate hydrogels as a matrix for neural stem cell growth.[41-43] Ashton et al.[50] previously demonstrated a method for creating alginate hydrogel scaffolds incorporated with poly(lactide-co-glycolide) microspheres with adjustable degradation rates in stem cell cultures. The authors highlighted a significant increase in the rate of expansion of neuronal progenitor cells cultured in degrading hydrogel alginates. Another study by Novikova et al.[51] in 2005 showed that alginate hydrogels combined with fibronectin promoted olfactory ensheathing cells proliferation. This study suggested the use of ECM when engineering biosynthetic scaffolds based on alginate hydrogels. Furthermore a study by Banerjee et al.[52] in 2009 investigated the effects the modulus of alginate hydrogels has on the proliferation and differentiation of neural stem cells. Kataoka et al.[53] also demonstrated nerve outgrowth and astrocyte reactions at the stump of 2 transected spinal cords of young rats implanted with alginates at the site of the lesion. Significant growth was seen in comparison to collagen gels serving as controls. Altering the concentration of alginate and calcium ions, the authors demonstrated enhancement in expression of B-tubulin III within alginate hydrogel scaffolds.[52]

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THERAPEUTIC POTENTIAL

1. SCI Overview

SCI is a potential field for alginate hydrogel implementation. SCI is a complex disorder that affects over 180,000 people annually worldwide.[10] It commonly manifests into long-term impairments such as loss of motor/sensory function and loss of autonomous function of breathing, sexual function, and bladder control.[19] The pathophysiology of SCI is complex, where the trauma to the spinal cord can institute a cascade effect of biochemical and cellular responses that trigger apoptosis in neurons and glial cells that lead to lesion development.[19] The functional deficits due to SCI are typically permanent because affected neurons have limited regenerative ability and are often exposed to inhibitory molecules that prevent regeneration.[54,55] Rehabilitative approaches and epidural stimulation remain the only treatment modalities, despite the significant efforts to find alternative therapeutic strategies. Advances in polymer science have identified that biomaterial hydrogels, such as alginate hydrogels, may promote spinal regeneration of damaged tissues in animal models.[56] The properties of alginates, including their versatility, biocompatibility, lack of toxicity, ease of gelation, and biomechanical similarity to that of the ECM, may be valuable for spinal cord regeneration.[31] As such, the utility of alginate hydrogels in spinal care has been explored extensively (Table 1).

2. Hydrogel Scaffolding

Prang et al.[57] demonstrated the feasibility of alginate hydrogel scaffolds for axonal regrowth using *in vitro* and adult rat models after acute SCI. In an entorhinal-hippocampal slice culture model, anisotropic capillary hydrogels supported directed central nervous system axonal growth and permitted longitudinally oriented reinnervation *in vitro* and integration into the spinal cord without major inflammatory reactions *in vivo*.[57] In a study in 2015 by Günther et al.,[58] 2-mm long alginate hydrogels seeded with bone marrow stromal cells (BMSCs) expressing brain-derived neurotrophic factor (BDNF) or green fluorescent protein as control were implanted into the C5 hemisection lesion of a rat spinal cord. On the 4-week assessment, numerous BMSCs appeared in the scaffold channels along with macrophages, blood vessels, and Schwann cells. Moreover, axon numbers were 3-4x higher in the alginate group compared to the control.[58] Lesions filled with BMSCs without alginate hydrogels presented random axon orientation, compared to axons in alginate-based scaffolds, which showed axons in linear orientation concerning the hydrogel channel wall.[58] These indications show that alginate hydrogel scaffolds can play a crucial role in guiding axonal regeneration. Another study by Tobias et al.[59] in 2001 found that BDNF-producing fibroblast grafts encapsulated within an alginate-poly-L-ornithine scaffold survived, proliferated, and continued to secrete BDNF for at least one month in culture. Encapsulation further permitted retention of bioactivity and allowed graft survival in a spinal cord despite the absence of immunosuppression. This subsequently fostered an environment adequate for axonal growth. In a further study in 2005, Tobias et al.[59] examined the effects of the same alginate-based grafts on subtotal cervical hemisections. The study assessed forelimb and hindlimb function and axonal growth in the absence of immunosuppression. Results showed that the alginate graft led to improved partial recovery of forelimb and hindlimb function compared to the group without the alginate graft. Immunohistochemical examination in the alginate graft group revealed an abundance of axonal promoters, including neurofilament (RT-97), 5-HT, CGRP, and GAP-43 along the injury site.[59] Axonal reorganization and behavioral recovery was induced by a BDNF releasing alginate graft, suggesting that alginate grafts are a feasible strategy for therapeutic recovery of injured SCI.[59,60] A recent study in 2019 by Schackel et al.[61] grafted poly-L-ornithine and laminin-coated alginate hydrogels into a cervical hemisection of adult female rats immediately postinjury. The authors reported the implants to remain firmly integrated and to exhibit signs of host cell migration and neurite extension further reinforcing its potential in axonal regeneration.

Table 1. Usage of biomaterial in clinical practice

Potential clinical applications for biomaterials
Use as medical implants for cartilage or bone tissue replacement
Facilitate drug delivery
Enhance neural and tissue regeneration
Promote tissue and wound healing
Act as biosensors for the detection of the physiological environment

3. Drug Delivery

Alginate hydrogels may also play a key role in drug delivery for SCI.[51,62,63] Drug delivery has also been studied *in vivo* SCI models.[31,64] Alginate hydrogels can serve as precise delivery vectors for these molecules to the desired target tissue.[65] Rolipram, a phosphodiesterase-4 inhibitor as neuroprotective agent, was prepared in microfibrous patches of alginate for controlled release *in vivo* delivery of high or low doses.[31,66] The results showed

improvement in functional recovery of motor systems following the drug delivery of low-dose rolipram. When animals were given high-dose rolipram patch treatments, there was a 50% decline in survival rates. This outcome highlights the value of alginate hydrogel encapsulation of drugs as drug-delivery platforms.[66] The injection of RhoA inhibitor (RhoAi) was also facilitated using an alginate hydrogel vector. In a rat SCI model, Devaux et al.[67] assessed the use of an alginate hydrogel for the delivery of RhoA inhibitors. The drug was experimentally tested both *in vivo* and *in vitro*, however, the authors demonstrated the importance of a delivery regimen to facilitate the neuronal reconnections and axonal regeneration *in vivo* using tissue-secreted media and proteomic analysis. Wen et al.[68] analyzed the union of alginate hydrogels with an integrin ligand, a signaling receptor that plays a crucial role in regulating progenitor cell proliferation. The *in vitro* results showed that the alginate model enhanced the encapsulation and differentiation of neural progenitor cells, indicating a further potential regenerative property.

4. Stem Cell and Neurotrophic Factor Delivery

Alginate hydrogels can also be used for the delivery of cell and neurotropic factors. In a study by Ansorena et al.,[69] the alginate hydrogel was used as a reservoir for glial-derived neurotrophic factor (GDNF) and injected into the hemisection of SCI rat models. After 6 weeks, the lesions of rats injected with the alginate hydrogel with GDNF had more key neurofilaments compared to controls.[69] The hydrogel group also had superior endothelial cell and nerve fiber infiltration at the lesion site, showing that the hydrogel can promote growth factor release better functional outcomes. Des Rieux et al.[70] investigated the use of vascular endothelial growth factor (VEGF)-containing hydrogels as a stimulating agent for a traumatized spinal cord. VEGF-loaded particles were mixed with fibrinogen and injected into the lesion of a spinal cord. Their results revealed that the local delivery of VEGF via an alginate-fibrinogen vector promoted plasticity in the injured spinal cord. Moreover, in a study by Liu et al.,[71] researchers constructed sodium alginate and naloxone (an opioid receptor antagonist) loaded macrophage-derived microvesicles to assess functional recovery in mice with SCI. Their results showed that the microvesicles could decrease the concentration of free calcium, thereby alleviating inflammatory factors such as tumor necrosis factor-α, interleukin (IL)-1β, IL-6 and increasing the anti-inflammatory expression of IL-10. In addition, motor functional improvement in mice was significant after treatment. A recent study by Zhang et al.[72] also found that alginate hydrogels combined with basic fibroblast growth factors (bFGFs) can prevent blood-spinal cord barrier destruction. Researchers found that a single *in situ* injection of the hydrogel combined with alginate and bFGF can have significant therapeutic effects together, rather than when treated alone. The study demonstrated that the hydrogel improved the blood-spinal cord barrier and functional recovery in mice, thereby potentially introductive a therapeutic strategy to approach SCI. Alginate hydrogels can act as an implant in cell-based therapies. Mesenchymal stem cells, embryonic and neural cells have been studied to replace defective cells and facilitate regeneration; however, they risk cell mortality after their transport. Therefore, alginate hydrogels have been incorporated as implants that can act by adhering to and protecting neurological cells. Barminko et al.[73] investigated the efficacy of encapsulating an implantable device with alginates for the delivery of human mesenchymal stem cells (hMSCs) in the treatment of SCI. The authors demonstrated functional maintenance of the hMSCs, and a curbed inflammatory reaction, both *in vivo* and *in vitro*. Similarly, gel encapsulation of Wnt3a-secreting fibroblasts in alginates yielded enhanced axonal recovery in rats SCI models than alginates or Wnt3a proteins alone.[74]

LIMITATIONS TO CLINICAL TRANSLATION

The benefits of alginate hydrogel in SCI may be limited by its long-term stability versus degradation.[75] Within the dynamic physiological environment, the hydrogel dissolves due to divalent ion release after exchange reactions with monovalent cations. The result is the release of homeostatic promoting calcium ions. As such, the gel may serve as a matrix for platelet and erythrocyte aggregation. Depending on the situation, this reaction may be desired or undesired. This could result in a cascade of negative reactions that could contribute to dysregulation within the intraspinal environment. This instability is one limiting factor in using alginate hydrogels as long-term survival *in vivo* is an important consideration in its clinical utility.[75,14] The alginate hydrogel has not been evaluated in clinical trials for its safety and potential risk to patients with SCI, despite being immunologically inert in animal studies. However, some commercially available alginates have been shown to contain cytotoxicity and mitogenic impurities that could elicit an unwanted immune response after transplantation.[76] This emphasizes the fundamental need for standardized cGMP-level purification and toxicity studies before use in the biotechnological setting.

Increasing the relevance of alginate hydrogels in clinical trials

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Table 2. Pitfalls of alginate hydrogel application in current clinical practice

Benefits
Biocompatible and biodegradable
Naturally derived compound
Multifunctional usage (drug delivery scaffolding cell-based therapies)
Has demonstrated positive preclinical outcomes
Easily modifiable to suite desired functionality
Drawbacks
Long-term stability and degradation biproducts not completely understood
Potential for unleashing adverse cations and immunological reactions
Not actively characterized clinically
Certain commercially available show cytotoxicity
Difficult adjusting composition to meet certain applications

would require a greater understanding of the biomaterial properties to determine appropriate therapies for human subjects.[31] A common approach with alginate hydrogels is adjusting their composition and makeup to meet a particular application's needs. Tailoring alginate hydrogels in human trials requires revisiting the different crosslinking strategies using molecules that are themselves safe for translation to humans. Similarly, the mechanism and biproducts of degradation in humans have yet to be fully characterized[10] (Table 2). In other fields of study, advances have been made that allow for the use of implantable alginate hydrogels in human subjects. Ongoing trials evaluating their role as a material for reconstructing the left ventricle in human subjects are currently ongoing (Clinicaltrail.gov ID: NCT04-781660).[77] Other clinical trials are exploring the feasibility and safety of alginate hydrogels to treat anal fistulas, diabetic foot ulcers, and other chronic wounds.[78,79]

FUTURE DIRECTIONS

The utilization of alginate in medicine is expected to evolve considerably into a more active role, especially in drug delivery, wound healing and tissue regeneration. With alginate's ability to be physically and chemically modified, we can expect future derivatives incorporated into a diverse range of biological systems, not just exclusively in the spine. The engineering of new alginate polymers with enhanced chemical and physical properties can develop various proteins with novel functions. Moreover, alginate hydrogels can have an advanced role in alternative technologies such as 3D bioprinting and microfluidics, increasing their versatility in the multiple spheres of biomedical research[80] Shang et al.[81] recently verified a gel growth model for 3D printing of hybrid calcium gluconate alginate hydrogels. The authors describe integrating collagen fibrils into the alginates scaffold to create cell-adhesions motifs within its chemical structure, creating ECM-like microenvironments. These 3D models will mitigate the complexity of designing cell growth, maturation and behavior. These prospects will pave the way for opportunities in drug treatments, cell therapies, and tissue transplantation.

CONCLUSION

Alginate hydrogels are efficient and promising substrates for tissue engineering, drug delivery, neural regeneration, and cell-based therapies for patients with SCI. With its ability to act as a pro-regenerative and antidegenerative agent, the alginate hydrogel has the potential to improve clinical outcomes. However, thus far, its translation to clinical practice has not been widely assessed. Nevertheless, with the current era of regenerative medicine, positive contributions may be anticipated in spine research and clinical care.

NOTES

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REFERENCES

1. Bhatia SK. Biomaterials for clinical applications. New York: Springer New York; 2010.
2. Loebsack A, Greene K, Wyatt S, et al. In vivo characterization of a porous hydrogel material for use as a tissue bulking agent. J Biomed Mater Res 2001;57:575-81.
3. Alizadeh A, Dyck SM, Karimi-Abdolrezaee S. Traumatic spinal cord injury: an overview of pathophysiology, models and acute injury mechanisms. Front Neurol 2019;10:282.
4. Gasperini L, Mano JF, Reis RL. Natural polymers for the microencapsulation of cells. J R Soc Interface 2014;11:20140817.
5. Nerurkar NL, Baker BM, Sen S, et al. Nanofibrous biologic laminates replicate the form and function of the annulus fibrosus. Nat Mater 2009;8:986-92.
6. Dash TK, Konkimalla VB. Poly-ϵ-caprolactone based formulations for drug delivery and tissue engineering: a review. J Control Release 2012;158:15-33.
7. Guarino V, Lewandowska M, Bil M, et al. Morphology and degradation properties of PCL/HYAFF11® composite scaffolds with multi-scale degradation rate. Compos Sci Technol 2010;70:1826-37.
8. Straley KS, Foo CWP, Heilshorn SC. Biomaterial design strategies for the treatment of spinal cord injuries. J Neurotrauma 2010;27:1-19.
9. Liu S, Sandner B, Schackel T, et al. Regulated viral BDNF delivery in combination with Schwann cells promotes axonal regeneration through capillary alginate hydrogels after spinal cord injury. Acta Biomater 2017;60:167-80.
10. Tang G, Zhou B, Li F, et al. Advances of naturally derived and synthetic hydrogels for intervertebral disk regeneration. Front Bioeng Biotechnol 2020;8:745.
11. Augst AD, Kong HJ, Mooney DJ. Alginate hydrogels as biomaterials. Macromol Biosci 2006;6:623-33.
12. Schierbaum F. Book review: polysaccharides and polyamides in the food industry. properties, production, and patents. Starch Stärke 2005;57:453.
13. Jeong HJ, Yun Y, Lee SJ, et al. Biomaterials and strategies for repairing spinal cord lesions. Neurochem Int 2021;144:104973.
14. Lee KY, Mooney DJ. Alginate: properties and biomedical applications. Prog Polym Sci 2012;37:106-26.
15. Madigan NN, McMahon S, O'Brien T, et al. Current tissue engineering and novel therapeutic approaches to axonal regeneration following spinal cord injury using polymer scaffolds. Respir Physiol Neurobiol 2009;169:183-99.
16. Dhoot NO, Tobias CA, Fischer I, et al. Peptide-modified alginate surfaces as a growth permissive substrate for neurite outgrowth. J Biomed Mater Res A 2004;71:191-200.
17. Haug A, Smidsrød O, Wachtmeister CA, et al. Fractionation of alginates by precipitation with calcium and magnesium ions. Acta Chem Scand 1965;19:1221-6.
18. Haug A, Claeson K, Hansen SE, et al. Fractionation of alginic acid. Acta Chem Scand 1959;13:601-3.
19. Assunção-Silva RC, Gomes ED, Sousa N, et al. Hydrogels and cell based therapies in spinal cord injury regeneration. Stem Cells Int 2015;2015:948040.
20. Möller L, Krause A, Dahlmann J, et al. Preparation and evaluation of hydrogel-composites from methacrylated hyaluronic acid, alginate, and gelatin for tissue engineering. Int J Artif Organs 2011;34:93-102.
21. Matyash M, Despang F, Ikonomidou C, et al. Swelling and mechanical properties of alginate hydrogels with respect to promotion of neural growth. Tissue Eng Part C Methods 2014;20:401-11.
22. West ER, Xu M, Woodruff TK, et al. Physical properties of alginate hydrogels and their effects on in vitro follicle development. Biomaterials 2007;28:4439-48.
23. Du HC, Jiang L, Geng WX, et al. Evaluation of xenogeneic extracellular matrix fabricated from CuCl-conditioned mesenchymal stem cell sheets as a bioactive wound dressing material. J Biomater Appl 2017;32:472-83.
24. Lambricht L, De Berdt P, Vanacker J, et al. The type and composition of alginate and hyaluronic-based hydrogels influence the viability of stem cells of the apical papilla. Dent Mater 2014;30:e349-61.
25. Sarker B, Papageorgiou DG, Silva R, et al. Fabrication of alginate-gelatin crosslinked hydrogel microcapsules and evaluation of the microstructure and physico-chemical properties. J Mater Chem B Mater Biol Med 2014;2:1470-82.
26. Ghasemiyeh P, Mohammadi-Samani S. Hydrogels as drug delivery systems; pros and cons. Trends Pharm Sci 2019;5:7-24.
27. Krebs MD, Salter E, Chen E, et al. Calcium phosphate-DNA nanoparticle gene delivery from alginate hydrogels induces in vivo osteogenesis. J Biomed Mater Res A 2010;92:1131-8.
28. Lawson MA, Barralet JE, Wang L, et al. Adhesion and growth of bone marrow stromal cells on modified alginate hydrogels. Tissue Eng 2004;10:1480-91.
29. Gao J, Fan D, Song P, et al. Preparation and application of pH-responsive composite hydrogel beads as potential delivery carrier candidates for controlled release of berberine hydrochloride. R Soc Open Sci 2020;7:200676.

 https://doi.org/10.14245/ns.2244186.093

30. Melrose J, Smith S, Ghosh P, et al. Differential expression of proteoglycan epitopes and growth characteristics of intervertebral disc cells grown in alginate bead culture. Cells Tissues Organs 2001;168:137-46.
31. Grijalvo S, Nieto-Díaz M, Maza RM, et al. Alginate Hydrogels as Scaffolds and Delivery Systems to Repair the Damaged Spinal Cord. Biotechnol J 2019;14:e1900275.
32. Mano JF, Silva GA, Azevedo HS, et al. Natural origin biodegradable systems in tissue engineering and regenerative medicine: present status and some moving trends. J R Soc Interface 2007;4:999-1030.
33. Tabata Y. Biomaterial technology for tissue engineering applications. J R Soc Interface 2009;6 Suppl 3:S311-24.
34. Schmocker A, Khoushabi A, Frauchiger DA, et al. A photopolymerized composite hydrogel and surgical implanting tool for a nucleus pulposus replacement. Biomaterials 2016; 88:110-9.
35. Li J, Illeperuma WRK, Suo Z, et al. Hybrid hydrogels with extremely high stiffness and toughness. ACS Macro Lett 2014; 3:520-3.
36. Ma Z, Yang C, Song W, et al. Chitosan hydrogel as siRNA vector for prolonged gene silencing. J Nanobiotechnology 2014;12:23.
37. Shu XZ, Zhu KJ. The influence of multivalent phosphate structure on the properties of ionically cross-linked chitosan films for controlled drug release. Eur J Pharm Biopharm 2002;54:235-43.
38. Yao KD, Peng T, Goosen MFA, et al. pH-sensitivity of hydrogels based on complex forming chitosan: Polyether interpenetrating polymer network. J Appl Polym Sci 1993;48: 343-54.
39. Khong TT, Aarstad OA, Skjåk-Bræk G, et al. Gelling concept combining chitosan and alginate-proof of principle. Biomacromolecules 2013;14:2765-71.
40. Li Z, Ramay HR, Hauch KD, et al. Chitosan-alginate hybrid scaffolds for bone tissue engineering. Biomaterials 2005;26: 3919-28.
41. Mao S, Sun W, Kissel T. Chitosan-based formulations for delivery of DNA and siRNA. Adv Drug Deliv Rev 2010;62: 12-27.
42. Han HD, Mora EM, Roh JW, et al. Chitosan hydrogel for localized gene silencing. Cancer Biol Ther 2011;11:839-45.
43. Li H, Ji Q, Chen X, et al. Accelerated bony defect healing based on chitosan thermosensitive hydrogel scaffolds embedded with chitosan nanoparticles for the delivery of BMP2 plasmid DNA. J Biomed Mater Res A 2017;105:265-73.
44. Iwasaki N, Yamane ST, Majima T, et al. Feasibility of polysaccharide hybrid materials for scaffolds in cartilage tissue engineering: evaluation of chondrocyte adhesion to polyion complex fibers prepared from alginate and chitosan. Biomacromolecules 2004;5:828-33.
45. Straccia MC, d'Ayala GG, Romano I, et al. Alginate hydrogels coated with chitosan for wound dressing. Mar Drugs 2015;13:2890-908.
46. Steinle H, Ionescu TM, Schenk S, et al. Incorporation of synthetic mRNA in injectable chitosan-alginate hybrid hydrogels for local and sustained expression of exogenous proteins in cells. Int J Mol Sci 2018;19:1313.
47. Yang Y, Wang X, Yang F, et al. A universal soaking strategy to convert composite hydrogels into extremely tough and rapidly recoverable double-network hydrogels. Adv Mater 2016;28:7178-84.
48. Machida-Sano I, Ogawa S, Ueda H, et al. Effects of composition of iron-cross-linked alginate hydrogels for cultivation of human dermal fibroblasts. Int J Biomater 2012;2012:820513.
49. Perale G, Rossi F, Sundstrom E, et al. Hydrogels in spinal cord injury repair strategies. ACS Chem Neurosci 2011;2: 336-45.
50. Ashton RS, Banerjee A, Punyani S, et al. Scaffolds based on degradable alginate hydrogels and poly(lactide-co-glycolide) microspheres for stem cell culture. Biomaterials 2007;28:5518-25.
51. Novikova LN, Mosahebi A, Wiberg M, et al. Alginate hydrogel and matrigel as potential cell carriers for neurotransplantation. J Biomed Mater Res A 2006;77:242-52.
52. Banerjee A, Arha M, Choudhary S, et al. The influence of hydrogel modulus on the proliferation and differentiation of encapsulated neural stem cells. Biomaterials 2009;30:4695-9.
53. Kataoka K, Suzuki Y, Kitada M, et al. Alginate enhances elongation of early regenerating axons in spinal cord of young rats. Tissue Eng 2004;10:493-504.
54. Quencer RM, Bunge RP. The injured spinal cord: imaging, histopathologic clinical correlates, and basic science approaches to enhancing neural function after spinal cord injury. Spine 1996;21:2064-6.
55. Bodley R. Imaging in chronic spinal cord injury--indications and benefits. Eur J Radiol 2002;42:135-53.
56. Siddiqui AM, Khazaei M, Fehlings MG. Translating mechanisms of neuroprotection, regeneration, and repair to treatment of spinal cord injury. Prog Brain Res 2015;218:15-54.
57. Prang P, Müller R, Eljaouhari A, et al. The promotion of oriented axonal regrowth in the injured spinal cord by alginate-

based anisotropic capillary hydrogels. Biomaterials 2006;27:3560-9.
58. Günther MI, Weidner N, Müller R, et al. Cell-seeded alginate hydrogel scaffolds promote directed linear axonal regeneration in the injured rat spinal cord. Acta Biomater 2015;27:140-50.
59. Tobias CA, Han SSW, Shumsky JS, et al. Alginate encapsulated BDNF-producing fibroblast grafts permit recovery of function after spinal cord injury in the absence of immune suppression. J Neurotrauma 2005;22:138-56.
60. Tobias CA, Dhoot NO, Wheatley MA, et al. Grafting of encapsulated BDNF-producing fibroblasts into the injured spinal cord without immune suppression in adult rats. J Neurotrauma 2001;18:287-301.
61. Schackel T, Kumar P, Günther M, et al. Peptides and astroglia improve the regenerative capacity of alginate gels in the injured spinal cord. Tissue Eng Part A 2019;25:522-37.
62. Grulova I, Slovinska L, Blaško J, et al. Delivery of alginate scaffold releasing two trophic factors for spinal cord injury repair. Sci Rep 2015;5:13702.
63. Francis NL, Hunger PM, Donius AE, et al. Strategies for neurotrophin-3 and chondroitinase ABC release from freeze-cast chitosan-alginate nerve-guidance scaffolds. J Tissue Eng Regen Med 2017;11:285-94.
64. Abasalizadeh F, Moghaddam SV, Alizadeh E, et al. Alginate-based hydrogels as drug delivery vehicles in cancer treatment and their applications in wound dressing and 3D bioprinting. J Biol Eng 2020;14:8.
65. Khang G. Handbook of intelligent scaffolds for tissue engineering and regenerative medicine. 2nd ed. Boca Raton (FL): CRC Press; 2017.
66. Downing TL, Wang A, Yan ZQ, et al. Drug-eluting microfibrous patches for the local delivery of rolipram in spinal cord repair. J Control Release 2012;161:910-7.
67. Devaux S, Cizkova D, Mallah K, et al. RhoA inhibitor treatment at acute phase of spinal cord injury may induce neurite outgrowth and synaptogenesis. Mol Cell Proteomics 2017;16:1394-415.
68. Wen H, Xiao W, Biswas S, et al. Alginate hydrogel modified with a ligand interacting with α3β1 integrin receptor promotes the differentiation of 3D neural spheroids toward oligodendrocytes in vitro. ACS Appl Mater Interfaces 2019;11:5821-33.
69. Ansorena E, De Berdt P, Ucakar B, et al. Injectable alginate hydrogel loaded with GDNF promotes functional recovery in a hemisection model of spinal cord injury. Int J Pharm 2013;455:148-58.
70. des Rieux A, De Berdt P, Ansorena E, et al. Vascular endothelial growth factor-loaded injectable hydrogel enhances plasticity in the injured spinal cord. J Biomed Mater Res A 2014;102:2345-55.
71. Liu X, Jiang X, Yu Q, et al. Sodium alginate and naloxone loaded macrophage-derived nanovesicles for the treatment of spinal cord injury. Asian J Pharm Sci 2022;17:87-101.
72. Zhang R, Xie L, Wu F, et al. ALG-bFGF Hydrogel inhibiting autophagy contributes to protection of blood-spinal cord barrier integrity via PI3K/Akt/FOXO1/KLF4 pathway after SCI. Front Pharmacol 2022;13:828896.
73. Barminko J, Kim JH, Otsuka S, et al. Encapsulated mesenchymal stromal cells for in vivo transplantation. Biotechnol Bioeng 2011;108:2747-58.
74. Park JH, Min J, Baek SR, et al. Enhanced neuroregenerative effects by scaffold for the treatment of a rat spinal cord injury with Wnt3a-secreting fibroblasts. Acta Neurochir 2013;155:809-16.
75. Leone G, Torricelli P, Chiumiento A, et al. Amidic alginate hydrogel for nucleus pulposus replacement. J Biomed Mater Res A 2008;84:391-401.
76. Zhang Z, Ortiz O, Goyal R, et al. Biodegradable polymers. In: Lanza RP, Vacanti J, Langer RS, editor. Principles of tissue engineering. Amsterdam: Elsevier; 2014. p. 441-73.
77. First in man study of implantable alginate hydrogel [Internet]. Bethesda (MD): ClinicalTrials.gov; 2021 [cited 2021 Apr 2]. Available from: https://clinicaltrials.gov/ct2/show/NCT04781660?id=NCT04781660&draw=2&rank=1.
78. Feasibility and safety of the calcium alginate hydrogel sealant for the treatment of cryptoglandular fistula-in-ano: phase I/IIa clinical trial [Internet]. Bethesda (MD): ClinicalTrials.gov; 2021 [cited 2021 Apr 2]. Available from: https://clinicaltrials.gov/ct2/show/NCT04740086?id=NCT04740086&draw=2&rank=1.
79. Clinical Trial using the proteolytic fraction P1G10 from V. cundinamarcensis to heal diabetic foot ulcer (P1G10) [Internet]. Bethesda (MD): ClinicalTrials.gov; 2018 [cited 2021 Apr 2]. Available from: https://clinicaltrials.gov/ct2/show/NCT03700580?id=NCT03700580&draw=2&rank=1.
80. Łabowska MB, Cierluk K, Jankowska AM, et al. A review on the adaption of alginate-gelatin hydrogels for 3D cultures and bioprinting. Materials (Basel) 2021;14:858.
81. Shang W, Liu Y, Wan W, et al. Hybrid 3D printing and electrodeposition approach for controllable 3D alginate hydrogel formation. Biofabrication 2017;9:025032.

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Editorial

Commentary on "The Role of Alginate Hydrogels as a Potential Treatment Modality for Spinal Cord Injury: A Comprehensive Review of the Literature"

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See the article "The Role of Alginate Hydrogels as a Potential Treatment Modality for Spinal Cord Injury: A Comprehensive Review of the Literature" via https://doi.org/10.14245/ns.2244186.093.

In this paper,[1] the authors identified 555 preclinical studies that used alginate scaffolds. The authors have discussed the role of alginate hydrogels as substrate, drug delivery, neural regeneration, and cell-based therapy for spinal cord injury (SCI). In the current scenario, tissue engineering for repairing the damaged spinal cord is essential, and hydrogels seem promising for tissue engineering.[2] In central nervous system injuries, including SCI, the primary approach is to fix what we have (left after primary injury) by preventing further cell death,[3] restoring axon regrowth,[4] and removing blockades. The second approach is built around it; this could be accomplished by tissue engineering, biomaterial, and cell therapy.[5] Finally, the restoration of impulse conduction in demyelinated axons could be achieved by building a "bridge" around the injured area. Regenerative cell therapy using different types of stem cells, different inoculation techniques, and scaffolds has undergone many trials, highlighting cell efficacies and limitations.[6]

Alginates are polysaccharides extracted from brown algae; these include *Laminaria hyperborea*, *Laminaria digitata, Laminaria japonica, Ascophyllum nodosum,* and *Macrocystis pyrifera*. Alginate is composed of M-residues and G-residues arranged in diaxial links, and the ratio of 2 polymers depends on the algae of origin. Alginate hydrogels boost cell proliferation and differentiation before implantation. The use of alginate hydrogels is encouraging in the SCI therapy as it could be utilized as a substrate to make a bridge and could also be exploited in drug delivery and cell therapy.[7] Once integrated, their soft, porous, 3-dimensional structure can sustain injured spine tissue. Interestingly, alginates resemble hyaluronic acid, a brain and spinal cord extracellular matrix component, suggesting it could be a promising material for tissue engineering. Furthermore, a hydrogel can occupy the injured site and take shape for *in situ* gelations. The authors also summarised the studies suggesting that alginates are "antidegenerative" and "pro-regenerative," making them attractive candidates for SCI research.

The authors also discussed the studies where alginate-encapsulated brain-derived neurotrophic factor-producing fibroblast grafts restore spinal cord function without immune suppression,[8] and microvesicles with sodium alginate and naloxone improve functional recov-

ery after SCI.[9] The advantages of using alginate hydrogels are that they are natural, biocompatible, biodegradable, and have multifunctional usage, and they are easily modifiable to suit the desired functionality. However, alginate hydrogel application has certain limitations; they can cause adverse cations leading to immunological reactions, they are not clinically characterized, and sometimes it is difficult to adjust the composition to meet specific applications. In addition, the molecular weights might fluctuate due to their easy chemical modification. The other issue is long-term term stability and degradation as by-products are not entirely known.

In summary, alginate hydrogels have been shown to support neural stem cell development in several investigations as summarised by authors, and they could be promising for tissue engineering, medication delivery, axon regrowth, brain regeneration, and cell-based SCI treatments.

Conflict of Interest: The author has nothing to disclose.

REFERENCES

1. Jarrah R, El Sammak S, Onyedimma C, et al. The role of alginate hydrogels as a potential treatment modality for spinal cord injury: a comprehensive review of the literature. Neurospine 2022;19:272-80.
2. Walsh CM, Wychowaniec JK, Brougham DF, et al. Functional hydrogels as therapeutic tools for spinal cord injury: new perspectives on immunopharmacological interventions. Pharmacol Ther 2022 Jun;234:108043. https://doi.org/10.1016/j.pharmthera.2021.108043. [Epub].
3. Fiani B, Kondilis A, Soula M, et al. Novel methods of necroptosis inhibition for spinal cord injury using translational research to limit secondary injury and enhance endogenous repair and regeneration. Neurospine 2021;18:261-70.
4. Kumar H, Lim CS, Choi H, et al. Elevated TRPV4 levels contribute to endothelial damage and scarring in experimental spinal cord injury. J Neurosci 2020;40:1943-55.
5. Kim HY, Kumar H, Jo MJ, et al. Therapeutic efficacy-potentiated and diseased organ-targeting nanovesicles derived from mesenchymal stem cells for spinal cord injury treatment. Nano letters 2018;18:4965-75.
6. Takami T, Shimokawa N, Parthiban J, et al. Pharmacologic and regenerative cell therapy for spinal cord injury: WFNS spine committee recommendations. Neurospine 2020;17:785-96.
7. Prang P, Müller R, Eljaouhari A, et al. The promotion of oriented axonal regrowth in the injured spinal cord by alginate-based anisotropic capillary hydrogels. Biomaterials 2006;27:3560-9.
8. Tobias CA, Han SS, Shumsky JS, et al. Alginate encapsulated BDNF-producing fibroblast grafts permit recovery of function after spinal cord injury in the absence of immune suppression. J Neurotrauma 2005;22:138-56.
9. Liu X, Jiang X, Yu Q, et al. Sodium alginate and naloxone loaded macrophage-derived nanovesicles for the treatment of spinal cord injury. Asian J Pharm Sci 2022;17:87-101.

Title: Dove of Peace
Year: 1949
Artist: Pablo Picasso

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Review Article

Established and Emerging Therapies in Acute Spinal Cord Injury

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Acute spinal cord injury (SCI) is devastating for patients and their caretakers and has an annual incidence of 20–50 per million people. Following initial assessment with appropriate physical examination and imaging, patients who are deemed surgical candidates should undergo decompression with stabilization. Earlier intervention can improve neurological recovery in the post-operative period while allowing earlier mobilization. Optimized medical management is paramount to improve outcomes. Emerging strategies for managing SCI in the acute period stem from an evolving understanding of the pathophysiology of the injury. General areas of focus include ischemia prevention, reduction of secondary injury due to inflammation, modulation of the cytotoxic and immune response, and promotion of cellular regeneration. In this article, we review established, emerging, and novel experimental therapies. Continued translational research on these methods will improve the feasibility of bench-to-bedside innovations in treating patients with acute SCI.

Keywords: Spinal cord injury, Acute, Pathophysiology, Therapeutics

INTRODUCTION

Spinal cord injuries (SCIs) are devastating traumatic events in the lives of patients, often resulting in severe and/or permanent neurologic disabilities. Nearly half a million people are living permanently disabled in the United States due to traumatic SCI, and 12,000–15,000 patients per year incur new injuries.[1,2] Further, the incidence of SCI varies by country with most developed countries reporting incidences of 20–50 per million.[3,4] The event can result in an assortment of immediate sequelae and long-term complications including loss of motor and sensory function, loss of autonomic function, and increased risk of medical complications and death.[5]

As traumatic SCI more commonly occurs in young, healthy adults, the associated quality-adjusted life year and economic loss can be immense.[6] Despite recent gains in understanding of the pathogenesis and improved acute management of SCI, there remains an ongoing need to investigate novel molecular targets and therapeutics for treatment in the acute injury period, with the goal of maximizing patient recovery and preventing chronic manifestations of the injury. While the timing of surgery for decompression and stabilization of acute SCI has been well studied,[7] the evidence for most medical treatments of the acute neurological injury are less well supported. This review discusses the established current management strategies and expands on emerging therapeutic strategies for acute SCI. Additionally, we discuss an updated review of experimental therapies, from bench to bedside.

MECHANISM OF INJURY IN SPINAL CORD INJURY

SCI can result either from high-energy trauma (e.g., motor vehicle accidents, diving, sports) or lower impact trauma, which often occurs in the presence of underlying degenerative or congenital spinal spondylosis. The cervical spinal cord is the most

commonly affected region due to the lack of bony and muscular protection relative to thoracic and lumbar segments.[8] The mechanism of spinal cord damage is generally divided into primary and secondary processes. Primary injury encompasses the initial insult, such as compression, penetrating injury, or strain on neural tissue or vascular structures. Subsequent perfusion disruption progresses to local hypoxia and can be worsened by systemic vasogenic shock. Hypoxic cell death induces the multifaceted, progressive process of secondary injury during the following hours to weeks. Ischemia caused by primary injury activates release of vasoactive proteins and cytokines, and the resulting edema and inflammation promote cytoskeletal and mitochondrial damage and immune cell infiltration. The zone of injury then expands due to reactive oxygen species (ROS) accumulation and oxidative damage, lactic acidosis, fibrin and platelet accumulation, toxic excitatory neurotransmitter release, and axonal demyelination, leading to progressive tissue death and scarring.

CLINICAL PRESENTATION

Initial management of patients with suspected acute traumatic SCI follows established trauma guidelines to manage the airway, breathing, and circulation. Immobilization is necessary to prevent further possible damage in all patients with suspected SCI (characterized, for example, by polytrauma, neck/back spinal pain, dysesthesia, loss of consciousness, or a mechanism of injury with the potential to cause an SCI).[9-11]

Patients with SCI can present with either complete injury, defined as a lack of motor or sensory function in the anal and perineal region (representing the lowest sacral segments S4–S5), or incomplete injury with varying degrees of motor and sensory function caudal to the level of the injury.[12] The American Spinal Injury Association (ASIA) scoring system is used to stratify injury severity, ranging from complete injury (ASIA-A) to normal neurological exam (ASIA-E), to standardize assessment and treatment of SCI.[2] In addition, patients can present with spinal shock, an often-transient physiologic depression of spinal cord function secondary to cell damage which can be tracked with progressive recovery of anatomical reflexes including the bulbocavernosus, anal cutaneous, and plantar reflexes.[12] Spinal shock and medication effects may obscure accurate ASIA scoring, particularly in the first 48–72 hours after injury.[13] This process is distinct from neurogenic shock, a condition of autonomic dysregulation from injury to spinal levels C1–T6 and/or associated sympathetic ganglia, which is characterized by persistent hypotension, bradycardia, and hypothermia.[12]

ESTABLISHED ACUTE MANAGEMENT STRATEGIES

Computed tomography of the entire spine is indicated in the initial evaluation of traumatic SCI patients.[14] ASIA motor scores and neurologic level of injury have the most consistent prognostic value regarding outcome.[15] Magnetic resonance imaging has utility for guiding surgical intervention and prognostication and should be performed when available but should not delay surgical treatment in a neurologically declining patient.[12,15] Standardization of magnetic resonance changes of increasing severity in acute SCI is increasing, with the BASIC score serving as one example.[16] Surgical candidacy should be promptly determined through assessment of a worsening neurological examination along with signs and symptoms of instability and progressive compression.

Direct spinal cord compression is the most frequent mechanism of SCI and can progress following the initial injury, prompting a need for emergent surgical decompression. A meta-analysis including 16 studies involving nearly 4,000 patients found that patients who receive early spinal surgery (<24 hours following injury) experience greater neurological recovery, shorter length of stay, lower hospitalization costs, and a lower incidence of complications than those who undergo surgery >24 hours following injury.[17] Another recent multicenter clinical trial compared early and delayed surgical treatment (defined as ≤ 24 hours after injury and after ≥ 2 weeks of conservative therapy, respectively) and assessed motor recovery using the ASIA motor score, spinal cord independence measure, and independent ambulation capacity for 1 year. The study found that the 2 treatment paradigms were not significantly different; however, motor recovery at 2-week, 3-month, and 6-month follow-ups were improved with early surgical treatment, indicating accelerated recovery.[18] These results align with several large, well-documented trials and underscore the importance of early decompression to improve potential for motor recovery following SCI.[19-21]

Medical management has an essential role in the optimization of patients with SCI.[12,22] Hemodynamic control is crucial in the early stages of acute SCI to reduce potential ischemic injury, with goal mean arterial pressures (MAPs) of 85–90 mmHg for 5–7 days suggested for improved functional outcomes.[23] Other crucial tenets of management include prevention of pulmonary (i.e., pneumonia), gastrointestinal (i.e., bowel obstruction), and urologic (i.e., dysautonomic uropathy) complications caused by

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loss of voluntary and autonomic control.[12,14] As such, current multidisciplinary clinical studies are examining, for example, the use of low versus high tidal volume mechanical ventilation in patients requiring intubation in acute SCI (NCT04912583) and the use of early epidural and sacral nerve stimulation as an adjunct for improving bladder function (NCT03083366).[24,25] The utility of methylprednisolone (MPSS) administration has been discussed extensively in the literature and, while initially thought to improve outcomes based on the early North American Spinal Cord Injury Study (NASCIS) results, subsequent large studies have not demonstrated this benefit.[26-28] Moreover, a consistently increased risk of steroid-associated complications including infection was found. Recent animal studies have found that high-dose steroid administration may actually increase the extravasation of plasma components after SCI and can enhance tissue swelling and edema.[29] Therefore, routine administration of high-dose steroids is no longer recommended; a short course may, however, be considered in young, otherwise healthy adults presenting < 8 hours from injury based on expert consensus.[27,28,30] Early physical rehabilitation, nutritional optimization, and mental health consultation are indicated, and have been shown to improve functionality and quality of life.[31-33] These therapies continue to be studied, for example, in clinical trials assessing the effects of interval versus continuous aerobic training on autonomic dysreflexia in the acute phase of SCI (NCT05061160).

EXPERIMENTAL ACUTE MANAGEMENT STRATEGIES

Emerging therapeutic strategies for acute SCI can be classified by the biological mechanism which they are designed to address, prevent, or reverse. Mechanisms largely discussed in

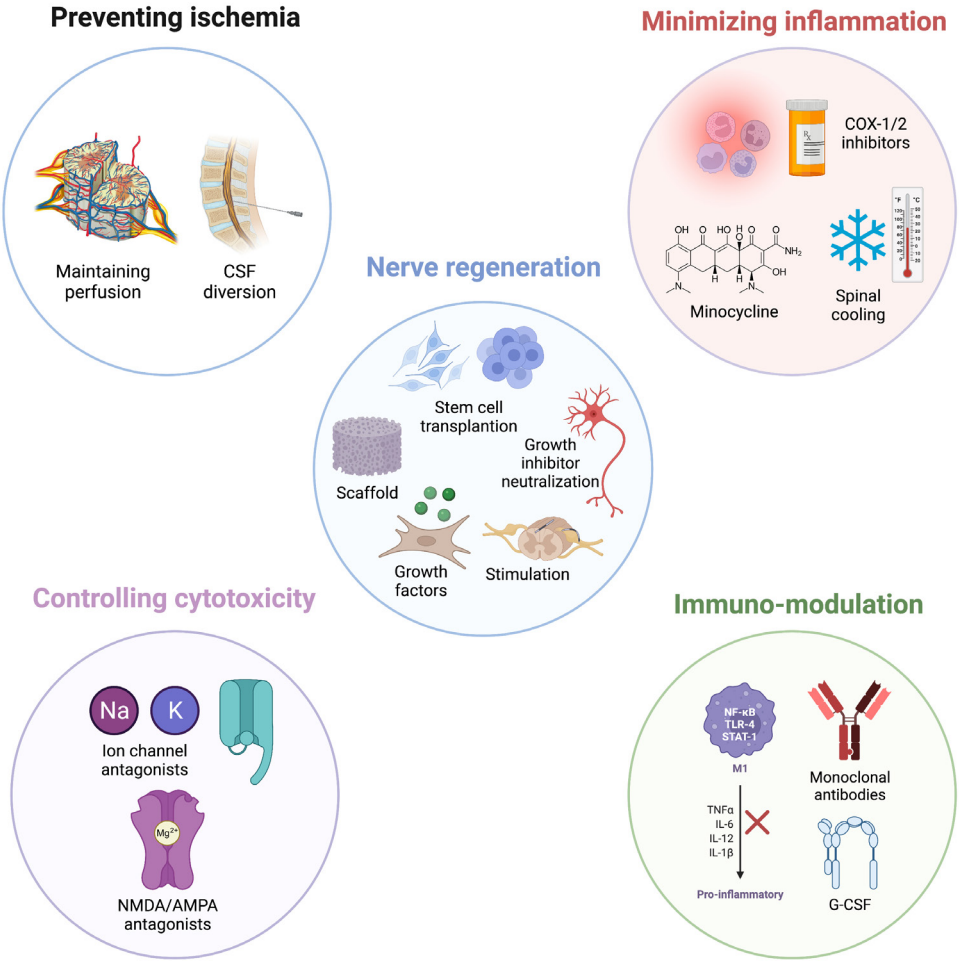

Fig. 1. Emerging therapies for acute spinal cord injury. CSF, cerebrospinal fluid; COX, cyclooxygenase; NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; TNF, tumor-necrosis factor; IL, interleukin; G-CSF, granulocyte-colony stimulating factor.

the literature to date can be grouped into categories as described below based on the current understanding of SCI pathophysiology (Fig. 1, created with BioRender.com).

1. Preventing Ischemia

In the early stages of SCI, bleeding caused by disruption of local vasculature can lead to ischemic hypoxia within spinal grey matter. Hypoxia in these highly metabolically active structures leads to neuronal dysfunction, demyelination, and the initiation of apoptosis and necrosis.[34] Uncorrected ischemia can cause secondary damage due to the cumulative effects of cellular swelling and the initial macrophage-mediated inflammatory response which may last between 3–24 hours following the inciting event.[34] Furthermore, without proper blood flow, the highly vascular and regenerative astrocytic environment is less equipped to repair axonal and neuronal damage. Maintaining adequate perfusion systemically and within the remaining spinal vascular beds is essential for mitigating the pathological consequences of SCI.

States of neurogenic shock can further compound the ischemic burden. Prompt correction of hypotension with fluid resuscitation, transfusion, or traditional vasopressors can be difficult due to the disruption of local capillary auto-regulatory mechanisms. Agents including dopamine and midodrine have been attempted in clinical trials with varying levels of success and no high-level evidence supports the use of one pressor over another.[35] When compared with norepinephrine, dopamine maintained MAP to a similar degree but was associated with a higher intrathecal pressure (ITP) and consequentially decreased spinal cord perfusion pressure (SCPP); dopamine use was also associated with higher rates of vasopressor-associated complications.[22] A handful of case reports and small clinical trials of midodrine note successful acute maintenance of blood pressure and orthostatic symptoms with no serious adverse effects but lacked long-term follow-up.[36] Importantly, hypertension should be avoided in acute SCI to lower the risk of hyperemia and hemorrhage.

Cerebrospinal fluid (CSF) diversion has potential to alleviate ischemia caused by venous edematous leakage following SCI through the reduction of ITP. This strategy was extrapolated from the cranial trauma practice of ventriculostomy placement and the vascular surgery literature's investigation of the use of lumbar drains in aortic dissection to support cord perfusion.[37] A preclinical study utilizing a pig SCI model previously demonstrated a significant and sustainable improvement in blood flow and SCPP with CSF drainage.[38] An early human study was undertaken with 22 patients randomized to undergo CSF drainage within 48 hours of injury versus not.[39] Lumbar drainage was not associated with significant side effects but also did not demonstrate definite neurologic benefit, though the authors cited a low power as one potential cause. Subsequent larger studies demonstrated more significant benefits with adequate safety profiles; however, a well-defined effect remains to be reproducibly demonstrated.[40] Patch duraplasty is another method of lowering ITP on the injured cord and can be performed during initial surgical decompression.[41] One study found that laminectomy with patch duraplasty resulted in lower ITP and improved spinal perfusion pressure compared with laminectomy alone in acute SCI; additionally, ASIA impairment and bowel/bladder function was improved in the duraplasty group. However, low power contributed to a lack of statistically significant differences in clinical outcomes.[42] These studies underscore the overall difficulty in performing well powered and large-scale human trials on acute SCI.

Hyperbaric oxygen (HBO), when administered early, may counteract spinal cord ischemia and hypoxia, potentially reducing apoptosis, oxidative damage, inflammation, and edema, and promoting angiogenesis and autophagy. Recent clinical studies have initiated therapy within 9–20 hours of injury with varying time-courses, demonstrating varying degrees of neurologic improvement.[43] Technical parameters (onset, duration, frequency, and pressure) and evaluation of benefits in more heterogenous samples of SCI presentations remain to be investigated. Two clinical studies are ongoing in China (NCT03112941) and Austria (NCT03101982).

2. Minimizing Inflammation-Induced Secondary Damage

The inflammatory cascade occurring hours to days following the primary of insult of SCI likely contributes to worsened neurological outcomes.[34] This secondary damage acts on the injured spinal cord through cellular and systemic factors that worsen compression, ischemia, and scarring.[44] Synthesis of proinflammatory prostaglandins and cytokines, calcium-dependent nitric oxide, opioid peptides, and necroptotic factors have been shown to augment inflammatory secondary damage in the acute stages of injury. To address this component of the injury, several commonplace pharmacological agents have demonstrated efficacy in maintaining blood flow and protecting from cellular damage in preclinical studies.[34] Cyclooxygenase inhibitors including ibuprofen and meclofenamate as well as nonselective opioid antagonists such as naloxone have been shown to improve blood flow and enhance functional results in animal spinal cord contusion models.[45-48] Still, few trials have attempted to establish the ef-

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fects of these agents in human SCI. In 1990, NASCIS II found no neurologic benefit with the administration of naloxone throughout the first 24 hours after SCI compared to placebo, although those recommendations are being revisited more broadly.[26] A phase-I clinical trial involving 12 patients investigating the use of ibuprofen administration in acute SCI is in progress (NCT-02096913).

Minocycline, a tetracycline antibiotic, has demonstrated multiple neuroprotective effects against secondary injury progression in SCI.[34] Minocycline impedes generation of proinflammatory cytokines (IL-1beta, tumor-necrosis factor [TNF]-alpha, cyclooxygenase-2), hinders expression of proapoptotic caspase-1/-3, and inhibits inducible nitric oxide synthase.[49,50] Successful preclinical studies showed enhanced tissue sparing and motor recovery within 3–4 weeks following SCI in mice.[51,52] A phase-II clinical trial demonstrated that patients with acute incomplete cervical SCI can benefit from early minocycline administration.[53] The study reported a 14-point ASIA motor score recovery in patients receiving minocycline administration for 7 days following injury compared with placebo.[53]

Spinal cooling is a nonpharmacologic method that has been explored for its potential to ameliorate biochemical secondary injury. One study utilized a combination of surgical decompression, steroid administration, and regional hypothermia in 20 patients and saw an improvement from initial ASIA-A impairment in 13 patients.[54] The lack of randomized comparative control arms in this study and the few other case reports/small clinical series available limit the generalizability of spinal cord cooling in acute SCI; however, the promising initial results and absence of reported adverse effects may warrant further study.[12]

3. Controlling Cytotoxic Response

The acute cytotoxic response to SCI is another targetable pathomechanism. Calcium, sodium, and potassium ion dysregulation as well as release of high levels of glutamate from damaged neural tissue can cause excitotoxicity and oxidative damage. Signaling cascades that lead to ROS formation and lipid peroxidation increase the likelihood of neuronal cell death. Inhibiting free radical formation through various antioxidants including cyclosporin A, vitamins C, D, and E, selenium, lithium, polyethylene glycol-superoxide dismutase, and *OXR1* gene-enhancing therapy, have all shown promise in maintaining cell viability in animal models.[34] One 16-participant, phase-I/II clinical trial of lithium in China (NCT01471613) is the first human trial to incorporate one of these agents as an adjunct in acute management strategies.

Uncontrolled activation of voltage-gated sodium channels has been hypothesized as an important step in the cytotoxic response leading to secondary spinal trauma. Riluzole is a benzothiazole that inhibits voltage-gated sodium channel-mediated glutamate release and recently gained approval for the treatment of amyotrophic lateral sclerosis. Previous animal studies have documented reduced neuronal loss and sensorimotor improvement with Riluzole administration following SCI, likely through inhibition of glutamate release and subsequent reduction of calcium-signaling induced apoptosis reduction.[55] A successful phase-I trial involving 36 patients found that 50 mg of Riluzole orally every 12 hours for 14 days enhanced motor recovery in cervical SCI at 3 months postinjury compared with a matched control group.[55] Similar motor enhancement was not found at 6-month follow-up. A transient increase in liver enzymes in the Riluzole group prompted questions of pharmacotoxicity, however its safety profile has yet to be presented in larger studies. The AO Spine North America Research Network is currently conducting the Riluzole in Acute Spinal Cord Injury Study, a multicenter randomized trial designed to evaluate the therapeutic application of Riluzole in acute SCI.

Antagonism of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/ N-methyl-D-aspartate (NMDA) receptors has been postulated as a mechanism of reducing excitatory amino acid (glutamate) toxicity in the hyperacute phase of SCI. These neurotransmitters reach toxic levels within 15 minutes of injury and typically peak for less than 120 minutes.[34] Gacyclidine, an NMDA receptor antagonist, has been evaluated in a phase-II double-blind, randomized evaluation of 280 patients with SCI.[56] However, this study revealed no significant improvement in ASIA scores compared with placebo treatment. Still, other NMDA antagonists such as magnesium have been shown in preclinical studies to reduce excitotoxicity and inflammation. Organized phase-I/II clinical trials have yet to be completed examining this therapy in acute SCI.

Calcium-channel blockers (CCB) can significantly reduce the pathological influx of calcium following SCI and improve perfusion through regulation of vascular smooth muscle tone. The utility of nimodipine has been studied, most notably in a French clinical trial of 106 patients with SCI randomized to receive MPSS, nimodipine, MPSS and nimodipine, or placebo within 8 hours of injury for 7 days duration. Neither additional neurologic benefit nor significant adverse effects in the nimodipine treatment group versus control were noted.[27] Still, concerns for systemic hypotension in the context of injured auto-regulatory mechanisms in cervicothoracic SCI should prompt caution when

considering CCBs during acute management. Finally, potassium channel antagonists such as the fast potassium channel blocker fampridine may have potential therapeutic benefit through improvement of axonal conduction in SCI and are currently being tested in phase-III trials.[34]

4. Modulating the Immune Response

Immunomodulative therapies are currently under investigation for the treatment of acute SCI. Peripheral immune cells including macrophages, neutrophils, and T cells trigger an inflammatory response following injury that can last several days. Importantly, this response can cause cavitary lesion growth, further damaging surrounding spinal cord. Inflammatory cytokines including IL-1beta, TNF-alpha, and IL6 are produced in response to the injury and are followed by release of the neuroprotective IL-10.[34,57] Microglia, the resident immune cells of the central nervous system, are known to have a central role in modulating this response.[58] One phase-I/II trial currently underway in China is examining the use of TNF-alpha monoclonal antibodies in acute SCI (NCT04988425). Enrollment is expected to reach 90 participants, and results are anticipated in late 2023.

Granulocyte-colony stimulating factor (G-CSF) is a cytokine glycoprotein that has increasingly been demonstrated to enhance neurogenesis and reduce TNF-alpha and IL1-beta expression levels at SCI sites.[59] Randomized phase-I/IIa studies have shown ASIA motor score improvement and a lack of significant adverse events with G-CSF therapy for acute SCI.[60] A phase-III clinical trial in Japan was recently completed with results to be published in the near future.[61]

5. Nerve Regeneration Techniques

One of the most promising aims in experimental therapeutics for SCI remains establishing methods for neuronal and axonal regeneration. Current approaches focus on stem cell implantation, growth factor conditioning, neural growth inhibitor binding, tissue scaffolding, and neuromodulation. While these methods have historically been engineered to address chronic SCI, focusing regenerative efforts closer to the primary insult could theoretically expedite healing and functional recovery.

1) Stem cell implantation

The potential of stem cell therapy to induce or enhance endogenous neural regeneration and/or improve functional recovery has continued to undergo rigorous research. Stem cell therapies under investigation encompass autologous bone-marrow mononuclear cells (BM-MSCs)—including hematopoietic stem cells (HSCs) and mesenchymal stem cells—and other cell types including neural progenitor cells (NPCs), olfactory ensheathing cells (OECs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs).

Bone-marrow derived mononuclear cells have the advantage of reduced immune rejection and possible synergism between HSCs and MSCs, improving angiogenesis and matrix repair.[30] On the other hand, BM-MSCs are difficult to purify and culture *in vitro*, and they possess limited differentiation potential.[30] Clinical trials of these therapies have shown promising but mixed results. After autologous HSC (CD-34+ and CD-133+) transplantation in 19 patients with complete SCI (ASIA-A), 37% of patients saw segmental sensory improvement (ASIA-B), 10% saw motor improvement (ASIA-C), and the remaining 53% saw no improvement (ASIA-A) within a 42–60 months follow-up period.[62] Relative to HSCs, MSCs possess higher neuronal differentiation potential, and small clinical trials have demonstrated safety and variable efficacy in improving spasticity, sensorimotor, and sphincter function in both complete and incomplete chronic SCI patients.[30,63] A meta-analysis of 328 patients demonstrated improved ASIA scores in 42% of cases after 1 year but noted the limited availability of clinical trial data and standardized methods.[64] Numerous clinical trials are ongoing, including a phase-II/III trial of MSCs in chronic ASIA-B patients by Pharmicell Co. (Seoul, Korea) and a trial of adipose-derived MSCs in ASIA-A, ASIA-B, and ASIA-C patients by Mayo Clinic. These trials were set to conclude in 2020 and 2023, respectively.[65]

NPCs are native and multipotent and differentiate into neuronal-restricted precursors and glial-restricted precursors. NPC transplants readily integrate into the host milieu, induce axonal regeneration and extension, hasten remyelination, attenuate glial scar formation, and afford immunomodulation and neuroprotection.[66] A phase-I/IIa open-label nonrandomized controlled clinical trial did demonstrate AISA score improvement by at least 2 points in 5 of 19 NPC transplant patients, compared to 1 of 15 control patients.[67] Other clinical trials, such as an open-label phase-I trial by Neuralstem (now Seneca BioPharma, Germantown, MD, USA), are ongoing. Challenges currently faced include difficult isolation of NPCs, the small number of therapy candidates, and the high cost of research.[67]

OECs are glial cells that support olfactory receptor axonal growth into the olfactory bulb. Specifically, they express neurotrophins that promote neurogenesis and reduce risk of astrocyte hypertrophy. They are readily harvested autologously from the olfactory bulb and nasal mucosa and do not require patient

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immunosuppression. OECs are limited by inadequate source quantity and present differentiation and purification challenges similar to other regenerative options. Numerous clinical trials have been conducted, and a meta-analysis of 1,193 patients treated with OECs found no significant adverse effects, but methodological and technical concerns prevented determination of any significant efficacy as well.[68] Clinical trials in Poland (NCT03933072) and the United Kingdom (NCT02870426) are slated to conclude in 2023.

ESCs and iPSCs have similarly impressive differentiation potential, promising substantial efficacy; human ESCs are indeed capable of differentiation into NPCs and, subsequently, regionally specific neuronal subtypes.[69] Their pluripotency means ESCs and iPSCs do carry an associated genomic instability and risk of malignancy. The ethical stature of ESC use is also disputed. Non-human investigation of ESC- and iPSC-based treatment of SCI has demonstrated feasibility, but clinical trials are so far limited.[70,71] The Geron Corporation (Foster City, CA, USA) began a clinical trial of ESCs for SCI therapy in 2010, enrolling 5 patients before stopping the trial a year later. Not all patients enrolled had received a transplant.[30] Keio University in Tokyo, Japan, has received approval for a clinical trial of iPSC therapy for ASIA-A patients, which is ongoing.[30,71]

Overall, while these data are promising in the quest to determine the best neuro-regenerative substrates in SCI, more work is required to establish efficacy and safety in the acute postinjury setting to determine long-term effects on functional recovery. Additionally, no head-to-head trials have as of yet been conducted; subsequent investigation should help to focus efforts on optimizing sourcing, delivery, and conditioning of transplanted cells.

2) Growth factor conditioning

Acidic fibroblast growth factor (aFGF) is a mitogenic, pluripotent heparin-binding protein that has been shown to enhance neuronal growth and mitigates scarring in SCI in numerous animal studies.[72,73] Human clinical trials have steadily increased in number since an initial case report demonstrating marked functional recovery of a patient with chronic SCI who was treated with 4 survival nerve grafts along with an aFGF fibrin glue and could ambulate independently with a walker at 2.5 years postinjury.[74] A different group conducted 2 more studies, 1 on 9 cervical SCI patients and a follow-up study with 60 patients (50/50 cervical and thoracolumbar SCI), and found that the use of aFGF fibrin glue resulted in significant enhancement of ASIA motor and sensory scores.[75,76] These observational studies were limited by their lack of randomization and control arms. Recombinant human aFGF (compound ES135) is currently undergoing a multicenter double blind, randomized placebo control phase-III study (NCT03229031). Hepatocyte growth factor (HGF) can enhance neuronal survival and decrease astroglial scar lesion size by increasing angiogenesis and axon regeneration.[77] Intrathecal recombinant human HGF injection has been shown to improve neurological status in rat studies.[78] Based on this, a phase-I/II trial of intrathecal recombinant HGF involving patients with acute cervical SCI found that all patients had improved Frankel scores at 72 hours.[79]

3) Inhibiting neural growth inhibitors

Cethrin (VX-210) is a recombinant inhibitor of the Rho pathway which is involved in the regulation of cytoskeleton formation.[30] Inhibition of Rho has been shown in rodent thoracic contusion models to promote axonal outgrowth and improve motor function.[80] Following a phase-I/IIa clinical study that demonstrated the safety and tolerability of Cethrin for acute cervical and thoracic SCI in human patients, a double-blinded, placebo-controlled, multicenter trial (SPRING) has been developed to demonstrate therapeutic benefit, with preliminary results posted (NCT02669849).

Elezanumab is a monoclonal antibody that binds to and neutralizes repulsive guidance molecule A, an inhibitor of axonal growth and regulator of neuronal cell death.[81] A phase-II clinical trial is currently underway to evaluate the effects of Elezanumab in acute traumatic cervical SCI (NCT04295538).

4) Tissue scaffolding

Biomaterial tissue scaffolding is one promising method for facilitating SCI repair. Natural or synthetic biomaterial polymers have been shown in animal models to enhance nervous tissue regeneration by promoting survival and outgrowth of transplanted cells and providing an environment to concentrate neurotrophic growth factors.[12,30] Limited efficacy has been redemonstrated in humans. A large multicenter trial entitled INSPIRE launched in 2014 to determine the benefit of a synthetic polymer scaffold poly(lactic-co-glycolic acid)-b-poly(L-lysine) in subjects with thoracic ASIA-A impairment, has completed enrollment and expected to conclude in 2024 (NCT02138110). Multiple clinical trials led by the Chinese Academy of Sciences are investigating the application of NeuroRegen, a collagen scaffold, in concert with other experimental strategies including stem cell therapy and epidural stimulation.

Gangliosides including the glycosphingolipid ganglioside-1

(GM-1) are complex acidic glycolipids that constitute a major component of the cell membrane. Experimental evidence in animal studies has shown potential in the regeneration and growth of damaged nervous tissue leading to functional improvement.[82] One phase-II trial showed enhanced 1-year ASIA motor score improvement following daily administration of GM-1 for 18–32 days following injury.[68] However, meta-analyses evaluating potential therapeutic benefits of GM-1 across studies failed to support its widespread use for SCI.[83] Still, it has been suggested that studies with more optimized methodology (i.e., potentializing GM-1 administration with HBO and/or refining outcome measurement) may be warranted with this potential therapeutic.[83]

5) Neuromodulation

Epidural stimulation (ES) is an emerging treatment strategy that has demonstrated promise in the treatment of chronic SCI in both animals and humans.[84-86] It is theorized that oscillating electrical fields may stimulate neuronal growth and remyelination and excite remaining neuronal networks at the site of the lesion.[87] Individual patients with predominantly lumbar injuries have demonstrated motor improvement with ES, including partial and full weight-bearing and overground ambulation, even with complete injuries.[88,89] Similarly promising results of upper limb motor recovery have been observed.[89] Notably, a recent study demonstrated activity-specific stimulation programs that enabled 3 individuals with complete sensorimotor paralysis to regain trunk and leg motor functions within 1 day of stimulation.[90] Several clinical trials targeting these broader functional metrics (e.g., volitional movement, autonomic function, bladder training, and sensory feedback) are underway.

FUTURE PERSPECTIVES

Table 1 summarizes the current and developing investigational therapeutic tools for treating acute SCI. Numerous methods are being developed in animal models that may soon be tested in clinical trials designed to demonstrate functional benefit in SCI. Necroptosis is a caspase-independent mechanism of programmed cell death that occurs following cellular injury in which cellular contents are not packaged into apoptotic bodies and instead leak into the extracellular space, promoting a proinflammatory state through triggering of innate and adaptive immune systems.[91] The process is dependent on receptor-interacting serine/threonine kinase 1 and 3 and studies have shown that it may be one of the primary forms of cell death following traumatic SCI.[91] Inhibition of this pathway is suspected to attenuate secondary damage and minimize cell death.[92]

Autologous omental transplantation has been proposed as a method to introduce blood- and lymph-rich tissue to injured spinal cord tissue.[93] Relatively small human trials in the 1990s showed continued viability of omental grafts in chronic SCI patients but failed to demonstrate objective functional improvement, and interest in its SCI treatment potential fell flat for a time.[94] However, omental transplant therapy has progressed in other clinical settings, including flap transposition on the brain surface for neovascularization and neurotrophic effects in epileptic or ischemic brain injury.[95] Interest in omental angiogenesis as a treatment for SCI has revived in recent years, and trials in rats have improved neural preservation, reduced injury cavity, and promoted neovascularization of the injured site.[93]

A newer addition to the regenerative cellular therapies discussed in the literature is peripheral nerve derived stem cells (PNSCs). Spheroid forms of PNSCs have demonstrated therapeutic potential through neurotrophic factor release and extracellular matrix expression, leading to significant functional recovery, neuronal regeneration, and neuropathic pain reduction in animal models.[96]

Estrogen-based therapies are also an emerging avenue or research. Estradiol is known to provide CNS neuroprotection in animal models of SCI, traumatic brain injury, and ischemic brain injury.[97] The therapeutic capability of a third-generation selective estrogen receptor modulator, bazedoxifine, was studied in rats.[98] Bazedoxifine was shown to suppress inflammatory response and promote remyelination by inhibiting the mitogen-activated protein kinase/nuclear factor-kappa B (NF-κB) pathway and enhancing oligodendrocyte precursor cell differentiation and oligodendrocyte proliferation. There are complex and profound implications of estrogen therapy due to its natural maintenance and alteration of normal physiology. Still, there is hope that estrogen therapies may play some role in SCI treatment.

Entinostat is a class I histone deacetylase (HDAC) inhibitor directed primarily against HDAC1 and HDAC3. HDAC inhibitors have been shown to inhibit NF-κB mediated microglial activation, thus reducing SCI-induced inflammation.[99] Treatment of a mouse SCI model with Entinostat resulted in improved grip strength, Basso Mouse Scale score for locomotion, spinal edema, cell death, and local NLRP3 inflammasome activation.[99]

Another method of counteracting inflammation induced by SCI may be found in IgM's homeostatic role against IgG autoimmune response. One study found that IgM-knockout mice with induced C6–7 SCI showed significantly greater impair-

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Table 1. Summary of investigational therapeutic tools and their corresponding evidence for management of acute SCI

Therapeutic goal	Investigational tool	Investigational status/current findings
Prevent ischemia	Vasopressors	Norepinephrine, dopamine, midodrine Limited evidence supporting one pressor over another
	CSF diversion	Lumbar puncture & patch duraplasty may improve SCPP and ASIA scores in low-power studies
	Hyperbaric oxygen	Optimized technical parameters remain undefined
Minimize inflammatory damage	COX-inhibitors, nonselective opioid antagonists	Improved blood flow and functional status in animals. Human clinical trials underway
	Minocycline	Phase-II clinical trials demonstrated improved functional status
	Spinal cooling	ASIA motor score improvement in small, non-RCT trials
Block cytotoxic response	Free radical inhibition	Few studies of antioxidant therapy in humans Adjunctive lithium is being studied in a phase-I/II trial.
	Riluzole	Small, phase-I trial showed short term motor improvement. Transaminase elevation raises concerns for pharmacotoxicity Multicenter RCT (RISCIS) underway
	AMPA/NMDA antagonists	Phase-II double-blind, randomized trial of gacyclidine showed no significant benefit versus placebo Other antagonists (e.g., magnesium) have promising preclinical results
	Ion channel modulators	Nimodipine (CCB): No apparent benefit or adverse effects in RCT. Concern for systemic hypotension Fampridine (K-channel blocker): Phase-III trial underway
Immunomodulation	TNF-alpha mAb	Phase-I/II clinical trial underway
	G-CSF	Phase-I/II trials showed ASIA motor score improvement Phase III trial underway
Nerve regeneration	Stem cell therapies	Sourcing, potency, and clinical benefit vary by cell type. Numerous clinical trials are underway Future efforts should optimize sourcing, delivery, and conditioning of transplant cells
	Growth factor conditioning	aFGF: Phase I/II clinical trials demonstrate ASIA motor and sensory improvement. Phase-III trial underway HGF: Phase I/II trials showed improvement in Frankel grade
	Neural growth inhibitor blockers	Cethrin: Phase-I/IIa successful; Phase-IIb/III (SPRING trial) underway Elezanumab: Phase-II trial underway
	Tissue scaffolding	PLGA: Multicenter trial (INSPIRE) underway NeuroRegen: Multiple trials underway GM-1: Unclear benefit; clinical methodologies need optimization
	Neuromodulation (ES)	Small studies demonstrate promising functional recovery. Several clinical trials underway
Future perspectives	Necroptosis inhibition (RIPK-1/3 inhibition)	Under preclinical investigation
	Omental transplant	
	Peripheral nerve derived stem cell therapy	
	Selective estrogen receptor modulator therapy	
	HDAC1/3 inhibition (Entinostat)	
	IgM therapy	

SCI, spinal cord injury; CSF, cerebrospinal fluid; SCPP, spinal cord perfusion pressure; ASIA, American Spine Injury Association; COX, cyclooxygenase; RCT, randomized clinical trial; RISCIS, Riluzole in Spinal Cord Injury Study; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartate; CCB, calcium-channel blocker; K, potassium; TNF, tumor-necrosis factor; mAb, monoclonal antibody; G-CSF, granulocyte-colony stimulating factor; aFGF, acidic fibroblast growth factor; HGF, hepatocyte growth factor; PLGA, poly (lactic-co-glycolic acid)-b-poly(L-lysine); RIPK, receptor-interacting protein kinase; HDAC, histone deacetylase; ES, epidural stimulation; GM-1, ganglioside-1.

ment in neurobehavioral recovery compared to their wild-type counterparts, including deteriorated coordination and reduced fore- and hind-limb swing speed and print-area, which serve as gait parameters.[100] IgM-knockout mice also exhibited increased lesion size, less white matter sparing, and enhanced deposition of complement-fixing IgG antibodies in the spinal cord. These newer methods will continue to be studied closely by the scientific community hoping to grow the armamentarium available to treat this multifaceted disorder.

CONCLUSION

Emerging strategies for managing SCI in the acute period stem from an evolving understanding of the pathophysiology of the disorder and focus on preventing ischemia, reducing secondary injury due to inflammation and necroptosis, modulating the cytotoxic and immune response, and promoting cellular regeneration. There is significant research ongoing in preclinical and clinical studies examining a wide array of surgical and non-surgical therapies. A major hurdle to wide acceptance of any of the emerging treatments is designing an appropriate clinical trial to test them. Continued translational research on these methods will improve the feasibility of bench-to-bedside innovations in treating patients with acute SCI.

NOTES

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REFERENCES

1. Hadley MN, Walters BC, Aarabi B, et al. Clinical assessment following acute cervical spinal cord injury. Neurosurgery 2013;72 Suppl 2:40-53.
2. Roberts TT, Leonard GR, Cepela DJ. Classifications In Brief: American Spinal Injury Association (ASIA) Impairment Scale. Clin Orthop Relat Res 2017;475:1499-504.
3. Singh A, Tetreault L, Kalsi-Ryan S, et al. Global prevalence and incidence of traumatic spinal cord injury. Clin Epidemiol 2014;6:309-31.
4. Ackery A, Tator C, Krassioukov A. A global perspective on spinal cord injury epidemiology. J Neurotrauma 2004;21:1355-70.
5. Simpson LA, Eng JJ, Hsieh JT, et al. The health and life priorities of individuals with spinal cord injury: a systematic review. J Neurotrauma 2012;29:1548-55.
6. Furlan JC, Gulasingam S, Craven BC. The Health Economics of the spinal cord injury or disease among veterans of war: A systematic review. J Spinal Cord Med 2017;40:649-64.
7. Moghaddamjou A, Fehlings MG. The beneficial effect of early surgical decompression for acute spinal cord injury: time is spine. Neurospine 2021;18:20-2.
8. Alizadeh A, Dyck SM, Karimi-Abdolrezaee S. Traumatic spinal cord injury: an overview of pathophysiology, models and acute injury mechanisms. Front Neurol 2019;10:282.
9. Kumar N, Osman A, Chowdhury JR. Traumatic spinal cord injuries. J Clin Orthop Trauma 2017;8:116-24.
10. Hadley MN, Walters BC, Grabb PA, et al. Cervical spine immobilization before admission to the hospital. Neurosurgery 2002;50(3 Suppl):S7-17.
11. Zileli M, Osorio-Fonseca E, Konovalov N, et al. Early management of cervical spine trauma: WFNS Spine Committee Recommendations. Neurospine 2020;17:710-22.
12. Wang TY, Park C, Zhang H, et al. Management of acute traumatic spinal cord injury: a review of the literature. Front Surg 2021;8:698736.
13. Snyder R, Verla T, Ropper AE. Practical application of recent advances in diagnostic, prognostic, and therapeutic modalities for spinal cord injury. World Neurosurg 2020;136:330-6.
14. Fehlings MG, Tetreault LA, Wilson JR, et al. A clinical practice guideline for the management of acute spinal cord injury: introduction, rationale, and scope. Global Spine J 2017;7(3 Suppl):84S-94S.
15. Mputu Mputu P, Beauséjour M, Richard-Denis A, et al. Early predictors of neurological outcomes after traumatic spinal cord injury: a systematic review and proposal of a conceptual framework. Am J Phys Med Rehabil 2021;100:700-11.
16. Parthiban J, Zileli M, Sharif SY. Outcomes of spinal cord injury: WFNS Spine Committee Recommendations. Neuro-

spine 2020;17:809-19.
17. Qiu Y, Chen Y, Xie Y, et al. Comparative analysis of the efficacy of early and late surgical intervention for acute spinal cord injury: a systematic review and meta-analysis based on 16 studies. Int J Surg 2021;94:106098.
18. Chikuda H, Koyama Y, Matsubayashi Y, et al. Effect of early vs delayed surgical treatment on motor recovery in incomplete cervical spinal cord injury with preexisting cervical stenosis: a randomized clinical trial. JAMA Netw Open 2021;4:e2133604.
19. Fehlings MG, Vaccaro A, Wilson JR, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One 2012;7:e32037.
20. Dvorak MF, Noonan VK, Fallah N, et al. The influence of time from injury to surgery on motor recovery and length of hospital stay in acute traumatic spinal cord injury: an observational Canadian cohort study. J Neurotrauma 2015;32:645-54.
21. Badhiwala JH, Wilson JR, Witiw CD, et al. The influence of timing of surgical decompression for acute spinal cord injury: a pooled analysis of individual patient data. Lancet Neurol 2021;20:117-26.
22. Lee YS, Kim KT, Kwon BK. Hemodynamic management of acute spinal cord injury: a literature review. Neurospine 2021;18:7-14.
23. Hawryluk G, Whetstone W, Saigal R, et al. Mean arterial blood pressure correlates with neurological recovery after human spinal cord injury: analysis of high frequency physiologic data. J Neurotrauma 2015;32:1958-67.
24. Hatton GE, Mollett PJ, Du RE, et al. High tidal volume ventilation is associated with ventilator-associated pneumonia in acute cervical spinal cord injury. J Spinal Cord Med 2021;44:775-81.
25. Redshaw JD, Lenherr SM, Elliott SP, et al. Protocol for a randomized clinical trial investigating early sacral nerve stimulation as an adjunct to standard neurogenic bladder management following acute spinal cord injury. BMC Urol 2018;18:72.
26. Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. JAMA 1997;277:1597-604.
27. Pointillart V, Petitjean ME, Wiart L, et al. Pharmacological therapy of spinal cord injury during the acute phase. Spinal Cord 2000;38:71-6.
28. Matsumoto T, Tamaki T, Kawakami M, et al. Early complications of high-dose methylprednisolone sodium succinate treatment in the follow-up of acute cervical spinal cord injury. Spine (Phila Pa 1976) 2001;26:426-30.
29. Cabrera-Aldana EE, Ruelas F, Aranda C, et al. Methylprednisolone administration following spinal cord injury reduces aquaporin 4 expression and exacerbates edema. Mediators Inflamm 2017;2017:4792932.
30. Takami T, Shimokawa N, Parthiban J, et al. Pharmacologic and regenerative cell therapy for spinal cord injury: WFNS Spine Committee Recommendations. Neurospine 2020;17:785-96.
31. Hicks AL, Martin KA, Ditor DS, et al. Long-term exercise training in persons with spinal cord injury: effects on strength, arm ergometry performance and psychological well-being. Spinal Cord 2003;41:34-43.
32. Post MW, van Leeuwen CM. Psychosocial issues in spinal cord injury: a review. Spinal Cord 2012;50:382-9.
33. Dhall SS, Hadley MN, Aarabi B, et al. Nutritional support after spinal cord injury. Neurosurgery 2013;72 Suppl 2:255-9.
34. Zhang Y, Al Mamun A, Yuan Y, et al. Acute spinal cord injury: pathophysiology and pharmacological intervention (review). Mol Med Rep 2021;23:417.
35. Ploumis A, Yadlapalli N, Fehlings MG, et al. A systematic review of the evidence supporting a role for vasopressor support in acute SCI. Spinal Cord 2010;48:356-62.
36. Mojtahedzadeh M, Taghvaye-Masoumi H, Najafi A, et al. Management of hypotension and bradycardia caused by spinal cord injury. The usefulness of midodrine and methylxanthines. Iran J Pharm Res 2019;18:2131-5.
37. Khan NR, Smalley Z, Nesvick CL, et al. The use of lumbar drains in preventing spinal cord injury following thoracoabdominal aortic aneurysm repair: an updated systematic review and meta-analysis. J Neurosurg Spine 2016;25:383-93.
38. Martirosyan NL, Kalani MY, Bichard WD, et al. Cerebrospinal fluid drainage and induced hypertension improve spinal cord perfusion after acute spinal cord injury in pigs. Neurosurgery 2015;76:461-8; discussion 468-9.
39. Kwon BK, Curt A, Belanger LM, et al. Intrathecal pressure monitoring and cerebrospinal fluid drainage in acute spinal cord injury: a prospective randomized trial. J Neurosurg Spine 2009;10:181-93.
40. Squair JW, Bélanger LM, Tsang A, et al. Spinal cord perfusion pressure predicts neurologic recovery in acute spinal

cord injury. Neurology 2017;89:1660-7.
41. Tykocki T, Poniatowski Ł, Czyż M, et al. Intraspinal pressure monitoring and extensive duroplasty in the acute phase of traumatic spinal cord injury: a systematic review. World Neurosurg 2017;105:145-52.
42. Phang I, Werndle MC, Saadoun S, et al. Expansion duroplasty improves intraspinal pressure, spinal cord perfusion pressure, and vascular pressure reactivity index in patients with traumatic spinal cord injury: injured spinal cord pressure evaluation study. J Neurotrauma 2015;32:865-74.
43. Patel NP, Huang JH. Hyperbaric oxygen therapy of spinal cord injury. Med Gas Res 2017;7:133-43.
44. Schwartz G, Fehlings MG. Secondary injury mechanisms of spinal cord trauma: a novel therapeutic approach for the management of secondary pathophysiology with the sodium channel blocker riluzole. Prog Brain Res 2002;137:177-90.
45. Chaves RHF, Souza CC, Furlaneto IP, et al. Influence of tramadol on functional recovery of acute spinal cord injury in rats. Acta Cir Bras 2018;33:1087-94.
46. Harada N, Taoka Y, Okajima K. Role of prostacyclin in the development of compression trauma-induced spinal cord injury in rats. J Neurotrauma 2006;23:1739-49.
47. Young W, Flamm ES, Demopoulos HB, et al. Effect of naloxone on posttraumatic ischemia in experimental spinal contusion. J Neurosurg 1981;55:209-19.
48. Winkler T, Sharma HS, Stålberg E, et al. Opioid receptors influence spinal cord electrical activity and edema formation following spinal cord injury: experimental observations using naloxone in the rat. Neurosci Res 1994;21:91-101.
49. Scholz R, Sobotka M, Caramoy A, Stempfl T, Moehle C, Langmann T. Minocycline counter-regulates pro-inflammatory microglia responses in the retina and protects from degeneration. J Neuroinflammation 2015;12:209.
50. Tikka TM, Koistinaho JE. Minocycline provides neuroprotection against N-methyl-D-aspartate neurotoxicity by inhibiting microglia. J Immunol 2001;166:7527-33.
51. Wells JE, Hurlbert RJ, Fehlings MG, et al. Neuroprotection by minocycline facilitates significant recovery from spinal cord injury in mice. Brain 2003;126(Pt 7):1628-37.
52. Squair JW, Ruiz I, Phillips AA, et al. Minocycline reduces the severity of autonomic dysreflexia after experimental spinal cord injury. J Neurotrauma 2018;35:2861-71.
53. Casha S, Zygun D, McGowan MD, et al. Results of a phase II placebo-controlled randomized trial of minocycline in acute spinal cord injury. Brain 2012;135(Pt 4):1224-36.
54. Hansebout RR, Hansebout CR. Local cooling for traumatic spinal cord injury: outcomes in 20 patients and review of the literature. J Neurosurg Spine 2014;20:550-61.
55. Nagoshi N, Nakashima H, Fehlings MG. Riluzole as a neuroprotective drug for spinal cord injury: from bench to bedside. Molecules 2015;20:7775-89.
56. Kim YH, Ha KY, Kim SI. Spinal cord injury and related clinical trials. Clin Orthop Surg 2017;9:1-9.
57. Thompson CD, Zurko JC, Hanna BF, et al. The therapeutic role of interleukin-10 after spinal cord injury. J Neurotrauma 2013;30:1311-24.
58. Brockie S, Hong J, Fehlings MG. The role of microglia in modulating neuroinflammation after spinal cord injury. Int J Mol Sci 2021;22:9706.
59. Nishio Y, Koda M, Kamada T, et al. Granulocyte colony-stimulating factor attenuates neuronal death and promotes functional recovery after spinal cord injury in mice. J Neuropathol Exp Neurol 2007;66:724-31.
60. Derakhshanrad N, Saberi H, Yekaninejad MS, et al. Granulocyte-colony stimulating factor administration for neurological improvement in patients with postrehabilitation chronic incomplete traumatic spinal cord injuries: a double-blind randomized controlled clinical trial. J Neurosurg Spine 2018;29:97-107.
61. Koda M, Hanaoka H, Fujii Y, et al. Randomized trial of granulocyte colony-stimulating factor for spinal cord injury. Brain 2021;144:789-99.
62. Al-Zoubi A, Jafar E, Jamous M, et al. Transplantation of purified autologous leukapheresis-derived CD34+ and CD133+ stem cells for patients with chronic spinal cord injuries: long-term evaluation of safety and efficacy. Cell Transplant 2014;23 Suppl 1:S25-34.
63. Vaquero J, Zurita M, Rico MA, et al. Intrathecal administration of autologous mesenchymal stromal cells for spinal cord injury: Safety and efficacy of the 100/3 guideline. Cytotherapy 2018;20:806-19.
64. Aghayan HR, Arjmand B, Yaghoubi M, et al. Clinical outcome of autologous mononuclear cells transplantation for spinal cord injury: a systematic review and meta-analysis. Med J Islam Repub Iran 2014;28:112.
65. Ahuja CS, Mothe A, Khazaei M, et al. The leading edge: Emerging neuroprotective and neuroregenerative cell-based therapies for spinal cord injury. Stem Cells Transl Med 2020;9:1509-30.
66. Fischer I, Dulin JN, Lane MA. Transplanting neural progenitor cells to restore connectivity after spinal cord injury. Nat

 https://doi.org/10.14245/ns.2244176.088

Rev Neurosci 2020;21:366-83.
67. Shin JC, Kim KN, Yoo J, et al. Clinical trial of human fetal brain-derived neural stem/progenitor cell transplantation in patients with traumatic cervical spinal cord injury. Neural Plast 2015;2015:630932.
68. Badhiwala JH, Ahuja CS, Fehlings MG. Time is spine: a review of translational advances in spinal cord injury. J Neurosurg Spine 2018;30:1-18.
69. Ronaghi M, Erceg S, Moreno-Manzano V, et al. Challenges of stem cell therapy for spinal cord injury: human embryonic stem cells, endogenous neural stem cells, or induced pluripotent stem cells? Stem Cells 2010;28:93-9.
70. Keirstead HS, Nistor G, Bernal G, et al. Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. J Neurosci 2005;25:4694-705.
71. Nagoshi N, Tsuji O, Nakamura M, et al. Cell therapy for spinal cord injury using induced pluripotent stem cells. Regen Ther 2019;11:75-80.
72. Ko CC, Tu TH, Wu JC, et al. Acidic fibroblast growth factor in spinal cord injury. Neurospine 2019;16:728-38.
73. Zhou Y, Wang Z, Li J, et al. Fibroblast growth factors in the management of spinal cord injury. J Cell Mol Med 2018;22: 25-37.
74. Ko CC, Tu TH, Wu JC, et al. Functional improvement in chronic human spinal cord injury: Four years after acidic fibroblast growth factor. Sci Rep 2018;8:12691.
75. Wu JC, Huang WC, Tsai YA, et al. Nerve repair using acidic fibroblast growth factor in human cervical spinal cord injury: a preliminary phase I clinical study. J Neurosurg Spine 2008;8:208-14.
76. Wu JC, Huang WC, Chen YC, et al. Acidic fibroblast growth factor for repair of human spinal cord injury: a clinical trial. J Neurosurg Spine 2011;15:216-27.
77. Kitamura K, Iwanami A, Nakamura M, et al. Hepatocyte growth factor promotes endogenous repair and functional recovery after spinal cord injury. J Neurosci Res 2007;85:2332-42.
78. Kitamura K, Fujiyoshi K, Yamane J, et al. Human hepatocyte growth factor promotes functional recovery in primates after spinal cord injury. PLoS One 2011;6:e27706.
79. Kitamura K, Nagoshi N, Tsuji O, et al. Application of hepatocyte growth factor for acute spinal cord injury: the road from basic studies to human treatment. Int J Mol Sci 2019; 20:1054.
80. Dergham P, Ellezam B, Essagian C, et al. Rho signaling pathway targeted to promote spinal cord repair. J Neurosci 2002; 22:6570-7.
81. Jacobson PB, Goody R, Lawrence M, et al. Elezanumab, a human anti-RGMa monoclonal antibody, promotes neuroprotection, neuroplasticity, and neurorecovery following a thoracic hemicompression spinal cord injury in non-human primates. Neurobiol Dis 2021;155:105385.
82. Geisler FH, Dorsey FC, Coleman WP. Recovery of motor function after spinal-cord injury--a randomized, placebo-controlled trial with GM-1 ganglioside. N Engl J Med 1991; 324:1829-38.
83. Marcon RM, Cristante AF, de Barros Filho TE, et al. Potentializing the effects of GM1 by hyperbaric oxygen therapy in acute experimental spinal cord lesion in rats. Spinal Cord 2010;48:808-13.
84. Angeli CA, Boakye M, Morton RA, et al. Recovery of overground walking after chronic motor complete spinal cord injury. N Engl J Med 2018;379:1244-50.
85. Selfslagh A, Shokur S, Campos DSF, et al. Non-invasive, brain-controlled functional electrical stimulation for locomotion rehabilitation in individuals with paraplegia. Sci Rep 2019; 9:6782.
86. Jack AS, Hurd C, Martin J, et al. Electrical stimulation as a tool to promote plasticity of the injured spinal cord. J Neurotrauma 2020;37:1933-53.
87. Eisdorfer JT, Smit RD, Keefe KM, et al. Epidural electrical stimulation: a review of plasticity mechanisms that are hypothesized to underlie enhanced recovery from spinal cord injury with stimulation. Front Mol Neurosci 2020;13:163.
88. Krucoff MO, Gramer R, Lott D, et al. Spinal cord stimulation and rehabilitation in an individual with chronic complete L1 paraplegia due to a conus medullaris injury: motor and functional outcomes at 18 months. Spinal Cord Ser Cases 2020;6:96.
89. Choi EH, Gattas S, Brown NJ, et al. Epidural electrical stimulation for spinal cord injury. Neural Regen Res 2021;16:2367-75.
90. Rowald A, Komi S, Demesmaeker R, et al. Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. Nat Med 2022;28:260-71.
91. Fiani B, Kondilis A, Soula M, et al. Novel methods of necroptosis inhibition for spinal cord injury using translational research to limit secondary injury and enhance endogenous repair and regeneration. Neurospine 2021;18:261-70.
92. Wang Y, Wang J, Wang H, et al. Necrosulfonamide attenu-

ates spinal cord injury via necroptosis inhibition. World Neurosurg 2018;114:e1186-91.
93. Fay LY, Lin YR, Liou DY, et al. The application of an omentum graft or flap in spinal cord injury. Int J Mol Sci 2021;22:7930.
94. Clifton GL, Donovan WH, Dimitrijevic MM, et al. Omental transposition in chronic spinal cord injury. Spinal Cord 1996;34:193-203.
95. Di Nicola V. Omentum a powerful biological source in regenerative surgery. Regen Ther 2019;11:182-91.
96. Lee HL, Yeum CE, Lee H, et al. Peripheral nerve-derived stem cell spheroids induce functional recovery and repair after spinal cord injury in rodents. Int J Mol Sci 2021;22:4141.
97. Raghava N, Das BC, Ray SK. Neuroprotective effects of estrogen in CNS injuries: insights from animal models. Neurosci Neuroecon 2017;6:15-29.
98. Kim Y, Roh EJ, Joshi HP, et al. Bazedoxifene, a selective estrogen receptor modulator, promotes functional recovery in a spinal cord injury rat model. Int J Mol Sci 2021;22:11012.
99. Dai C, Liu B, Peng B, et al. Entinostat improves motor function and neuronal damage via downregulating NLRP3 inflammasome activation after spinal cord injury. Front Pharmacol 2021;12:774539.
100. Ulndreaj A, Vidal PM, Forgione N, et al. IgM immunoglobulin influences recovery after cervical spinal cord injury by modulating the IgG autoantibody response. eNeuro 2021;8:ENEURO.0491-19.2021.

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Editorial

Commentary on "Established and Emerging Therapies in Acute Spinal Cord Injury"

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Spinal cord injury (SCI) is a severe neurological disease commonly caused by traumas or variety diseases which can lead to complete or incomplete neural function deficiency.[1] Among all the directly or indirectly causal external factors resulting in SCI, the trauma, which including traffic accidents, falls and sports/recreation, are the most common etiologies of SCI.[2] Due to severe incapacitation of the limbs below the injured segment after SCI, SCI not only causes considerable physical suffering and mental distress to patients themselves, but also incurs substantial economic burdens for families and society.[3] According to incomplete statistics, SCI affects more than 2 million people worldwide. Therefore, finding ways to repair damage to spinal cord tissue is a common goal in modern medicine. Of course, understanding the molecular and cellular mechanisms contributing to the pathophysiology of SCI is essential for developing more effective therapeutic interventions.

In the current study, Dr. Gadot et al.[4] have provided thoroughly review of the SCI, which including the mechanisms of SCI injury, SCI patient's clinical presentation, and established acute management strategies. All these subsections have focused the classical view about the mainly pathological changes during the SCI process, and novel understanding for SCI, as well as ongoing studies carried by worldwide.

In general, the pathophysiological types of SCI are characterized as acute, secondary and chronic phases.[5] Primary damage to the spinal cord occurs as a direct result of the initial trauma, such as compression, shearing, laceration, transection, stretch, or distraction, leading to immediate hemorrhage or vasospasm and rapid cell death.[6] Concomitantly, Secondary injury closely follows in an ongoing way characterized by further damage to neuronal and glial cells and is accompanied by paralysis, intense pain, and progressive neurological damage.[7] This phase usually occurs within minutes after injury and can last for weeks even months. The concomitant and consecutive pathological events in this phase involve the immune response, inflammation, apoptotic cell death, and formation of cystic cavitations and astroglial scars.[8] Authors have provided novel reviews on these aspect in the section of "experimental acute management strategies" which containing 5 subsections for discussed and explored the details in each cited literatures in the categories of current novel understandings of SCI pathophysiology.

Conflict of Interest: The author has nothing to disclose.

REFERENCES

1. Ernst M, Ljutow A, Stockinger L, et al. Variability in clinical and neurophysiological evaluation of pain development following acute spinal cord injury: a case report. Spinal Cord Ser Cases 2021;7:72.
2. Lee YS, Kim KT, Kwon BK. Hemodynamic management of acute spinal cord injury: a literature review. Neurospine 2021;18:7-14.
3. Esmorís-Arijón I, Galeiras R, Salvador de la Barrera S, et al. Characteristics and survival of patients with acute traumatic spinal cord injury above t6 with prolonged intensive care unit stays. World Neurosurg 2021;152:e721-8.
4. Gadot R, Smith DN, Prablek M, et al. Established and emerging therapies in acute spinal cord injury. Neurospine 2022;19:283-96.
5. Kim SH. Finding a better way to manage cervical spine trauma and spinal cord injury. Neurospine 2020;17:708-9.
6. Morano JM, Morano MJ, Wagner NE, et al. Management of acute traumatic brain injury and acute spinal cord injury. Int Anesthesiol Clin 2021;59:17-24.
7. Hiremath SV, Karmarkar AM, Kumar A, et al. Factors associated with post-acute functional status and discharge dispositions in individuals with spinal cord injury. J Spinal Cord Med 2022;45:126-36.
8. Buchtler K, Carrard V, Jochum H, et al. Body experience during post-acute rehabilitation in individuals after a traumatic spinal cord injury: a qualitative interview-based pilot study. Spinal Cord Ser Cases 2021;7:14.

Title: Girl Before A Mirror
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Review Article

Genetic Odyssey to Ossification of the Posterior Longitudinal Ligament in the Cervical Spine: A Systematic Review

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Despite numerous studies, the pathogenesis of ossification of the posterior longitudinal ligament (OPLL) is still unclear. Previous genetic studies proposed variations in genes related to bone and collagen as a cause of OPLL. It is unclear whether the upregulations of those genes are the cause of OPLL or an intermediate result of endochondral ossification process. Causal variations may be in the inflammation-related genes supported by clinical and updated genomic studies. OPLL demonstrates features of genetic diseases but can also be induced by mechanical stress by itself. OPLL may be a combination of various diseases that share ossification as a common pathway and can be divided into genetic and idiopathic. The phenotype of OPLL can be divided into continuous (including mixed) and segmental (including localized) based on the histopathology, prognosis, and appearance. Continuous OPLL shows substantial overexpression of osteoblast-specific genes, frequent upper cervical involvement, common progression, and need for surgery, whereas segmental OPLL shows moderate-to-high expression of these genes and is often clinically silent. Genetic OPLL seems to share clinical features with the continuous type, while idiopathic OPLL shares features with the segmental type. Further genomic studies are needed to elucidate the relationship between genetic OPLL and phenotype of OPLL.

Keywords: Ossification of posterior longitudinal ligament, Myelopathy, Genomics, *NLRP1*, *BMP*, *SSH2*

INTRODUCTION

Ossification of the posterior longitudinal ligament (OPLL; MIM 602475) is a hyperostotic condition that results in ectopic calcification of the posterior longitudinal ligament (PLL) and leads to a reduced range of motion and potential spinal cord compromise.[1,2] OPLL was first reported by Key in 1838 and described in detail by Tsukimoto in 1960.[3,4] Two centuries have passed since the discovery of this disease, and nearly a century has passed since the specific form of the disease was confirmed, but we still do not know the exact cause, pathogenesis, and treatment of OPLL.[5-8] Numerous studies over the last several decades have suggested the involvement of multiple etiologic factors in the development of OPLL, including genetic factors, mechanical stress, nutrition, and secondary changes caused by systemic disease.[9]

With regard to the pathogenesis of OPLL, on one hand, OPLL demonstrates racial differences in its incidence, which is especially high in East Asian males.[10,11] A previous study in North America showed that the prevalence of OPLL varied among races: 4.8% in Asian Americans, 1.3% in Caucasian Americans, 1.9% in Hispanic Americans, and 3.2% in Native Americans.[12]

The prevalence of OPLL was found to be 26% in the parents and 29% in the siblings of probands from 347 OPLL families, which is significantly higher than that in the general population.[13] This findings imply that OPLL is a genetic disease. On the other hand, the nongenetic factors associated with OPLL include age, diabetes mellitus, obesity, exercise, and mechanical stress. The majority of OPLL cases occur after age 50, which means that OPLL is related to degenerative disease. Previous studies also reported that OPLL was associated with a vitamin A-rich diet, plasma pentosidine levels, and femoral neck bone mineral density.[12,14,15]

Many investigators have performed case-control association studies, affected sibling-pair linkage studies, and candidate gene association studies, and they identified many genes or loci that are linked to OPLL susceptibility. However, replication studies have failed to verify these results, even in the same ancestry groups as the original studies.[16] Next-generation sequencing (NGS) has recently emerged, and the genetic odyssey of OPLL has moved to a new direction. The purpose of this study was to review systematically and summarize genetic and genomic studies on OPLL of the cervical spine, and to make a suggestion which will help us to guide our future OPLL studies.

MATERIALS AND METHODS

A comprehensive literature search was performed using PubMed, Embase, and the Cochrane Library for all journal articles published from January 2000 through October 2021. We also manually searched reference lists. Key words used in the search included "ossification of the posterior longitudinal ligament," "genetics," and "genomics." The terms were searched individually or in combination. Appropriate articles for our review were selected based on scientific investigations on the genetic inheritance and susceptibility patterns of OPLL in humans. The search results were screened by title and abstract for the following exclusion criteria: duplicate studies; case reports, letters, comments, reviews, or technical notes; animal studies; and OPLL in the thoracic spine. After eliminating the excluded papers, full-text articles were obtained, and studies were thoroughly screened again using the same exclusion criteria. We excluded the following articles: combined diseases such as diffuse idiopathic skeletal hyperostosis (DISH) and ankylosing spondylitis (AS); redundant papers; and those without any description of mean values, the standard deviation, or the number of patients in each group. We limited our results to articles in the English language. In the case of overlapping study populations, we excluded patients described twice or used the most recent publication.

RESULTS

1. Systematic Search and Identification of Relevant Papers

An initial literature search using the chosen subject headings identified 129 studies in PubMed, 138 studies in Embase, and 2 studies in the Cochrane Central Register of Controlled Trials. Among these 269 studies, 71 were duplicates and were thus excluded. After screening titles and abstracts, 86 of the 198 remaining papers were excluded from our analysis because they were case reports, review articles, letters, technical notes, or animal experiments. Ten papers written in Japanese or Chinese were excluded, and 6 studies that dealt with OPLL in the thoracic and lumbar spine were excluded. The remaining 96 studies were subjected to a full-text review, and another 35 were excluded. These 26 articles were excluded because the studies used a mixed group including patients with other rheumatic diseases such as AS (n = 21), no description of the standard deviation (n = 8), and indirect comparative studies or single group studies (n = 6). Finally, this systematic search found 39 gene-expression screening studies using real-time quantitative polymerase chain reaction, 6 genome-wide association studies (GWAS), 2 NGS studies, 7 proteomic tissue expression analyses, and 7 micro-RNA expression analyses. A detailed process is shown in Fig. 1.

2. Pathogenesis I: Review of Studies That Conducted Screening of a Few Genes

Many research groups have proposed that genes related to bone, collagen, and inflammation might be associated with the initiation and progression of OPLL by using several methods such as genetic linkage analysis, positional cloning, and association studies.[17] The expression levels of the osteoblast-specific genes encoding alkaline phosphatase (ALP), osteocalcin (OCN), and type I collagen (COL I), were upregulated in OPLL patients, as shown in Table 1.[18-23] However, it remains unclear whether upregulated expression of bone and collagen-related genes is the cause of this disease or an intermediate result of the ossification process.[21] In addition, some ossification-related genes such as *BMP, RUNX2,* and *TGFB* families were introduced as causal genes in the development of OPLL based on genotyping.[21,24-26] The logic of these studies is that some suspected genetic variations that researchers assumed to be causal variations showed statistically significant differences in case-control studies. This may be valid if only a few variations demonstrate sta-

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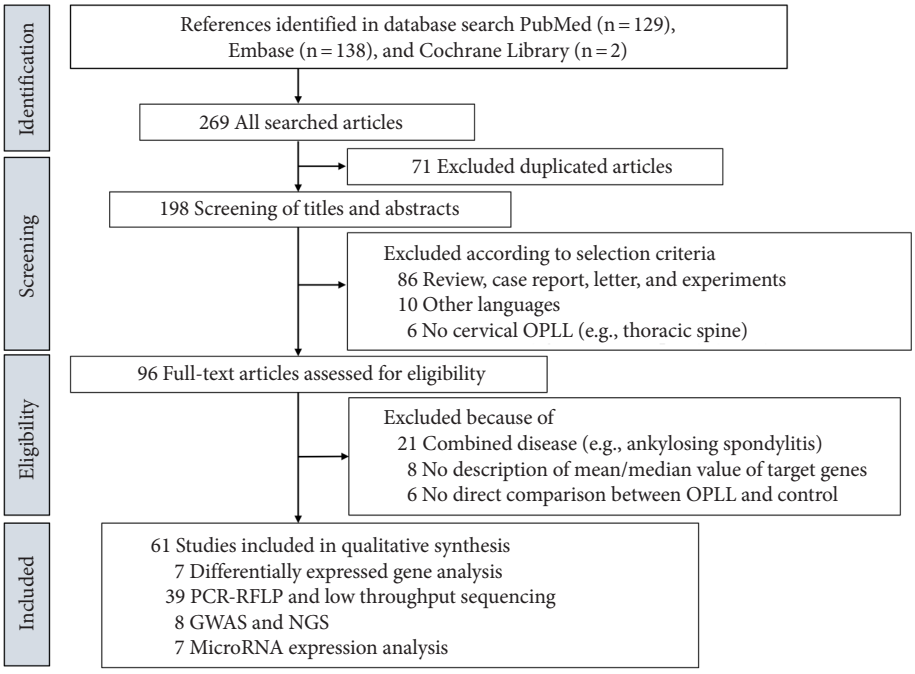

Fig. 1. Flow diagram of the identification of relevant studies. Ossification of the posterior longitudinal ligament (OPLL) indicates ossification of the posterior longitudinal ligament. PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; GWAS, genome-wide association study; NGS, next-generation sequencing.

Table 1. Differential expression ratio of OPLL for the various osteogenic marker gene

Study	No. of OPLL	No. of controls	ALP		OCN		COL I	
			DE	p-value	DE	p-value	DE	p-value
Yamamoto et al.[21] 2002	5	5	1.55	< 0.05	N/D	N/D	N/D	N/D
Tsukahara et al.[22] 2006	3	3	1.76	SD, 0.04	2.83	0.08	1.66	0.16
Yang et al.[19,20] 2011	20	18	1.79	< 0.01	1.72	< 0.01	1.62	< 0.01
Tanaka et al.[23] 2011	18	14	1.8	N/D	N/D	N/D	1.1	N/D
Yang et al.[18] 2020	21	16	2.71	< 0.001	2.71	< 0.001	3.31	< 0.001

OPLL, ossification of the posterior longitudinal ligament; ALP, alkaline phosphatase; OCN, osteocalcin; COL I, type I collagen; DE, differential expression; SD, standard deviation; N/D, no description.

tistically significant differences between the 2 groups. However, there were thousands of variations show statistically significant differences in case-control studies. Even if, those variations were closely related with the OPLL, it is unknown whether they were causal variation or intermediate results.

3. Pathogenesis II: Review of Genomic Variation Discovery Studies

Genomic variation detection can be divided into discovery and screening.[27] Discovery involves the identification of variations that are not yet known, while screening pertains to known variations.[27] Causative genetic variations of OPLL have not been clearly elucidated, and genomic studies must discover all genes, excluding the researcher's prejudice. Nakajima et al.[16] performed the first GWAS study that discovered variant loci in the whole genome, and they identified 6 susceptibility loci for OPLL. Their subsequent study suggested that *RSPO2* might be a susceptibility gene for OPLL based on genetic and functional data.[28] However, the *RSPO2* gene did not show a significant difference in other researchers' studies, including a whole-exome sequencing (WES) study.[29]

Two WES studies that used the most up-to-date and precise methods to discover causal variations were published by researchers from Korea and China.[29,30] One paper included 28 patients with OPLL (67%, continuous/mixed type) and suggested that variants of the *PTCH1* and *COL17A1* genes might contribute

to the development of OPLL.[30] *PTCH1* is related to basal cell carcinoma, and no precise relationship was found between the results of the study and clinical findings. Seven years have passed since the paper was published, but no further study by the authors has yet been published. The other WES study included 74 OPLL patients (100% with the continuous/mixed type and a ≥40% occupying ratio) and 26 controls and was published this year.[29] A characteristic of this paper is that the patients group was selected very precisely and that it probably included more patients with OPLL caused by genetic diseases than other previous studies. The authors proposed that the causal variations of genetic OPLL might be auto-/local inflammation-related genes such as *NLRP1, SSH2,* and *CYP4B1*.[29] Previous genetic studies also suggested that the inflammatory response were related to OPLL.[31,32] In a clinical study, serum level of C-reactive protein (CRP) as well-known inflammatory marker was higher in the OPLL group than in the control group, and the group with progression of OPLL showed much higher CRP levels than the group with nonprogression of OPLL.[33] The researchers suggested that inflammation might relate the development or progression of OPLL.[33] Genetic vulnerability of inflammation-related genes may be a causal factor of OPLL. Further biomarker studies are needed.

MiRNAs are small noncoding RNAs that regulate gene expression in numerous biological or pathological processes by binding with target mRNAs to affect their translation or stability, and they are thought to regulate cell reprogramming and differentiation.[34] Many miRNAs previously reported in network studies were addressed the association with osteogenesis.[34] Previous studies described significant upregulation of the expression of ossification-related *RUNX2, ALP,* and *OSX* genes by miR-181a-5p, while the inhibition of miR-181a-5p by treatment with antagomir had the opposite effects.[34,35] Other investigators demonstrated that the GG genotype of miR-499 was associated with a significantly higher risk of OPLL in the segmental OPLL group.[36] More studies are needed to prove the pathogenesis of OPLL by miRNA.

4. Pathogenesis III: Role of Mechanical Stress in the Development/Progression of OPLL

It has been reported that the abnormal distribution of mechanical stress is closely correlated with the process of OPLL.[37] Mechanical stress could induce osteogenic differentiation of PLL fibroblasts *in vitro*, which is expressed as the upregulation of osteogenic markers, including OCN, ALP, and COL I.[38,39] Other researchers reported that numerous genes showed upregulated expression levels in response to mechanical stress, such as *ALP, BMP2, BMP4,* osteopontin, *CBFA1, OCN,* integrin-β1, and endothelin-1; furthermore, mechanical stress elevated prostacyclin synthesis in ligament cells derived from OPLL patients and induced osteogenic differentiation.[12,40] This evidence suggests that mechanical stress itself induces ossification of the ligament at highly stressed regions such as the low cervical spine.

One hand, a recent epidemiological study reported that the prevalence of OPLL has increased in North American and European populations from 0.1% to 2.5%.[41] The number of surgical cases of OPLL has tripled in 12 years across the United States (US).[41] Because the incidence of genetic disease is hard to increase like this, the rapid increase of OPLL patients in the last decade may be related with mechanical stress. On the other hand, 7.5% of Asians and Pacific islander living in the US underwent surgery for the OPLL, which was higher than the 4.9% of all Americans.[41] Assuming that the lifestyle of the people living in US is similar, the fact that severe OPLL requiring surgery is especially frequent in Asians means that Asians have a genetic vulnerability under similar mechanical stress. This reflects that severe OPLL resulting from a genetic vulnerability needs to be distinguished from mild OPLL caused by mechanical stress.

5. Two Distinct Phenotypes of OPLL

One reason for the uncertain pathogenesis is that OPLL is a disease named based on a radiological finding regardless of cause and pathogenesis. According to the definition of the disease name, all patients showing any ossification or calcification at the PLL can be diagnosed with OPLL. The disease needs to be classified based on its cause and pathogenesis because ectopic osteogenesis (ossification and calcification) is frequently found even in healthy people in various organs and tissues, including connective tissues, blood vessels, and skeletal muscle.[17,42,43] In addition, some systemic diseases such as hypoparathyroidism, DISH, AS, and potentially schizophrenia sometimes induce paravertebral ligamentous ossification.[12,14,15,44,45] Therefore, clinically insignificant calcifications or ossification of PLL may be better excluded from the diagnosis of OPLL.

It is well known that OPLL can be classified into 4 types based on the shape of the ossified region using plain radiographs of the cervical spine in the lateral view: continuous, segmental, mixed, and localized. However, researchers suggested that it would be better to divide OPLL into only 2 types (continuous and segmental) based on the histopathology, prognosis, and appearance.[44] The mixed type of OPLL is regarded as a subcategory in which segmental ossification is added to the continuous

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type of OPLL. The localized type of OPLL is referred to as the circumscribed or unclassified type of OPLL, and is regarded as a kind of the segmental type of OPLL. Differential points between continuous/mixed and segmental/localized OPLL are described in Table 2.

A previous study demonstrated that ALP activity in continuous OPLL, segmental OPLL, and non-OPLL was 2.56 ± 0.05, 1.21 ± 0.11, and 1.00 ± 0.05, respectively.[17] Other researchers also reported that the expression level of ALP, OCN, and COL I showed significant step-wide decrease, which was found most prominently in continuous OPLL, followed in order by segmental OPLL and non-OPLL.[37,44,46-48] The researchers stated that spinal ligament cells derived from continuous OPLL tended to be more easily mineralized than those from segmental OPLL patients.[17] From a clinical point of view, continuous OPLL requires careful observation of cervical myelopathy, whereas segmental OPLL is often clinically silent. A previous meta-analysis demonstrated that the continuous/mixed type accounted for 77% of the patients who underwent surgery due to cervical myelopathy with OPLL.[10] The progression rate of ossification was reported to be 75% in patients with continuous OPLL and 38% in those with segmental OPLL.[44] Another study showed 72% of patients with continuous/mixed OPLL had involvement in the upper cervical region such as C2.[29] It may be necessary to distinguish clinically significant continuous OPLL from the asymptomatic segmental type based on genetic, biochemical, and clinical differences.[29,44]

Table 2. Two different phenotypes of cervical OPLL

Item	Continuous/ mixed	Segmental/ localized
Upper cervical (C2, 3) involve	Frequent	Rare
Lower cervical (C5/6/7) involve	Sometimes	Frequent
Mean age	Younger	Older
Progression rate	Fast	Slow
Need for surgical treatment	Sometimes	Rare

OPLL, ossification of the posterior longitudinal ligament.

6. Suggestion for the Development of OPLL

We may summarize 2 mechanisms and 2 types of OPLL, as shown in Fig. 2. One is named idiopathic OPLL, which may be triggered by mechanical stress, comorbid diseases, and specific nutritional patterns. Mechanical stress to the cervical spine is usually focused on low cervical spine, high mobile segments.[49,50] Segmental OPLL usually occur at the segments, but continuous OPLL usually involve upper cervical spine. Segmental or localized OPLL may be developed by this mechanism. This type

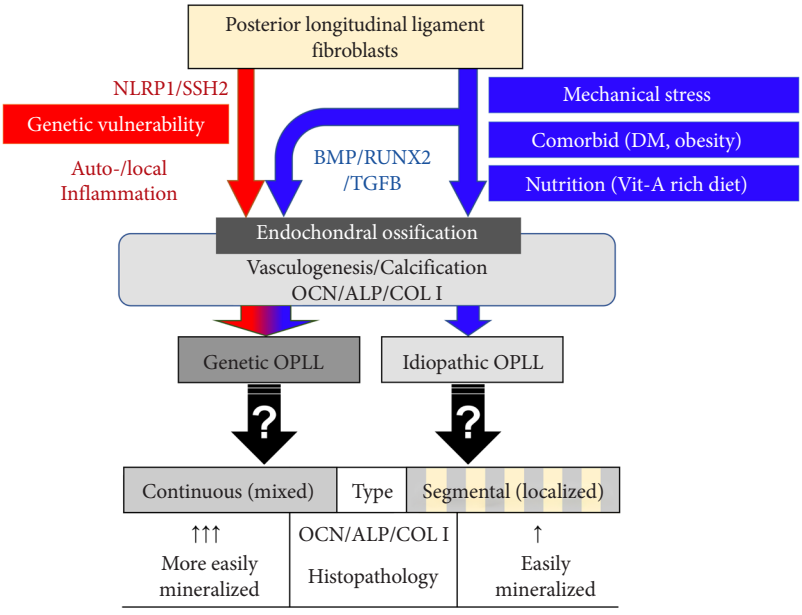

Fig. 2. Hypothetic pathogenesis of ossification of the posterior longitudinal ligament (OPLL). The phenotype of OPLL is divided into continuous (including mixed) and segmental (including localized). The continuous type of OPLL demonstrates much higher expression of endochondral ossification genes encoding osteocalcin (OCN), alkaline phosphatase (ALP), and type I collagen (COL I) than the segmental type of OPLL. Genetic OPLL showed involvement of less stressed cervical region such as C2 and frequent surgical treatment, which is similar with continuous type of OPLL. DM, diabetes mellitus; Vit-A, vitamin A.

may show moderate over expression of ALP, OCN, and COL I. Rapid increase of surgery for OPLL over the past 10 years may mean that OPLL can be developed regardless of genetic vulnerability because it is difficult to triple the number of genetic diseases for 10 years.[41] The other is named genetic OPLL, which occurs in patients with variations in inflammatory genes such as *NLRP1* and *SSH2*. Levels of inflammatory biomarkers such as CRP were found to remain high in OPLL patients and were positively associated with OPLL progression. Genetic OPLL may even show involvement in the upper cervical regions with less mechanical stress. In an epidemiologic study from US, Asian American underwent 53% more spine surgeries than the US overall. This may mean that genetic OPLL often seems to induce cervical myelopathy and more often requires surgical treatment than the idiopathic OPLL and genetic OPLL needs to surgical treatments more than idiopathic OPLL.[51,52] These features of genetic OPLL are observed in continuous OPLL. Although the genetic differences among types of ossification remain to be elucidated, genetic and genomic studies may provide new etiologic insights into how the type of OPLL relates to the causal genetic variation and the prognosis.

7. Limitations

There are some limitations that need to be acknowledged and addressed regarding the present study. The first limitation concerns a narrative review. We tried to search all genetic and genomic studies and offer clear evidence. We performed a systematic search and found 60 papers. Most of searched studies suggested misleading candidate genes that studied with single or a few genes and variants addressed one at a time by single team with small sample size.[53] The authors tried to summary all reported results without bias because following the systematic review protocol could rather lose objectivity. The second, there are few evidence that genetic OPLL make continuous type ossification. It is entirely our hypothesis. Although genetic OPLL showed similar feature with continuous type of OPLL, there are many things that are difficult to explain by the reason. Further studies are necessary to find out the difference in genetic variations by type of OPLL.

CONCLUSION

OPLL may develop from genetic vulnerabilities and idiopathic factors, including mechanical stress. It is not clear whether OPLL is a complex genetic disease or a combination of various diseases that share a process of calcification/ossification as a common pathway. Genetic OPLL seems to share clinical features with the continuous type, while idiopathic OPLL shares them with the segmental type. Further genomic studies with clear phenotypic classifications may provide further insights into the disease.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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REFERENCES

1. Lee JK, Ham CH, Kwon WK, et al. A new classification for cervical ossification of the posterior longitudinal ligament based on the coexistence of segmental disc degeneration. J Korean Neurosurg Soc 2021;64:69-77.
2. Abiola R, Rubery P, Mesfin A. Ossification of the posterior longitudinal ligament: etiology, diagnosis, and outcomes of nonoperative and operative management. Global Spine J 2016;6:195-204.
3. Key CA. On paraplegia depending on disease of the ligaments of the spine. Guys Hosp Rep 1838;3:17-34.
4. Tsukimoto H. A case report: autopsy of syndrome of compression of spinal cord owing to ossification within spinal canal of cervical spines. Nippon Geka Hokan 1960;29:1003-7.
5. Kim SY, Hyun SJ, Kim KJ, et al. Surgical outcomes according to dekyphosis in patients with ossification of the posterior longitudinal ligament in the thoracic spine. J Korean Neurosurg Soc 2020;63:89-98.
6. Shin HK, Park JH. Posterior floating laminotomy as a new decompression technique for posterior cervical spinal fusion surgery. J Korean Neurosurg Soc 2021;64:901-12.

 https://doi.org/10.14245/ns.2244038.019

7. Lee S, Roh SW, Jeon SR, et al. A prognostic factor for prolonged mechanical ventilator-dependent respiratory failure after cervical spinal cord injury : maximal canal compromise on magnetic resonance imaging. J Korean Neurosurg Soc 2021;64:791-8.
8. Jung JM, Jahng AL, Hyun SJ, et al. Comparison of spinal canal expansion following cervical laminoplasty based on the preoperative lamina angle : a simulation study. J Korean Neurosurg Soc 2021;64:229-37.
9. Zhang W, Wei P, Chen Y, et al. Down-regulated expression of vimentin induced by mechanical stress in fibroblasts derived from patients with ossification of the posterior longitudinal ligament. Eur Spine J 2014;23:2410-5.
10. Lee CH, Sohn MJ, Lee CH, et al. Are there differences in the progression of ossification of the posterior longitudinal ligament following laminoplasty versus fusion?: a meta-analysis. Spine (Phila Pa 1976) 2017;42:887-94.
11. Lee SH, Son DW, Shin JJ, et al. Preoperative radiological parameters to predict clinical and radiological outcomes after laminoplasty. J Korean Neurosurg Soc 2021;64:677-92.
12. Yan L, Gao R, Liu Y, et al. The pathogenesis of ossification of the posterior longitudinal ligament. Aging Dis 2017;8:570-82.
13. Terayama K. Genetic studies on ossification of the posterior longitudinal ligament of the spine. Spine (Phila Pa 1976) 1989;14:1184-91.
14. Boody BS, Lendner M, Vaccaro AR. Ossification of the posterior longitudinal ligament in the cervical spine: a review. Int Orthop 2019;43:797-805.
15. Yoshimura N, Nagata K, Muraki S, et al. Prevalence and progression of radiographic ossification of the posterior longitudinal ligament and associated factors in the Japanese population: a 3-year follow-up of the ROAD study. Osteoporos Int 2014;25:1089-98.
16. Nakajima M, Takahashi A, Tsuji T, et al. A genome-wide association study identifies susceptibility loci for ossification of the posterior longitudinal ligament of the spine. Nat Genet 2014;46:1012-6.
17. Furukawa KI. Pharmacological aspect of ectopic ossification in spinal ligament tissues. Pharmacol Ther 2008;118:352-8.
18. Yang Y, Lin Z, Chen J, et al. Autophagy in spinal ligament fibroblasts: evidence and possible implications for ossification of the posterior longitudinal ligament. J Orthop Surg Res 2020;15:490.
19. Yang HS, Lu XH, Chen DY, et al. Upregulated expression of connexin43 in spinal ligament fibroblasts derived from patients presenting ossification of the posterior longitudinal ligament. Spine (Phila Pa 1976) 2011;36:2267-74.
20. Yang HS, Lu XH, Chen DY, et al. Mechanical strain induces Cx43 expression in spinal ligament fibroblasts derived from patients presenting ossification of the posterior longitudinal ligament. Eur Spine J 2011;20:1459-65.
21. Yamamoto Y, Furukawa K, Ueyama K, et al. Possible roles of CTGF/Hcs24 in the initiation and development of ossification of the posterior longitudinal ligament. Spine (Phila Pa 1976) 2002;27:1852-7.
22. Tsukahara S, Ikeda R, Goto S, et al. Tumour necrosis factor alpha-stimulated gene-6 inhibits osteoblastic differentiation of human mesenchymal stem cells induced by osteogenic differentiation medium and BMP-2. Biochem J 2006;398:595-603.
23. Tanaka S, Kudo H, Asari T, et al. P2Y1 transient overexpression induced mineralization in spinal ligament cells derived from patients with ossification of the posterior longitudinal ligament of the cervical spine. Calcif Tissue Int 2011;88:263-71.
24. Chang F, Li L, Gao G, et al. Role of Runx2 polymorphisms in risk and prognosis of ossification of posterior longitudinal ligament. J Clin Lab Anal 2017;31:e22068.
25. Li P, Liu Z, Liu J, et al. RUNX2 and IL-15RA polymorphisms associated with OPLL in the Han and Mongolian population. J Pak Med Assoc 2020;70 [Special Issue]:98-104.
26. Kim KH, Kuh SU, Park JY, et al. Association between BMP-2 and COL6A1 gene polymorphisms with susceptibility to ossification of the posterior longitudinal ligament of the cervical spine in Korean patients and family members. Genet Mol Res 2014;13:2240-7.
27. Kwok PY, Chen X. Detection of single nucleotide polymorphisms. Curr Issues Mol Biol 2003;5:43-60.
28. Nakajima M, Kou I, Ohashi H, et al. Identification and functional characterization of RSPO2 as a susceptibility gene for ossification of the posterior longitudinal ligament of the spine. Am J Hum Genet 2016;99:202-7.
29. Lee CH, Kim KT, Kim CH, et al. Unveiling the genetic variation of severe continuous/mixed-type ossification of the posterior longitudinal ligament by whole-exome sequencing and bioinformatic analysis. Spine J 2021;21:1847-56.
30. Wei W, He HL, Chen CY, et al. Whole exome sequencing implicates PTCH1 and COL17A1 genes in ossification of the posterior longitudinal ligament of the cervical spine in Chinese patients. Genet Mol Res 2014;13:1794-804.
31. Chen D, Chen Y, Li T, et al. Role of Cx43-mediated NFsmall

ka, CyrillicB signaling pathway in ossification of posterior longitudinal ligament: an in vivo and in vitro study. Spine (Phila Pa 1976) 2017;42:E1334-41.
32. Yuan X, Guo Y, Chen D, et al. Long non-coding RNA MALAT1 functions as miR-1 sponge to regulate Connexin 43-mediated ossification of the posterior longitudinal ligament. Bone 2019;127:305-14.
33. Kawaguchi Y, Nakano M, Yasuda T, et al. Serum biomarkers in patients with ossification of the posterior longitudinal ligament (OPLL): inflammation in OPLL. PLoS One 2017;12:e0174881.
34. Liu N, Zhang Z, Li L, et al. MicroRNA-181 regulates the development of ossification of posterior longitudinal ligament via epigenetic modulation by targeting PBX1. Theranostics 2020;10:7492-509.
35. Xu C, Chen Y, Zhang H, et al. Integrated microRNA-mRNA analyses reveal OPLL specific microRNA regulatory network using high-throughput sequencing. Sci Rep 2016;6:21580.
36. Lim JJ, Shin DA, Jeon YJ, et al. Association of miR-146a, miR-149, miR-196a2, and miR-499 polymorphisms with ossification of the posterior longitudinal ligament of the cervical spine. PLoS One 2016;11:e0159756.
37. Inamasu J, Guiot BH, Sachs DC. Ossification of the posterior longitudinal ligament: an update on its biology, epidemiology, and natural history. Neurosurgery 2006;58:1027-39; discussion -39.
38. Shi L, Miao J, Chen D, et al. Endoplasmic reticulum stress regulates mechanical stress-induced ossification of posterior longitudinal ligament. Eur Spine J 2019;28:2249-56.
39. Furukawa KI. Current topics in pharmacological research on bone metabolism: molecular basis of ectopic bone formation induced by mechanical stress. J Pharmacol Sci 2006;100:201-4.
40. Yoon HH, Lee HJ, Min J, et al. Optimal ratio of Wnt3a expression in human mesenchymal stem cells promotes axonal regeneration in spinal cord injured rat model. J Korean Neurosurg Soc 2021;64:705-15.
41. Bernstein DN, Prong M, Kurucan E, et al. National trends and complications in the surgical management of ossification of the posterior longitudinal ligament (OPLL). Spine 2019;44:1550-7.
42. Lee S, Jung SK, Kim HB, et al. Postoperative non-pathological fever following posterior cervical fusion surgery : is laminoplasty a better preventive method than laminectomy? J Korean Neurosurg Soc 2020;63:487-94.
43. Lee JH, Han IH, Kim DH, et al. Spine computed tomography to magnetic resonance image synthesis using generative adversarial networks : a preliminary study. J Korean Neurosurg Soc 2020;63:386-96.
44. Kudo H, Furukawa K, Yokoyama T, et al. Genetic differences in the osteogenic differentiation potency according to the classification of ossification of the posterior longitudinal ligament of the cervical spine. Spine (Phila Pa 1976) 2011;36:951-7.
45. Lee HJ, Kim IS, Hong JT. Physiologic cervical alignment change between cervical spine x-ray and computed tomography. J Korean Neurosurg Soc 2021;64:784-90.
46. Chiba K, Yamamoto I, Hirabayashi H, et al. Multicenter study investigating the postoperative progression of ossification of the posterior longitudinal ligament in the cervical spine: a new computer-assisted measurement. J Neurosurg Spine 2005;3:17-23.
47. Kawaguchi Y, Kanamori M, Ishihara H, et al. Progression of ossification of the posterior longitudinal ligament following en bloc cervical laminoplasty. J Bone Joint Surg Am 2001;83:1798-802.
48. Hori T, Kawaguchi Y, Kimura T. How does the ossification area of the posterior longitudinal ligament thicken following cervical laminoplasty? Spine (Phila Pa 1976) 2007;32:E551-6.
49. Otluoglu GD, Konya D, Toktas ZO. The influence of mechanic factors in disc degeneration disease as a determinant for surgical indication. Neurospine 2020;17:215-20.
50. Shin JJ, Kim B, Kang J, et al. Clinical, radiographic, and genetic analyses in a population-based cohort of adult spinal deformity in the older population. Neurospine 2021;18:608-17.
51. Papavero L, Schmeiser G, Kothe R, et al. Degenerative cervical myelopathy: a 7-letter coding system that supports decision-making for the surgical approach. Neurospine 2020;17:164-71.
52. Riew KD. Review of vertebral body sliding osteotomy for cervical myelopathy with rigid kyphosis. Neurospine 2020;17:648-9.
53. Ioannidis JP. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. Milbank Q 2016;94:485-514.

 https://doi.org/10.14245/ns.2244038.019

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Original Article

What Can Legacy Patient-Reported Outcome Measures Tell Us About Participation Bias in Patient-Reported Outcomes Measurement Information System Scores Among Lumbar Spine Patients?

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Objective: Patient-Reported Outcomes Measurement Information System (PROMIS) is a validated tool for assessing patient-reported outcomes in spine surgery. However, PROMIS is vulnerable to nonresponse bias. The purpose of this study is to characterize differences in patient-reported outcome measure scores between patients who do and do not complete PROMIS physical function (PF) surveys following lumbar spine surgery.
Methods: A prospectively maintained database was retrospectively reviewed for primary, elective lumbar spine procedures from 2015 to 2019. Outcome measures for Patient Health Questionnaire-9 (PHQ-9), visual analogue scale (VAS) back & leg, Oswestry Disability Index (ODI), and 12-item Short Form health survey physical composite summary (SF-12 PCS) were recorded at both preoperative and postoperative (6 weeks, 12 weeks, 6 months, 1 year, 2 years) timepoints. Completion rates for PROMIS PF surveys were recorded and patients were categorized into groups based on completion. Differences in mean scores at each timepoint between groups was determined.
Results: Eight hundred nine patients were included with an average age of 48.1 years. No significant differences were observed for all outcome measures between PROMIS completion groups preoperatively. Postoperative PHQ-9, VAS back, VAS leg, and ODI scores differed significantly between groups through 1 year (all $p < 0.05$). SF-12 PCS differed significantly only at 6 weeks ($p = 0.003$).
Conclusion: Patients who did not complete PROMIS PF surveys had significantly poorer outcomes than those that did in terms of postoperative depressive symptoms, pain, and disability. This suggests that patients completing PROMIS questionnaires may represent a healthier cohort than the overall lumbar spine population.

Keywords: Patient-reported outcomes, Patient-Reported Outcomes Measurement Information System, Lumbar spine

INTRODUCTION

As the frequency of spinal procedures has steadily increased, so too has the use of patient-reported outcome measures (PROMs). Legacy PROMs such as the Oswestry Disability Index (ODI), visual analogue scale (VAS) and the 12-item Short Form health survey (SF-12) measure perceptions of pain, disability, and physical function (PF), but are dated in their ability to provide more personalized assessment. More recent metrics such as the Patient-Reported Outcomes Measurement Information System

(PROMIS) utilize computer adaptive testing which customizes questions based on previous responses and provides more efficient and focused assessments of patient-reported outcomes (PROs). Additionally, PROMIS surveys have demonstrated minimal floor and ceiling effects, and their use among spine patients is well-validated.[1-4]

Although PROs are of utmost importance to accurately track postoperative improvement, noncompliance is nearly inevitable with any self-report measure and bias may be thereby introduced. Participation bias (also known as nonresponse bias) can occur when there are significant differences between respondents and nonrespondents and may lead to an inaccurate representation of the population at large. Previous studies have demonstrated several important differences between respondents and nonrespondents to PROM surveys. Parrish et al.[5] examined demographic and perioperative variables as predictors of survey completion and reported that patients of African-American or Hispanic race and those with radicular pain were less likely to complete surveys. Conversely, older individuals and patients with more severe depressive symptoms were more likely to complete PROMIS PF questionnaires. Furthermore, several other studies demonstrated higher completion rates among older individuals, and those with postoperative complications, whereas male sex, younger age, lower socioeconomic status and non-White race were reported as predictors of decreased compliance.[6-8]

The variability in demographics and perioperative characteristics that may predict respondent and nonrespondent status may have implications for the outcomes experienced by these patients as well. If key differences in PROs exist between respondents and nonrespondents, the data obtained by these surveys may be unrepresentative of the patient population as a whole and, if taken at face value, may misguide clinical decision making or lead some patients to receive inappropriate or inadequate care. Given that it is predicated on the *absence* of data, participation bias is inherently difficult to quantify. Several orthopedic studies have employed different tactics, such as telephone outreach, to quantify outcomes in nonrespondents.[9-11] One avenue to elucidate PROM trends in nonrespondents that has not been well explored is the use of data from "partial-respondents" who may have completed other PROMs, but not PROMIS PF. The establishment of strong correlations between PROMIS PF and VAS, ODI, and SF-12 at multiple timepoints for both lumbar and cervical spine patients may allow for an alternative route to quantify outcome measures of nonrespondents.[2,3,12] More specifically, use of completed legacy PROMs to extrapolate important data about potential PROMIS scores could provide insight to the true status of postoperative PF among nonrespondents. As the popularity and applications of PROMIS surveys continue to expand, it becomes more important than ever to quantify the impact of participation bias on their results. This study aims to explore the extent of participation bias for PROMIS PF in a cohort of lumbar spine patients by analyzing differences in legacy PROM scores between PROMIS respondents and nonrespondents.

MATERIALS AND METHODS

1. Patient Population

Prior to study onset, this study was approved by the Institutional Review Board of Rush University Medical Center (ORA #14051301) and written informed consent were obtained from patients. A private registry of prospectively maintained spine surgery data was retrospectively reviewed for patients that underwent primary, elective lumbar spine procedures, which included fusions, decompressions, and discectomies between the dates of May 2015 and July 2019. Revision procedures along with surgeries indicated for traumatic, infectious, or malignant etiologies were excluded.

2. Data Collection

The following patient demographic characteristics were collected: age, sex, body mass index (BMI), preoperative smoking status, diabetic status, American Society of Anesthesiologists (ASA) physical status classification, Charlson Comorbidity Index (CCI), ethnicity, and insurance/payment type received. Preoperative spinal pathologies were classified as herniated nucleus pulposus (new-onset or recurrent), degenerative spondylolisthesis, isthmic spondylolisthesis, and scoliosis. Perioperative characteristics were recorded including operative duration (in minutes), estimated blood loss (EBL; in mL), and postoperative length of stay (in hours). PROMs assessing pain (VAS back and leg), disability (ODI), PF (SF-12 physical component summary [SF-12 PCS]), and depressive symptoms (Patient Health Questionnaire-9 [PHQ-9]) were collected at preoperative and 6-week, 12-week, 6-month, and 1-year postoperative timepoints. All PROMs were completed either during clinic appointments using a hand-held tablet device or remotely using the patients' personal devices through an online portal. Patients completing PROMs during clinic appointments were required to finish surveys before meeting with clinicians to avoid any biases.

3. Statistical Analysis

All statistical tests and calculations were performed using

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Stata 16.1 (StataCorp, College Station, TX, USA). Descriptive statistics were reported for patient demographic characteristics, preoperative spinal diagnoses, and perioperative variables. Perioperative variables were reported separately for patients who underwent lumbar fusion and patients who underwent lumbar decompression/discectomy. Outlier analysis was performed to identify patients with operative duration, EBL, or length of stay >3 standard deviations above or below the mean value. Outliers were excluded to limit the amount of bias introduced by highly atypical cases. Patients were categorized at each timepoint as PROMIS respondents or nonrespondents based on whether they had completed a PROMIS PF survey corresponding to that given timepoint. Chi-square and Student t-test were used to compare demographic and perioperative variables between PROMIS respondents and nonrespondents. Student t-test for independent samples was used to compare scores for each of the other included PROMs between PROMIS respondents and nonrespondents at each timepoint. A p-value of ≤0.05 was set as the threshold for statistical significance for all tests.

RESULTS

A total of 827 eligible lumbar spine patients were initially identified. Following removal of outliers, 809 patients were included in final analysis. The overall cohort had a mean age of 48.1 years and a majority were male (66.9%) and nonobese (BMI <30 kg/m^2; 56.7%). The mean ASA classification was 1.9 and mean CCI score was 1.4. Ethnicity ($p<0.001$) and insurance/payment type ($p<0.001$) were significantly associated with PROMIS completion status (Table 1). The study cohort included 335 lumbar fusion patients among whom degenerative spondylolisthesis was the most common preoperative spinal pathology (49.0%) and means for perioperative variables were as follows: operative duration 136.6±45.8 minutes, EBL 52.1±30.4 mL, and length of stay 32.7±21.5 hours. The study cohort included 474 lumbar decompression/discectomy patients among whom herniated nucleus pulposus was the most common spinal pathology (82.7%) and means for perioperative variables were as follows: operative duration 46.0±16.7 minutes, EBL 26.9±9.2 mL, and length of stay 5.8±7.6 hours. No perioperative variables significantly differed between PROMIS PF respondents and nonrespondents for either procedure type (Table 2).

No significant preoperative differences in any of the included PROMs were observed between PROMIS respondents and nonrespondents. PHQ-9 scores were significantly more severe for nonrespondents at 6 weeks (3.3 vs. 5.7, $p<0.001$), 12 weeks (3.6 vs. 5.4, $p=0.005$), 6 months (3.7 vs. 5.3, $p=0.007$), and 1 year (4.0 vs. 5.7, $p=0.042$). VAS back pain scores were significantly higher for nonrespondents at 6 weeks (3.1 vs. 3.8, $p=0.004$), 12 weeks (3.2 vs. 4.1, $p=0.003$), 6 months (3.3 vs. 4.3, $p=0.002$), and 1 year (3.2 vs. 4.5, $p=0.004$). VAS leg pain scores were significantly higher for nonrespondents at 6 weeks (2.8 vs. 3.6, $p=0.004$), 12 weeks (2.8 vs. 3.4, $p=0.047$), 6 months (2.8 vs. 3.7, $p=0.011$), and 1 year (2.7 vs .3.9, $p=0.011$). ODI scores indicat-

Table 1. Patient demographics

Demographic	Total (n=809)	Completed PROMIS PF (n=570)	Incomplete PROMIS PF (n=239)	p-value†
Age (yr)	48.1±13.3	48.0±13.2	48.2±13.6	0.918
Sex				0.603
Female	268 (33.1)	192 (33.7)	76 (31.8)	
Male	541 (66.9)	378 (66.3)	163 (68.2)	
Body mass index (kg/m^2)				0.617
<30	450 (56.7)	320 (57.3)	130 (55.3)	
≥30	344 (43.2)	239 (43.8)	105 (44.7)	
Smoking status				0.506
Nonsmoker	707 (87.4)	501 (87.9)	206 (86.2)	
Smoker	102 (12.6)	69 (12.1)	33 (13.3)	
Diabetes				0.067
Nondiabetic	743 (91.8)	530 (93)	213 (89.1)	
Diabetic	66 (8.2)	40 (7.0)	26 (10.9)	
ASA PS classification	1.9±0.6	1.8±0.6	1.9±0.6	0.244
CCI score	1.4±1.5	1.3±1.5	1.4±1.5	0.823
Ethnicity				<0.001*
White	562 (69.7)	437 (76.9)	125 (52.5)	
African-American	82 (10.2)	49 (8.6)	33 (13.9)	
Hispanic	107 (13.3)	48 (8.5)	59 (24.8)	
Asian	31 (3.9)	22 (3.9)	9 (3.8)	
Other	24 (3.0)	12 (2.1)	12 (5.0)	
Insurance				<0.001*
Medicare/Medicaid	25 (3.1)	18 (3.2)	7 (2.9)	
Workers' compensation	212 (26.3)	112 (19.7)	100 (41.8)	
Private	570 (70.6)	438 (77.1)	132 (55.2)	

Values are presented as mean±standard deviation or number (%).
PROMIS PF, Patient-Reported Outcomes Measurement Information System physical function; ASA PS, American Society of Anesthesiologists physical status; CCI, Charlson Comorbidity Index.
*$p<0.05$, statistically significant differences. †p-values calculated using t-test for independent samples (continuous) or chi-square analysis (categorical).

Table 2. Spinal pathology and operative characteristics

Characteristic	Total	Completed PROMIS PF	Incomplete PROMIS PF	p-value†
Lumbar fusion	(n = 335)	(n = 236)	(n = 99)	
Spinal pathology				
Degenerative spondylolisthesis	164 (49.0)	118 (50.0)	46 (45.5)	0.555
Isthmic spondylolisthesis	88 (26.3)	59 (25.0)	29 (29.3)	0.415
Recurrent HNP	45 (13.4)	27 (11.4)	18 (18.2)	0.099
Degenerative scoliosis	35 (10.5)	26 (11.0)	9 (9.1)	0.599
Operative time‡ (min)	136.6 ± 45.8	137.1 ± 45.7	135.3 ± 46.3	0.749
Estimated blood loss (mL)	52.1 ± 30.4	51.1 ± 29.5	54.6 ± 32.5	0.351
Length of stay (hr)	32.7 ± 21.5	31.5 ± 19.5	35.6 ± 25.4	0.114
Lumbar decompression/discectomy	(n = 474)	(n = 334)	(n = 140)	
Spinal pathology				
HNP	392 (82.7)	270 (80.8)	122 (87.1)	0.098
Central stenosis	362 (76.4)	257 (77.0)	105 (75.0)	0.649
Foraminal stenosis	254 (53.6)	178 (53.3)	76 (54.3)	0.843
Operative time‡ (min)	46.0 ± 16.7	46.0 ± 15.9	46.0 ± 18.6	0.995
Estimated blood loss (mL)	26.9 ± 9.2	26.5 ± 7.1	27.7 ± 12.9	0.225
Length of stay (hr)	5.8 ± 7.6	5.4 ± 6.9	6.5 ± 9.0	0.158

Values are presented as number (%) or mean ± standard deviation.
PROMIS PF, Patient-Reported Outcomes Measurement Information System physical function; HNP, herniated nucleus pulposus.
†p-values calculated using t-test for independent samples (continuous) or chi-square analysis (categorical). ‡Skin incision to skin closure.

ed significantly more severe disability for nonrespondents at 6 weeks (27.6 vs. 35.0, $p < 0.001$), 12 weeks (25.2 vs. 33.9, $p < 0.001$), 6 months (24.1 vs. 323, $p < 0.001$), and 1 year (22.8 vs. 31.7, $p = 0.009$). SF-12 PCS scores were significantly poorer for nonrespondents at 6 weeks (35.9 vs. 32.5, $p = 0.003$), but not at any other timepoint (all $p \geq 0.090$). A summary of postoperative PROM improvement by respondent group can be found in Table 3.

DISCUSSION

Defined as key differences in nonrespondents and respondents to a survey in a given population that may influence overall results, participation bias (also known as nonresponse bias) is a concern for clinical research, particularly those focused on PROMs. Such biases can be influenced both by the rate of response and the degree of difference between respondents and nonrespondents. Given that this bias is predicated on the *absence* of data, it is particularly difficult to quantify. Previous studies have utilized a variety of different methods to explore participation bias in surgical patients and report a wide range of results. Our analysis indicates significant differences in both the physical and mental health PROM scores of lumbar spine patients between respondents and nonrespondents to PROMIS PF surveys. These differences raise concerns for nonnegligible participation bias in the PROMIS scores of lumbar spine patients.

The challenging task of quantifying participation bias in PROs has necessitated a good deal of creativity on the part of researchers. One method employed by multiple orthopedic studies involves the use of a relatively generic, mail-based survey to categorize "respondents" and "nonrespondents," followed by self-reported and more objective clinical data collection at subsequent follow-up appointments. Both Kwon et al.[13] and Kim et al.[14] conducted such analyses using a mail-based survey assessing satisfaction and functional status in patients undergoing total knee arthroplasty.

Telephone-based outreach has also been utilized by several groups to connect with patients that did not respond to initial survey requests. In a study of patients from the Danish Shoulder Arthroplasty Registry, Polk et al.[15] utilized both postal reminders and telephone contact to increase completion rates of the Western Ontario Osteoarthritis of the Shoulder index from 65% to 82%. Højmark et al.[11] also studied nonrespondents to a

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Table 3. Outcomes by PROMIS completion status

Variable	Completed PROMIS PF	Incomplete PROMIS PF	p-value†
PHQ-9			
Preoperative	6.0 ± 5.7 (448)	6.9 ± 6.6 (144)	0.117
6 Weeks	3.3 ± 4.4 (347)	5.7 ± 6.0 (147)	< 0.001*
12 Weeks	3.6 ± 5.2 (257)	5.4 ± 6.0 (105)	0.005*
6 Months	3.7 ± 5.2 (232)	5.3 ± 6.1 (142)	0.007*
1 Year	4.0 ± 5.7 (189)	5.7 ± 6.0 (65)	0.042*
VAS back			
Preoperative	6.1 ± 2.6 (553)	6.5 ± 3.0 (183)	0.130
6 Weeks	3.1 ± 2.7 (435)	3.8 ± 2.8 (188)	0.004*
12 Weeks	3.2 ± 2.8 (316)	4.1 ± 2.7 (133)	0.003*
6 Months	3.3 ± 2.9 (255)	4.3 ± 2.8 (132)	0.002*
1 Year	3.2 ± 2.8 (179)	4.5 ± 2.9 (49)	0.004*
VAS leg			
Preoperative	5.9 ± 2.8 (556)	6.1 ± 2.8 (182)	0.311
6 Weeks	2.8 ± 2.7 (434)	3.6 ± 3.0 (187)	0.001*
12 Weeks	2.8 ± 2.8 (316)	3.4 ± 2.8 (134)	0.047*
6 Months	2.8 ± 3.0 (255)	3.7 ± 2.8 (132)	0.011*
1 Year	2.7 ± 3.0 (180)	3.9 ± 3.2 (49)	0.011*
Oswestry Disability Index			
Preoperative	41.5 ± 17.2 (556)	42.9 ± 17.8 (182)	0.319
6 Weeks	27.6 ± 18.8 (436)	35.0 ± 21.9 (188)	< 0.001*
12 Weeks	25.2 ± 19.8 (315)	33.9 ± 20.3 (137)	< 0.001*
6 Months	24.1 ± 20.4 (256)	32.3 ± 20.4 (132)	< 0.001*
1 Year	22.8 ± 20.7 (177)	31.7 ± 20.9 (49)	0.009*
SF-12 PCS			
Preoperative	31.1 ± 8.0 (539)	32.1 ± 8.4 (155)	0.159
6 Weeks	35.9 ± 10.0 (424)	32.5 ± 9.3 (122)	0.003*
12 Weeks	37.9 ± 11.1 (329)	35.8 ± 9.0 (71)	0.141
6 Months	39.5 ± 11.4 (268)	37.9 ± 11.6 (86)	0.265
1 Year	40.7 ± 11.3 (241)	37.6 ± 12.7 (47)	0.090

Values are presented as mean ± standard deviation (number).
PROMIS PF, Patient-Reported Outcomes Measurement Information System physical function; PHQ-9, Patient Health Questionnaire-9; VAS, visual analogue scale; SF-12 PCS, 12-item Short Form health survey physical composite score.
*$p < 0.05$, statistically significant differences. †p-values calculated using t-test for independent samples.

mail-based survey from the Danish national spine database (DaneSpine) at 1 year follow-up by initiating contact through a structured telephone interview. Though this study is one of few to examine PROM participation bias in a cohort of spine patients, Cabitza et al.[9] also utilized telephone-based follow-up, but used a slightly less conventional method of characterizing and studying "nonrespondents." These authors utilized phone-based reminders at 3 separate timepoints, and timed the third reminder such that patient responses had essentially ceased before this final outreach was attempted. Predicated on the idea that patients engaged by the third reminder otherwise would likely not have responded, outcome response data from these patients were used as a "proxy" for "true nonrespondents."

Our group's collection of a variety of different PROMs at multiple postoperative intervals allows us the opportunity to use data from "partial-respondents" who complete some PROMs but not others, to extrapolate potential trends for missing surveys. A number of previous studies have demonstrated robust correlations between PROMIS PF and the other physical health-related "legacy" PROMs utilized in our study. In their 2-year PROMIS validation study, Jenkins et al.[3] demonstrated strong correlations of PROMIS PF with VAS back, VAS leg, ODI, and SF-12 at both short- and long-term follow-up in patients undergoing transforaminal lumbar interbody fusion. This finding has been similarly reproduced in other studies across a number of procedures including lumbar fusions and microdiscectomies,[16-18] with the exception of Vaishnav et al, who reported a weak correlations of PROMIS PF with SF-12 preoperatively.[19] Based on these well-documented correlations, we can be confident that the completed PROM data we do have may provide useful information regarding the potential PROMIS scores for those that did not complete the PROMIS questionnaire. These relationships indicate that in cases where "legacy" PROM scores differ significantly between PROMIS respondents and nonrespondents, PROMIS scores may differ as well.

We identified 2 key demographic variables that were significantly associated with PROMIS completion. Specifically, the nonrespondent group included a larger proportion of patients who were African-American or Hispanic, and patients who made payments through workers' compensation. Parrish et al.[5] previously examined demographic factors associated with PROMIS survey completion and reported similar trends of lower survey completion among African-American and Hispanic spine patients. While their study did not replicate our results regarding workers' compensation patients, several investigations have reported poorer lumbar surgery outcomes among African-American and workers' compensation populations.[20,21] These observed demographic variations in PROMIS response rates may contribute to and/or exacerbate the apparent response bias demonstrated in our results.

Although our analysis demonstrated substantial discrepan-

cies in postoperative PROM scores, preoperative PROM scores did not significantly differ for any measure between PROMIS respondents and nonrespondents. This trend was demonstrated for both mental and physical health measures and may be particularly strong given that the greatest number of participants were included at these preoperative timepoints. Other studies of participation bias have reported similar results, with negligible preoperative differences between respondents and nonrespondents, even when significant differences emerged postoperatively.[9,14] One potential explanation for this observation is that differences in response rates may be influenced by patient experiences, perceptions, or outcomes of surgery. Perhaps patients hold relatively similar perceptions of surgery at the preoperative timepoint, given that they have all decided to pursue elective procedures, but these perceptions may diverge following varying postoperative outcomes and experiences. In fact, a number of studies have demonstrated that postoperative satisfaction is significantly associated with rates of survey completion.[10,14]

In contrast with our preoperative results, PROMIS PF nonrespondents reported significantly worse back pain, leg pain, and disability at all postoperative timepoints. In their study of total knee arthroplasty patients, Kim et al.[14] demonstrated poorer mean scores and less postoperative improvement in pain, functionality, and Knee Society knee scores in patients that did not respond to their initial, mail-based survey. Cabitza et al.[9] also demonstrated poorer pain outcomes among survey nonrespondents in their cohort of hip, knee, and spine patients. However, others, such as Højmark et al.[11] and Kwon et al.[13] reported no significant difference in pain scores between respondents and nonrespondents.

PF, as measured by SF-12 PCS, demonstrated the least postoperative difference between PROMIS respondents and nonrespondents, with the nonresponding group demonstrating worse scores at the 6-week timepoint only. In previous validation studies, SF-12 PCS demonstrated some of the strongest, most consistent correlations with PROMIS PF.[3,4] Given that these measures are both specifically designed to assess physical functioning, the relative lack of difference in SF-12 PCS scores between PROMIS respondents and nonrespondents may be reassuring in terms of the validity of PROMIS data for drawing conclusions about the entire cohort. Our results conflict again with that of Kwon et al.[13] and also with Cabitza et al.[9] in this regard, as these studies both reported significantly poorer SF PF scores among survey nonrespondents.

In addition to the differences, we observed in physical health measures, patient-reported depressive symptoms, as measured by PHQ-9, were also significantly more severe at all postoperative timepoints for patients that did not complete PROMIS. Literature related to participation bias in measures of depression among surgical patients is quite limited. Cabitza et al.[9] was one of very few studies to include a measure of mental health status and, in contrast with their results regarding physical health, demonstrated no significant difference in SF mental component summary scores between respondents and nonrespondents. Several previous studies in more general medical populations have also reported minimal effects of participation bias with regard to depressive symptoms or mental health outcomes.[22,23] Nonetheless, the substantial differences we observed in depressive symptoms is concerning, especially considering evidence for a connection between PHQ-9 scores and physical outcomes in patients undergoing spine surgery.[24-26]

The primary limitation of this study is that our use of legacy PROMs as a proxy for PROMIS scores did not allow us to study "complete nonrespondents" who did not complete any PROM surveys at all. These patients may differ from the 2 groups examined in our study in several important ways, and future studies of participation bias should consider alternative ways to capture outcomes in these patients. Additionally, all procedures in this study were performed by a single attending surgeon at the same academic institution. Therefore, the ability to generalize our results regarding PROMIS nonrespondents to other populations may be limited. A follow-up study using a multicenter design and an innovative method of engaging nonrespondents could be helpful to address these limitations. However, the current study provides a novel analysis of PROM trends in patients that did not complete the PROMIS PF survey, and presents important data regarding the potential for participation bias in this measure among lumbar spine patients.

CONCLUSION

No significant preoperative differences were observed for any of the assessed PROM scores between PROMIS respondents and nonrespondents. PROMIS nonrespondents demonstrated significantly poorer postoperative back pain, leg pain, disability, and depressive symptoms than respondents through 1-year following surgery. PF, as quantified by SF-12 PCS, generally did not differ between respondents and nonrespondents. Our results indicate that some degree of nonresponse bias may exist for PROMIS surveys, leading to a potential underestimation of PF deficits in the overall lumbar spine cohort, particularly at

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short-term postoperative timepoints. Efforts should be taken whenever possible to maximize survey completion and the outcomes of nonrespondents should be considered alongside available survey data.

NOTES

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REFERENCES

1. Boody BS, Bhatt S, Mazmudar AS, et al. Validation of Patient-Reported Outcomes Measurement Information System (PROMIS) computerized adaptive tests in cervical spine surgery. J Neurosurg Spine 2018;28:268-79.
2. Patel AA, Dodwad SM, Boody BS, et al. Validation of patient Reported Outcomes Measurement Information System (PROMIS) computer adaptive tests (CATs) in the surgical treatment of lumbar spinal stenosis. Spine (Phila Pa 1976) 2018;43:1521-8.
3. Jenkins NW, Parrish JM, Cha EDK, et al. Validation of PROMIS physical function in MIS TLIF: 2-year follow-up. Spine (Phila Pa 1976) 2020;45:E1516-22.
4. Parrish JM, Jenkins NW, Brundage TS, et al. PROMIS physical function predicts postoperative pain and disability following anterior cervical discectomy and fusion. Clin Spine Surg 2020;33:382-7.
5. Parrish JM, Jenkins NW, Patel DV, et al. Demographic and perioperative factors associated with Patient-reported Outcomes Measurement Information System (PROMIS) survey completion. Clin Spine Surg 2020;33:E519-24.
6. Solberg TK, Sørlie A, Sjaavik K, et al. Would loss to follow-up bias the outcome evaluation of patients operated for degenerative disorders of the lumbar spine? Acta Orthop 2011;82:56-63.
7. Tyser AR, Abtahi AM, McFadden M, et al. Evidence of non-response bias in the Press-Ganey patient satisfaction survey. BMC Health Serv Res 2016;16(a):350.
8. Hutchings A, Neuburger J, Grosse Frie K, et al. Factors associated with non-response in routine use of patient reported outcome measures after elective surgery in England. Health Qual Life Outcomes 2012;10:34.
9. Cabitza F, Dui LG, Banfi G. PROs in the wild: assessing the validity of patient reported outcomes in an electronic registry. Comput Methods Programs Biomed 2019;181:104837.
10. Imam MA, Barke S, Stafford GH, et al. Loss to follow-up after total hip replacement: a source of bias in patient reported outcome measures and registry datasets? Hip Int 2014;24:465-72.
11. Højmark K, Støttrup C, Carreon L, et al. Patient-reported outcome measures unbiased by loss of follow-up. Single-center study based on DaneSpine, the Danish spine surgery registry. Eur Spine J 2016;25:282-6.
12. Parrish JM, Jenkins NW, Nolte MT, et al. A Validation of Patient Health Questionnaire-9 for cervical spine surgery. Spine (Phila Pa 1976) 2020;45:1668-75.
13. Kwon SK, Kang YG, Chang CB, et al. Interpretations of the clinical outcomes of the nonresponders to mail surveys in patients after total knee arthroplasty. J Arthroplasty 2010;25:133-7.
14. Kim J, Lonner JH, Nelson CL, et al. Response bias: effect on outcomes evaluation by mail surveys after total knee arthroplasty. J Bone Joint Surg Am 2004;86:15-21.
15. Polk A, Rasmussen JV, Brorson S, et al. Reliability of patient-reported functional outcome in a joint replacement registry. A comparison of primary responders and non-responders in the Danish Shoulder Arthroplasty Registry. Acta Orthop 2013;84:12-7.
16. Haws BE, Khechen B, Guntin JA, et al. Validity of PROMIS in minimally invasive transforaminal lumbar interbody fusion: a preliminary evaluation. J Neurosurg Spine 2018;29:28-33.
17. Bhatt S, Boody BS, Savage JW, et al. Validation of Patient-reported Outcomes Measurement Information System computer adaptive tests in lumbar disk herniation surgery. J Am Acad Orthop Surg 2019;27:95-103.
18. Khechen B, Haws BE, Patel DV, et al. PROMIS physical function score strongly correlates with legacy outcome measures

in minimally invasive lumbar microdiscectomy. Spine (Phila Pa 1976) 2019;44:442-6.
19. Vaishnav AS, McAnany SJ, Iyer S, et al. Psychometric evaluation of Patient-reported Outcomes Measurement Information System physical function computer adaptive testing in minimally invasive lumbar spine surgery: an analysis of responsiveness, coverage, discriminant validity, and concurrent validity. J Am Acad Orthop Surg 2020;28:717-29.
20. Gum JL, Glassman SD, Carreon LY. Is type of compensation a predictor of outcome after lumbar fusion? Spine (Phila Pa 1976) 2013;38:443-8.
21. Elsamadicy AA, Kemeny H, Adogwa O, et al. Influence of racial disparities on patient-reported satisfaction and short- and long-term perception of health status after elective lumbar spine surgery. J Neurosurg Spine 2018;29:40-5.
22. Linnenkamp U, Gontscharuk V, Brüne M, et al. Using statutory health insurance data to evaluate non-response in a cross-sectional study on depression among patients with diabetes in Germany. Int J Epidemiol 2020;49:629-37.
23. Vink JM, Willemsen G, Stubbe JH, et al. Estimating non-response bias in family studies: application to mental health and lifestyle. Eur J Epidemiol 2004;19:623-30.
24. Patel DV, Yoo JS, Khechen B, et al. PHQ-9 score predicts postoperative outcomes following minimally invasive transforaminal lumbar interbody fusion. Clin Spine Surg 2019;32:444-8.
25. Alvi MA, Berg J, Goyal A, et al. Mental illnesses among patients undergoing elective anterior cervical discectomy and fusion: analysis from the National Readmissions Database. Clin Neurol Neurosurg 2020;193:105765.
26. Tuck AN, Scribani MB, Grainger SD, et al. The 9-item Patient Health Questionnaire (PHQ-9): an aid to assessment of patient-reported functional outcomes after spinal surgery. Spine J 2018;18:1398-405.

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Effects of Anterior Plating on Achieving Clinically Meaningful Improvement Following Single-Level Anterior Cervical Discectomy and Fusion

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Objective: The clinical utility of anterior cervical plating for anterior cervical discectomy and fusion (ACDF) procedures remains controversial. This study aims to compare the impact of cervical plating on achievement of minimum clinically important difference (MCID) up to 2 years following ACDF.
Methods: Patients undergoing primary, single-level ACDF procedures were grouped based on whether their procedure included application of an anterior cervical plate. Demographics, preoperative spinal diagnoses, operative characteristics, and patient-reported outcome measures (PROMs) were compared between plating groups. Achievement of an MCID was assessed using the following previously established thresholds: 12-item Short Form health survey physical component summary (SF-12 PCS) 8.1, visual analogue scale (VAS) neck 2.6, VAS arm 4.1, Neck Disability Index (NDI) 8.5. Rates of MCID achievement were compared between groups.
Results: The cohort included 192 patients of whom 102 received plating and 90 received no plating. Plating status was significantly associated with Charlson Comorbidity Index and insurance status. Operative duration and estimated blood loss were significantly greater for the plating group. Both groups demonstrated significant improvements at the majority of postoperative timepoints. Significant intergroup differences in PROM improvement were demonstrated for VAS neck and NDI at 6 weeks. Rates of MCID achievement differed significantly between groups for NDI at 6 weeks, and 12 weeks, and SF-12 PCS overall.
Conclusion: Patients improved significantly in terms of pain, disability and physical function, regardless of plating status, and with the exception of early neck pain and disability, these improvements were similar between groups. Patients that underwent plating as part of their ACDF procedure achieved an MCID for physical function at lower rates overall.

Keywords: Cervical vertebrae, Spinal fusion, Visual analogue scale, Patient-reported outcome measures

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) is a commonly performed spinal procedure to treat cervical radiculopathy and myelopathy, with approximately 130,000 performed in the United States every year.[1-3] The procedure itself provides significant benefits, with one study reporting 78% of patients were satisfied with their surgical outcomes.[4] Part of the success associated with ACDF may be owed to substantial evolution in operative techniques since its introduction. While autografts alone were initially used to achieve fusion, use of metal plates and screws to decrease subsidence, and now the integration of titanium or polyether ether ketone interbody cages have contributed to continually effective treatment of cervical spine pathologies.

Plating has been utilized to strengthen the graft area, provide

stability, and help maintain sagittal alignment;[5] however, its benefits are still heavily debated due to associated complications such as esophageal irritation or damage, injury to vasculature, higher rates of adjacent segment disease (ASD), and dysphagia.[6-8] In addition to soft tissue damage, challenges to the integrity of the plate instrumentation can occur with screw misalignment, plate loosening, or breakage causing subsequent damage to surrounding tissues.[9]

Although the stability added to the area of implantation by anterior plating may be advantageous, its associated complications may raise concerns when considering its use in addition to an interbody cage. With the rise of stand-alone cages that anchor directly into the vertebral bodies, the use of anterior plates has been further called into question. ACDF procedures using a stand-alone cage have demonstrated reduced rates of common postsurgical complications, such as dysphagia and ASD.[10,11] Although use of stand-alone cages has become common practice for ACDF, this technique is not without its own reported disadvantages, such as increased subsidence, vertebral dislocation, and kyphosis.[12]

The currently available literature provides no clear consensus as to whether a stand-alone cage or a cage-plate combination is preferable, as compelling pros and cons have been presented for each and similar rates of fusion have been reported.[8,11] One method that may aid in resolving this debate is the use of patient-reported outcome measures (PROMs) to quantify patient perceptions of health and functional status. A number of studies have explored the use of plates and stand-alone cages and their subsequent effects on PROMs but provide inconclusive evidence. For instance, studies focusing on perceptions of disability and pain have demonstrated no significant differences between ACDF procedures utilizing stand-alone cages vs. cages with anterior plating.[13,8] Conversely, several investigators have reported outcomes that favor one technique over the other.[13-15]

Although the use of PROMs may offer a patient-centered perspective on key clinical symptoms, a simple comparison of their values fails to capture a change which patients perceive as a true clinical difference. More recent use of the minimum clinically important difference (MCID) may provide physicians with better insight into the true difference in postoperative symptoms. Defined as the smallest meaningful difference in scores that a patient perceives as beneficial,[16] MCID is a useful metric with strong evidence as a predictor of patient satisfaction and functional clinical improvement following ACDF.[17,18] However, MCID achievement rates have yet to be empirically applied to the question of whether to include anterior plating with ACDF procedures. Therefore, this study endeavors to determine the impact of cervical plating on achievement of MCID up to 2 years following ACDF.

MATERIALS AND METHODS

1. Patient Population

Prior to study commencement, this study was approved by the Institutional Review Board of Rush University Medical Center (ORA #14051301) and written informed consent were obtained from patients. A prospectively maintained surgical database was retrospectively reviewed for ACDF procedures from June 2005 to July 2020. Inclusion criteria were primary, single-level ACDF procedures for degenerative pathology. Exclusion criteria were patients without clear identification regarding the use of an anterior interbody plate, patients without preoperative PROM data, and patients undergoing surgery to treat traumatic, infectious, or malignant conditions. All procedures were performed by a single, fellowship-trained spine surgeon at the same academic institution. Anterior plate instrumentation consisted of low-profile titanium devices which were fixed to the anterior spine with 2 screws placed into the cranial and caudal vertebral bodies each. Stand-alone cage devices were composed of polyether ether ketone and were fixed to the superior and inferior endplates via one locking screw each.

2. Data Collection

Patient demographic information was collected which included age, gender, body mass index (BMI; categorized as nonobese: BMI <30 kg/m^2 and obese: BMI ≥ 30 kg/m^2), smoking status, diabetic status, American Society of Anesthesiologists classification (ASA; categorized as $\leq$II and $>$II), Charlson Comorbidity Index score (CCI; categorized as <1 and ≥ 1), ethnicity, and insurance/payment received. Pre-existing spinal pathologies and operative characteristics were recorded for all patients and included operative duration (from skin incision to skin closure, in minutes), estimated blood loss (EBL; in mL), and postoperative length of stay (in hours). Rates of arthrodesis by the 1-year postoperative timepoint were confirmed using computed tomography (CT) scans of the lumbar spine. Additionally, preoperative and final postoperative lateral radiographs were reviewed and measured to determine global cervical lordosis, segmental lordosis, and cervical sagittal vertical axis (SVA) at the operated level. Rates of revision for clinically significant subsidence were also calculated for all patients. PROMs were administered at preoperative and postoperative (6 weeks, 12 weeks, 6 months, 1 year,

 https://doi.org/10.14245/ns.2142214.107

2 years) timepoints and included 12-Item Short Form physical component summary (SF-12 PCS), visual analogue scale (VAS) for neck and arm pain, and Neck Disability Index (NDI).

3. Statistical Analysis

All statistical tests and calculations were performed using Stata IC 16.1 (StataCorp, College Station, TX, USA). Patients were sorted into 2 groups based on whether they had an anterior plate placed as part of their ACDF procedure. Demographic characteristics, pre-existing spinal pathologies, operative and radiographic variables were compared between groups using chi-square analysis and Student t-test for independent samples for categorical and continuous variables, respectively. Change in PROM scores (ΔPROM) was calculated as the difference of each postoperative score from preoperative baseline. A paired Student t-test compared postoperative to preoperative scores to assess improvement following ACDF. Student t-test for independent samples was used to assess differences in ΔPROM between groups at each timepoint. Achievement of MCID was determined by comparing ΔPROM values to the following previously established thresholds: SF-12 PCS (8.1),[19] VAS arm (4.1),[19] VAS neck (2.6),[19] NDI (8.5).[19] Association of MCID achievement between groups was assessed using chi-square analysis at each postoperative timepoint and overall (whether MCID had been achieved at any timepoint). A p-value of ≤0.05 was set as the threshold for statistical significance for all statistical tests.

RESULTS

A total of 192 patients were included, of whom 102 received anterior plating and 90 did not. The cohort's mean age was 47.4 years, 59.9% were male, and 48.4% were obese. Herniated nucleus pulposus was the most common preoperative spinal pathology. Mean operative duration was 53.2 minutes, mean EBL was 35.9 mL, and mean length of stay was 19.0 hours. CCI (p=0.012) and insurance/payment collected (p=0.027) were the only demographic characteristics significantly associated with plating status (Table 1). None of the included patients had a history of osteopenia or osteoporosis. None of the reported spinal pathologies were significantly associated with plating status. Operative duration (57.2 minutes vs. 48.8 minutes, p<0.001) and EBL (40.2 mL vs. 31.1 mL, p=0.001) were significantly greater for the plating group. None of the preoperative or postoperative sagittal alignment parameters differed between groups (p>0.050, all). By 1 year postoperatively, radiographic evidence of arthrodesis was demonstrated in 98.4% of patients and did not vary significantly between groups. All 3 patients (2 plate, 1 no plate) who failed to demonstrate arthrodesis underwent revision fusion procedures at the index level. Sufficient follow-up data to assess fusion status was unavailable for 7 patients (Table 2). Clinically significant subsidence was not observed among any of the patients in either group.

Significant postoperative improvements were demonstrated

Table 1. Patient demographics

Demographic	No plate (n=90)	Plate (n=102)	p-value†
Age (yr)	45.6±8.5	48.1±11.5	0.312
Sex			0.391
Female	39 (43.3)	38 (37.3)	
Male	51 (56.7)	64 (62.8)	
Body mass index (kg/m²)			0.684
<30	45 (50.0)	54 (52.9)	
≥30	45 (50.0)	48 (47.1)	
Smoking status			0.099
Nonsmoker	78 (86.7)	79 (77.5)	
Smoker	12 (13.3)	23 (22.6)	
Diabetes			0.227
Diabetic	6 (6.7)	12 (11.8)	
Nondiabetic	84 (93.3)	90 (88.2)	
ASA PS classification			0.508
≤II	66 (73.3)	79 (77.5)	
>II	24 (26.7)	23 (22.6)	
CCI score			0.012*
<1	30 (33.3)	18 (17.7)	
≥1	60 (66.7)	84 (82.4)	
Ethnicity			0.353
White	63 (70.0)	76 (74.5)	
African-American	12 (13.3)	14 (13.7)	
Hispanic	7 (7.8)	7 (6.9)	
Asian	1 (1.1)	3 (2.9)	
Other	7 (7.8)	2 (2.0)	
Insurance			0.027*
Medicare/Medicaid	3 (3.3)	13 (12.8)	
Workers' compensation	27 (30.0)	36 (35.3)	
Private	60 (66.7)	53 (52.0)	

Values are presented as mean±standard deviation or number (%).
ASA PS, American Society of Anesthesiologists physical status; CCI, Charlson Comorbidity Index.
*p<0.05, statistically significant differences. †p-values calculated using an unpaired t-test or chi-square test to determine differences between groups.

Table 2. Perioperative characteristics

Characteristic	No plate (n = 90)	Plate (n = 102)	p-value†
Spinal pathology			
Degenerative disc disease	5 (5.6)	2 (2.0)	0.185
Central stenosis	24 (26.7)	32 (31.4)	0.474
Radiculopathy	20 (22.2)	19 (18.6)	0.537
Myelopathy	2 (2.2)	1 (1.0)	0.489
Myeloradiculopathy	67 (74.4)	76 (74.5)	0.992
Herniated nucleus pulposus	84 (93.3)	95 (93.1)	0.957
Operative time (min)	48.8 ± 11.1	57.2 ± 13.4	< 0.001*
Estimated blood loss (mL)	31.1 ± 12.0	40.2 ± 21.7	0.001*
Length of stay (hr)	17.9 ± 15.1	20.1 ± 22.0	0.431
Arthrodesis‡	85 (98.8)	97 (98.0)	0.645
Cervical lordosis (°)			
Preoperative	8.4 ± 6.0	9.5 ± 7.2	0.385
Postoperative	10.5 ± 6.9	10.8 ± 8.8	0.828
Change	2.1 ± 6.5	1.3 ± 7.3	0.547
Segmental lordosis (°)			
Preoperative	3.9 ± 2.6	4.1 ± 3.9	0.704
Postoperative	4.9 ± 3.8	6.2 ± 4.5	0.083
Change	1.0 ± 5.0	2.2 ± 5.5	0.227
Cervical sagittal vertical axis (mm)			
Preoperative	26.9 ± 9.1	28.0 ± 11.1	0.605
Postoperative	27.7 ± 9.7	28.7 ± 9.4	0.568
Change	0.7 ± 6.9	0.8 ± 6.7	0.978

Values are presented as number (%) or mean ± standard deviation.
*p < 0.05, statistically significant differences. †p-values calculated using an unpaired t-test or chi-square test to determine differences between groups. ‡Insufficient follow-up data was available to determine fusion status for 7 patients.

in both groups for all PROMs at all timepoints ($p \leq 0.030$), except SF-12 PCS at 2 years ($p = 0.100$) for the no plating group and SF-12 PCS, and NDI at 6 weeks ($p = 0.358$, $p = 0.066$), VAS arm at 1 year ($p = 0.145$), and VAS neck, VAS arm, and NDI at 2 years ($p = 0.347$, $p = 0.576$, $p = 0.058$) for the plating group (Table 3). ΔPROM was significantly lower in the plating group for VAS neck (1.9 vs. 3.1, $p = 0.018$) and NDI (5.0 vs. 13.6, $p = 0.010$) at 6 weeks only. No other significant intergroup differences in ΔPROM were observed. A majority of patients achieved an overall MCID for all measures, except for SF-12 PCS in the plating group (41.0%). Achievement of MCID varied significantly by group for NDI at 6 weeks (37.3% vs. 58.9%, $p = 0.025$) and 12 weeks (72.6% vs. 48.9%, $p = 0.017$), and SF-12 PCS overall (41.0% vs. 59.7%, $p = 0.022$) (Table 4).

DISCUSSION

Following the introduction of stand-alone interbody cages, the utility of anterior plating for ACDF procedures remains controversial. While satisfactory outcomes have been achieved with both techniques, plating has been associated with increased incidence of dysphagia and ASD, while greater rates of subsidence and less restoration of cervical lordosis have been reported with stand-alone cages.[8,11,20] Previous studies examining PROMs are similarly inconclusive regarding the advantage of one technique over the other.[8,13,20,21] The present study seeks to address this ongoing controversy through the lens of MCID in PROMs for pain, disability, and physical function.

CCI and insurance status differed significantly between groups. The plating group had a higher proportion of patients with a CCI score of 1 or greater, indicating that more of these patients had some medical comorbidity. Narain et al.[22] previously demonstrated that ACDF patients with a CCI of 2 or greater are less likely to achieve MCID in NDI than those with lower comorbidity burden. While we chose to assess a lower comorbidity threshold (< 1 vs. ≥ 1), it is possible that the difference in comorbidity burden between groups may have affected our results. Additionally, a larger proportion of the plating group consisted of patients with workers' compensation or Medicare/Medicaid payments. A retrospective analysis by Goldberg et al.[23] reported no significant differences in long-term, patient-reported functional outcomes between workers' compensation and non-workers' compensation patients following ACDF. Therefore, this difference in workers' compensation status is unlikely to represent a significant confounder in the present study.

Prevalence of preoperative spinal pathologies did not significantly vary between groups. Operative duration was significantly longer and EBL was significantly greater for the plating group than the no plating group. Similar operative findings have been reported by previous studies.[11,14] A systematic review of ACDF with stand-alone cage vs traditional cage and plate techniques by Cheung et al.[8] demonstrated that on average, ACDF procedures without use of an anterior plate were associated with 9.90 mL less blood loss ($p < 0.01$) than those with a plate. Vaishnav et al.[14] also reported significantly shorter operative time for cage-only procedures. Interestingly, although they did not demonstrate a direct association of dysphagia with plating, they did demonstrate that increased operative time was correlated with rates of postoperative dysphagia, a complication that has been reported in association with anterior plating by several other studies.[11,20,21] While the observed difference in blood loss was

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Table 3. PROM improvement following ACDF

Variable	No plate			Plate			p-value‡
	Mean ± SD	ΔPROM	p-value†	Mean ± SD	ΔPROM	p-value†	
SF-12 PCS							
Preoperative	36.1 ± 8.7	-	-	39.6 ± 9.8	-	-	-
6 Weeks	38.2 ± 8.8	3.6 ± 8.6	0.014*	38.8 ± 10.6	1.3 ± 9.9	0.358	0.254
12 Weeks	42.6 ± 8.7	5.9 ± 8.1	< 0.001*	45.0 ± 10.5	4.3 ± 7.7	< 0.001*	0.287
6 Months	42.7 ± 10.1	8.5 ± 11.0	< 0.001*	41.4 ± 9.4	6.4 ± 9.2	0.002*	0.421
1 Year	43.1 ± 10.9	8.2 ± 12.6	0.004*	43.7 ± 10.3	4.6 ± 6.4	0.004*	0.255
2 Years	41.7 ± 19.3	6.6 ± 14.4	0.100	46.0 ± 11.5	6.5 ± 8.3	0.027*	0.988
VAS neck							
Preoperative	6.5 ± 2.2	-	-	5.9 ± 2.4	-	-	-
6 Weeks	3.2 ± 2.4	3.1 ± 2.3	< 0.001*	3.9 ± 2.7	1.9 ± 3.1	< 0.001*	0.018*
12 Weeks	3.0 ± 2.5	3.4 ± 2.5	< 0.001*	3.0 ± 2.5	2.9 ± 3.0	< 0.001*	0.348
6 Months	3.0 ± 2.8	3.5 ± 2.8	< 0.001*	2.6 ± 2.5	3.2 ± 3.2	< 0.001*	0.687
1 Year	3.1 ± 2.6	2.9 ± 3.0	< 0.001*	3.9 ± 3.0	1.9 ± 3.6	0.025*	0.258
2 Years	4.1 ± 2.4	2.7 ± 2.3	0.001*	4.8 ± 3.6	1.5 ± 4.5	0.347	0.421
VAS arm							
Preoperative	6.0 ± 2.6	-	-	6.2 ± 2.5	-	-	-
6 Weeks	1.9 ± 2.1	3.8 ± 2.8	< 0.001*	3.3 ± 2.8	2.7 ± 3.5	< 0.001*	0.081
12 Weeks	2.4 ± 2.6	3.4 ± 3.0	< 0.001*	3.1 ± 3.2	3.1 ± 3.8	< 0.001*	0.684
6 Months	2.2 ± 2.6	3.4 ± 3.1	< 0.001*	3.3 ± 3.2	2.8 ± 3.4	< 0.001*	0.358
1 Year	2.8 ± 2.9	2.5 ± 3.4	< 0.001*	4.7 ± 3.0	1.5 ± 4.5	0.145	0.374
2 Years	4.0 ± 3.0	2.0 ± 2.2	0.003*	3.3 ± 4.1	1.2 ± 5.5	0.576	0.642
NDI							
Preoperative	44.8 ± 19.9	-	-	39.1 ± 17.7	-	-	-
6 Weeks	29.3 ± 18.7	13.6 ± 14.7	< 0.001*	33.2 ± 21.3	5.0 ± 19.0	0.066	0.010*
12 Weeks	27.3 ± 20.9	17.0 ± 15.0	< 0.001*	27.6 ± 20.5	12.1 ± 21.6	< 0.001*	0.198
6 Months	22.9 ± 20.9	21.6 ± 18.2	< 0.001*	24.5 ± 22.6	15.7 ± 22.1	< 0.001*	0.177
1 Year	26.2 ± 21.5	16.3 ± 19.2	< 0.001*	21.7 ± 20.0	15.3 ± 22.9	0.012*	0.866
2 Years	28.7 ± 21.4	13.1 ± 14.9	0.004*	21.6 ± 19.2	21.6 ± 24.4	0.058	0.323

PROM, patient-reported outcome measure; ACDF, anterior cervical discectomy and fusion; SD, standard deviation; SF-12 PCS, 12-item Short Form health survey physical component summary; VAS, visual analogue scale; NDI, Neck Disability Index.
*$p < 0.05$, statistically significant differences. †p-values calculated using a paired t-test to assess within-group improvement from preoperative baseline. ‡p-values calculated using a t-test for independent samples to assess intergroup differences in PROM score improvement (ΔPROM).

statistically significant, we agree with other authors that such a relatively small difference is unlikely to be clinically relevant.[8] However, the increased operative duration associated with anterior plating may be cause for slightly more concern. Any amount of time under general anesthesia is not without risk. If this time can be minimized through the use of a stand-alone cage, this should be carefully considered in preoperative planning.

While some have suggested that anterior plating may lend additional stability to the operative segment, we were unable to detect a significant difference in fusion rates between the 2 groups. These results are largely in line with previous literature which similarly reports satisfactory rates of arthrodesis regardless of plating status.[8,11] Preoperatively, neither segmental nor global sagittal alignment significantly differed between groups, which confirms that preoperative kyphosis is unlikely to represent a significant source of bias in our study. Postoperatively, neither mean angles nor pre-post change significantly differed for segmental nor global cervical lordosis measurements. These find-

Table 4. MCID achievement rates

Variable	No plate	Plate	p-value†
SF-12 PCS			
6 Weeks	13 (33.3)	13 (25.0)	0.384
12 Weeks	18 (40.0)	23 (33.8)	0.504
6 Months	17 (44.7)	11 (42.3)	0.847
1 Year	11 (45.8)	4 (20.0)	0.072
2 Years	7 (46.7)	4 (36.4)	0.599
Overall	40 (59.7)	34 (41)	0.022*
VAS neck			
6 Weeks	33 (53.2)	23 (41.1)	0.187
12 Weeks	40 (67.8)	27 (52.9)	0.111
6 Months	31 (58.5)	29 (61.7)	0.744
1 Year	14 (41.2)	9 (42.9)	0.902
2 Years	5 (33.3)	4 (44.4)	0.586
Overall	53 (76.8)	40 (65.6)	0.156
VAS arm			
6 Weeks	26 (45.6)	21 (40.4)	0.582
12 Weeks	21 (41.2)	20 (40.8)	0.971
6 Months	19 (38.8)	19 (44.2)	0.599
1 Year	9 (26.5)	6 (30.0)	0.780
2 Years	3 (20.0)	2 (28.6)	0.655
Overall	36 (57.1)	33 (57.9)	0.934
NDI			
6 Weeks	33 (58.9)	19 (37.3)	0.025*
12 Weeks	37 (72.6)	23 (48.9)	0.017*
6 Months	33 (68.8)	26 (65.0)	0.709
1 Year	17 (51.5)	10 (55.6)	0.782
2 Years	9 (60.0)	4 (57.1)	0.899
Overall	51 (82.3)	36 (66.7)	0.053

Values are presented as number (%).
MCID, minimum clinically important difference; SF-12 PCS, 12-item Short Form health survey physical component summary; VAS, visual analogue scale; NDI, Neck Disability Index.
*$p < 0.05$, statistically significant differences. †p-values calculated using a chi-square test to assess MCID achievement between groups.

ings are in agreement with 2 previous meta-analyses which demonstrated nonsignificant change in segmental or global cervical sagittal alignment.[8,21] Additionally, we detected no significant difference in change of SVA between groups. Effects of anterior plating on postoperative sagittal alignment may be more dramatic for procedures that include multiple spinal levels. For example, in a study of 2-level ACDF, Kwon et al.[12] demonstrated significantly greater increase in cervical lordosis and greater decrease in SVA for patients receiving anterior plates compared to stand-alone cages. Therefore, biomechanical change may be a more important factor in the decision to utilize anterior plating with more extensive procedures, but may not be the most important deciding factor for single-level fusions. Results of previous studies regarding risk of implant subsidence are mixed, with Cheung et al.[8] reporting increased rates associated with stand-alone cages and Nambiar et al.[21] reporting no significant difference between groups. In the present study, no cases of frank subsidence were observed among patients in either group, suggesting an agreement with Nambiar et al.'s result. This agreement may be related to the single-level nature of both the current study and those included in Nambiar et al.'s systematic review.

Our analysis revealed early (6 weeks) differences between groups in terms of postoperative improvements in VAS neck and NDI, with the plating group demonstrating significantly less improvement in both metrics. One possible explanation for these short-term differences could be related to longer time to recover due to the additional operative trauma of anterior plating, which involves additional instrumentation and may require a larger operative window. However, no significant long-term differences in "raw" improvement scores were observed. While mean change scores in NDI, VAS neck, and SF-12 PCS did demonstrate several points of difference at some longitudinal timepoints, the high degree of variability observed in these scores likely contributed to the nonsignificant intergroup difference observed for these measures. Results of previous studies regarding pain and disability outcomes based on the use of anterior plating have been mixed. Etemadifar et al.[15] and Kim et al.[24] both observed a significant difference in postoperative NDI, favoring the cage-only technique. Additionally, Oliver et al.[13] and Vaishnav et al.[14] demonstrated more favorable VAS neck outcomes for patients who received anterior plating. Interestingly, Oliver et al.[13] also demonstrated more favorable long-term VAS arm outcomes for patients that did not undergo anterior plating. However, a number of other studies have demonstrated no significant differences in terms of VAS arm, VAS neck, and NDI at short- or long-term follow-up between patients undergoing ACDF with and without anterior plating.[8,11,21,25]

It should be noted that previous studies have primarily compared mean PROM scores between groups, while we compared the magnitude of change in these scores. Our method may allow for more relevant comparison by better accounting for preoperative PROM scores. Furthermore, while a multitude of previous studies have assessed the association of anterior plating with VAS and NDI, few if any have explored physical function

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outcomes. Our analysis of PROM values did not demonstrate significant differences between groups in either short- or long-term improvement in the included physical function measure.

While a number of comparisons have been made in terms of "raw" PROM values, the lack of reported data regarding rates of clinically meaningful improvement represents a substantial shortcoming of the available literature regarding the use of anterior plating in ACDF procedures. In line with our findings regarding ΔPROM, plating was associated with lower rates of short-term MCID achievement in NDI. However, the more favorable ΔPROM findings in VAS neck were not similarly borne out in our MCID analysis.

Overall, a greater proportion of patients in the no plating group achieved an MCID in SF-12 PCS. Evidence for mechanical/structural benefits of one technique over the other have been relatively consistent but cite pros and cons for each. Although decreased segmental range of motion is often to be desired following fusion procedures, perhaps the increased neck stiffness reported to be associated with plating[26] might hamper the physical capabilities of some patients. Additionally, several previous studies have demonstrated increased rates of ASD associated with anterior plating.[8,20] It is possible that early symptoms of such degeneration at adjacent disc levels could explain some of the observed differences in physical function improvement.

While our study is the first to assess the impact of anterior plating on MCID achievement, it is subject to several notable limitations. Our assessment relied heavily on data obtained from self-reported questionnaires, which are inherently vulnerable to bias. Since our express purpose was to quantify results in terms of patient perceptions, some such bias was likely unavoidable. Additionally, all ACDF procedures were performed by a single experienced spine surgeon at a single academic institution, which may limit the generalizability of our results. Despite these limitations, the present study utilizes a robust sample size, includes longitudinal follow-up data (through 2 years postoperatively), and is the first to include an analysis of MCID achievement to assess ACDF outcomes based on the use or exclusion of anterior plating.

CONCLUSION

Patients generally demonstrated favorable outcomes and significant improvements in PROM following ACDF, regardless of whether their procedure included anterior plating. In terms of mean PROM score improvement, only short-term neck pain and disability were less favorable for the plating group. Rates of MCID achievement were likewise generally similar for ACDF procedures involving both techniques, and a majority of patients in both groups met these thresholds for neck pain, arm pain, and disability. Clinically meaningful improvements in early (6 weeks, 12 weeks) disability and overall physical function were more common amongst the cage-only group. While the use of anterior plating has both pros and cons for patients undergoing ACDF, clinically important improvements in disability and physical function may be more likely without the use of a plate.

NOTES

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REFERENCES

1. Yue WM, Brodner W, Highland TR. Long-term results after anterior cervical discectomy and fusion with allograft and plating: a 5- to 11-year radiologic and clinical follow-up study. Spine (Phila Pa 1976) 2005;30:2138-44.
2. Matz PG, Holly LT, Groff MW, et al. Indications for anterior cervical decompression for the treatment of cervical degenerative radiculopathy. J Neurosurg Spine 2009;11:174-82.
3. Saifi C, Fein AW, Cazzulino A, et al. Trends in resource utilization and rate of cervical disc arthroplasty and anterior cervical discectomy and fusion throughout the United States from 2006 to 2013. Spine J 2018;18:1022-9.
4. Cauthen JC, Kinard RE, Vogler JB, et al. Outcome analysis of noninstrumented anterior cervical discectomy and interbody fusion in 348 patients. Spine (Phila Pa 1976) 1998;23:188-92.
5. Song KJ, Choi BY. Current concepts of anterior cervical discectomy and fusion: a review of literature. Asian Spine J 2014;

8:531-9.
6. Wang Z, Jiang W, Li X, et al. The application of zero-profile anchored spacer in anterior cervical discectomy and fusion. Eur Spine J 2015;24:148-54.
7. Chen Y, Chen H, Wu X, et al. Comparative analysis of clinical outcomes between zero-profile implant and cages with plate fixation in treating multilevel cervical spondilotic myelopathy: a three-year follow-up. Clin Neurol Neurosurg 2016;144:72-6.
8. Cheung ZB, Gidumal S, White S, et al. Comparison of anterior cervical discectomy and fusion with a stand-alone interbody cage versus a conventional cage-plate technique: a systematic review and meta-analysis. Global Spine J 2019;9:446-55.
9. Viswanathan VK, Manoharan SR. To plate or not to plate after a single- or two-level anterior cervical discectomy: fusion with cage-plate construct or stand-alone cage. Asian Spine J 2017;11:1-3.
10. Overley SC, Merrill RK, Leven DM, et al. A matched cohort analysis comparing stand-alone cages and anterior cervical plates used for anterior cervical discectomy and fusion. Global Spine J 2017;7:394-9.
11. Zhou J, Li J, Lin H, et al. A comparison of a self-locking stand-alone cage and anterior cervical plate for ACDF: Minimum 3-year assessment of radiographic and clinical outcomes. Clin Neurol Neurosurg 2018;170:73-8.
12. Kwon WK, Kim PS, Ahn SY, et al. Analysis of associating factors with C2-7 sagittal vertical axis after two-level anterior cervical fusion: comparison between plate augmentation and stand-alone cages. Spine (Phila Pa 1976) 2017;42:318-25.
13. Oliver JD, Goncalves S, Kerezoudis P, et al. Comparison of outcomes for anterior cervical discectomy and fusion with and without anterior plate fixation: a systematic review and meta-analysis. Spine (Phila Pa 1976) 2018;43:E413-22.
14. Vaishnav AS, Saville P, McAnany S, et al. Predictive factors of postoperative dysphagia in single-level anterior cervical discectomy and fusion. Spine (Phila Pa 1976) 2019;44:E400-7.
15. Etemadifar M, Andalib A, Shafiee H, et al. Comparison of the outcomes of cage-stand-alone with cage-with-plate fixation in one level and two levels for treating cervical disk diseases. J Craniovertebr Junction Spine 2018;9:170-4.
16. Brozek JL, Guyatt GH, Schünemann HJ. How a well-grounded minimal important difference can enhance transparency of labelling claims and improve interpretation of a patient reported outcome measure. Health Qual Life Outcomes 2006;4:69.
17. Chotai S, Sivaganesan A, Parker SL, et al. Patient-specific factors associated with dissatisfaction after elective surgery for degenerative spine diseases. Neurosurgery 2015;77:157-63.
18. Andresen AK, Paulsen RT, Busch F, et al. Patient-reported outcomes and patient-reported satisfaction after surgical treatment for cervical radiculopathy. Global Spine J 2018;8:703-8.
19. Parker SL, Godil SS, Shau DN, et al. Assessment of the minimum clinically important difference in pain, disability, and quality of life after anterior cervical discectomy and fusion: clinical article. J Neurosurg Spine 2013;18:154-60.
20. Yang Z, Zhao Y, Luo J. Incidence of dysphagia of zero-profile spacer versus cage-plate after anterior cervical discectomy and fusion: a meta-analysis. Medicine (Baltimore) 2019;98:e15767.
21. Nambiar M, Phan K, Cunningham JE, et al. Locking stand-alone cages versus anterior plate constructs in single-level fusion for degenerative cervical disease: a systematic review and meta-analysis. Eur Spine J 2017;26:2258-66.
22. Narain AS, Hijji FY, Khechen B, et al. Risk factors associated with failure to reach minimal clinically important difference in patient-reported outcomes following anterior cervical discectomy and fusion. Int J Spine Surg 2019;13:262-9.
23. Goldberg EJ, Singh K, Van U, et al. Comparing outcomes of anterior cervical discectomy and fusion in workman's versus non-workman's compensation population. Spine J 2002;2:408-14.
24. Kim SY, Yoon SH, Kim D, et al. A prospective study with cage-only or cage-with-plate fixation in anterior cervical discectomy and interbody fusion of one and two levels. J Korean Neurosurg Soc 2017;60:691-700.
25. Tabaraee E, Ahn J, Bohl DD, et al. Comparison of surgical outcomes, narcotics utilization, and costs after an anterior cervical discectomy and fusion: stand-alone cage versus anterior plating. Clin Spine Surg 2017;30:E1201-5.
26. Shimamoto N, Cunningham BW, Dmitriev AE, et al. Biomechanical evaluation of stand-alone interbody fusion cages in the cervical spine. Spine (Phila Pa 1976) 2001;26:E432-6.

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Original Article

Analysis of the Incidence and Risk Factors of Postoperative Delirium in Patients With Degenerative Cervical Myelopathy

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Objective: The purpose of this study is to analyze various risk factors that can cause postoperative delirium (POD) in degenerative cervical myelopathy (DCM) patients, which may affect normal recovery and outcomes after surgery, and to help deal with them in advance and to take a medical approach.
Methods: A total of 148 patients aged 60 years or older who underwent laminoplasty or anterior cervical discectomy and fusion (ACDF) for DCM from 2008 to 2015 were included in this study. Incidence and multiple risk factors for development of POD were analyzed.
Results: POD occurred in 24 patients (16.2%). Among the 148 patients, 78 received laminoplasty, of whom 19 patients (24%) experienced delirium; the other 70 patients underwent ACDF, of whom 5 patients (7.1%) experienced delirium. History of Parkinson disease (odds ratio [OR], 178.242; p = 0.015), potassium level (OR, 3.764; p = 0.031), and surgical approach of laminoplasty over ACDF (OR, 8.538; p = 0.008) were found to be significant risk factors in a multivariate analysis. Age (OR, 1.056; p = 0.04) and potassium level (OR, 3.217; p = 0.04) were significant risk factors in the laminoplasty group.
Conclusion: The findings of this study suggest that the incidence and risk factors for POD may vary in patients with DCM. It is necessary to understand multiple factors that affect the development of POD.

Keywords: Delirium, Postoperative care, Cervical myelopathy, Laminoplasty

INTRODUCTION

Postoperative delirium (POD) refers to any acute change in cognition, including fluctuating awareness, deficit attention, memory impairment, disorientation, or other behavioral disorders that occur within 30 days after surgery.[1,2] The overall complication rate was reported at 13% in patients with posterior lumbar fusion according to the data of National Inpatient Sample.[3] Delirium is one of the most common postoperative complications (10%–77%) and occurs after various surgical treatments including orthopedic, pelvic, and aortic surgeries.[4,5] POD worsens surgical outcomes, increases hospitalization period, raises the medical cost, and increases postoperative morbidity and mortality.[6] There are many causes of delirium. Preoperative cognitive impairment, drug abuse or alcoholism, diabetes, hearing or vision impairment, various types of surgery, excessive bleeding, and acute anemia are known as factors of POD. Older age is the most common cause in relation to orthopedic and cardiac surgeries, as well as anesthesia.[7,8]

A few studies on POD after spinal surgery have been conducted and identified various associated factors, including age, baseline comorbidities, preoperative cognition, neurological diseases, and operation duration.[9-12] However, these studies included all spinal surgery patients with no consideration for factors related to the prevalence of delirium, whose occurrence varies according to the type and method of spinal surgery. Thus,

these studies provide no descriptions of whether the degree of delirium would vary according to the severity of the disease, the surgical levels, or the specific surgical method.[13,14]

Early surgical treatment is usually recommended at degenerative cervical myelopathy because it not only causes clinical manifestations such as clumsiness of hands, abnormal gait, and bowel or bladder dysfunctions, but also can cause irreversible neurological damage to the spinal cord as the lesion progresses.[15,16] Surgical methods for DCM can vary according to the extent and location of the lesion.[17,18] Anterior cervical discectomy and fusion (ACDF) or anterior corpectomy and fusion (ACF) can be performed in the anterior approach, and posterior cervical laminoplasty or posterior laminectomy and fusion can be performed in the posterior approach to relieve the compressed spinal cord, improve blood flow in the spinal cord, and prevent nerve damage. Typically, in the presence of lesions extending over 3 or more segments and in cases where lordosis of the cervical spine is well maintained in myelopathy with cervical stenosis, posterior laminoplasty or posterior laminectomy and fusion are usually recommended.[17,18]

As far as the authors know, no study has yet provided any data on the incidence and risk factors of POD in patients with DCM. Furthermore, active rehabilitation after surgery is extremely important because DCM patients may have poor outcomes when they have POD.

Laminoplasty is known as one of the most performed surgical procedures in Asia for DCM. Thus, this study is aimed to investigate whether the incidence of delirium is higher after laminoplasty than ACDF, which is known as the most common surgical method for the cervical spine, evaluated for comparison with the results of the study.

MATERIALS AND METHODS

1. Study Population

This study included 148 patients aged 60 years or older who underwent surgery ACDF or laminoplasty surgeries for DCM or myelo-radiculopathy at our clinic from 2008 to 2015. Of these 148 patients who underwent surgery, 78 patients underwent laminoplasty, and 70 patients underwent ACDF. In the patient group who underwent laminoplasty, all had symptoms and signs associated with myelopathy, and the causes of myelopathy were ossification of the posterior longitudinal ligament (OPLL) (n=62), cervical spinal stenosis (n=10), and herniated nucleus pulposus (HNP) (n=6). Among patients who underwent ACDF, 57 patients had symptoms and signs associated with myeloradiculopathy. The causes of them were HNP (n=48), spinal stenosis (n=3), HNP with spinal stenosis (n=3), and HNP with OPLL (n=3). Thirteen patients who underwent ACDF had only myelopathy and were diagnosed with HNP (n=6), spinal stenosis (n=2), HNP with spinal stenosis (n=2), and HNP with OPLL (n=3) (Table 1).

Table 1. The etiologies of myelopathy

Etiology	Laminoplasty (n=78)	ACDF (n=70)
Myelopathy		
OPLL	62	-
HNP	6	6
HNP with OPLL	-	3
HNP with cervical spinal stenosis	-	2
Cervical spinal stenosis	10	2
Myeloradiculopathy		
HNP	-	48
HNP with OPLL	-	3
HNP with cervical spinal stenosis	-	3
Cervical spinal stenosis	-	3

ACDF, anterior cervical discectomy and fusion; OPLL, ossification of the posterior longitudinal ligament; HNP, herniated nucleus pulposus.

An inclusion criterion was patients who underwent laminoplasty or ACDF aged 60 years or older due to DCM at our institution. Exclusion criteria were patients who have had previous cervical spine surgery, patients who were received a combination of surgery with laminoplasty and ACDF, patients who underwent laminoplasty or ACDF due to myelopathy caused by trauma, tumors and congenital stenosis, patients who received laminoplasty or ACDF under age 60 years old, and extension of surgical levels to C2 or T1. The criteria for ACDF were soft disc herniation, instability of a degenerative nature, concomitant severe axial neck pain, and cervical kyphosis. ACF is an alternative to multilevel ACDF, but ACF was not included in our study because of small number of cases. The criteria of laminoplasty were multilevel cervical stenosis, patients with advanced multilevel spondylosis, OPLL, and patients with at least 10° of cervical lordosis to allow posterior shift or the spinal cord for indirect compression.

The mean age was 66.7 years (56.5–76.9) in the laminoplasty group and 67.2 years (60.9–73.4) in the ACDF group, with no statistical difference between these 2 groups (p=0.747). The male to female ratio was 60:18 in the laminoplasty group and 36:34 in the ACDF group, with a statistically significant differ-

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Table 2. Demographics of participants according to surgical method

Variable	Laminoplasty (n = 78)	ACDF (n = 70)	p-value
Age (yr)	66.74 ± 10.22	67.2 ± 6.25	0.747
Sex, male:female	60:18	36:34	0.02*
Operated level	3.13 ± 0.85	1.93 ± 0.80	< 0.01*
mJOA score (preoperative)	12.43 ± 3.61	15.16 ± 2.26	< 0.01*
mJOA score (postoperative)	14.04 ± 3.53	16.24 ± 2.31	< 0.01*
Operation time (min)	258.31 ± 80.83	230.07 ± 94.63	0.052
EBL (mL)	774.36 ± 440.90	562.71 ± 327.67	0.001*
Hospital stay (day)	15.15 ± 10.92	11.50 ± 4.85	0.009*

Values are presented as mean ± standard deviation.
ACDF, anterior cervical discectomy and fusion; mJOA, modified Japanese Orthopedic Association score; EBL, estimated blood loss.
Chi-square test for categorical variables, independent t-test for continuous variables.
*p < 0.05, statistically significant differences.

Table 3. The criteria for diagnosis of postoperative delirium

DSM-5 (Diagnostic and Statistical Manual of Mental disorders, 5th version)
The presence of delirium requires all the criteria to be met:
Disturbance in attention and awareness
Disturbance develops acutely and tends to fluctuate in severity
At least one additional disturbance in cognition
Disturbances are not better explained by a pre-existing dementia
Disturbances do not occur in the context of a severely reduced level of arousal or coma
Evidence of an underlying organic cause or causes
CAM (Confusion Assessment Method)
The presence of delirium requires features 1 and 2 and either 3 or 4:
Acute change in mental status with a fluctuating course (feature 1)
Inattention (feature 2)
Disorganized thinking (feature 3)
Altered level of consciousness (feature 4)

ence in the chi-square test (p = 0.02). The extent of surgery was 3.13 levels (2.87–3.39) in the laminoplasty group and 1.93 levels (1.74–2.12) in the ADCF group on average, showing a statistically significant difference (p < 0.01). The preoperative modified Japanese Orthopedic Association (mJOA) score for laminoplasty patients was 12.43/18 (8.82–16.04) and that for ACDF patients was 15.16/18 (12.90–17.42), which also showed a statistically significant difference (p < 0.01). The postoperative mJOA score for laminoplasty patietnts was 14.04/18 (10.51–17.57) and that for ACDF patients was 16.24 (13.93–18.55), showed a statistical difference (p < 0.01) (Table 2).

2. Diagnosis of POD

Based on the medical records of patients receiving replies after consulting a specialist in the neurology or psychiatry department and the medical records that evaluated the patient's condition after surgery, POD were analyzed retrospectively, and the diagnosis of POD was made in the following way.

The surgeons who performed the surgeries and 2 attending physicians evaluated the cognitive status of patients every day during the period after the surgery until discharge. The evaluation included disturbance in attention and disturbance in awareness. Based on the Diagnostic and Statistical Manual of Mental Disorders-V criteria (Table 3), delirium was determined: disturbance occurrence within a few hours or days after the surgery, a change in baseline attention and awareness, and a fluctuation in severity was assessed by asking patients about orientation such as time, place and person and evaluating whether hallucinations or other psychiatric symptoms occurred every 8 hours after surgery.[19,20] Besides, patients who did not associate with a pre-existing established neurocognitive disorder were diagnosed with having delirium and underwent consultation with a neurologist or psychiatrist.[2,21-23]

Since the surgeons who performed the surgeries and 2 attending physicians evaluated the cognitive status of patients were not a neurologists or psychiatrists, authors tried to reduce the error of diagnosis by consulting in a specialized field, and thus seek advice from neurologists or psychiatrists. The neurologist or psychiatrist reevaluated suspected patients who received consultations and ultimately diagnosed them with delirium. All of the patients described in the paper included only those identified and confirmed as delirium through neurology or psychiatric consultation. The delirium diagnosis was finally determined based on the confusion assessment method (CAM).

3. Anesthesia and Drug Regimen

All patients underwent cervical spine surgery under general anesthesia, and anesthesia was induced and maintained according to our clinic's standard regimen. Anesthesia was induced with IV propofol and maintained with sevoflurane and remifentanil (0.25–0.5 μg/kg per min). At the end of the surgery, neostigmine (0.05 mg/kg), and glycopyrrolate (0.01 mg/kg) were used to recover from neuromuscular block during extuba-

tions. They were used once in the process of removing the tube.

4. Risk Factor

The following known risk factors were compared. Age, sex, baseline comorbidities, osteoporosis, bone mineral density (BMD) score, hemoglobin and hematocrit, sodium, chloride, potassium, hypotension (systolic blood pressure < 80 mmHg) immediately after the surgery or during surgery. Patients' height, weight, body mass index (BMI), smoking status, American Society of Anesthesiologists (ASA) physical status classification above II, intraoperative blood loss, blood transfusion, transfusion volume, drugs used to control pain such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophens, and other pain killers, duration of hospitalization, days to wait for hospitalization from admission to surgery, operation time, intensive care unit (ICU) care, and duration of ICU care were reviewed. Postoperative complications comprised of patients' medical conditions requiring consults from other specialists, including acute kidney injury, pneumonia, pulmonary edema, urinary tract infection, atrial fibrillation, insomnia, vertigo, and anxiety were also compared. However, these complications were heterogeneous and lacked in number for individual analysis.[4,5,7,13,14,24,25]

5. Statistical Analysis

The cross-tabulation analysis was performed by using Pearson chi-square test for the incidence of POD after laminoplasty and ACDF. In analyzing the risk factors, Pearson chi-square test (parametric test), Fisher exact test (nonparametric test), and cross-tabulation analysis were conducted for categorical variables. An independent t-test (parametric test) and Mann-Whitney U-test (nonparametric test) were performed for continuous variables. Multivariate logistic regression test was conducted on factors with p-values lower than 0.05 in univariate analysis. Statistical analysis was performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). Statistical significance was set at a significance probability (p-value) < 0.05.

6. Ethics

This study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital (Ref. No. 720127) and performed in accordance with the guidelines and regulations.

RESULTS

1. Incidence of POD

Delirium occurred in 24 patients out of 148 patients with DCM aged 60 years or older who underwent laminoplasty or ACDF. The incidence of POD was 16.2%. Among those 148 patients who underwent surgery, 78 patients received laminoplasty, and 19 (24%) of them experienced delirium. Seventy patients underwent ACDF and 5 (7.1%) of them experienced delirium. The odds ratio (OR) for POD in the laminoplasty and ACDF groups was 4.18 (95% confidence interval [CI], 1.47–11.9) (Table 4).

Table 4. Incidence and odds ratio of postoperative delirium in patients with DCM

POD	Laminoplasty	ACDF	Odds ratio (95% CI)	p-value
(+)	19/78 (24.3)	5/70 (7.1)	4.18 (1.47–11.9)	0.005*
(-)	59/78 (75.7)	65/70 (92.9)		
Total	78	70		

Values are presented as number (%).
DCM, degenerative cervical myelopathy; ACDF, anterior cervical discectomy and fusion; CI, confidence interval; POD, postoperative delirium.
*p < 0.05, statistically significant differences.

2. Risk Factors for POD

The risk factors for developing POD that were found to be statistically significant were age, neurologic disease, dementia, Parkinson disease, stroke history, hyponatremia, hyperkalemia, and ASA physical status classification > II, blood transfusion, transfusion volume, and ICU care. (age, p < 0.001; neurologic disease, p = 0.009; dementia, p = 0.001; Parkinson disease, p = 0.001; stroke history, p = 0.001; hyponatremia, p = 0.012; hyperkalemia, p = 0.048; ASA physical status classification > II, p = 0.002; transfusion volume, p = 0.013; blood transfusion, p = 0.001; ICU care, p = 0.003) (Table 5).

Multivariate logistic regression analysis was performed on the above factors including surgical method. Parkinson disease (OR, 178.242; p = 0.015), potassium level (OR, 3.764; p = 0.031), and surgical method (laminoplasty over ACDF) (OR, 8.538; p = 0.008) were statistically significant for the development of POD (Table 6).

In the patient group who underwent laminoplasty, the risk factors for POD that were found to be statistically significant were the patient's age (p = 0.008), Parkinson disease (p = 0.012), sodium level (p = 0.023), potassium level (p = 0.047), and ICU care (p = 0.033) (Table 7).

Multivariate logistic regression analysis was performed on the above factors. Age (OR, 1.056; p = 0.04), and potassium level (OR, 3.217; p = 0.04) were statistically significant for the de-

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Table 5. Analysis of risk factors for postoperative delirium in patients with DCM

Variable	POD (-) (n = 124)	POD (+) (n = 24)	p-value
Sex			0.503
Male	79 (63.7)	17 (70.8)	
Female	45 (36.2)	7 (29.1)	
Age (yr)	73.2 ± 10.2	65.7 ± 7.66	0.000*
Smoking	22 (17.7)	5 (20.8)	0.720
Cardiovascular disease	41 (33.0)	6 (25)	0.437
Pulmonary disease	9 (7.25)	1 (4.16)	0.581
Endocrinal disease	30 (24.1)	8 (33.3)	0.348
Diabetes mellitus	27 (21.7)	7 (29.1)	0.431
Renal disease	4 (3.22)	2 (8.33)	0.246
Neurologic disease	12 (9.67)	7 (29.1)	0.009*
Dementia	0 (0)	2 (8.33)	0.001*
Parkinson disease	1 (0.80)	3 (12.5)	0.001*
Liver disease	5 (4.03)	1 (4.16)	0.976
Hypertension	52 (41.9)	13 (54.1)	0.269
Stroke	3 (2.41)	3 (12.5)	0.022*
MDD	6 (4.83)	0 (0)	0.271
Osteoporosis	5 (4.03)	1 (4.16)	0.976
BMD score	-1.1 ± 1.74	-0.7 ± 1.56	0.427
Hemoglobin	13.0 ± 1.97	13.7 ± 1.47	0.350
Hematocrit	36.5 ± 3.18	37.7 ± 3.91	0.201
Sodium	138. ± 4.78	140. ± 3.62	0.012*
Chloride	102. ± 3.80	103. ± 3.15	0.077
Potassium	4.47 ± 0.54	4.28 ± 0.41	0.048*
Intraoperative hypotension	5 (4.03)	1 (4.16)	0.976
Height (cm)	161.97 ± 8.50	160.90 ± 8.22	0.804
Weight (kg)	62.7 ± 13.0	65.1 ± 11.1	0.350
Body mass index	24.1 ± 3.99	24.8 ± 3.59	0.420
ASA PS classification > II	37 (29.8)	15 (62.5)	0.002*
Intraoperative blood loss (mL)	787.5 ± 550.3	652.3 ± 368.4	0.134
Blood transfusion	22 (17.7)	12 (50)	0.001*
Transfusion volume (mL)	363.3 ± 423.9	144.5 ± 383.5	0.013*
Postoperative opioid use	17 (13.7)	4 (16.6)	0.704
Postoperative NSAIDs use	77 (62.0)	16 (66.6)	0.672
Postoperative acetaminophen use	50 (40.3)	13 (54.1)	0.209
Postoperative other pain killer use	58 (46.7)	8 (33.3)	0.225
Postoperative complications	19 (15.3)	7 (29.1)	0.103
Duration of admission (day)	18.3 ± 11.2	19.9 ± 11.1	0.580
Duration of preoperative period (day)	3.9 ± 7.2	2.3 ± 1.7	0.337
Operation time (min)	245.75 ± 89.98	240.83 ± 81.79	0.804
ICU care	19 (15.3)	10 (41.6)	0.003*
Duration of ICU care period (day)	0.87 ± 2.04	0.67 ± 3.71	0.801

Values are presented as number (%) or mean ± standard deviation.
DCM, degenerative cervical myelopathy; POD, postoperative delirium; MDD, manic depressive disorders; BMD, bone mineral density; ASA PS, American Society of Anesthesiologists physical status; NSAIDs, nonsteroidal anti-inflammatory drugs; ICU, intensive care unit.
*$p < 0.05$, statistically significant differences.

Table 6. Multivariate analysis of risk factors of postoperative delirium in patients with DCM

Variable	Odds ratio	95% CI	p-value
Age	1.078	0.998–1.164	0.056
Neurologic disease	0.329	0.020–5.319	0.434
Dementia	14,582,368,637.117		0.999
Parkinson disease	178.242	2.686–11,827.268	0.015*
Stroke	33.308	0.993–1,117.692	0.050
Sodium	0.881	0.770–1.009	0.067
Potassium	3.764	1.131–12.525	0.031*
ASA PS classification >II	0.730	0.183–2.919	0.657
Blood transfusion	2.889	0.352–23.711	0.323
Transfusion volume	1.000	0.998–1.002	0.993
ICU	3.260	0.850–12.507	0.085
Surgical method (laminoplasty over ACDF)	8.538	1.729–42.149	0.008*

DCM, degenerative cervical myelopathy; CI, confidence interval; ASA PS, American Society of Anesthesiologists physical status; ICU, intensive care unit; ACDF, anterior cervical discectomy and fusion.
*$p < 0.05$, statistically significant differences.

velopment of POD in the patients who underwent laminoplasty (Table 8). This was not analyzed in ACDF due to the low (n = 5).

DISCUSSION

Several studies on POD have been conducted on patients that underwent spinal surgery, investigating the incidence and risk factors. According to the literature, the incidence of the delirium after spinal surgery is reported at 11%–61%.[12-14,25] Various risk factors have also been reported.[12,22,25,26] According to a retrospective study, which analyzed data from more than 500,000 patients with various degenerative diseases of the lumbar spine including herniated lumbar discs, spondylolisthesis, and lumbar spinal stenosis, the risk factors of POD were identified as age (≥65 years), sex (female), alcohol/drug abuse, depression, psychotic disorders, and neurological disorders.[13]

However, previous studies on spinal surgery have covered on a wide range of spinal disorders including HNP, spinal stenosis, myelopathy, tumors, and trauma across a variety of regions treated with various surgical methods, they did not characterize the POD associated with certain specific disorders.[22,26,27] Furthermore, although not many, some of meta-analysis were conducted by extracting data from other studies, the methods for determining POD were heterogeneous.[12]

1. Incidence of POD

In the study, delirium occurred in 24 out of 148 elderly patients (16.2%) aged 60 years or older who underwent cervical spine surgery, similar to the results of previous studies, which reported an incidence of 11%–61% (Table 4).[12-14,25]

There was difference of incidence rates of POD between surgical methods and multivariate analysis demonstrated higher risk of POD in laminoplasty patients according to our results. This shows that there is a difference in the development of POD depending on the surgical method even for the same disease. This finding deviates substantially from those of previous similar studies. As a result, the studies overlooked the characteristics present in the incidence of delirium. This approach could make medical professionals overly cautious about the incidence of delirium for surgeries with a low frequency of delirium, while making them erroneously comfortable with surgeries with a high risk of delirium incidence. Thus, it should be noted that POD after spinal surgery can vary depending on the type and selection of surgical methods. This is particularly related to the fact that spinal surgery, unlike surgery in any other parts, has been performed through various methods depending on the surgical levels and the characteristics of the disease, despite surgery for a similar disease in the same area.

2. Risk Factors of the POD

According to this study, the risk factors that affect the incidence of POD following cervical spine surgery were age, neurologic disease, dementia, Parkinson disease, stroke history, hemoglobin, hyponatremia, hyperkalemia, and ASA physical sta-

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Table 7. Analysis of risk factors for postoperative delirium following laminoplasty

Variable	POD (-) (n = 59)	POD (+) (n = 19)	p-value
Sex			0.386
Male	44 (74.6)	16 (84.2)	
Female	15 (25.4)	3 (15.8)	
Age (yr)	65.2 ± 9.5	72.1 ± 10.5	0.008*
Smoking	7 (11.8)	5 (26.3)	0.107
Cardiovascular disease	8 (13.6)	2 (10.5)	0.731
Pulmonary disease	4 (6.8)	1 (5.3)	0.814
Endocrinal disease	11 (18.6)	5 (26.3)	0.471
Diabetes mellitus	11 (18.6)	5 (26.3)	0.471
Renal disease	3 (5.1)	1 (5.3)	0.976
Neurologic disease	5 (8.5)	3 (15.8)	0.361
Dementia	0 (0)	1 (5.3)	0.076
Parkinson disease	0 (0)	2 (10.5)	0.012*
Liver disease	2 (3.4)	0 (0)	0.416
Hypertension	25 (42.4)	9 (47.4)	0.703
Stroke	1 (1.7)	2 (10.5)	0.082
MDD	2 (3.4)	1 (5.3)	0.416
Osteoporosis	5 (8.5)	1 (5.3)	0.648
BMD score	-1.0 ± 1.4	-1.2 ± 1.9	0.746
Hemoglobin	12.5 ± 1.4	12.8 ± 1.4	0.548
Hematocrit	37.2 ± 3.7	37.4 ± 3.8	0.914
Sodium	140.1 ± 3.6	137.6 ± 4.9	0.023*
Chloride	103.6 ± 3.3	102.2 ± 3.7	0.138
Potassium	4.2 ± 0.4	4.4 ± 0.5	0.047*
Intraoperative hypotension	11 (18.6)	6 (31.6)	0.744
Height (cm)	162.7 ± 8.5	162.6 ± 7.2	0.119
Weight (kg)	65.8 ± 9.8	62.3 ± 11.0	0.160
Body mass index	24.8 ± 2.5	23.5 ± 3.1	0.201
ASA PS classification > II	24 (40.7)	11 (57.9)	0.189
Intraoperative blood loss (mL)	683.9 ± 297.9	828.6 ± 342.9	0.558
Blood transfusion	13 (22.0)	8 (42.1)	0.086
Transfusion volume (mL)	180.4 ± 439.5	290.5 ± 395.7	0.335
Postoperative opioid use	12 (20.3)	3 (15.7)	0.662
Postoperative NSAIDs use	38 (64.4)	13 (68.4)	0.749
Postoperative acetaminophen use	30 (50.8)	11 (57.9)	0.593
Postoperative other pain killer use	28 (47.4)	6 (31.6)	0.225
Postoperative complications	4 (6.8)	2 (10.5)	0.311
Duration of admission (day)	18.3 ± 11.2	19.9 ± 11.1	0.580
Duration of preoperative period (day)	3.9 ± 7.2	2.3 ± 1.7	0.337
Operation time (min)	253.2 ± 57.9	253.2 ± 62.2	0.715
Duration of postoperative period (day)	14.3 ± 10.7	17.6 ± 11.2	0.580
ICU care	13 (22.0)	9 (47.4)	0.033*
Duration of ICU care period (day)	1.2 ± 5.3	1.0 ± 2.2	0.918

Values are presented as number (%) or mean ± standard deviation.
POD, postoperative delirium; MDD, manic depressive disorders; BMD, bone mineral density; ASA PS, American Society of Anesthesiologists physical status; NSAIDs, nonsteroidal anti-inflammatory drugs; ICU, intensive care unit.
*$p < 0.05$, statistically significant differences.

Table 8. Multivariate analysis of risk factors of postoperative delirium following laminoplasty

Variable	Odds ratio	95% CI	p-value
Age	1.056	1.004–1.124	0.04*
Parkinson disease	154	0.000–154.000	0.99
ICU care	2.457	0.658–7.037	0.17
Sodium	0.879	0.762–1.013	0.75
Potassium	3.217	1.456–11.174	0.04*

CI, confidence interval; ICU, Intensive care unit.
*$p < 0.05$, statistically significant differences.

tus classification >II, transfusion volume, blood transfusion, and ICU care (Table 5). Among these factors, Parkinson disease, potassium, and surgical method (laminoplasty over ACDF) were statistically significant for the development of POD in multiple regression analysis (Table 6). When we looked at the factors involved in the occurrence of the POD for each surgery, the factors that found to be statistically significant were patient's age, Parkinson disease, low sodium level, high potassium level, ICU care in patients who underwent laminoplasty (Table 7). A multivariate logistic regression test conducted on the above factors and revealed that age and high potassium level alone were significant factors in the development of POD (Table 8). Thus, if any patient who receives laminoplasty due to DCM is old or has an electrolyte imbalance (high potassium level), he or she will require more caution due to a higher probability of POD. However, the factors affect ACDF were not analyzed in the study, because the incidence of POD unexpectedly lowers in ACDF (n=5), making it difficult to statistically analyze the associated factors and have a statistical significance with it.

In this study, we tried to investigate factors that are known to affect spinal surgery, and examined the relations between these factors and the development of POD.

The smoking status is a known factor that can affect surgical outcomes.[28] The toxic agents in cigarette smoke induce atherosclerotic and microvascular changes, which build up gradually with time and remain even years after quitting. Especially in older smokers, these changes are linked to cognitive decline and dementia, as well as vascular disease, which increase the risk of developing delirium.[9] In our study, however, smoking was not found to increase the risk of POD (Tables 5, 7). Dementia and delirium (an acute confused state) are also known to be associated with drug toxicity.[29] Especially, elderly people are more likely than young people to develop cognitive impairments associated with medication use because renal and liver functions are often impaired in elderly people. Anticholinergic medications are common causes of both acute and chronic cognitive impairment. Psychoactive drugs, antidepressants and anticonvulsants can cause dementia and delirium.[30] The use of NSAIDs, opioids, and other pain killers did not affect the development of POD in this study. However, there are reports of drug-induced cognitive impairment by these agents, so care should be taken when using painkillers after surgery.[30] Other factors associated with surgery including blood transfusion, operation, blood loss, operation time, postoperative complications, ICU care, and duration of admission were not found to be significant. This is a finding that is different from other studies.[12,13] We assume that this was due to our study being a single-center study where surgeries and postoperative care were performed under uniform protocols. More heterogeneous cohort might lead to different results in future studies.

In addition, patient with existing neurological disorders such as dementia or Parkinson disease have been reported to develop POD, and authors included them as one of the causes of the delirium in the study. Our results demonstrated that patients with Parkinson disease had higher risk for development of POD. This is a similar result of a recent systematic review, which suggested that people with Parkinson disease may be at increased risk of delirium.[11] According to a study of Caplan[10] diagnosing delirium in the presence of pre-existing dementia is difficult and gets harder as either progresses because their symptoms are intertwined. Prolonged delirium becomes permanent cognitive impairment, and severe dementia is often manifested by multiple symptoms that are similar to those of delirium. As the neuro-inflammatory mechanism in delirium is actually mediated by the effect of glucose, and not the inflammatory changes in the brain, they suggest that glucose could be the link between dementia and delirium pathophysiology, given that dementia is characterized by insulin resistance and impairments in glucose metabolism and delirium may be working likewise.[31,32] As if to support this hypothesis, recent studies of F-fluorodeoxyglucose positron emission tomography in delirium reveal a novel and unique pattern of glucose hypometabolism that correlates with neuropsychological functions.[33] Parkinson disease, dementia and neurologic disease were found to be meaningful factor in the occurrence of POD in cervical spine surgery, and Parkinson disease was also a meaningful factor in our results. Therefore, patients with neurological disorders such as Parkinson disease and dementia need to take special care of the occurrence of POD if they operate on cervical spine surgery.

Preoperative comorbidities such as liver disease, renal disease, cardiovascular disease, pulmonary disease, hypertension,

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endocrine disease, diabetes mellitus, BMI, BMD, and osteoporosis were also analyzed but they were not found to be meaningful factors associated with POD in the study. There is little research on whether gender affects the occurrence of the POD. According to a study of age- and sex-related peculiarities of patients with delirium in the cardiac ICU,[34] it was shown that delirium is a severe complication that more often affects men amongst patients < 65 years old and more frequently affects women in the age group of ≥ 85 years. Male patients < 65 years old, who develop delirium, should be treated with more caution because they tend to have more serious forms of disorder and a poorer prognosis.[34] Age was also found to a meaningful factor to develop the POD in our study, however, sex was not found to be a meaningful risk factor of POD (Tables 5, 7).

3. Reasons for a Difference in POD

Based on our observations, there was a difference in the occurrence of delirium between ACDF and laminoplasty in the study. We potentially suggest the reason why the incidence of POD was higher following laminoplasty than ACDF as follows.

The preoperative mJOA score was 12.43/18 in the laminoplasty group and that of the ACDF group was 15.16/18. The preoperative mJOA score was statistically significantly lower in the laminoplasty group ($p < 0.001$; 95% CI, -3.726 to -1.735) (Table 2), suggesting the preoperative neurological status in the patients who underwent laminoplasty was worse and this status might influence the development of POD. In addition, the operation levels were 1.93 levels in the ACDF group and 3.13 levels in the laminoplasty group on average. This indicates wider and more extensive surgical area in the patient group that underwent laminoplasty. These patients would have considered the operation to be more dangerous and this might have affected the results. Furthermore, 74 patients underwent laminoplasty mainly due to the symptoms of myelopathy, characterized by hand clumsiness, gait disturbance, and bowel or bladder dysfunctions, while the other group of patients underwent ACDF mainly due to symptoms of myeloradiculopathy (77%) accompanied by radiculopathy and mild myelopathy. For these reasons, we inferred that the incidence of POD was relatively higher in the laminoplasty group than in the ACDF group, which was commonly performed in cervical spine surgery. Further studies are required to determine whether these reasons actually contributed to the incidence of POD.

4. Diagnosis and Treatment of the POD

In this study, we tried to diagnose POD using the diagnostic criteria and methods currently in practice at the clinical site (Diagnostic and Statistical Manual of Mental disorders, 5th version, DSM-5),[35,36] and tried to double-check it through consultation with neurology or psychiatry, the specialty of the disease.

According to the guidance of the specialists, various treatments, ranging from drug treatment to supportive therapy, were carried out depending on the degree of the patient's symptoms. The treatment of POD combines drug therapy and supportive treatment for the situation.[9,37] First of all, it is necessary to secure hemodynamic stability and correct electrolyte imbalance after surgery. If the symptoms are not severe, and in the early stages, it continuously provides information on time, place, and person, and creates an environment where patients can sleep without interruption during bedtime. Early ambulation and movement can also help treat patients, and it is also necessary to create an environment to help patients recover by using the items needed for each patient.

5. Limitations

This study has some limitations as follows. First, this study, as a retrospective study, has a limitation in that the sample size was not sufficiently large because the study was conducted at a single institution. Also, the retrospective nature limited acquisition of standardized data on postoperative pain, which can be a risk factor of POD. Second, as in this study, as far as authors know, there are very few research methods that objectively evaluate the preoperative cognitive function of patients. All of the patients who participated in this study showed no cognitive dysfunction in the preoperative evaluation according to the criteria of DSM-5 and CAM. However, objectively assessing the cognitive status of patients before surgery, along with objectively assessing the cognitive function of patients after surgery, can be one of the key factors in determining the results of the study associated with POD. Third, although we intended to compare and analyze factors affecting the POD according to the method of surgery in DCM, we'd like to emphasize that we can create a bias in the interpretation of the results by not including all factors that may be related to the occurrence of POD. Moreover, we concede that although patients had same diagnosis, underlying etiologies and baseline characteristics such as severity of preoperative symptoms, levels requiring treatment were insufficiently standardized for analysis and this can create bias. In future studies, there should be stricter conditioning for confounders, such as matching or weighting in larger numbers. In addition, in the course of analyzing the factors affecting the occurrence of POD between surgical methods, the incidence of

POD unexpectedly lowers in ACDF (n=5), making it difficult to statistically analyze the associated factors and have a statistical meaning with it. We look forward to further research on this. Lastly, this study also did not include other surgical methods for DCM, such as posterior laminectomy and fusion or ACF, due to the small number of cases. As it is not easy to review the characteristics depending on all surgical methods for DCM, this study was focused on laminoplasty, which is regarded as one of the most common surgical procedures in Asia for DCM.

CONCLUSION

It is important for surgeons to understand various factors that can affect the development of POD in patients with DCM, which can help to potentially prevent its occurrence.

NOTES

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REFERENCES

1. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29:1370-9.
2. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941-8.
3. Kalakoti P, Missios S, Maiti T, et al. Inpatient outcomes and postoperative complications after primary versus revision lumbar spinal fusion surgeries for degenerative lumbar disc disease: a national (nationwide) Inpatient Sample Analysis, 2002-2011. World Neurosurg 2016;85:114-24.
4. Takeuchi M, Takeuchi H, Fujisawa D, et al. Incidence and risk factors of postoperative delirium in patients with esophageal cancer. Ann Surg Oncol 2012;19:3963-70.
5. Brauer C, Morrison RS, Silberzweig SB, et al. The cause of delirium in patients with hip fracture. Arch Intern Med 2000;160:1856-60.
6. Marcantonio ER. Postoperative delirium: a 76-year-old woman with delirium following surgery. JAMA 2012;308:73-81.
7. Bin Abd Razak HR, Yung WY. Postoperative delirium in patients undergoing total joint arthroplasty: a systematic review. J Arthroplasty 2015;30:1414-7.
8. Koster S, Hensens AG, Schuurmans MJ, et al. Risk factors of delirium after cardiac surgery: a systematic review. Eur J Cardiovasc Nurs 2011;10:197-204.
9. Raats JW, Steunenberg SL, de Lange DC, et al. Risk factors of post-operative delirium after elective vascular surgery in the elderly: a systematic review. Int J Surg 2016;35:1-6.
10. Caplan GA. Delirium superimposed upon dementia. J Am Med Dir Assoc 2019;20:1382-3.
11. Lawson RA, Richardson SJ, Yarnall AJ, et al. Identifying delirium in Parkinson disease: a pilot study. Int J Geriatr Psychiatry 2020;35:547-52.
12. Zhu C, Wang B, Yin J, et al. Risk factors for postoperative delirium after spinal surgery: a systematic review and meta-analysis. Aging Clin Exp Res 2020;32:1417-34.
13. Fineberg SJ, Nandyala SV, Marquez-Lara A, et al. Incidence and risk factors for postoperative delirium after lumbar spine surgery. Spine (Phila Pa 1976) 2013;38:1790-6.
14. Ushida T, Yokoyama T, Kishida Y, et al. Incidence and risk factors of postoperative delirium in cervical spine surgery. Spine (Phila Pa 1976) 2009;34:2500-4.
15. Toledano M, Bartleson JD. Cervical spondylotic myelopathy. Neurol Clin 2013;31:287-305.
16. Iyer A, Azad TD, Tharin S. Cervical spondylotic myelopathy. Clin Spine Surg 2016;29:408-14.
17. Fehlings MG, Barry S, Kopjar B, et al. Anterior versus posterior surgical approaches to treat cervical spondylotic myelopathy: outcomes of the prospective multicenter AOSpine North America CSM study in 264 patients. Spine (Phila Pa 1976) 2013;38:2247-52.
18. Lawrence BD, Jacobs WB, Norvell DC, et al. Anterior versus posterior approach for treatment of cervical spondylotic myelopathy: a systematic review. Spine (Phila Pa 1976) 2013;38 (22 Suppl 1):S173-82.
19. Robinson TN, Raeburn CD, Tran ZV, et al. Postoperative delirium in the elderly: risk factors and outcomes. Ann Surg

2009;249:173-8.
20. Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994;271:134-9.
21. Cavallari M, Dai W, Guttmann CRG, et al. Longitudinal diffusion changes following postoperative delirium in older people without dementia. Neurology 2017;89:1020-7.
22. Brown CH 4th, LaFlam A, Max L, et al. Delirium after spine surgery in older adults: incidence, risk factors, and outcomes. J Am Geriatr Soc 2016;64:2101-8.
23. Rudolph JL, Marcantonio ER, Culley DJ, et al. Delirium is associated with early postoperative cognitive dysfunction. Anaesthesia 2008;63:941-7.
24. Takeuchi D, Honda K, Shinohara T, et al. Incidence, clinical course, and risk factors of amiodarone-induced thyroid dysfunction in Japanese adults with congenital heart disease. Circ J 2015;79:1828-34.
25. Morino T, Hino M, Yamaoka S, et al. Risk factors for delirium after spine surgery: an age-matched analysis. Asian Spine J 2018;12:703-9.
26. Susano MJ, Scheetz SD, Grasfield RH, et al. Retrospective analysis of perioperative variables associated with postoperative delirium and other adverse outcomes in older patients after spine surgery. J Neurosurg Anesthesiol 2019;31:385-91.
27. Elsamadicy AA, Adogwa O, Vuong VD, et al. Association of intraoperative blood transfusions on postoperative complications, 30-day readmission rates, and 1-year patient-reported outcomes. Spine (Phila Pa 1976) 2017;42:610-5.
28. Hessler JB, Brönner M, Etgen T, et al. Smoking increases the risk of delirium for older inpatients: a prospective population-based study. Gen Hosp Psychiatry 2015;37:360-4.
29. Shinohara Y. Delirium caused by intramuscular administration of biperiden. J Neuropsychiatry Clin Neurosci 2010;22:E15.
30. Moore AR, O'Keeffe ST. Drug-induced cognitive impairment in the elderly. Drugs Aging 1999l;15:15-28.
31. Steen E, Terry BM, Rivera EJ, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease--is this type 3 diabetes? J Alzheimers Dis 2005;7:63-80.
32. De Felice FG, Lourenco MV, Ferreira ST. How does brain insulin resistance develop in Alzheimer's disease? Alzheimers Dement 2014;10(1 Suppl):S26-32.
33. Haggstrom LR, Nelson JA, Wegner EA, Caplan GA. 2-18F-fluoro-2-deoxyglucose positron emission tomography in delirium. J Cereb Blood Flow Metab 2017;37:3556-67.
34. Serpytis P, Navickas P, Navickas A, et al. Age- and gender-related peculiarities of patients with delirium in the cardiac intensive care unit. Kardiol Pol 2017;75:1041-50.
35. European Delirium Association; American Delirium Society. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Med 2014;12:141.
36. Sepulveda E, Franco JG, Trzepacz PT, et al. Delirium diagnosis defined by cluster analysis of symptoms versus diagnosis by DSM and ICD criteria: diagnostic accuracy study. BMC Psychiatry 2016;16:167.
37. Robinson TN, Eiseman B. Postoperative delirium in the elderly: diagnosis and management. Clin Interv Aging 2008;3:351-5.

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Cost-Utility Analysis Compared Between Radiotherapy Alone and Combined Surgery and Radiotherapy for Symptomatic Spinal Metastases in Thailand

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Objective: To investigate the patient quality of life and cost-utility compared between radiotherapy alone and combined surgery and radiotherapy for spinal metastasis (SM) in Thailand.
Methods: Patients with SM with an indication for surgery during 2018–2020 were prospectively recruited. Patients were assigned to either the combination surgery and radiotherapy group or the radiotherapy alone group. Quality of life was assessed by EuroQol-5D-5L (EQ-5D-5L) questionnaire, and relevant healthcare costs were collected pretreatment, and at 3-month and 6-month posttreatment. Total lifetime cost and quality-adjusted life-years (QALYs) were estimated for each group.
Results: Twenty-four SM patients (18 females, 6 males) were included. Of those, 12 patients underwent combination treatment, and 12 underwent radiotherapy alone. At 6-month posttreatment, 10 patients in the surgery group, and 11 patients in the nonsurgery group remained alive for a survival rate of 83.3% and 91.7%, retrospectively. At 6-month posttreatment, the mean utility in the combination treatment group was significantly better than in the radiotherapy alone group (0.804 ± 0.264 vs. 0.518 ± 0.282, respectively; $p = 0.011$). Total lifetime costs were 59,863.14 United States dollar (USD) in the combination treatment group and 24,526.97 USD in the radiation-only group. The incremental cost-effectiveness ratio using 6-month follow-up data was 57,074.01 USD per QALY gained.
Conclusion: Surgical treatment combined with radiotherapy to treat SM significantly improved patient quality of life compared to radiotherapy alone during the 6-month posttreatment period. However, combination treatment was found not to be cost-effective compared to radiotherapy alone for SM at the Thailand willingness-to-pay threshold of 5,113 USD/QALY.

Keywords: Patient quality of life, Cost-utility, Radiotherapy alone, Combined surgery and radiotherapy, Spinal metastasis

INTRODUCTION

Spinal metastasis results from cancer cells that spread from the primary tumor, which is located somewhere else in the body. Spinal metastasis can cause severe pain, impaired ambulation, and neurological deficit–all of which significantly adversely affect patient quality of life. Several studies reported favorable results of palliative surgery combined with radiotherapy for improving pain, ambulation, and quality of life compared to radiotherapy alone.[1-5] As such, palliative surgery plays an important role in the multidisciplinary management of spinal metastasis.

However, the additional cost of surgery combined with radiotherapy makes combination therapy for spinal metastasis much more expensive than radiotherapy alone. From a study conducted in Denmark, Tipsmark et al.[6] reported the cost of radiotherapy alone to be 36,616 euro (EUR), whereas the cost of surgery with decompression, instrumentation, and reconstruction was 87,814 EUR.

Cost-utility analysis (CUA), which evaluates both clinical and economic outcomes, provides important evidence-based information that helps clinicians and policymakers in decision-making relative treatment strategy. CUA studies that compared surgical treatment and radiotherapy alone for the treatment of spinal metastasis have been reported in Japan, the United Kingdom, Belgium, Canada, and the United States. The results of those studies showed combination surgery and radiotherapy to be cost-effective compared to radiotherapy alone for treating spinal metastasis in developed countries.[2,7-10]

Studies in the cost-effectiveness of surgery for spinal metastasis patients in developing countries, such as Thailand, are limited. Accordingly, the aim of this study was to investigate the patient quality of life and cost-utility compared between radiotherapy alone and combined surgery and radiotherapy for spinal metastasis in Thailand.

MATERIALS AND METHODS

This prospective cohort study was conducted at the Faculty of Medicine Siriraj Hospital, Mahidol University–Thailand's largest medical school and national tertiary referral center. The protocol for this study received approval from the Siriraj Institutional Review Board (protocol number: 395/2561[EC3]), and written informed consent was obtained from each enrolled study patient.

1. Subjects

Patients aged 18 years or older with spinal metastasis with an indication for surgery during 2018–2020 were prospectively recruited. Diagnosis of spinal metastasis was made by radiological or pathological methods. Indications for surgery included intractable pain, spinal instability, and neurological symptom. Patients having one or more of the following were excluded: (1) curative surgery, (2) posterior instrumentation more than 10 levels, (3) previous history of radiotherapy at the affected spine level, and/or (4) impaired consciousness that prevented completion of the study questionnaire.

2. Study Procedures

Eligible patients that accepted our invitation to join the study were educated about the study objective and protocol. The spinal instability neoplastic score was used to assess the severity of spinal instability. All patients underwent intensive adjuvant treatments, radiotherapy, rehabilitation, and palliative care. All patients were offered the opportunity to undergo surgical treatment, and the patient made the final decision. The patients who decided to undergo surgery were allocated to the combination surgery and radiotherapy group, and those not willing to undergo surgery were allocated to the radiotherapy alone group. In both groups, chemotherapy was performed if indicated. The modified Tokuhashi and Tomita scores were used to evaluate the prognosis of spinal metastasis. Each patient's general condition was assessed using Frankel classification grading.

3. Surgical Procedures

The patients who undergo surgery were a posterior approach. Debulking tumor from the posterolateral aspect after laminectomy was performed, and the posterior stabilization was achieved using a pedicle screw-rod system. The range of stabilization was decided based on bone quality, the number of affected vertebrae, and deformity. After surgery, postoperative rehabilitation was adjusted case by case depending on patients' status with immobilization support devices.

4. Sample Size Calculation

The sample size was based on a mean of health state values between the radiotherapy alone and the combined surgery and radiotherapy at 12 months (0.019 ± 0.027, 0.448 ± 0.451, respectively) from the study of Miyazaki et al.[2] Two-sided, 2-independent means sample size calculation was used at the 0.05 significance level for the difference. The power of the test was 0.2. Thus, the number of each group was 12 patients.

5. Statistical Analysis

Demographic and clinical characteristics of study participants were analyzed descriptively. Categorical data were reported as frequency and percentage, and normally distributed continuous data were reported as mean ± standard deviation. Fisher exact test and Student t-test were used to comparing categorical data and normally distributed continuous data, respectively. The Kaplan-Meier method was used to estimate the survival function from lifetime data. All statistical analyses were performed using IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA), and a 2-tailed p-value that less than 0.05 was considered statistically significant.

6. Economic Evaluation

A CUA was performed to compare the cost and health status between the combined use of surgery and radiotherapy and radiotherapy alone in patients with spinal metastasis. The intervention of interest was palliative surgery that provides better quality of life, but the cost of treatment is higher. We performed the analysis using a societal perspective and lifetime time horizon as recommended by the Thailand health technology assessment (HTA) guideline.[11] Our findings are presented as an incremental cost-effectiveness ratio (ICER) in United States dollar (USD) per quality-adjusted life years (QALYs) gained. The interpretation of the cost-effectiveness of the surgery was based on an official willingness-to-pay (WTP) threshold of 160,000 Thai Baht (THB)/QALY (5,113 USD/QALY), as reported by the Thai Health Economic Working Group.[12] An annual discount rate of 3% was used for both costs and health outcomes.

7. Economic Model

According to expert opinion and our review of the literature, the health status outcome should include both ambulatory status and pain improvement after the treatment. A decision tree was constructed to divide patients into 2 groups–those who received surgical treatment and those who did not. After treatment, the patients in each group were classified into 1 of the 4 following outcomes of treatment: ambulatory with less pain, nonambulatory with less pain, ambulatory without pain improvement, and nonambulatory without pain improvement (Fig. 1A). After that, a Markov model with 3-month cycle durations was adopted to capture the lifetime costs and health outcomes of the treatment. In the Markov model, patients could remain either in the same state or in transition to a poorer state due to the progression of the disease. In this model, we assumed that patients underwent surgery only one time and that no patients would transition to an improved health state, as shown in Fig. 1B.

8. Input Parameters

The transition probabilities and utility of each group were obtained from the result of the cohort included in this study. The disease-specific mortality rate was based on the overall local control rate of the disease from studies conducted by Bishop et al.[13] and Pessina et al.[14] The probability of ambulatory and nonambulatory status before treatment was obtained from the studied cohort. Regarding the adoption of societal perspective, in this study, we included both direct medical costs (e.g., nursing service, medication, diagnostic imaging) and direct nonmedical costs (e.g., food, transportation). Indirect costs of patients were not included due to our assumption that lost or impaired ability to work or engage in leisure activities due to morbidity would be captured in the disutility of QALY.[15] Direct costs of treatment, hospital visit rates (both outpatient and inpatient), and utility data were obtained from the studied cohort. Direct nonmedical costs were obtained from a standard cost list in the Thailand HTA guideline.[16] All costs were converted to 2020 USD using an exchange rate of 1 USD = 31.3 THB and the consumer price index.[17] Detail and sources of the model input parameters used in this study are shown in Table 1.

9. Cost-Utility Analysis

The primary outcome of the base case analysis was the ICER obtained from a comparison between the combined surgery and radiotherapy treatment strategy versus radiotherapy alone.

One-way sensitivity analyses were performed to study the effects of altering uncertainty parameters within the 95% confidence interval (CI) ranges, including all clinical effects, transitional probabilities, costs, and utilities, on the ICER from the model. In cases where the 95% CI range was unavailable, a range of mean ± 15% was applied. The results of 1-way sensitivity analysis are presented using a tornado diagram. A probabilistic sensitivity analysis (PSA) was performed using Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA) to simultaneously examine the effects of all parameter uncertainties.[18] The distributions of each probability were assigned the following:[19] transitional probability, and utility parameters were specified to beta-distribution. Costs were assigned a gamma distribution. Relative risk of mortality parameters was given a lognormal distribution. A Monte Carlo simulation was run to obtain 1,000 different simulations reflecting a range of values for the total cost, outcomes, and ICER. The results of the PSA are

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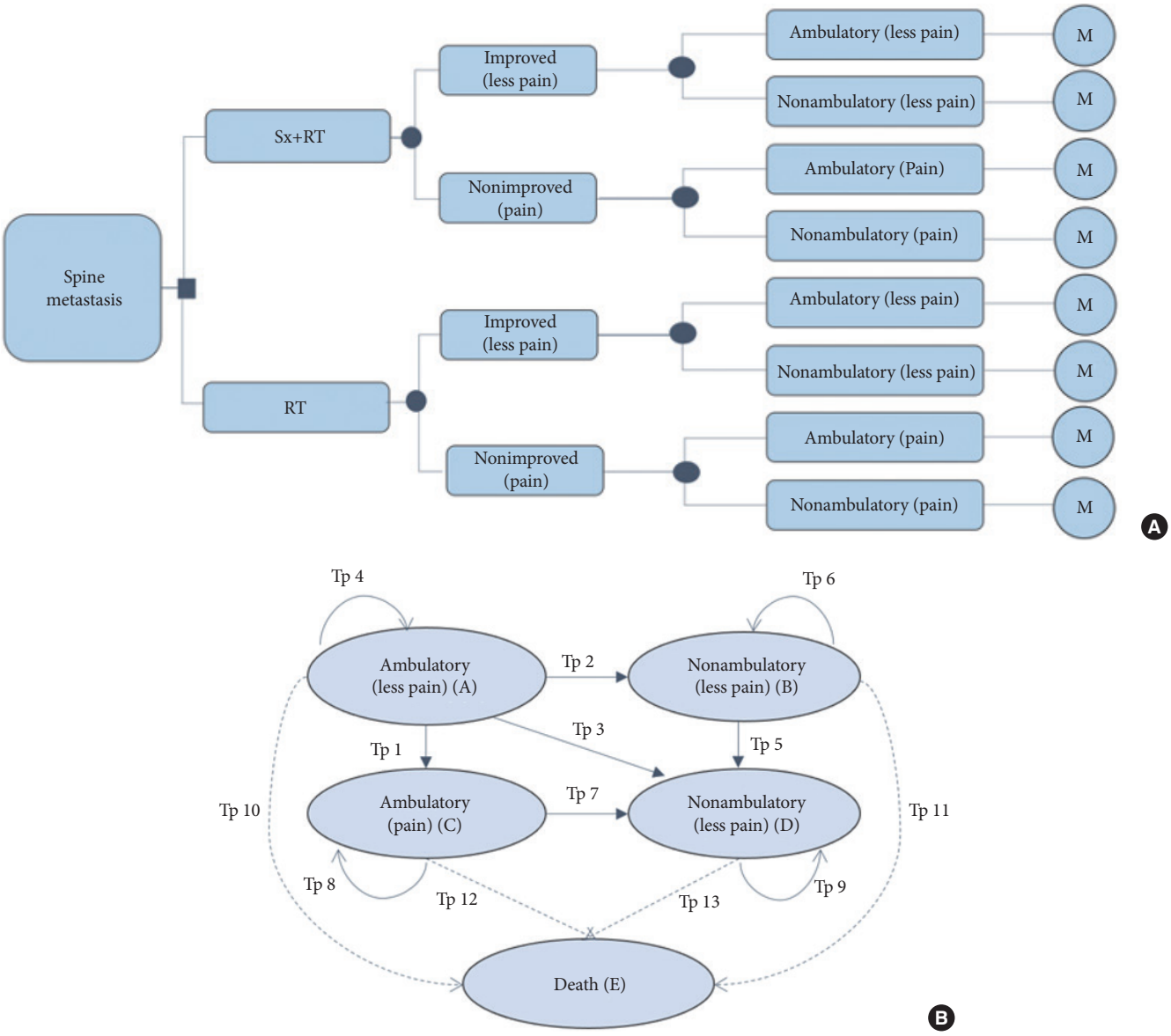

Fig. 1. Decision tree (A) and Markov model (B). A decision tree was constructed to divide patients into the 4 following groups according to the health status outcome of each treatment: ambulatory with less pain, nonambulatory with less pain, ambulatory with pain, and nonambulatory with pain. In the Markov model, patients could remain in the same health state or transition to worse health states. Sx+RT, combined surgery, and radiotherapy; RT, radiotherapy alone.

presented as a cost-effectiveness plane and a cost-effectiveness acceptability curve.

RESULTS

1. Clinical Results

Twenty-four patients were prospectively enrolled and followed for 6 months after treatment. There were 6 men and 18 women. Twelve patients underwent surgical treatment and radiotherapy. The others underwent only radiotherapy. Patient demographic and clinical characteristics are shown in Table 2. No statistically significant difference was observed for any of the parameters shown in Table 2 between the surgery group and the nonsurgery group. Patients with various types of cancer were included (Table 2). All patients in both groups underwent radiotherapy. The average back pain score at the 3-month follow-up in the surgery group was significantly lower than the average score in the radiotherapy alone group (31.67 ± 30.92 vs. 55.45 ± 20.67, respectively; p = 0.024), but there was no significant difference between groups for pain at the 6-month follow-

Table 1. Input parameters used in the health economic model

Parameter	Distribution	Base case	Range	References
Probability of ambulatory/nonambulatory status before treatment				
Ambulatory	Beta	0.723	SD 0.204	Primary data
Nonambulatory	Beta	0.160	SD 0.149	Primary data
Transition probabilities				
Ambulate (less pain)				
To ambulate (pain) - Sx+RT	Beta	0.0055	0.005–0.006	Primary data
To nonambulatory (less pain) - Sx+RT	Beta	0.0055	0.005–0.006	Primary data
To nonambulatory (pain) - Sx+RT	Beta	0.0055	0.005–0.006	Primary data
To ambulate (pain) - RT	Beta	0.0067	0.006–0.007	Primary data
To nonambulatory (less pain) - RT	Beta	0.0067	0.006–0.007	Primary data
To nonambulatory (pain) - RT	Beta	0.0067	0.006–0.007	Primary data
Nonambulatory (less pain)				
To nonambulatory (pain) - Sx+RT	Beta	0.0055	0.005–0.006	Primary data
To nonambulatory (pain) - RT	Beta	0.0067	0.006–0.007	Primary data
Ambulate (pain)				
To nonambulatory (pain) - Sx+RT	Beta	0.0055	0.005–0.006	Primary data
To nonambulatory (pain) - RT	Beta	0.0067	0.006–0.007	Primary data
Disease-specific mortality rate - Sx+RT	Log-normal	0.41	SE 0.06	(13, 14)
Relative risk of survival in RT vs. Sx+RT	Log-normal	0.60	SE 0.16	-1
Utilities				
Sx+RT				
Ambulatory (less pain)	Beta	0.743	SD 0.130	Primary data
Nonambulatory (less pain)	Beta	0.340	SD 0.051	Primary data
Ambulatory (pain)	Beta	0.732	SD 0.110	Primary data
Nonambulatory (pain)	Beta	0.160	SD 0.024	Primary data
RT				
Ambulatory (less pain)	Beta	0.743	SD 0.320	Primary data
Nonambulatory (less pain)	Beta	0.340	SD 0.051	Primary data
Ambulatory (pain)	Beta	0.732	SD 0.300	Primary data
Nonambulatory (pain)	Beta	0.160	SD 0.024	Primary data
Costs of treatment (USD/3 months)				
Total cost of ambulatory (less pain) - Sx+RT	Gamma	5,346	4,811–5,881	Primary data
Total cost of nonambulatory (less pain) - Sx+RT	Gamma	2,834	2,551–3,118	Primary data
Total cost of ambulatory (pain) - Sx+RT	Gamma	6,822	6,140–7,504	Primary data
Total cost of nonambulatory (pain) - Sx+RT	Gamma	6,221	5,599–6,843	Primary data
Total cost of ambulatory (less pain) - RT	Gamma	3,778	3,400–4,156	Primary data
Total cost of nonambulatory (less pain) - RT	Gamma	2,834	2,551–3,118	Primary data
Total cost of ambulatory (pain) - RT	Gamma	3,699	3,329–4,069	Primary data
Total cost of nonambulatory (pain) - RT	Gamma	8,695	7,825–9,564	Primary data
Chemotherapy (USD)	Gamma	2,030	1,144–2,915	Primary data
Radiotherapy (USD)	Gamma	1,097	963–1,232	Primary data
Surgical procedure (USD)	Gamma	2,155	1,995–2,314	Primary data
Implant (USD)	Gamma	1,780	1,651–1,909	Primary data

(*continued*)

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Table 1. Input parameters used in the health economic model (continued)

Parameter	Distribution	Base case	Range	References
Direct nonmedication cost				
Food (USD/visit)	Gamma	62	55–68	(16)
Transportation (USD/visit)	Gamma	167	154–181	(16)
Indirect cost–care giver (USD/visit)	Gamma	112	70–154	(16)

Sx+RT, combined surgery and radiotherapy; RT, radiotherapy alone; USD, United States dollar.

up. Ambulatory status and the survival rate were also not significantly different between the 2 treatment groups (Table 3).

The mean preoperative utility value was 0.592 ± 0.314 in the surgery group, and 0.479 ± 0.345 in the radiotherapy alone group (p = 0.402). At both the 3- and 6-month follow-up, the mean utility value in the surgery group was significantly higher than that in the radiotherapy alone group (3 months: 0.701 ± 0.328 vs. 0.433 ± 0.297, respectively; p = 0.018; and, 6 months: 0.804 ± 0.264 vs. 0.506 ± 0.270, respectively; p = 0.011) (Table 3).

2. Cost-Utility Analysis

1) Base case analysis

The estimated total lifetime cost per patient for surgery and radiotherapy versus radiotherapy alone was 59,863.14 USD versus 24,526.97 USD, respectively. The number of QALYs was 1.54 and 0.92 for the combination treatment group and the radiotherapy alone group, respectively. The ICER for the combination surgery and radiotherapy treatment was 57,074.01 USD per QALY gained compared to radiotherapy alone (Table 4). This finding demonstrates the combination treatment option to be non-cost-effective when judged according to the official WTP threshold in Thailand.

2) One-way sensitivity analysis

Fig. 2 shows the most influential variables in our model to be the utility of ambulatory status with less pain after combination surgery and radiotherapy, the utility of ambulatory status with less pain after radiotherapy alone, and relative risk of survival in radiotherapy alone versus combination surgery and radiotherapy. However, within the range of each parameter, none yielded a cost-effective result.

3) Probabilistic sensitivity analysis

Results of the PSA based on 1,000 Monte Carlo simulations are presented in a cost-effectiveness plane (Fig. 3A). Despite the variation in base case parameter inputs, most of the plots were in the upper-right quadrant, which suggests the combination surgery and radiotherapy treatment strategy to be more effective, but more expensive than radiotherapy alone. All simulations were plotted above the WTP threshold line, which means that none of the scenarios could be considered cost-effective in Thailand's healthcare setting. The results of the PSA are also presented as a cost-effectiveness acceptability curve, as shown in Fig. 3B. At the Thailand WTP threshold, the probability of the combination therapy strategy being cost-effective is zero. If the Thailand WTP was increased to 56,000 USD per QALY gained, the probability of surgery combined with radiotherapy being cost-effective was 50% compared to radiotherapy alone.

DISCUSSION

Many studies have investigated the cost-utility of the surgical treatment among spinal metastasis patients. Furlan et al.[8] reported an ICER of 250,307 USD per QALY when surgery plus radiotherapy was compared to radiotherapy alone. They adopted a Markov model approach and analyzed the results based on the data from the study of Patchell et al.[3] combined with Ontario-based physician fee and hospital cost data in Canada. They found and reported surgery plus radiotherapy to be cost-effective at a WTP threshold of 50,000 USD per QALY.[8] In Japan, Miyazaki et al.[2] also found surgical treatment to be cost-effective with an ICER of 42,003 USD per QALY gained at a WTP of 50,000 USD per QALY gained. Finally–in Belgium, Depreitere et al.[7] Reported an ICER for surgical management of spinal metastasis of 13,635 EUR per QALY compared to radiotherapy alone. Taken together, these reported findings indicate that palliative surgery is cost-effective for spinal metastasis patients in developed countries.

During the 6-month follow-up after treatment, our findings showed significant improvement in the quality of life of patients in the combined surgery and radiotherapy group compared to the quality of life of patients in the radiotherapy alone group. In this study, there was no significant difference in ambulation between the 2 groups. However, the radiotherapy alone group had

Table 2. Patient demographic and clinical characteristics compared between the combined surgery and radiotherapy (Sx+RT) group and the radiotherapy alone (RT) group

Characteristic	Sx+RT (n = 12)	RT alone (n = 12)	p-value
Female sex	8/12 (66.7)	10/12 (83.3)	0.538
Age (yr)	58.17 ± 11.06	62.25 ± 12.39	0.404
Frankel classification			0.640
Grades A, B and C	2 (16.7)	4 (33.3)	
Grades D and E	10 (83.3)	8 (66.7)	
Spinal level of compression			0.605
Cervical	1 (8.3)	2 (16.7)	
C, T	0 (0)	1 (8.3)	
C, TLS	1 (8.3)	1 (8.3)	
Lumbar	6 (50.0)	2 (16.7)	
Thoracic	2 (16.7)	2 (16.7)	
T, L	2 (16.7)	3 (25.0)	
TLS	0 (0)	1 (8.3)	
Position of spinal tumor			0.538
Anterior	2 (16.7)	1 (8.3)	
Anterior, posterior	1 (8.3)	0 (0)	
Anterior, lateral, posterior, anterior	5 (41.7)	8 (66.7)	
Lateral	4 (33.3)	3 (25.0)	
Revised Tokuhashi score			0.587
0–8	7 (58.3)	8 (66.7)	
9–11	4 (33.3)	4 (33.3)	
12–15	1 (8.3)	0 (0)	
Tomita score			0.411
4–5	2 (16.7)	4 (33.3)	
6–7	6 (50.0)	3 (25.0)	
8–10	4 (33.3)	5 (41.7)	
Spinal instability neoplastic score			> 0.999
0–6	0 (0)	0 (0)	
7–12	9 (75.0)	10 (83.3)	
13–18	3 (25.0)	2 (16.7)	
Primary tumor			0.622
Breast	2 (16.7)	4 (33.3)	
Colon	1 (8.3)	0 (0)	
Lungs	4 (33.3)	3 (25.0)	
Prostate	2 (16.7)	1 (8.3)	
Rectum	0 (0)	1 (8.3)	
Endometrium	1 (8.3)	0 (0)	
Supraglottis cancer	0 (0)	1 (8.3)	
Non-small cell lung cancer	1 (8.3)	1 (8.3)	
Hepatocellular carcinoma	1 (8.3)	0 (0)	
Thyroid	0 (0)	1 (16.7)	
Total	12 (100)	12 (100)	

Values are presented as number (%) or mean ± standard deviation.

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Table 3. Utility, ambulator, survival, and back pain visual analogue scale (VAS) score at different time points compared between the combined surgery and radiotherapy (Sx+RT) group and the radiotherapy alone (RT) group

Variable	Sx+RT	RT only	p-value
Pretreatment			
Utility	0.59 ± 0.31	0.48 ± 0.34	0.402
Ambulator	9 (75.0)	7 (58.3)	0.386
Survival	12 (100)	12 (100)	
Back pain VAS	50.75 ± 28.22	64.17 ± 36.30	0.243
Follow-up 3 months			
Utility	0.73 ± 0.28	0.48 ± 0.29	0.018*
Ambulator	11 (91.7)	10 (90.9)	0.949
Survival	12 (100)	11 (91.7)	0.307
Back pain VAS	31.67 ± 30.92	55.45 ± 20.67	0.024*
Follow-up 6 months			
Utility	0.80 ± 0.26	0.52 ± 0.28	0.011*
Ambulator	9 (90.0)	8 (72.7)	0.314
Survival	10 (83.3)	11 (91.7)	0.537
Back pain VAS	30.00 ± 33.00	37.18 ± 30.45	0.612

Values are presented as mean ± standard deviation or number (%).
*$p < 0.05$, statistically significant differences.

Table 4. Results of the base case analysis

Strategy	Cost (USD)	Effectiveness (QALYs)	Incremental cost (USD)	Incremental effectiveness (QALYs)	ICER (USD/QALYs)
Sx+RT	59,863.14	1.54	35,336.17	0.62	57,074.01
RT	24,526.97	0.92	-	-	-

Sx+RT, combined surgery and radiotherapy; RT, radiotherapy alone; USD, United States dollar; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

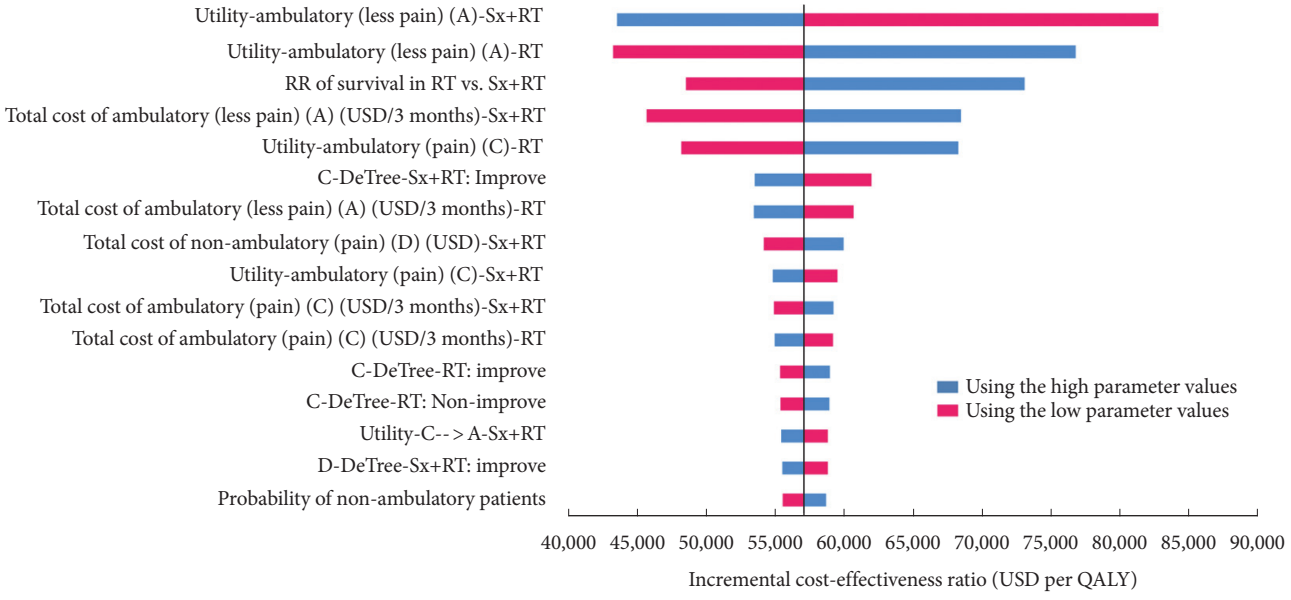

Fig. 2. Tornado diagram. This model illustrates the result of 1-way sensitivity analysis that was performed to study the effects of altering uncertainty parameters within the 95% confidence interval ranges, including all clinical effects, costs, utilities, and the discount rate on the ICER calculated from the model. ICER, incremental cost-effectiveness ratio; Sx+RT, combined surgery and radiotherapy; RT, radiotherapy alone; USD, United States dollar; QALY, quality-adjusted life-year.

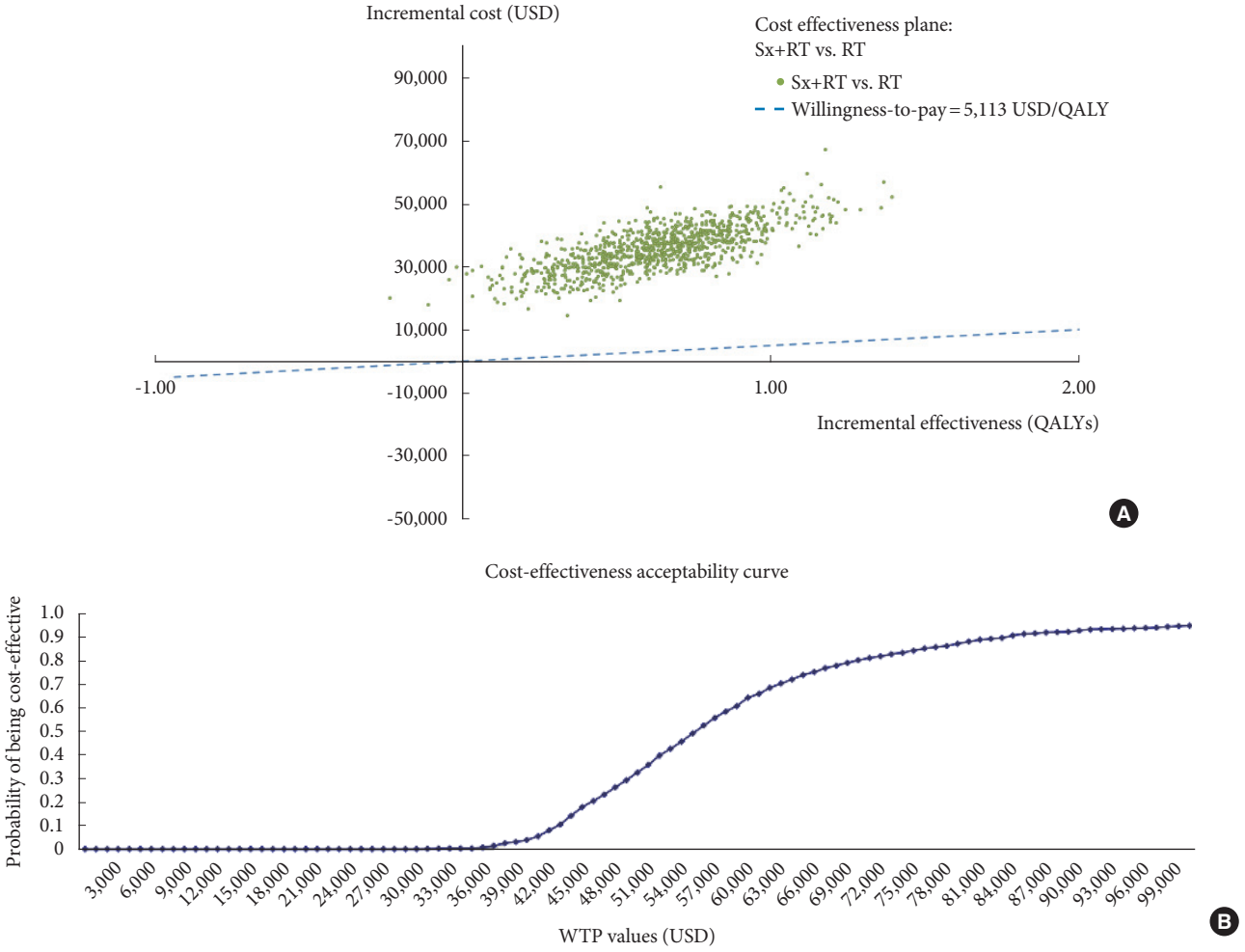

Fig. 3. Multivariate probabilistic sensitivity analysis. The result was based on 1,000 Monte Carlo simulations. The results are shown as a cost-effectiveness plane (A), and a cost-effectiveness acceptability curve (B). Sx+RT, combined surgery and radiotherapy; RT, radiotherapy alone; USD, United States dollar; QALY, quality-adjusted life-year.

less ambulatory status after 6 months. Therefore, the effectiveness of radiotherapy alone in terms of maintaining or restoring ambulatory status may be limited. A prior study also reported that surgical intervention significantly improved ambulation, pain relief, and quality of life in spinal metastasis patients.[20]

For the CUA, the ICER of the combined surgery and radiotherapy group relative to the radiotherapy alone group was 57,074.01 USD per QALY gained, which indicated that the surgery group is not cost-effective compared to the radiotherapy alone group. Moreover, the results of our sensitivity analyses showed no cost-effectiveness of the combination therapy regardless of the parameter values used. We conducted a literature review for studies that also compared combination treatment with radiotherapy alone in spinal metastasis (Table 5), and some previously reported results conflict with the results of our study. The observed differences between and among studies may be due to differences in the WTP threshold and cost of treatment of each country. However, the survival rate was not only affected by the choice of treatment but also other factors were included, so the highly selection of spinal metastatic patients who seemed to have better prognosis and outcome after the treatment was required. One of the significant prognostic factors in spinal metastasis patients was reported to be ambulatory status.[21] Schoenfeld et al.[9] reported a QALY of 0.800 among patients who received nonoperative treatment, and a QALY of 0.823 in patients with independent ambulatory status at presentation. In patients with nonambulatory status at presentation, they reported a QALY of 0.089 in patients who received nonoperative treatment and a QALY of 0.813 in patients who received operative treatment. The ICER for a surgical procedure was 899,700 USD per QALY and 48,600 USD per QALY in patients with independent ambulatory and nonambulatory status at pre-

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Table 5. Literature review for previous studies that compared cost-utility between radiotherapy alone and combined surgery (Sx) and radiotherapy (RT) for spinal metastasis

Variable	Furlan et al.[8] 2012	Miyazaki et al.[2] 2017	Turner et al.[10] 2018	Depreitere et al.[7] 2019	Schoenfeld et al.[9] 2021	The present study
Data collection year	Jan 2001–July 2005	2010–2014	2009–2015	2011–2015	2005–2017	2018–2020
Perspective	Public	Public	Societal	Societal	Health system	Societal
Country	Canada	Japan	United Kingdom	Belgium	United States	Thailand
Patient data	101 (50 Sx, 51 RT)	47 (31 Sx, 16 RT)	100 (50 Sx, 51 RT)	46 (38 Sx, 8 RT)	713 (370 Sx, 343 RT)	24 (12 Sx, 12 RT)
Primary tumor	Surgery group	Surgery group	-Breast 14 (14.7%)	Surgery group	-	Surgery group
	-Lung 13/50	-Lungs 8 (25.8%)	-Prostate 13 (13.7%)	-Breast (15.8%)		-Lung (33.3%)
	-Prostate 9/50	-Sarcoma 6 (19.3%)	-Renal 10 (10.5%)	-Gastric and lung (10.5%)		-Breast and prostate (16.7%)
	Radiation group	Radiation group		Radiation group		Radiation group
	-Lung 13/50	-Kidney 4 (25%)		-Breast (50%)		-Breast (33.3%)
	-Prostate 10/50	-Sarcoma 3 (18.7%)				-Lung (25%)
Cost	Surgery group	Surgery group	Surgery group	Surgery group	Independent ambulatory status at presentation	Surgery group
	Mean overall costs: 583,809.21 USD (95% CI, 61,813.80–2,235,090.76)	Total medical cost: 25,770 ± 7,750 USD	-The median community tariff: 38,802 pounds (IQR, 13,085–83,893)	-The median total cost of treatment 15,462 EUR (IQR, 10,911–23,116, mean 16,989 EUR, SD 8,148 EUR)	-Nonoperative treatment: 53,299 USD	-Total cost: 59,859.95 USD
	Radiation group	Radiation group	Radiation group	Radiation group	-Operative treatment: 73,777 USD	Radiation group
	Mean overall costs: 554,323.01 USD (95% CI, 59,407.05–2,211,295.22)	Total medical cost: 8,615 ± 12,273 USD	-The median total tariff: 45,141 pounds (IQR, 19,423–90,231)	-The mean total cost: 9,354 EUR	Nonambulatory status at presentation	-Total cost: 24,525.45 USD
					-Nonoperative treatment: 38,330 USD	
					-Operative treatment: 73,481 USD	
Utility assessment	-	1 Year	Mean follow-up: 24.8 months (SD 11.8)	24 Months	12 Months	6 Months
Utility result						
Sx	-	0.448 ± 0.451	-	-	-	0.80 ± 0.26
RT	-	0.019 ± 0.027	-	-	-	0.52 ± 0.28

(*continued*)

Table 5. Literature review for previous studies that compared cost-utility between radiotherapy alone and combined surgery (Sx) and radiotherapy (RT) for spinal metastasis (continued)

Variable	Furlan et al.[8] 2012	Miyazaki et al.[2] 2017	Turner et al.[10] 2018	Depreitere et al.[7] 2019	Schoenfeld et al.[9] 2021	The present study
QALY						
Sx	0.57 (95% CI, 0.13–2.24)	0.433 ± 0.327	Median 0.28 (IQR, 0.04–0.99) Mean 0.64 (SD, 0.76)	Median postoperative QALY 070 (IQR, 0.18–1.70; mean, 0.95; SD, 0.96)	-Independent ambulatory status 0.823 -Nonambulatory status 0.813	1.54
RT	0.46 (95% CI, 0.06–3.14)	0.024 ± 0.028	Median 0.13 (IQR, 0.02–0.50) Mean 0.32 (SD, 0.45)	Median QALY 0.17 (IQR, 0.01–0.56; mean, 0.42; SD, 0.64) in QALY overestimation, and 0.01 (IQR, 0.01–0.35; mean, 0.26; SD, 0.36) in QALY underestimation scenario	-Independent ambulatory status 0.800 -Nonambulatory status 0.089	0.92
ICER	250,307.30 USD/QALY	42,003 USD/QALY	-	13,635 EUR/QALY	-Independent ambulatory status 899,700 USD -Nonambulatory status 48,600 USD	US 57,071.31 USD/QALY
Willingness-to-pay per QALY	50,000 USD	50,000 USD	-	37,300 EUR	100,000–150,000 USD	5,113 USD (160,000 THB)
Exchange rates	2010 USD	2014 USD	2015–2016 financial year	2015–2016 financial year	2019 USD	2020 USD

USD, United States dollar; EUR, euro; IQR, interquartile range; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

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sentation, respectively. Similar to the result reported by Schoenfeld et al.[9] our results showed significant improvement in utility among surgical patients with nonambulatory status to be a factor that positively influences cost-effectiveness, so the observed improvement in utility and survival in the surgery group strongly influenced cost-effectiveness in this economic model.

There were many methods of surgery that may have affected the outcomes. Lee et al.[22] compared the postoperative result between palliative, debulking and en bloc surgery in spinal metastases. The result showed the debulking surgery group had the highest postoperative complications than the others but no difference in the improvement of neurological deficit after surgery. The proper surgical option on each patient may improve outcomes.[22] Additionally, stereotactic body radiation therapy has become a fundamental tool for the treatment of spine metastasis that provided good local control, especially in radioresistant tumor.[23,24] The separation surgery followed by stereotactic radiation therapy was effective in decompression and long-term local control.[25] Compared with conventional radiotherapy, stereotactic body radiotherapy at a dose of 24 Gy in 2 daily fractions was superior to conventional external beam radiotherapy at a dose of 20 Gy in 5 daily fractions in improving the complete response rate for pain.[26] However, the receipt of stereotactic body radiotherapy is limited because of a lack of medical resources. So, most patients with spine metastases were treated with conventional radiotherapy usually with 10 fractions[27] same as in Thailand.

To our knowledge, our study is the first prospective cohort study to compare utility outcomes after treatment in spinal metastasis patients in a developing country. This study has several strengths. First, our study data were prospectively collected. Second, we adjusted the mortality rates of these patients by incorporating the Thai age-standardized mortality rate to reflect baseline health of Thai population. Third, all cost data were retrieved from reliable local sources. Fourth and last, we conducted a comprehensive literature review to determine the overall mortality rate and the progression of disease after treatment in both groups for use as model input parameters.

This study has some mentionable limitations. From the reference literature, a study reported by Miyazaki et al.[2] showed a more significant difference in the health state of the surgery group versus radiotherapy alone, and the follow-up time was longer than the 6-month follow-up in our study. Second, there was a limited sample size. Third, our center is a university hospital so the costs of care are higher than those charged by rural general and provincial hospitals in Thailand. The further multicenter study may be needed that includes all healthcare settings in Thailand.

CONCLUSION

Surgical treatment for spinal metastasis significantly improved the quality of life of spinal metastasis patients compared with radiotherapy alone over the evaluated 6-month posttreatment follow-up period. However, the surgical treatment strategy was not found to be cost-effective compared to radiotherapy alone at the current WTP threshold in Thailand. A highly selective strategy for identifying spinal metastasis patients before surgical treatment is suggested to optimize all modifiable measurement parameters for all stakeholders.

NOTES

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REFERENCES

1. de Ruiter GC, Nogarede CO, Wolfs JF, et al. Quality of life after different surgical procedures for the treatment of spinal metastases: results of a single-center prospective case series. Neurosurg Focus 2017;42:E17.

2. Miyazaki S, Kakutani K, Sakai Y, et al. Quality of life and cost-utility of surgical treatment for patients with spinal metastases: prospective cohort study. Int Orthop 2017;41:1265-71.
3. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 2005;366:643-8.
4. Schoenfeld AJ, Losina E, Ferrone ML, et al. Ambulatory status after surgical and nonsurgical treatment for spinal metastasis. Cancer 2019;125:2631-7.
5. Versteeg AL, Sahgal A, Rhines LD, et al. Health related quality of life outcomes following surgery and/or radiation for patients with potentially unstable spinal metastases. Spine J 2021;21:492-9.
6. Tipsmark LS, Bünger CE, Wang M, et al. Healthcare costs attributable to the treatment of patients with spinal metastases: a cohort study with up to 8 years follow-up. BMC Cancer 2015;15:354.
7. Depreitere B, Turner I, Vandoren C, et al. Cost-utility analysis of surgery and radiotherapy for symptomatic spinal metastases in a belgian specialist center. World Neurosurg 2019;125:e537-43.
8. Furlan JC, Chan KK, Sandoval GA, et al. The combined use of surgery and radiotherapy to treat patients with epidural cord compression due to metastatic disease: a cost-utility analysis. Neuro Oncol 2012;14:631-40.
9. Schoenfeld AJ, Bensen GP, Blucher JA, et al. The cost-effectiveness of surgical intervention for spinal metastases: a model-based evaluation. J Bone Joint Surg Am 2021 Jul 21;10.2106/JBJS.21.00023. https://doi.org/10.2106/JBJS.21.00023. [Epub].
10. Turner I, Kennedy J, Morris S, et al. Surgery and radiotherapy for symptomatic spinal metastases is more cost effective than radiotherapy alone: a cost utility analysis in a U.K. Spinal Center. World Neurosurg 2018;109:e389-97.
11. Teerawattananon Y, Chaikledkaew U. Thai health technology assessment guideline development. J Med Assoc Thai 2008;91 Suppl 2:S11-5.
12. Teerawattananon Y, Tritasavit N, Suchonwanich N, et al. The use of economic evaluation for guiding the pharmaceutical reimbursement list in Thailand. Z Evid Fortbild Qual Gesundhwes 2014;108:397-404.
13. Bishop AJ, Tao R, Rebueno NC, et al. Outcomes for spine stereotactic body radiation therapy and an analysis of predictors of local recurrence. Int J Radiat Oncol Biol Phys 2015;92:1016-26.
14. Pessina F, Navarria P, Carta GA, et al. Long-term follow-up of patients with metastatic epidural spinal cord compression from solid tumors submitted for surgery followed by radiation therapy. World Neurosurg 2018;115:e681-7.
15. Riewpaiboon A. Measurement of costs for health economic evaluation. J Med Assoc Thai 2014;97 Suppl 5:S17-26.
16. Riewpaiboon A. Standard cost lists for health economic evaluation in Thailand. J Med Assoc Thai 2014;97 Suppl 5:S127-34.
17. Indices BoTaE. Report for consumer price index of Thailand year 2020 [Internet]. Bangkok (Thailand): 2020 [cited 2021 Aug 5]. Available from: http://www.indexpr.moc.go.th/price_present/TableIndexG_region.asp?table_name=cpig_index_country&province_code=5&type_code=g&check_f=i&year_base=2562&nyear=2563.
18. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006.
19. Limwattananon S. Handling uncertainty of the economic evaluation result: sensitivity analysis. J Med Assoc Thai 2008;91 Suppl 2:S59-65.
20. Chen B, Xiao S, Tong X, et al. Comparison of the therapeutic efficacy of surgery with or without adjuvant radiotherapy versus radiotherapy alone for metastatic spinal cord compression: a meta-analysis. World Neurosurg 2015;83:1066-73.
21. Yang XG, Han Y, Wang F, et al. Is ambulatory status a prognostic factor of survival in patients with spinal metastases? An exploratory meta-analysis. Orthop Surg 2018;10:173-80.
22. Lee BH, Park JO, Kim HS, et al. Perioperative complication and surgical outcome in patients with spine metastases: retrospective 200-case series in a single institute. Clin Neurol Neurosurg 2014;122:80-6.
23. Pérez-Montero H, Godino O, Lozano A, et al. Long-term outcomes of spinal SBRT. Is it important to select the treatment time? Clin Transl Oncol 2022;24:276-87.
24. Zhang HR, Li JK, Yang XG, et al. Conventional radiotherapy and stereotactic radiosurgery in the management of metastatic spine disease. Technol Cancer Res Treat 2020;19:1533033820945798.
25. Ito K, Sugita S, Nakajima Y, et al. Phase 2 clinical trial of separation surgery followed by stereotactic body radiation therapy for metastatic epidural spinal cord compression. Int J Radiat Oncol Biol Phys 2022;112:106-13.
26. Sahgal A, Myrehaug SD, Siva S, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label,

multicentre, randomised, controlled, phase 2/3 trial. Lancet Oncol 2021;22:1023-33.
27. Kim E, McClelland S 3rd, Jaboin JJ, et al. Disparities in patterns of conventional versus stereotactic body radiotherapy in the treatment of spine metastasis in the United States. J Palliat Care 2021;36:130-4.

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Original Article

Conversational Artificial Intelligence for Spinal Pain Questionnaire: Validation and User Satisfaction

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Objective: The purpose of our study is to develop a spoken dialogue system (SDS) for pain questionnaire in patients with spinal disease. We evaluate user satisfaction and validated the performance accuracy of the SDS in medical staff and patients.
Methods: The SDS was developed to investigate pain and related psychological issues in patients with spinal diseases based on the pain questionnaire protocol. We recognized patients' various answers, summarized important information, and documented them. User satisfaction and performance accuracy were evaluated in 30 potential users of SDS, including doctors, nurses, and patients and statistically analyzed.
Results: The overall satisfaction score of 30 patients was 5.5 ± 1.4 out of 7 points. Satisfaction scores were 5.3 ± 0.8 for doctors, 6.0 ± 0.6 for nurses, and 5.3 ± 0.5 for patients. In terms of performance accuracy, the number of repetitions of the same question was 13, 16, and 33 (13.5%, 16.8%, and 34.7%) for doctors, nurses, and patients, respectively. The number of errors in the summarized comment by the SDS was 5, 0, and 11 (5.2%, 0.0%, and 11.6 %), respectively. The number of summarization omissions was 7, 5, and 7 (7.3%, 5.3%, and 7.4%), respectively.
Conclusion: This is the first study in which voice-based conversational artificial intelligence (AI) was developed for a spinal pain questionnaire and validated by medical staff and patients. The conversational AI showed favorable results in terms of user satisfaction and performance accuracy. Conversational AI can be useful for the diagnosis and remote monitoring of various patients as well as for pain questionnaires in the future.

Keywords: Conversational artificial intelligence, Pain questionnaire, Spoken dialogue system, Natural language process, Chatbot, Spine

INTRODUCTION

With the advent of the Fourth Industrial Revolution, efforts to apply artificial intelligence (AI) and machine learning in the medical field are actively underway.[1,2] In particular, imaging diagnosis, disease diagnosis, and prediction using clinical data and genomic Big data are medical fields of AI that currently receive the most attention.[3,4] AI technologies associated with natural language processing (NLU) are also being used in healthcare.[5] Conversational AI is an application of NLU and refers to AI technology that can talk to people, including chatbots or virtual agents.[6]

Unlike the written text-based chatbot, a computer system that can communicate by voice is called a spoken dialog system (SDS).[7] Unlike the command and control speech system that simply answers requests and cannot maintain the conversation continuously, a SDS can maintain the continuity of the conversation over long periods of time. SDSs are already being applied in everyday life through in-home AI speakers, such as Amazon Alexa (Amazon, Seattle, WA, USA).[8] Moreover, conversational AI

is being applied in various medical fields, such as patient education, medical appointments, and voice-based electronic medical record (EMR) creation.[7,9] Recent attempts have been made to collect medical data, such as patient-reported outcomes, health status checks and tracking, and remote home monitoring, using conversational AI.[7,10]

In assessing patient with spinal disease, doctor-patient dialogue about pain is the first step in diagnosis, and a pain questionnaire is the most important tool during follow-up after treatment or spine surgery. The purpose of our study was to develop a SDS for a pain questionnaire for patients with spinal diseases. We aimed to evaluate user satisfaction and validate the performance accuracy of the system in medical staff and patients. This study is a preliminary study for the development of an interactive medical robot. Based on the results of this study, a follow-up study on robot-based interactive questionnaire is planned.

MATERIALS AND METHODS

1. Development of the Pain Questionnaire Protocol

First, a pain questionnaire protocol for a SDS was developed by dividing the preoperative and postoperative pain questionnaires to assess the outcomes of patients undergoing spine surgery. The pain questionnaire consisted of questions to reflect the actual conversation between the medical staff and the patient. The items were created based on questions that medical staff usually ask during rounds of inpatients. The protocol included questions about the location, type, influencing factors, intensity, time of onset, and duration of pain. In addition, questions about the patient's psychological state, such as questions regarding mood, anxiety, and sleep quality, were included as indirect indicators of pain. Postoperative question items were replaced with question items about pain at the surgical site. Furthermore, a question about whether the patient's preoperative pain had improved or not was added. Questions about psychological status were the same as the preoperative questions. Each question was structured in a closed question format so that the pain questionnaire system could easily process the patients' responses. The developed pain questionnaire protocol is shown in Table 1.

2. Collection of Dialogue Dataset for the SDS

To build a database of patients' various expressions for NLU, real doctor-patient dialogue sets were collected. The study was approved by the Institutional Review Board (IRB No. 1905-023-079). Informed consent was obtained from all patients. A total of 1,314 dialogue sets were collected from 100 hospitalized patients who underwent spinal surgery between September 2019 and August 2021. One dialogue set was defined as one question and one answer. The age range was 22–82 years (mean, 62.6 years), and 47 patients were male. There were 48 spinal stenosis, 13 herniated disc herniation, 13 spinal infection, 11 spinal

Table 1. Questionnaire of the spoken dialogue system

Category	Description	Preoperative situation	Postoperative situation
Pain	Location	Where is the most painful area right now? If there are multiple areas, please tell them briefly in the order of the most pain.	Where do you feel most uncomfortable after surgery? If there are multiple parts, please tell them briefly in the order of discomfort.
	Type	How does the pain feel? Please express it like numbness or aching.	Has the pain that was very painful before the operation improved?
	Influence factor	1. What time of the day do you have the most pain?	1. Is there any pain at the surgical site?
		2. What posture hurts the most?	2. What posture hurts the most?
	Intensity	Please rate how severe the pain is on a scale of VAS 0–10.	Please rate how severe the pain is on a scale of VAS 0–10.
	Time and duration	1. Since when have you had pain?	Does the pain at the surgical site last all day?
		2. When did the pain get worse?	
Psychologic state	Mood	How are you feeling right now? Please tell me between good, average, and bad.	How are you feeling right now? Please tell me between good, average, and bad.
	Anxiety	Are you currently worried or anxious?	Are you currently worried or anxious?
	Quality	1. How many hours did you sleep?	1. How many hours did you sleep?
		2. Did you sleep well without waking up?	2. Did you sleep well without waking up?

VAS, visual analogue scale.

tumor, 8 spinal deformity, 4 spine trauma, and 3 myelopathy cases.

Three doctors asked inpatients questions naturally following the pain questionnaire protocol during the rounds, and the conversations were recorded using a voice recorder. The preoperative pain questionnaire was used the day before surgery, and the postoperative pain questionnaire was used between 3 and 7 days after surgery. The recordings were documented in the format of text and stored in a database for NLU. Additionally, the virtual conversations of the researchers were also collected, and 2,000 dialogue sets were used for the database.

3. Development of the SDS

The SDS was structured as shown in Fig. 1. The patient's response voice was entered into the speech recognition module and converted into text data. The text data was the input value of the NLU module. The NLU module played a role in understanding users' intentions by analyzing the intents, name entity recognition, and keywords in the user's answers. The output value of the NLU module was again entered into the dialog management module, which managed the flow of conversation between the user and SDS. It searched the database for information to be given to the user and outputted the content necessary for system utterance. The system utterance output was automatically generated in the format of text data through a natural language generation (NLG) module, which was again keyed into a speech synthesis module. The speech synthesis module finally completed system utterance generation by outputting the result in a voice format that the user can understand. The pain questionnaire SDS was developed using Python 3.8 for Windows 10. IBM Watson Text-to-Speech (IBM, Armonk, NY, USA) was used for utterance of the SDS. NLU was performed using IBM Watson Assistant and KoNLPy to understand the patient's intent from the text data.[11] The utterance was performed using the Google Cloud Speech-to-Text module (Google, Mountain View, CA, USA).

After analyzing the dialogue datasets obtained from the patients, patients' intents that express the character of pain and psychological state were classified into 95 in the intents column of IBM Watson Assistant. A total of 1,229 expression examples were registered in the user example of the intent column. A total of 770 examples for timing, duration, and influence factors were registered in the name entity column.

Fig. 2 shows the conversation flow of the pain questionnaire SDS for implementation of the questionnaire protocol in Table 1. The SDS starts by entering a unique identification number (UID) that anonymizes the patient's personal information and stores it in the virtual EMR. When the UID is entered, the SDS checks whether the UID exists in the database. If the UID exists, the SDS starts asking questions after repeating the previous questionnaire's summary. The SDS checks whether the answers to the 10 questions were obtained from the patient during the

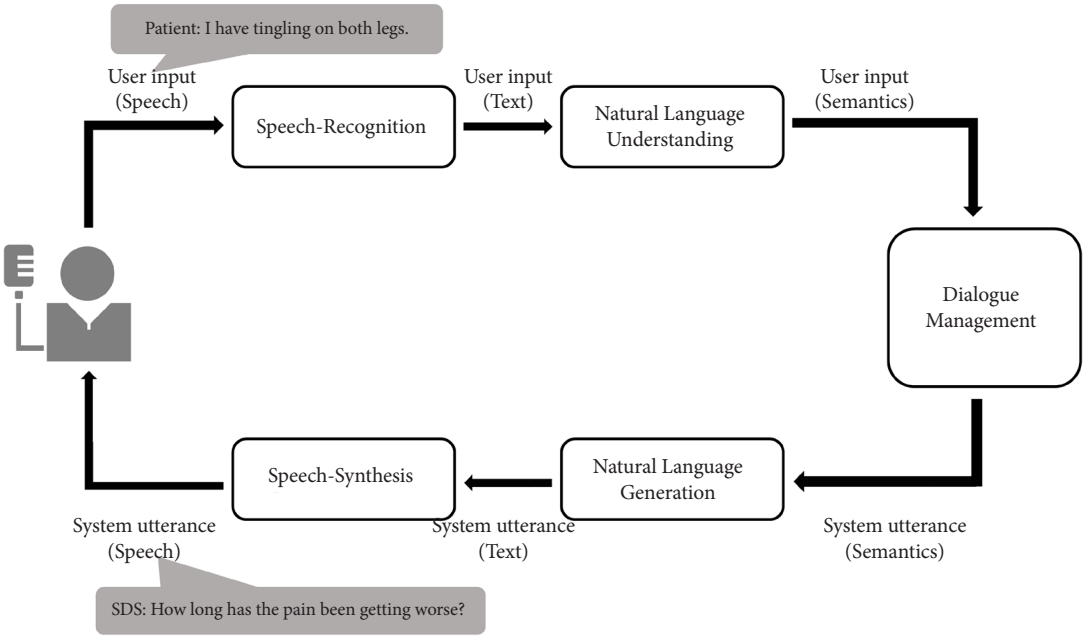

Fig. 1. Architecture of the spoken dialogue system (SDS).

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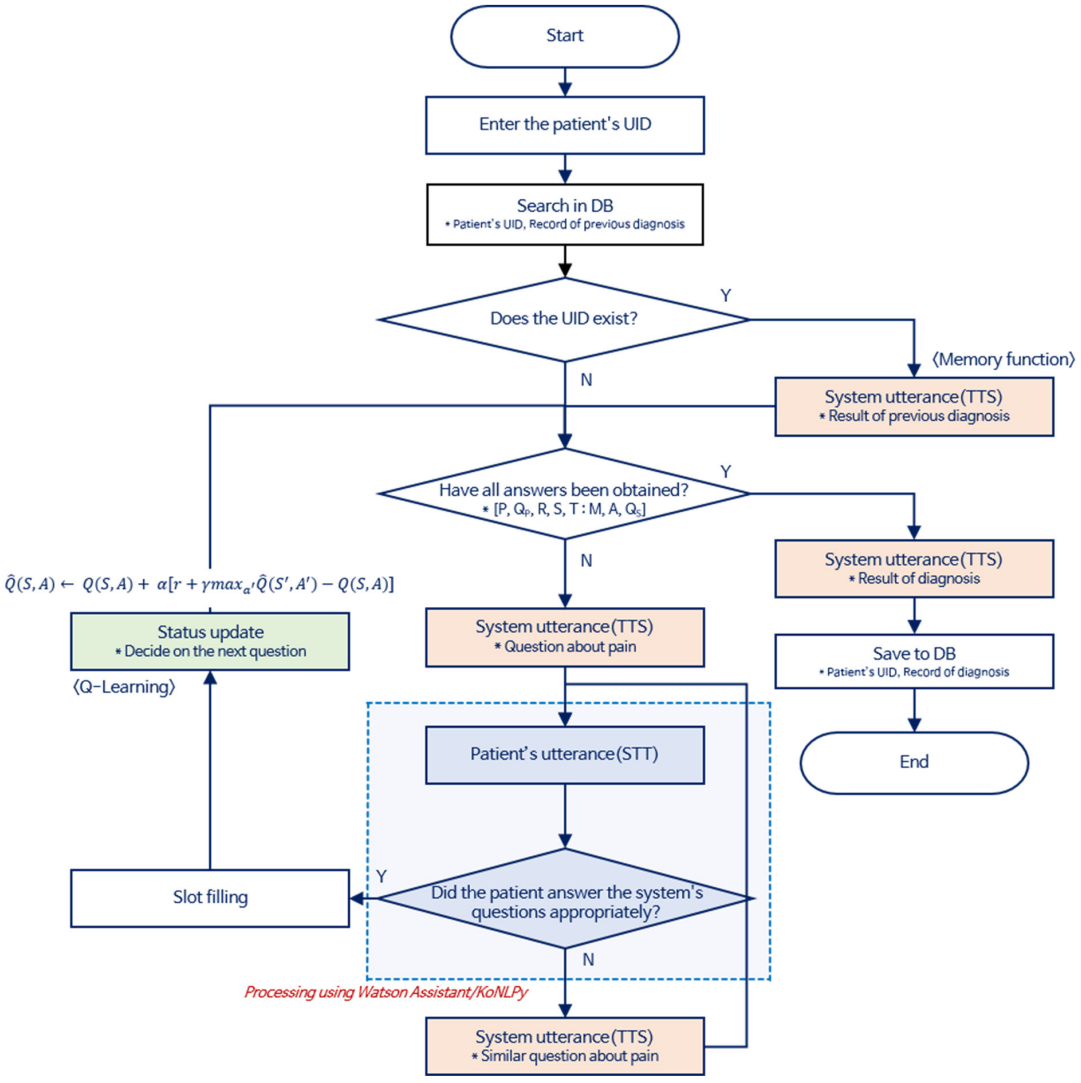

Fig. 2. Flow chart of the spoken dialogue system. UID, unique identification number; DB, database; STT, speech-to-text; TTS, text-to-speech.

Date : 2021-08-18 17:51:51
Position : ['wrist']
Quality : ['tingling']
R_factor1 : ['always']
R_factor2 : ['when using a computer']
Severity : 6
Timing2 : 1 week
Mood : good
Anxiety : no
Sleep1 : 7
Sleep2 : good

Fig. 3. Electric medical record linkage with the spoken dialogue system.

questionnaire. If proper information was not obtained, the SDS asks the question until proper information is obtained. When the patient's answer is not recognized, the SDS utters similar questions without repeating the same question. When the patient's answer is properly recognized, the Q-learning status is updated to determine the next question, and the SDS checks whether all answers are obtained. When all answers are obtained, the SDS utters the summarized result and finishes the questionnaire after saving the results in the form of text in the virtual EMR. An example of the questionnaire results that were transmitted to the virtual EMR is shown in Fig. 3. Supplementary video clip 1 is actual conversation video between SDS and a participant.

4. Validation and User Satisfaction for the SDS

User satisfaction and performance accuracy of the developed pain questionnaire SDS were evaluated. Validation of the SDS was performed for 3 user groups: doctors, nurses, and patients. The participants volunteered to be recruited. The study was approved by the Institutional Review Board of Pusan National University Hospital (IRB No. 2012-010-097). Informed consents were obtained from all patients. Ten participants were included in each group. The participants were pretrained to engage in routine conversations rather than simple short-answer conversations. The participants were provided with basic information about the purpose of the study and SDS, and we helped the participants adapt to the conversation with the SDS. The mean ages of the doctors, nurses, and patients were 35.3 years (range, 25–47 years), 31.2 years (range, 21–58 years), and 64.0 years (range, 48–82 years), respectively. The male-to-female ratios in doctors, nurses, and patients were 9:1, 10:0, and 5:5, respectively. Validation of the SDS was performed in a sitting position on the bed of an inpatient ward. The SDS was mounted on a laptop notebook and placed on a bed table. When the start button was pressed, a conversation was initiated automatically. The SDS first asked a question about pain and recognized the answer, and it followed up with further questions. After the last question and answer, the SDS uttered the summarized result to the users and ended the program immediately after the test, the participants completed a user satisfaction questionnaire about SDS. The questionnaire consisted of 10 items, including the accuracy of the SDS's voice, the degree of similarity to human conversation, and overall satisfaction, and followed the 7-point Likert scale.[7]

5. Statistical Analysis

To verify the performance accuracy of the SDS, the recognition error of the patient's answer, summary error, the causes of the errors, and summary omission of the summarized comment were analyzed. User satisfaction and accuracy between the participant groups were statistically analyzed using 1-way analysis of variance and *post hoc* Tukey honestly significant difference analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

1. User Satisfaction

The results of the user satisfaction survey are shown in Table 2. The overall satisfaction score of 30 participants, consisting of doctors, nurses, and patients, was measured with an average of 5.5 ± 1.4 points out of 7 points. The satisfaction score was 5.3 ± 0.8 for doctors, 6.0 ± 0.6 for nurses, and 5.3 ± 0.5 for patients. The nurse group showed a higher level of satisfaction, but there was no statistically significant difference in user satisfaction between the groups ($p = 0.136$). The average score for each item

Table 2. Survey results of the spoken dialogue system

Question items	Doctor	Nurse	Patient	p-value
Q1. I could understand SDS's words well.	6.6 ± 0.699	6.8 ± 0.422	5.7 ± 1.059	0.008*
Q2. The volume, speed, and sound quality of the SDS were adequate.	6.6 ± 0.699	6.7 ± 0.675	6.0 ± 1.155	0.171
Q3. SDS asked the proper questions.	5.4 ± 1.506	6.0 ± 0.816	5.2 ± 1.549	0.390
Q4. SDS gave an appropriate response.	4.9 ± 1.370	5.3 ± 1.418	5.4 ± 1.075	0.664
Q5. In conversation with SDS, I was able to fully express what I wanted to say.	4.6 ± 1.647	5.5 ± 1.179	4.5 ± 1.269	0.222
Q6. SDS seems to understand well what I'm saying.	4.7 ± 1.337	5.6 ± 1.265	4.7 ± 1.252	0.214
Q7. Conversations with SDS were not much different from conversations with people.	4.3 ± 1.337	5.4 ± 1.075	5.1 ± 1.370	0.153
Q8. I think positively about assisting my medical care through the SDS conversation.	5.5 ± 1.179	6.1 ± 0.568	5.0 ± 1.491	0.118
Q9. There was no objection to the conversation with SDS.	5.3 ± 1.494	6.5 ± 0.527	6.1 ± 0.994	0.057
Q10. The conversation with SDS was overall satisfactory.	5.3 ± 1.160	6.2 ± 0.919	5.4 ± 1.265	0.165
Mean	5.3 ± 0.777	6.0 ± 0.547	5.3 ± 0.522	0.136

Values are presented as mean ± standard deviation.
SDS, spoken dialogue system.
*One-way analysis of variance, *post hoc* Tukey honestly significant difference analysis was performed, the group that made the difference.

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was relatively high at >6 points for the items Q1, Q2, and Q9, which reflect the clarity and sound quality of the SDS's voice and positivity in conversation. The items, Q5, Q6, and Q7, which indicate the degree of similarity to conversations with real people, showed relatively low satisfaction. In terms of satisfaction among the participant groups for each item, the patients showed a statistically low score for item Q1 (p=0.008). Other items showed no statistical differences between the groups.

Table 3. Summary of errors in the spoken dialogue system

Participant	Total no. of question items	Total no. of questions	Recognition error	Summary error	Omission error
Doctor	96	109	13 (13.5)	5 (5.2)	7 (7.3)
Nurse	95	111	16 (16.8)	0 (0.0)	5 (5.3)
Patient	95	128	33 (34.7)	11 (11.6)	7 (7.4)
p-value			0.063	0.001*	0.857

Values are presented as number (%).
*One-way analysis of variance, *post hoc* Tukey honestly significant difference analysis was performed, the group that made the difference.

2. Performance Accuracy

The SDS asked 95 and 96 questions per group, respectively. The number of repeated questions asked by the SDS because it did not recognize the participant's answers was 13, 16, and 33 (13.5%, 16.8%, and 34.7%) in doctors, nurses, and patients, respectively. The difference in the number of repeated questions was not statistically significant among the 3 groups (p=0.063). However, the SDS did not recognize the answers of the patient group and tended to increase the repetition of questions. After

Table 4. Example of an actual conversation between the spoken dialogue system and a patient*

Question of spoken dialogue system	Answer of patient
Hello, it's interview time. I'll start the interview now. What is most uncomfortable symptom right now? If there are multiple parts, please tell them briefly in the order of the most pain.	Yes, My butt hurts. It hurts on both sides of the buttocks on the legs
How does the pain feel? Please express it like numbness or aching.	I get numb and numb. I have tingling when I walk.
How long has the pain been getting worse? Please answer with a period such as 1 day, 1 week, 1 month and 1 year.	No, what I'm doing here is that it hurt before the operation, but after the operation, it seems like yesterday.
I didn't hear well. When did the pain get worse? Please answer with a period such as 1 day, 1 week, 1 month and 1 year.	I can't remember how many years it was before the surgery, and it's been less than a week since I came in after the operation, but it's been 5 days since the operation.
Please rate how severe the pain is on a scale of 0-10.	It seems like the pain is something like 9 or 100 points or something. It hurts when I walk. Buttock. I can't get out of bed.
What time of day do you have severe pain? Please answer the time such as in the morning or before bed.	Mainly, I lay down and went to work, and when the bed goes up, I have to move my ass with it with that. The bed comes down and I can't do it properly with that. I need help.
I didn't hear well. When is the most painful time of the day? Please answer the time such as in the morning or before bed.	Usually, when I lie on the bed and then get up and try to get down from the bed to urinate, this buttock doesn't move properly. That's why I have to keep helping you so I can come down. I was sick. it's time. What, when will you come down?
Please tell me how you are feeling right now? Please answer your feeling between good, average and bad.	It's uncomfortable to sit right now.
Are you currently worried or anxious?	Yes
This is question about sleep quality. Did you sleep well without waking up?	Yes, I sleep well.
How many hours did you sleep last night?	Well, I didn't sleep for 3 days after surgery and I slept well last night.
I didn't hear well. how much time did you sleep yesterday?	How many hours. Well, 9 hours and 7 hours.
[Summarized comment of SDS] Yes, I see. Then I will inform you about the results of the questionnaire. Your pain area is your leg, and you have a tingling sensation, getting worse when you wake up. The intensity of the pain is 10, and the pain has gotten worse since about a week ago. And you say you feel bad and have anxiety. You said that you slept 9 hours and the quality of your sleep was good.	

*Translated questions and answers conducted in Korean into English.

the pain questionnaire was completed, the number of errors in the summarized comment was measured to be 5, 0, and 11 (5.2%, 0.0%, and 11.6%) for doctors, nurses, and patients, respectively. In particular, there were no summary error in nurses. There was a statistically significant difference between the groups ($p = 0.001$). The number of summarization omissions was 7, 5, and 7 (7.3%, 5.3%, and 7.4%), respectively, and there was no statistical difference between the groups ($p = 0.857$) (Table 3).

3. A Case of an Actual Conversation Between a Patient and the SDS

Table 4 shows the actual conversation content between the pain questionnaire SDS and a patient who was an 82-year-old woman. The patient reported a pain intensity score of 9 points for 2 or 3 days prior, but the SDS recognized it as a 10-point intensity for 1 week prior. Because the patient described her symptoms in great detail, it was difficult to accurately recognize specific factors, such as the timing and intensity of the pain. For example, when explaining the symptom duration, she did not mention the exact date, saying "It's been less than a week since I came in after the operation, but it's been 5 days since the operation." Even when talking about the score for pain intensity, she did not express it accurately. Even though the patient used a regional Korean dialect, the dialect had no effect on the processing results because the SDS processed the answers centered on the keywords. However, it was confirmed that the patient did not predict the end time of the utterance of the SDS and thus responded during the utterance of the SDS.

DISCUSSSION

Conversational AI is increasingly being used in medical healthcare field.[6,9] Conversational AI, such as voice chatbots and voice assistants, can provide primary medical education services that answer common questions based on knowledge databases. For example, if people ask a question about first aid in the case of a fever or insect bites, the SDS can tell the treatment method via voice.[12] Recently, hospitals have been actively introducing a doctor appointment service using chatbots.[13] Currently, the most actively researched field is document automation through voice recognition.[7,14] Speech recognition technology can dramatically reduce the time required to write medical records for doctors and nurses by automatically inputting data in the medical records. It has been reported that this technology has reduced the burden and fatigue experienced by doctors and nurses and increased the time spent caring for patients.[15] In addition, conversational AI can be used to automate patient data collection as the SDS used in this study can collect important medical history and patient-reported outcomes. It can also be used for remote home monitoring.[9,10,15]

The term, voice-based conversational AI, is used interchangeably with chatbot or voice assistant; however, the more specialized term is "spoken dialogue system." The SDS can be defined as a dialog software system that can communicate with people using voice.[16] SDS includes several NLU technologies, such as speech recognition, NLU, and NLG. Dialogue systems can be broadly classified into 4 categories depending on whether the type of dialogue is open or closed dialogue and whether the dialogue system is based on a retrieval or a generative model.[17] A retrieval model-based dialogue system called closed conversation responds to a specific topic with a premade answer. The pain questionnaire SDS is based on a retrieval model that allows a closed conversation. In many dialogue systems, the user initiates the conversation, and the conversation flow is determined by the user requesting information to the dialogue system.[16] The pain questionnaire SDS in our study has a flow of asking and processing information from the patients as the system takes the initiative in conversation.

This SDS was developed for the purpose of being mounted on a medical assistant robot that provides medical services to the inpatients, especially those undergoing spinal surgery since pre- and postoperative pain assessments in these patients are the most important items for diagnosis and treatment follow-up. Therefore, the conversation flow of the SDS actually followed the pre- and postoperative pain assessments for inpatients with spinal diseases. Although the SDS was developed with a focus on inpatients, it can be sufficiently used for first outpatient visits or remote monitoring due to the general content of the conversation.

In the user satisfaction evaluation of the SDS, there was no statistical difference in satisfaction among the 3 groups, but satisfaction of nurses was slightly higher than that of doctors and patients. In the nurse group, there was no summary errors; hence, the overall accuracy was high, and it is presumed that the expectation for the use of the SDS was reflected in the nurse groups with a high actual workload. On the other hand, it seems that doctors showed relatively low satisfaction because the accuracy of the SDS did not meet their expectations as they require a high level of information accuracy. As for the satisfaction of patients, the mean age was relatively older; hence, unfamiliarity with the digital system may have contributed to the low score. In particular, in item Q1, patients showed significantly lower satisfaction

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than medical staff; hence, their understanding of the SDS question may have been low. Therefore, the question content and method should be upgraded to be easier to understand for elderly patients. In the performance evaluation of the SDS, recognition errors in the patient group were significantly more in number. The high error rate may be due to the fact that many unstructured speech recognitions occurred because the patient's answer was long, specific, and varied as a routine expression. In addition, the patient's voice tended to be lower in volume and unclear; hence, the recognition error was likely to be high. On the other hand, due to their prior education for natural conversation, doctors and nurses tended to intentionally give clear and simple answers so that the SDS could recognize the answers themselves. There were cases in which the user could not predict the end time of the utterance of the SDS and answered before the end of the question. Therefore, it is necessary to improve the usability by adding system feedback so that patients can predict the end point of the SDS utterance. Finally, when users answered a question with multiple contents, the SDS recognized only one content. For example, when users answered about the location of the pain, they complained of pain in several locations, including the back, buttocks, and legs. However, the SDS only recognized only one of the 3 pain sites. This is because the SDS fills the slot by selecting only one keyword from the user's answer. Therefore, the SDS should be upgraded to recognize these types of answers.

To improve the overall accuracy of the SDS, it is necessary to significantly improve the current voice recognition technology. Despite the rapid development of voice recognition, the rate of its use is still 80% or less, which is not adequate for medical information that requires high accuracy.[18] In addition, it is important to secure the vocabulary and sentences for patients' expressions through the collection of more dialog sets from actual conversations between medical staff and patients. However, because the doctor-patient dialog is protected by the patient's right to privacy, collection of a large number of dialog sets is challenging, unlike general dialog sets that can be easily obtained from the internet.

Until now, commercialized conversational AI for collecting medical information through voice conversations with patients has not been developed. Conversational AI for collection of medical information can reduce the time and effort needed of medical staff by automating the questionnaire during the first outpatient visit in the future. In addition, it is expected that it will be applied in telemedicine and remote patient monitoring, which is receiving increasing interest due to the recent coronavirus disease 2019 pandemic. In particular, for older patients, collection of patient outcome reports using text-based chatbots or apps are limited due to presbyopia and difficulty in using smart devices. Therefore, it will be more useful if remote monitoring can be performed using conversational AI in elderly patients. If clinical decisions supporting AI and conversational AI are combined in the future, it could be applied to software in medical devices for diagnosis, treatment, and prevention beyond collecting medical information.[9]

SDS can be used for remote pain monitoring of spinal patients through automation of pain questionnaires for spine patients, and shortening of doctor consultation time through automation of initial consultations. In this case, the collection of pain information can be automated through follow-up of the patient before and after surgery, which can help in tracking the patient's prognosis. By frequently performing additional pain questionnaires as well as pain evaluation during rounds by medical staff, pain evaluation will be possible more frequently while reducing the medical staff's work loading.

A limitation of this study is the small number of test subjects; thus, there may be bias in the evaluation of user satisfaction and performance accuracy. Nevertheless, our study reports the first development of conversational AI for a spinal pain questionnaire. Our study can also provide an important starting point and reference for future related research as our findings validate the accuracy and satisfaction of real patients and medical staff. In the future, we hope to improve the SDS and evaluate user satisfaction and performance accuracy in a large sample of patients.

CONLUSION

This study is the first report in which voice-based conversational AI was developed for a spinal pain questionnaire that was validated by medical staff and patients. Conversational AI showed favorable results in terms of user satisfaction and performance accuracy. If a large amount of dialogue sets between patients and medical staff are collected and voice recognition technology is improved, it is expected that conversational AI can be used for diagnosis and remote monitoring of various patients as well as help in creating pain questionnaires in the near future.

NOTES

Supplementary Material: Supplementary video clip can be found via https://doi.org/10.14245/ns.2143080.540.

Conflict of Interest: The authors have nothing to disclose.

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REFERENCES

1. Nam KH, Seo I, Kim DH, et al. Machine learning model to predict osteoporotic spine with hounsfield units on lumbar computed tomography. J Korean Neurosurg Soc 2019;62:442-9.
2. Lee JH, Han IH, Kim DH, et al. Spine computed tomography to magnetic resonance image synthesis using generative adversarial networks: a preliminary study. J Korean Neurosurg Soc 2020;63:386-96.
3. Tran KA, Kondrashova O, Bradley A, et al. Deep learning in cancer diagnosis, prognosis and treatment selection. Genome Med 2021;13:152.
4. Kim M, Yun J, Cho Y, et al. Deep learning in medical imaging. Neurospine 2019;16:657-68.
5. Sarker A, Al-Garadi MA, Yang YC, et al. Defining patient-oriented natural language processing: a new paradigm for research and development to facilitate adoption and use by medical experts. JMIR Med Inform 2021;9:e18471.
6. Tudor Car L, Dhinagaran DA, Kyaw BM, et al. Conversational agents in health care: scoping review and conceptual analysis. J Med Internet Res 2020;22:e17158.
7. Mairittha T, Mairittha N, Inoue S. Evaluating a spoken dialogue system for recording systems of nursing care. Sensors (Basel) 2019;19:3736.
8. Shaughnessy AF, Slawson DC, Duggan AP. "Alexa, can you be my family medicine doctor?" The future of family medicine in the coming techno-world. J Am Board Fam Med 2021;34:430-4.
9. Jadczyk T, Wojakowski W, Tendera M, et al. Artificial intelligence can improve patient management at the time of a pandemic: the role of voice technology. J Med Internet Res 2021;23:e22959.
10. Piau A, Crissey R, Brechemier D, et al. A smartphone Chatbot application to optimize monitoring of older patients with cancer. Int J Med Inform 2019;128:18-23.
11. Park L, Cho S. Korean natural language processing in Python. Paper presented at Proceedings of the 26th Annual Conference on Human and Cognitive Language Technology; 2014 Oct 10-11; Chuncheon, Korea. Human and Language Technology; 2014.
12. García-Queiruga M, Fernández-Oliveira C, Mauríz-Montero MJ, et al. Development of the @Antidotos_bot chatbot tool for poisoning management. Farm Hosp 2021;45:180-3.
13. Palanica A, Flaschner P, Thommandram A, et al. Physicians' perceptions of Chatbots in health care: cross-sectional web-based survey. J Med Internet Res 2019;21:e12887.
14. White AA, Lee T, Garrison MM, et al. A randomized trial of voice-generated inpatient progress notes: effects on professional fee billing. Appl Clin Inform 2020;11:427-32.
15. Joseph J, Moore ZEH, Patton D, et al. The impact of implementing speech recognition technology on the accuracy and efficiency (time to complete) clinical documentation by nurses: a systematic review. J Clin Nurs 2020;29:2125-37.
16. Jurafsky D, Martin JH. Speech and language processing. London: Pearson; 2004.
17. Kojouharov S. Ultimate guide to leveraging NLP & machine learning for your Chatbot [Internet]. [cited 2016 Sep 18]. Available from: https://chatbotslife.com/ultimate-guide-to-leveraging-nlp-machine-learning-for-you-chatbot-531ff2dd870c.
18. Bajorek JP. Voice recognition still has significant race and gender biases [Internet]. Brighton (MA): Harvard Business Publishing; c2022 [2019 May 10]. Available from: https://hbr.org/2019/05/voice-recognition-still-has-significant-race-and-gender-biases.

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Original Article

Difference in the Cobb Angle Between Standing and Supine Position as a Prognostic Factor After Vertebral Augmentation in Osteoporotic Vertebral Compression Fractures

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Objective: We retrospectively analyzed patients with osteoporotic vertebral compression fracture (OVCF) undergoing vertebral augmentation to compare the Cobb angle changes in the supine and standing positions and the clinical outcomes.
Methods: We retrospectively extracted the data of OVCF patients who underwent vertebral augmentation. Back pain was assessed using a visual analogue scale (VAS). Supine and standing radiographs were assessed before treatment to determine the Cobb angle and compression ratio. Receiver operating characteristic curve analysis was performed to determine the optimal cutoff to predict favorable outcomes after vertebral augmentation.
Results: A total of 249 patients were included. We observed a statistically significant increase in the VAS score change with increasing Cobb angle and compression ratio ($p < 0.001$), and multivariate logistic regression analysis showed that a difference in the Cobb angle (odds ratio [OR], 1.27) and compression ratio (OR, 1.12) were the independent risk factors for predicting short-term favorable outcomes after vertebral augmentation. In addition, we found that the difference in the Cobb angle (OR, 1.05) was the only factor for predicting midterm favorable outcomes after vertebral augmentation. The optimal cutoff value of the difference in the Cobb angle for predicting midterm favorable outcomes was 35.526°.
Conclusion: We found that the midterm clinical outcome after vertebral augmentation was better when there was a difference of approximately 35% or more in the Cobb angle between the standing and supine positions. Surgeons should pay attention to the difference in the Cobb angle depending on the posture when deciding to perform vertebral augmentation in patients with OVCFs.

Keywords: Osteoporotic vertebral compression fracture, Vertebral augmentation, Cobb angle, Compression ratio

INTRODUCTION

The impact of osteoporosis has been increasingly recognized as the population ages. One of the main complications of osteoporosis is vertebral compression fractures.[1] Osteoporotic vertebral compression fractures (OVCFs) are a frequently encountered clinical problem and are becoming more important as the median age of the population continues to increase.[2] Most OVCFs are managed with a period of absolute bed rest or activity modification, narcotic analgesics, and braces.[3-5] However, approximately 150,000 vertebral compression fractures every year in the United States are refractory to these measures and require hospitalization, with prolonged periods of bed rest and narcotic analgesics.[2]

Currently, the main clinical diagnostic method for OVCFs is magnetic resonance imaging, and the proper determination of the fractured vertebra is the key to successful surgical treatment.[6] Patients with symptomatic OVCFs typically present with severe back pain following a minor injury. Until now, there has been little correlation between the degree of collapse of the vertebral body and the level of pain.[7] Some studies have reported that the changes in the supine lateral and standing lateral radiographs in thoracolumbar OVCFs[8,9] correlate with back pain.[10] Qian et al.[11] reported that improvement in symptoms after kyphoplasty is better in patients with wedge-shaped changes in the supine and standing positions. Based on a previous study, we hypothesized that the degree of difference in the Cobb angle according to the posture would affect the clinical outcomes after vertebral augmentation.

However, there are no reports on the relationship between the difference in the Cobb angle and clinical outcomes after vertebral augmentation. In this study, a retrospective analysis was performed in patients undergoing percutaneous vertebral augmentation to compare the Cobb angle changes in supine and standing positions and to illustrate their relevance to the short-term and midterm clinical outcomes after vertebral augmentation in patients with OVCFs.

MATERIALS AND METHODS

1. Study Design

We retrospectively extracted data of patients with thoracolumbar OVCF who underwent vertebral augmentation between January 1, 2010, and December 31, 2019.

We included patients with only 1-level of OVCF in the thoracolumbar vertebra between T11 and L2, a compression ratio of > 30%, and a bone mineral density (BMD) of less than -2.5 who underwent vertebral augmentation.

The exclusion criteria included patients younger than 55 years of age, with spinal canal invasion by retropulsion of bony fragments, spinal infection, and chronic back pain prior to trauma, including a history of previous spinal decompression or fusion surgery. Patients with severe cardiopulmonary comorbidity, cognitive disorders, or cerebral disease who could not communicate independently were excluded. The exclusion criteria included neurologic deficits, pathologic fractures, and unstable vertebral fractures involving the middle or posterior column of the spine. Patients over 80 years of age were excluded because there were cases of early surgery without conservative treatment for 2 weeks.

This study was approved by the Institutional Review Board of the Nowon Eulji Medical Center (2021-09-009) using the tenets of the World Medical Association Declaration of Helsinki (2018). The requirement for informed consent was waived because of the retrospective nature of the study. All individual records were anonymized prior to analysis.

2. Outcome Assessment

The clinical outcomes were measured using a visual analogue scale (VAS) score. The VAS score was measured before treatment and at 1 and 6 months after treatment. When assessing the VAS score, patients were asked to rate their pain on a scale from 0 to 10, with 0 representing no pain and 10 representing the worst pain. Therefore, patients were divided into a favorable outcome pain group (change in VAS score greater than 4) and an unfavorable outcome group (VAS score less than 4) for further analysis.

3. Imaging Assessment (Cobb Angle and Compression Ratio)

Supine and standing radiographs were assessed before treatment to determine the Cobb angle and compression ratio at the level of the fracture. The Cobb angle was measured as the angle between the superior endplate of the vertebral body above and the inferior endplate of the vertebral body below the fractured vertebral body (Fig. 1). From the lateral projection, the compression ratio (%) of the fractured vertebral body was calculated using the following equation: $\{1-2d/(c+e)\} \times 100$.

Differences in the Cobb angle and compression ratio from supine to standing position were reported using the following equation:

The difference in the Cobb angle (%) = (Cobb angle standing – Cobb angle supine)/Cobb angle standing × 100, Difference in compression ratio (%) = (compression ratio standing – compression ratio supine)/compression ratio standing × 100.

4. Surgical Procedures and Management

Patients were placed in a prone position on the operating table and received local or general anesthesia. Next, bone puncture trocars were placed bilaterally through the lateral margin of the pedicles at the fractured level and progressively passed through the pedicles into the vertebral body under C-arm guidance. An inflatable bone balloon was then used, and polymethylmethacrylate was carefully injected into the vertebral body. The injection was stopped if the cement reached the cortical edge of the vertebral body or leaked into extraosseous structures

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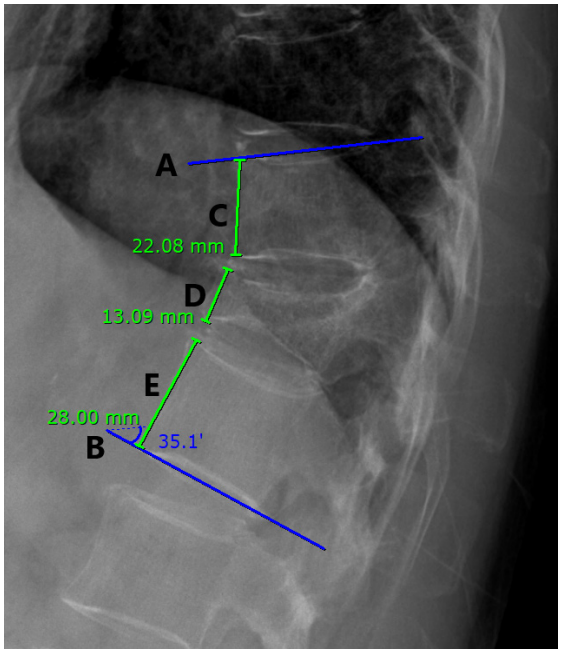

Fig. 1. Five lines (A–E) of the thoracolumbar vertebrae in x-ray radiographs were determined. The Cobb angle was measured using the angle between the superior endplate of the vertebral body above (line A) and the inferior endplate of the vertebral body below (line B) the fractured vertebral body. The length of the line (C, D, E) was used to calculate the compression ratio.

or veins. After the procedure, the patients were maintained in a prone position for 10–15 minutes. All patients were restricted to bed rest after the procedure and were encouraged to ambulate on the first day after augmentation. To assist ambulation, patients were required to wear a brace for at least 1 month.

5. Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median with interquartile range. Discrete variables were expressed as counts and percentages. The chi-square test and Student t-test were used to assess the differences between the favorable and unfavorable outcome groups. We constructed scatterplots with regression lines to represent the associations between the differences in the Cobb angle and compression ratio with changes in VAS score. Box plots with dot plots were used to visualize the association between the Cobb angle and compression ratio with the changes in the VAS score. Receiver operating characteristic curve analysis was performed to identify the optimal cutoff values of the difference in the Cobb angle and compression ratio for predicting the short-term and mid-term favorable outcomes in patients receiving vertebral augmentation for OVCFs. The differences in the Cobb angle and compression ratio with the maximum concurrent sensitivity and specificity were considered the optimal cutoff values. The odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using the univariate and multivariate logistic regression to determine the independent predictive factors for favorable outcomes in patients receiving cement augmentation for OVCFs. Sex, age, body mass index, Cobb angle in the standing position, Cobb angle in the supine position, difference in the Cobb angle, compression ratio in the standing position, compression ratio in the supine position, difference in compression ratio, hypertension, and diabetes, were entered into the multivariable model. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the R software ver. 3.5.2. (https://www.r-project.org/; R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Demographic characteristics of the patients (n = 249)

Characteristic	Value
Age (yr)	69.3 ± 5.6
Male sex	56 (22.5)
Body mass index (kg/m^2)	22.6 ± 3.1
Bone mineral density	-3.1 ± 0.5
Shape of fracture	
Wedge	141 (56.6)
Biconcave	67 (26.9)
Crush	41 (16.5)
VAS preoperation	7.4 ± 1.3
VAS 1 month	2.9 ± 1.2
Cobb angle at standing (°)	18.9 ± 5.7
Cobb angle at supine (°)	11.4 ± 3.7
Compression ratio at standing (%)	49.6 ± 7.2
Compression ratio at supine (%)	37.7 ± 5.6

Values are presented as mean ± standard deviation or number (%).
VAS, visual analogue scale.

RESULTS

1. Demographic Characteristics of the Patients

All the surgeries were completed in 249 patients. The male-to-female patient ratio was 56:193, and the mean age was 69.3 years. L1 was the most common level affected in 126 cases, followed by T12 in 77 cases, T11 in 25 cases, and L2 in 21 cases. The demographic characteristics of the patients are presented in Table 1.

2. Association Between the Cobb Angle and Compression Ratio With the VAS Score

Fig. 2 shows the significant positive correlations between the differences in the Cobb angle and the change in the VAS score. We observed a statistically significant increase in the VAS score change with an increase in the Cobb angle ($p < 0.001$) (Fig. 2A). In addition, we observed a statistically significant increase in the VAS score change with an increase in the compression ratio ($p < 0.001$) (Fig. 2B).

3. Differences in the Cobb Angle and Compression Ratio for Predicting the Short-term Favorable Outcomes After Vertebral Augmentation

A comparison of the short-term clinical outcomes in the patients is summarized in Table 2. There was no significant difference in the preoperative VAS score between the 2 groups (favorable outcome group 7.5 ± 1.2 versus unfavorable outcome group 7.4 ± 1.4). The Cobb angle and compression ratio when standing and differences in the Cobb angle and compression

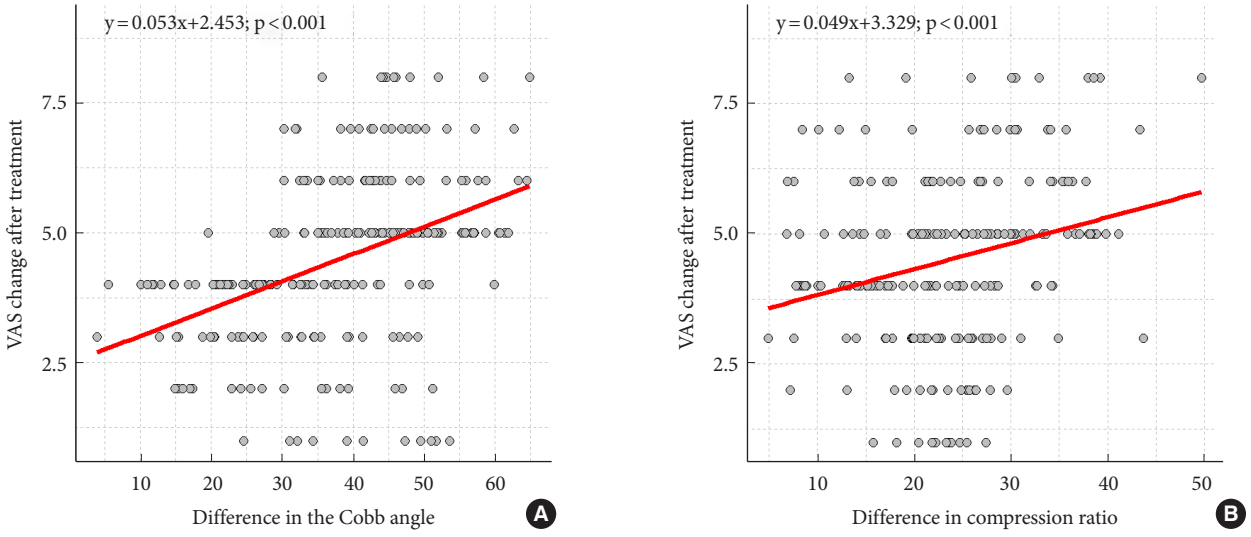

Fig. 2. A scatter plot with the linear regression line. Linear regression line showing the association between the difference in the Cobb angle and visual analogue scale (VAS) score after treatment (A) and difference in the compression ratio and VAS score after treatment (B).

Table 2. Comparisons of patients' variables according to the short-term clinical outcomes

Variable	Favorable outcome (n = 128)	Unfavorable outcome (n = 121)	p-value
Age (yr)	68.8 ± 5.2	69.9 ± 5.9	0.127
Male sex	34 (26.6)	22 (18.2)	0.152
Body mass index (kg/m^2)	22.5 ± 3.1	22.8 ± 3.1	0.521
Bone mineral density	-3.1 ± 0.5	-3.1 ± 0.5	0.389
VAS preoperation	7.5 ± 1.2	7.4 ± 1.4	0.286
VAS 1 month	1.8 ± 1.1	4.2 ± 1.3	< 0.001*
Cobb angle - standing (°)	20.3 ± 6.1	17.5 ± 4.8	0.001*
Cobb angle - supine (°)	11.1 ± 4.0	11.8 ± 3.3	0.107
Difference in Cobb angle (%)	45.7 ± 9.1	31.7 ± 11.2	< 0.001*
Compression ratio - standing (%)	51.1 ± 6.0	48.1 ± 7.9	0.001*
Compression ratio - supine (%)	37.5 ± 4.9	38.0 ± 6.2	0.442
Difference in compression ratio (%)	26.3 ± 8.4	20.6 ± 7.0	< 0.001*

Values are presented as mean ± standard deviation or number (%).
VAS, visual analogue scale.
*$p < 0.05$, statistically significant differences.

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ratio were higher in the favorable outcome group than in the unfavorable outcome group. Multivariate logistic regression analysis was performed to detect the factors associated with the favorable outcomes after surgery. As shown in Table 3, the differences in the Cobb angle (OR, 1.27; 95% CI, 1.16–1.40; p < 0.001) and compression ratio (OR, 1.12; 95% CI, 1.06–1.17; p < 0.001) were identified as the independent factors for predicting the short-term favorable outcomes after vertebral augmentation.

We observed a significant positive correlation between the differences in the Cobb angle and compression ratio with the change in VAS score (Fig. 2). The optimal cutoff values of the differences in the Cobb angle and compression ratio for predicting the short-term favorable outcomes after vertebral augmentation were 40.254 (area under the curve [AUC], 0.848; sensitivity, 74.2%; specificity, 82.6%; p < 0.001) and 26.493 (AUC, 0.703; sensitivity, 54.7%; specificity, 82.6%; p < 0.001), respectively (Fig. 3). When comparing the differences in the Cobb angle and compression ratio, the difference in the Cobb angle had a higher AUC for predicting the short-term favorable outcomes after vertebral augmentation.

Table 3. Multivariate logistic regression analysis for predicting the short-term favorable outcomes after vertebral augmentation based on various predictive factors

Variable	OR	95% CI	p-value
Age	0.95	0.89-1.02	0.149
Sex	2.27	0.95-5.42	0.065
Bone mineral density	0.48	0.22-1.04	0.063
Difference in Cobb angle	1.27	1.16-1.40	<0.001
Difference in compression ratio	1.12	1.06-1.17	<0.001

OR, odds ratio; CI, confidence interval.

4. Differences in the Cobb Angle and Compression Ratio for Predicting the Midterm Favorable Outcomes After Vertebral Augmentation

Of the 249 patients, 126 were followed up for more than 6 months. These patients were analyzed for the midterm clinical outcome after vertebral augmentation. A comparison of the midterm clinical outcomes in the patients is summarized in Table 4. The differences in the Cobb angle and compression ratio at supine were higher in the midterm favorable outcome group than in the unfavorable outcome group. Multivariate logistic regression analysis was performed to detect the factors associated with the favorable outcomes after surgery. As shown in Table 5, the difference in the Cobb angle (OR, 1.05; 95% CI, 1.02–1.09; p < 0.001) was found to be the only factor for predicting the midterm favorable outcomes after vertebral augmentation. In the favorable outcome group, hammer fracture occurred in 10.3% (7 of 68) of the patients, and in the unfavorable outcome group, hammer fracture occurred in 24.1% (14 of 58). There was no statistically significant difference between these results.

The optimal cutoff values of the difference in the Cobb angle for predicting the midterm favorable outcomes after vertebral augmentation were 35.526° (AUC, 0.676; sensitivity, 77.9%;

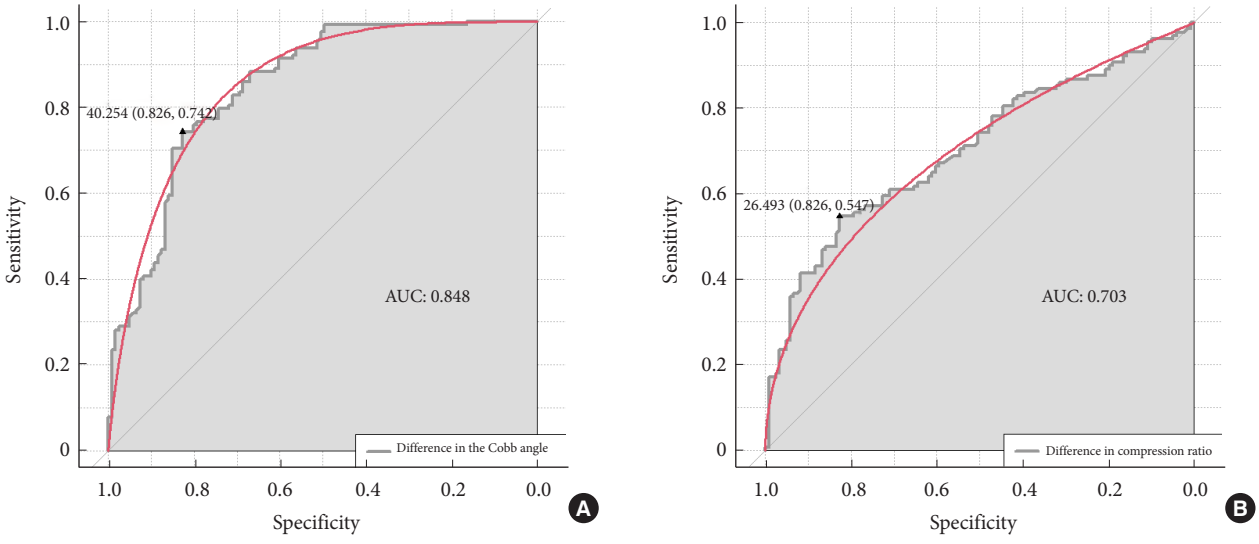

Fig. 3. Receiver operating characteristic (ROC) curve to identify the optimal cutoff values of the differences in the Cobb angle (A) and compression ratio (B) for the prediction of the short-term favorable outcomes after vertebral augmentation. AUC, area under the curve.

Table 4. A comparison of the patients' variables according to the midterm clinical outcomes

Variable	Favorable outcome (n = 68)	Unfavorable outcome (n = 58)	p-value
Age (yr)	69.1 ± 5.8	70.3 ± 6.1	0.257
Male sex	22 (32.4)	10 (17.2)	0.082
Body mass index (kg/m^2)	22.7 ± 3.3	22.9 ± 2.8	0.792
Bone mineral density	-3.1 ± 0.5	-3.2 ± 0.5	0.256
Cobb angle at standing (°)	20.7 ± 5.7	18.6 ± 5.0	0.030*
Cobb angle at supine (°)	11.8 ± 3.8	11.9 ± 3.5	0.846
Difference in Cobb angle (%)	42.9 ± 11.3	35.1 ± 12.4	< 0.001*
Compression ratio at standing (%)	50.6 ± 5.3	52.7 ± 4.8	0.021*
Compression ratio at supine (%)	37.3 ± 3.5	40.8 ± 4.4	< 0.001*
Difference in compression ratio (%)	25.6 ± 8.8	22.4 ± 6.7	0.021*
Hammer fracture	7 (10.3)	14 (24.1)	0.066

Values are presented as mean ± standard deviation or number (%).
*p < 0.05, statistically significant differences.

Table 5. Multivariate logistic regression analysis for predicting the midterm favorable outcomes after cement augmentation based on various predictive factors

Variable	OR	95% CI	p-value
Age	0.94	0.88–1.02	0.099
Sex	2.41	0.91–6.40	0.078
Bone mineral density	0.38	0.23–1.05	0.081
Difference of Cobb angle	1.05	1.02–1.09	< 0.001
Difference of compression ratio	0.63	0.37–1.07	0.087

OR, odds ratio; CI, confidence interval.

specificity, 53.4%; p < 0.001). The optimal cutoff value of the difference in compression ratio for predicting the midterm favorable outcomes after vertebral augmentation was 26.583 (AUC, 0.629; sensitivity, 54.4%; specificity, 72.4%; p < 0.001) (Fig. 4).

5. Differences in the Cobb Angle and Compression Ratio According to Shape of Fracture

The most common fracture shape was the wedge shape (56.6%). The biconcave and crush shapes were 26.9% and 16.5%, respec-

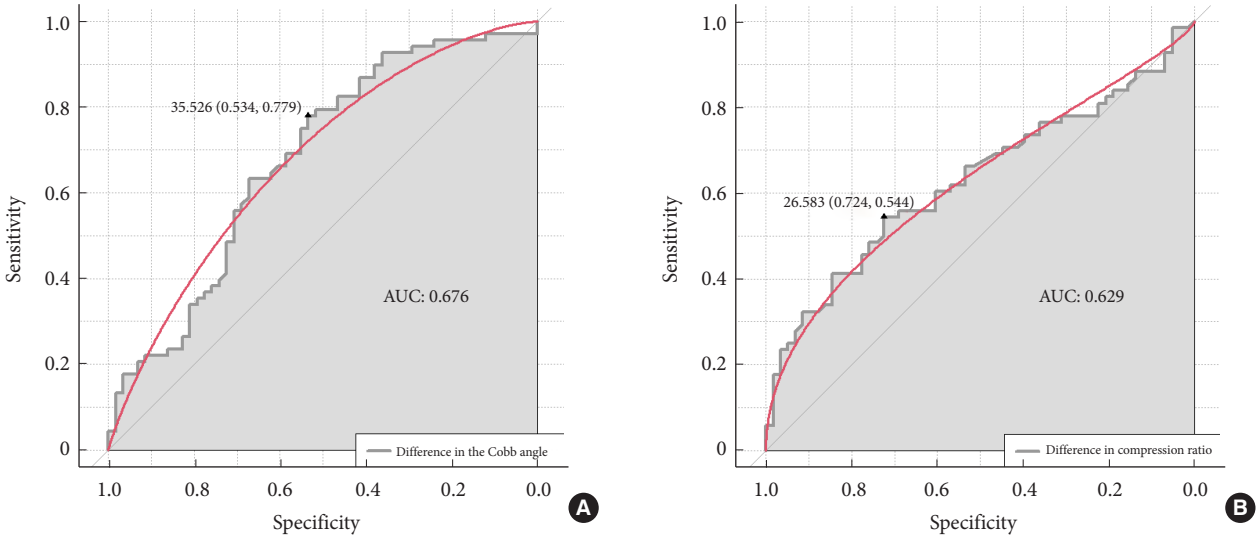

Fig. 4. Receiver operating characteristic (ROC) curve to identify the optimal cutoff values of the differences in the Cobb angle (A) and compression ratio (B) for the prediction of the midterm favorable outcomes after vertebral augmentation. AUC, area under the curve.

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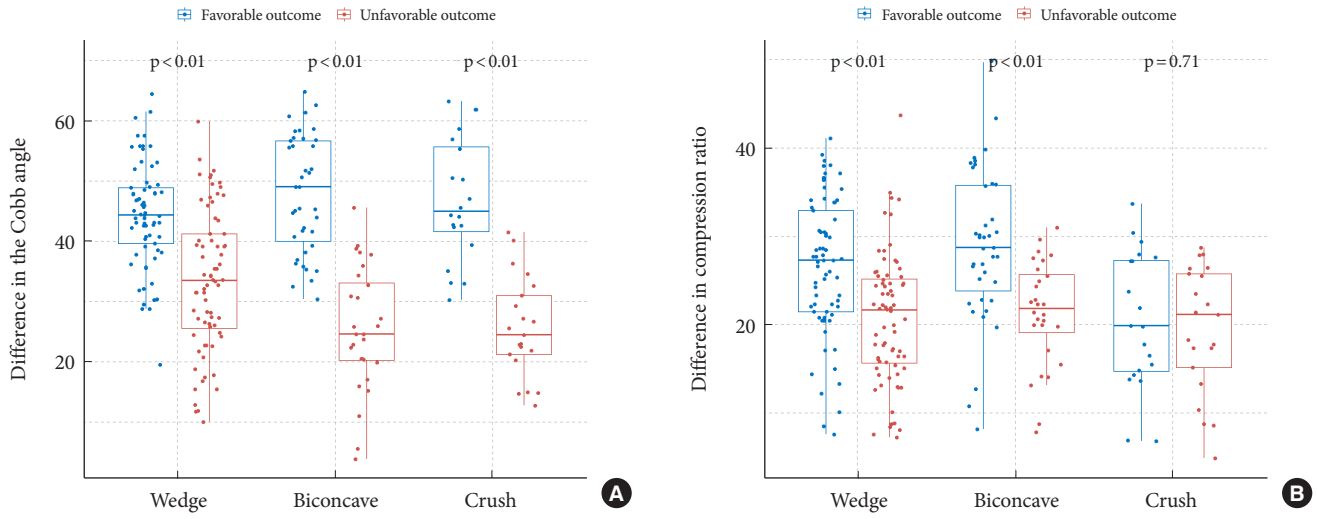

Fig. 5. Boxplots with dot plots of the differences in the Cobb angle (A) and compression ratio (B) classified according to the shape of the fracture.

tively. There was no significant difference in the Cobb angle or compression ratio according to the shape of the fracture. In the classification according to fracture shape, we found that the change in VAS score was significantly different from the differences in the Cobb angle and compression ratio (Fig. 5).

DISCUSSION

We found that the differences in the Cobb angle and compression ratio between the standing and supine positions were related to the short-term clinical outcome after vertebral augmentation. The optimal cutoff values of the differences in the Cobb angle and compression ratio for predicting the short-term favorable outcomes were 40.254° (AUC, 0.848) and 26.493° (AUC, 0.703), respectively. In addition, the optimal cutoff values of the differences in the Cobb angle and compression ratio for predicting the midterm favorable outcomes were 35.526° (AUC, 0.676) and 26.583° (AUC, 0.629), respectively. The difference in the Cobb angle was found to be the only factor for predicting the midterm favorable outcomes after vertebral augmentation. To the best of our knowledge, this study is the first study to suggest that the difference in the Cobb angle between the standing and supine positions is related to the clinical outcomes after vertebral augmentation in patients with OVCF.

Several treatments have been used to manage OVCFs. Typical treatments include conservative treatment, minimally invasive surgery (vertebral augmentation), and open surgery with spinal fusion. In many studies, cement augmentation was appropriate for treating OVCFs because it reduced pain and restored ambulation with minor complications in comparison to conservative treatment.[12-14] Vertebral augmentation provides significant, immediate, and sustained pain relief in patients with back pain from OVCFs. It rapidly improves physical function and the quality of life in patients with OVCFs. However, vertebral augmentation has adverse effects. Adjacent segment fractures and cement leakage have been reported.[15,16] The effectiveness of vertebral augmentation compared with conservative treatment is controversial.

Increase in the loading forces on the vertebral body and posterior tension forces increase pain after OVCFs.[17] A previous study reported that the degree of collapse of the vertebral body and the intensity of back pain are partially related.[7] The extent of radiologic collapse had no bearing on the length of hospital stay. However, in previous studies, measurements were only based on supine radiographs. The patients with compression fractures complained of more pain in the standing position than in the supine position. Based on this observation, we postulated that standing radiographs may provide some information about instability at the fracture level.

Qian et al.[11] reported that improvement in symptoms after kyphoplasty is better in patients with wedge-shaped changes in the supine and standing positions. There are 3 types of osteoporotic fractures: wedge-shaped, crush, or biconcave fractures.[18] In that study, only wedge-shaped compression fractures were analyzed. However, the wedge shape ratio cannot be measured in the biconcave compression fractures. Therefore, the Cobb angle and compression ratio, which can be measured even in the biconcave or crush shape fracture, were analyzed in this study.

Patients with symptomatic OVCFs typically present with severe back pain following a minor injury. Fracture site instability is thought to be the main cause of back pain in patients with OVCF.[19] Therefore, areas with severe instability should be targeted for vertebral augmentation. Pain relief can be expected when the instability is resolved by injecting cement into the fracture site. We observed a significant correlation between the differences in the Cobb angle and compression ratio with the short-term and midterm clinical outcomes after vertebral augmentation. Differences in the Cobb angle and change in compression ratio were identified as the independent factors for predicting short-term favorable outcomes after vertebral augmentation. In addition, difference in the Cobb angle was found to be the only factor for predicting the midterm favorable outcomes after vertebral augmentation. The results of our study showed that the more severe the instability, the better the postoperative outcome after vertebral augmentation. Based on the results of our study, it can be inferred that the pain after OVCFs is caused by instability in the fractured vertebrae. Instability at the fractured vertebrae is thought to be the main cause of back pain in patients with OVCF. Therefore, areas with severe instability should be targeted for vertebral augmentation. Pain relief can be expected when the instability is resolved by cement augmentation at the fracture site.

To measure the compression ratio, a total of the 3 heights of the fractured vertebral body and the adjacent 2 should be measured. On the other hand, to measure the Cobb angle, the angle between the superior endplate of the vertebral body above and the inferior endplate of the vertebral body below the fractured vertebral body should be measured. In addition, when measuring the compression ratio, an error may occur depending on which point is measured because it is measured from the fractured vertebral body. However, when measuring the Cobb angle, the normal vertebral bodies above and below the fractured vertebra are used, and the possibility of such an error is relatively small. When measuring the angles and heights, there is a possibility of interobserver error. However, if the number of measured values can be reduced, this error will reduce. It is easier to measure the Cobb angle than the compression ratio, with a reduced possibility of error.

Osteoporosis is one of the main factors that increase kyphosis after compression fracture. Bones with low quality cannot resist the vertebra's loads, leading to a loss in the vertebral body height.[20] Therefore, the height of the vertebral body may decrease more in the standing position, where the load on the spine increases, than in the supine position, where the load is less. Based on this, it can be expected that the more severe the osteoporosis, the greater the difference in the Cobb angle between the standing and supine positions. However, in our study, there was no significant correlation between the BMD and difference in the Cobb angle between the standing and supine positions. This result is probably because only patients with osteoporosis with an average BMD of -3.1 were included in this study. To elucidate the relationship between the BMD and difference in the Cobb angle between the standing and supine positions, a larger study including patients with osteopenia with BMD greater than -2.5 should be conducted in the future.

Many studies have proposed a high recurrent compression fracture rate after augmentation procedure, possibly related to an increase in the stiffness of the treated vertebra known as the "Hammer effect".[21,22] Kim et al.[23] found an increased risk of recurrent fracture of the adjacent level with increased height restoration after vertebroplasty. According to previous studies, the risk of recurrent fracture occurrence appears to be greater in kyphoplasty (45%–75%)[24,25] than in vertebroplasty (0%–16%).[23,26] In our study, 16.7% (21 of 126) of the recurrent fractures occurred after kyphoplasty. It is thought that the lower incidence of recurrent fractures in our study compared to that of previous studies was due to the short observation period of 6 months. Because there is a possibility of hammer fracture after augmentation, surgeons must carefully consider the difference in the Cobb angle between the standing and supine positions when deciding whether to operate.

In Korea, the national health insurance service system allows kyphoplasty when there is OVCF with a compression ratio of >30% and noncontrolled pain despite medical treatment and bed rest for more than 3 weeks. We found that the changes in the Cobb angle and compression ratio between the standing and supine positions were significantly related to the clinical outcomes after surgery. Based on these results, it is necessary to consider the differences according to the posture, and not based on the simple compression ratio, before determining the management of OVCF.

Surgical treatment should be considered in cases of nonunion or osteonecrosis, and spinal cord compression after conservative treatment has failed. To date, various surgical procedures have been reported, including vertebroplasty or kyphoplasty, spinal fusion,[27,28] vertebroplasty with posterior spinal fusion,[29] and posterior spinal shortening.[30] Surgical treatment of OVCF has been challenging for surgeons, because there are potential risks of instrumentation failure, including screw loosening, pseudarthrosis, and postoperative infection due to bone fragility in elderly patients with several comorbidities. OVCFs can be man-

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aged with cement augmentation which is a less invasive procedure than spinal fusion. However, the most appropriate method should be selected based on the patient's condition and understanding of each surgical method.

Our study has some limitations. First, it was a retrospective study and included a relatively small number of patients with a relatively short follow-up period. Since our study was retrospective, it was more likely to be affected by various types of bias compared to a randomized controlled study. Second, only patients who underwent cement augmentation were included. The decision of vertebral augmentation was made only by the surgeon, which might have introduced a selection bias. A study on the difference in the Cobb angle and the degree of pain according to the posture is needed even in patients who have not undergone surgery. Third, although the Cobb angle and the degree of compression ratio after cement augmentation may be related to the clinical outcomes, the analysis of the postoperative Cobb angle and compression ratio was omitted in this study. Fourth, patients over 80 years of age were excluded. A recent study has shown that cement augmentation is a safe treatment for OVCFs in very elderly patients.[31] Studies involving patients over 80 years of age should be conducted in the future. Fifth, since the spine has a normal physiological curvature, there is a difference in the Cobb angle for each segment. Therefore, it is necessary to analyze the difference in the Cobb angle between the standing and supine positions mentioned in this study for each segment. Therefore, a larger, randomized controlled case study with a long-term follow-up is required in the future. Despite these limitations, our study is the first to suggest that the difference in the Cobb angle between the standing and supine positions is related to the clinical outcomes after vertebral augmentation in patients with OVCF.

CONCLUSION

We found that the differences in the Cobb angle and compression ratio between the standing and supine positions were related to the short-term and midterm clinical outcomes after vertebral augmentation in patients with OVCFs. Furthermore, the difference in the Cobb angle was found to be the only factor for predicting the midterm favorable outcomes after vertebral augmentation. The optimal cutoff values of the difference in the Cobb angle for predicting the midterm favorable outcomes was 35.526°. The outcome was better when there was a difference of approximately 35% or more in the Cobb angle between the standing and supine positions. To the best of our knowledge, this study is the first to suggest that the difference in the Cobb angle between the standing and supine positions is related to the clinical outcomes after vertebral augmentation in patients with OVCF. Surgeons should pay attention to the difference in the Cobb angle depending on the posture when deciding to perform vertebral augmentation in patients with OVCFs.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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REFERENCES

1. Itshayek E, Miller P, Barzilay Y, et al. Vertebral augmentation in the treatment of vertebral compression fractures: review and new insights from recent studies. J Clin Neurosci 2012; 19:786-91.
2. Riggs BL, Melton LJ. Involutional osteoporosis. N Engl J Med 1986;314:1676-86.
3. Cooper C, Atkinson EJ, O'Fallon WM, et al. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. J Bone Miner Res 1992;7:221-7.
4. Rao RD, Singrakhia MD. Painful osteoporotic vertebral fracture. Pathogenesis, evaluation, and roles of vertebroplasty and kyphoplasty in its management. J Bone Joint Surg Am 2003;85:2010-22.
5. Francis RM, Baillie SP, Chuck AJ, et al. Acute and long-term management of patients with vertebral fractures. QJM 2004;

97:63-74.
6. Yamato M, Nishimura G, Kuramochi E, et al. MR appearance at different ages of osteoporotic compression fractures of the vertebrae. Radiat Med 1998;16:329-34.
7. Lee YL, Yip KM. The osteoporotic spine. Clin Orthop Relat Res 1996;(323):91-7.
8. Mehta JS, Reed MR, McVie JL, et al. Weight-bearing radiographs in thoracolumbar fractures: do they influence management? Spine 2004;29:564-7.
9. McKiernan F, Faciszewski T. Intravertebral clefts in osteoporotic vertebral compression fractures. Arthritis Rheum 2003;48:1414-9.
10. Toyone T, Toyone T, Tanaka T, et al. Changes in vertebral wedging rate between supine and standing position and its association with back pain: a prospective study in patients with osteoporotic vertebral compression fractures. Spine 2006;31:2963-6.
11. Qian L, Pan J, Liu ZD, et al. The correlation between vertebral wedge-shaped changes in X-ray imaging at supine and standing positions and the efficacy of operative treatment of thoracolumbar spinal fracture in the elderly. Spinal Cord 2013;51:904-8.
12. Lee HM, Park SY, Lee SH, et al. Comparative analysis of clinical outcomes in patients with osteoporotic vertebral compression fractures (OVCFs): conservative treatment versus balloon kyphoplasty. Spine J 2012;12:998-1005.
13. Diamond TH, Champion B, Clark WA. Management of acute osteoporotic vertebral fractures: a nonrandomized trial comparing percutaneous vertebroplasty with conservative therapy. Am J Med 2003;114:257-65.
14. Alvarez L, Alcaraz M, Pérez-Higueras A, et al. Percutaneous vertebroplasty: functional improvement in patients with osteoporotic compression fractures. Spine (Phila Pa 1976) 2006; 31:1113-8.
15. Klazen CAH, Lohle PNM, de Vries J, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. Lancet 2010;376:1085-92.
16. Mpotsaris A, Abdolvahabi R, Hoffleith B, et al. Percutaneous vertebroplasty in vertebral compression fractures of benign or malignant origin: a prospective study of 1188 patients with follow-up of 12 months. Dtsch Arztebl Int 2011;108: 331-8.
17. Yaman O, Zileli M, Şentürk S, et al. Kyphosis after thoracolumbar spine fractures: WFNS Spine Committee Recommendations. Neurospine 2021;18:681-92.
18. Ismail AA, Cooper C, Felsenberg D, et al. Number and type of vertebral deformities: epidemiological characteristics and relation to back pain and height loss. European Vertebral Osteoporosis Study Group. Osteoporos Int 1999;9:206-13.
19. Barr JD, Barr MS, Lemley TJ, et al. Percutaneous vertebroplasty for pain relief and spinal stabilization. Spine 2000;25: 923-8.
20. Sadatsune DA, Costa PP, Caffaro MF, et al. Thoracolumbar burst fracture: correlation between kyphosis and function after surgical treatment. Rev Bras Ortop 2015;47:474-8.
21. Baroud G, Bohner M. Biomechanical impact of vertebroplasty. Postoperative biomechanics of vertebroplasty. Joint Bone Spine 2006;73:144-50.
22. Baroud G, Nemes J, Heini P, et al. Load shift of the intervertebral disc after a vertebroplasty: a finite-element study. Eur Spine J 2003;12:421-6.
23. Kim SH, Kang HS, Choi JA, et al. Risk factors of new compression fractures in adjacent vertebrae after percutaneous vertebroplasty. Acta Radiol 2004;45:440-5.
24. Fribourg D, Tang C, Sra P, et al. Incidence of subsequent vertebral fracture after kyphoplasty. Spine (Phila Pa 1976) 2004; 29:2270-6; discussion 2277.
25. Gaitanis IN, Hadjipavlou AG, Katonis PG, et al. Balloon kyphoplasty for the treatment of pathological vertebral compressive fractures. Eur Spine J 2005;14:250-60.
26. Tanigawa N, Komemushi A, Kariya S, et al. Radiological follow-up of new compression fractures following percutaneous vertebroplasty. Cardiovasc Intervent Radiol 2006;29:92-6.
27. Kaneda K, Asano S, Hashimoto T, et al. The treatment of osteoporotic-posttraumatic vertebral collapse using the Kaneda device and a bioactive ceramic vertebral prosthesis. Spine (Phila Pa 1976) 1992;17(8 Suppl):S295-303.
28. Ataka H, Tanno T, Yamazaki M. Posterior instrumented fusion without neural decompression for incomplete neurological deficits following vertebral collapse in the osteoporotic thoracolumbar spine. Eur Spine J 2009;18:69-76.
29. Matsuyama Y, Goto M, Yoshihara H, et al. Vertebral reconstruction with biodegradable calcium phosphate cement in the treatment of osteoporotic vertebral compression fracture using instrumentation. J Spinal Disord Tech 2004;17:291-6.
30. Saita K, Hoshino Y, Kikkawa I, et al. Posterior spinal shortening for paraplegia after vertebral collapse caused by osteoporosis. Spine 2000;25:2832-5.
31. Galivanche AR, Toombs C, Adrados M, et al. Cement augmentation of vertebral compression fractures may be safely considered in the very elderly. Neurospine 2021;18:226-33.

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Original Article

Learning Curve of ROSA ONE Spine System for Transpedicular Screw Placement

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Objective: The study investigated our institutional learning curve for the ROSA ONE spine system (ROSA) based on ROSA usage time.
Methods: ROSA was designed to provide high accuracy for spinal pedicle screw placement through a built-in tracking technique. This study was conducted from November 2018 to January 2021. The time taken to complete each step of the robotic workflow was recorded. Patient demographics, comorbidities, surgical indications, and number of screw placements were examined in subgroup analysis. The Curve Fitting-General package (a part of NCSS 2021 software) was used to fit a mathematical model to the learning curve. Patient demographics, imaging data, and surgical time were reviewed retrospectively.
Results: A total of 167 patients who had undergone surgery were included. The mean total ROSA usage time was 107.1 ± 27.3 minutes. The estimated learning rate was 90.4%, and the largest slope change occurred close to the time of the 20th surgery. The observed overall learning trend in the 4-screw group could be attributed to screw planning. The presence of scoliosis ($p = 0.73$) or spondylolisthesis ($p = 0.70$) did not significantly influence the mean total time (TT) for all patients; however, the mean TT differed significantly ($p < 0.01$) among subgroups stratified by body mass index, screw number placement, and thoracic spine involvement.
Conclusion: To the best of our knowledge, this is the first study to examine the learning curve for the various crucial steps of ROSA-guided pedicle screw placement. The indicative learning curve involved 20 patients who had undergone surgery.

Keywords: Learning curve, Transpedicular screw, Spinal fusion, ROSA ONE spine system

INTRODUCTION

In recent decades, substantial advances have been made in pedicle screw techniques for treating spinal diseases.[1] Three-column fixations, which provide the most rigid form of posterior stabilization, are commonly used to treat spinal degenerative disease, fractures, and deformities. Nevertheless, pedicle screw malposition, particularly pedicle violation (which often occurs when performing freehand techniques), is still an unavoidable problem. Multiple surgical techniques (e.g., image-guided or navigation devices and robot-assisted pedicle screw placement) have been developed to improve the precision of pedicle screw placement and reduce pedicle violation risk.[2,3] Robot-assisted techniques provide noninferior to superior benefits relative to freehand techniques in terms of pedicle screw placement accuracy, pain scores, Oswestry Disability Index

scores, and intraoperative radiation exposure time (i.e., shorter exposure time) as well as equivalent postoperative stay.[2] New technologies are increasingly being applied to improve the capabilities of established systems. Three major robotic systems are currently used for spine surgery, namely the Renaissance Robotic Surgical System (Mazor Robotics, Caesarea, Israel), Ti-Robot Orthopaedic Robotic System (TINAVI Medical Technologies, Beijing, China), and the newly U.S. Food and Drug Administration (FDA)-approved ROSA robot (Medtech, Montpellier, France).[4]

Although robot-assisted spine surgery allows for efficient and accurate hardware placement, this technology is relatively new and is seldom used by spine surgeons. The newly FDA-approved ROSA robot was designed to aid spinal surgeons in performing minimally invasive spine procedures. The ROSA ONE spine system (ROSA) was designed to provide assisting spinal pedicle screw placement through a built-in tracking technique. However, few studies have examined the use of this technology and have developed corresponding guidelines. New surgical technologies such as the ROSA robotic system have a substantial learning curve.[5] In 2018, our institute became the first in Asia to utilize ROSA, which has been utilized in 171 spinal surgeries so far. Therefore, the present study investigated our institutional learning curve for ROSA based on ROSA usage time.

MATERIALS AND METHODS

1. Study Design and Subjects

A retrospective chart review (the requirement for informed consent was waived by the relevant Institutional Review Board) of data pertaining to the period from November 2018 to January 2021 was conducted. The demographic, preoperative, and intraoperative data of 167 patients who underwent thoracic and lumbosacral pedicle screw placement with minimally invasive navigated robotic guidance using intraoperative computed tomography (CT, O-arm device) were analyzed. A total of 171 surgeries were included; 4 surgeries were excluded because they were not performed as per the current surgical workflow. The included surgeries were all elective surgeries for spinal diseases requiring spinal fixation, which included degenerative spondylolisthesis, scoliosis, spinal stenosis, vertebral compression fracture, vertebral body malignancies, cord compression, and disc disease. The decision to perform robot-assisted or conventional posterior instrumentation was made on the basis of clinical findings independent of the present study. The time taken for each step of the robotic workflow was recorded. Subgroup analysis of patient demographics, comorbidities, surgical indications, and number of screw placements were conducted. The spinal level of screw fixation (thoracic, lumbar, or sacral level) was recorded accordingly. Of the 167 patients, 158 patients had bone mineral density (BMD) results. Pedicle variation and deformities such as scoliosis and spondylolisthesis were graded as per the Nash and Moe grading method and Meyerding classification, respectively.

2. Surgical Technique

In the operating room, after the general anesthesia, the patient is put on the radiolucent surgical table with prone position and 2 bolsters are positioned longitudinally beneath both sides of trunk. The surgical region is sterilized and draped, and the O-arm device and ROSA are positioned. After the percutaneous reference pin is fixed in the right iliac wing, the ROSA registration is started. The fiducial box which is held by ROSA arm is placed above surgical region, and the 3-dimensional (3D) image acquisition is performed by O-arm device afterwards. The 3D transformation is conducted through the ROSA workstation. The surgeon plans the 3D trajectory of screw by the ROSA workstation. The ROSA workstation provides several choices of the screw simulation with distinguished diameter and length, as well as different color for the operative side. After the screw planning, the surgeon scrubs again for the guide pin placement under the ROSA guide. Subsequently, the 3D image confirmation of guide pin placement by the O-arm device is performed (Fig. 1). When necessary, decompression, fusion, or other surgical procedures are subsequently performed using minimally invasive techniques[6] before the pedicle screws are placed along the pin. Eventually, the surgical arm is removed, and the wounds were closed.

3. Surgical Workflow

In order to analyze the learning curve of the ROSA ONE Spine System, we segmented the ROSA usage time into the 4 periods as follows (Fig. 2):[4]

1) Step 1: ROSA installation (S1)

This step includes the sterile draping of the surgical region and devices, percutaneous insertion of the reference pin on the right iliac wing or spine process, and the performance of ROSA boot-up registration.

2) Step 2: image acquisition (S2)

The intraoperative 3D image acquisition of the surgical re-

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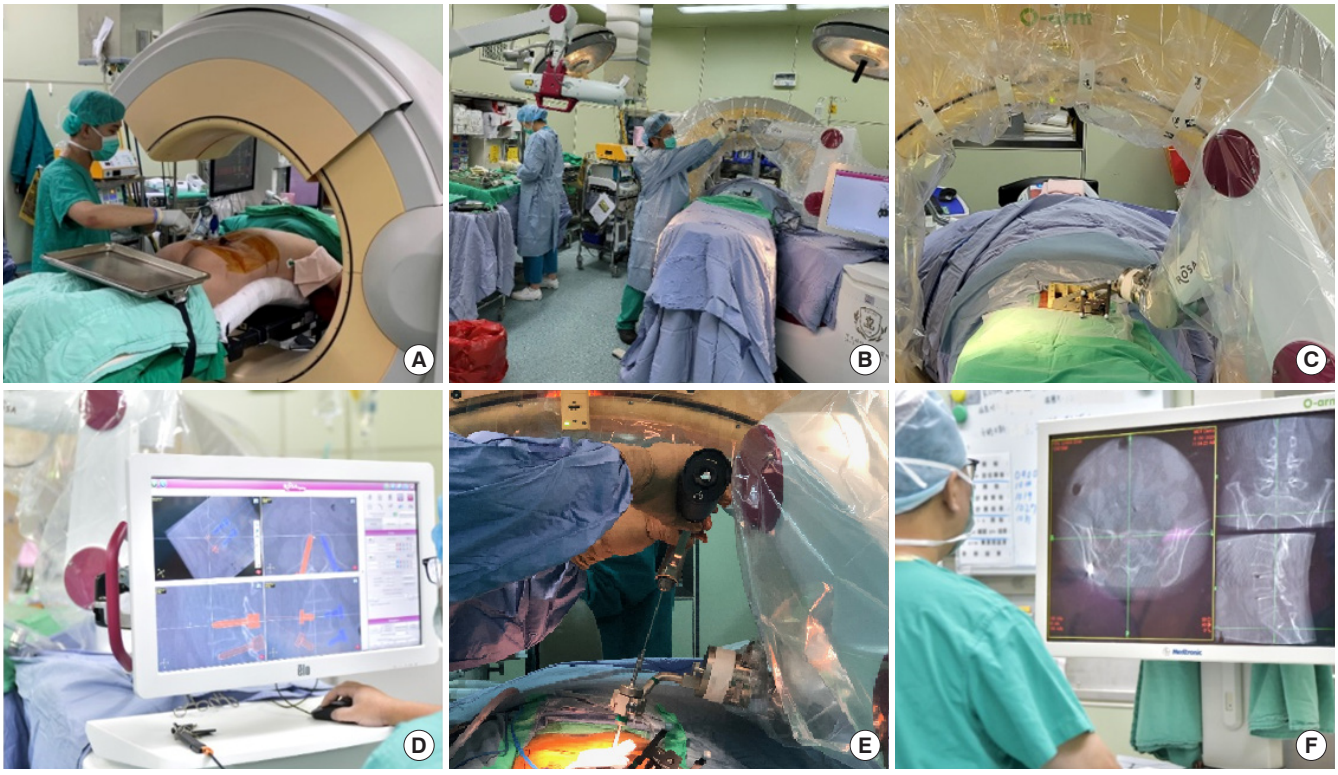

Fig. 1. (A) Sterile draping the surgical region. (B) Overview of operation room and ROSA registration. (C) Three-dimensional (3D) acquisition with fiducial box in position. (D) Screw planning by using the ROSA workstation. (E) Drilling and guide-wire placing under ROSA guide. (F) 3D image confirmation of the guide pin placement.

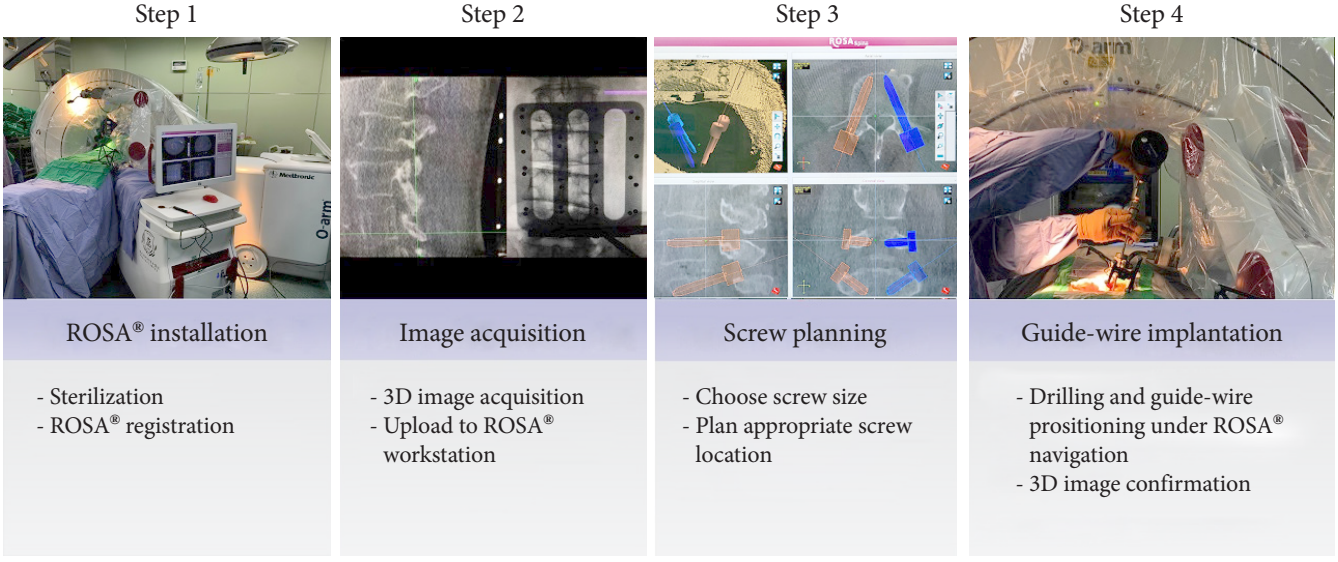

Fig. 2. Steps of surgical workflow. Step 1: ROSA installation step comprising sterilization and ROSA registration. Step 2: image acquisition step comprising 3-dimensional (3D) image acquisition and uploading of data to ROSA workstation. Step 3: screw planning step comprising selection of appropriate screw size and determination of appropriate screw location. Step 4: guide-wire implantation step comprising drilling and guide-wire positioning through ROSA navigation with 3D image confirmation.

gion is conducted using the O-arm device with installed reference devices, and 3D transformation is conducted through the ROSA workstation.

3) Step 3: screw planning (S3)

The surgeon plans the 3D trajectory (including the screw entry point, direction, and paramedian longitudinal skin incision) for the minimally invasive surgical approach by using the ROSA workstation.

4) Step 4: guide pin placement (S4)

This step includes robotic auto-tracking movement to the planned skin surface, soft tissue deepening, bone drilling, and placing the guide-wire needle into the vertebrae. The steps are repeated to complete the implantation of all guiding pins, after which CT image confirmation of guide pin placement (through the O-arm device) is performed.

Total time (TT) of ROSA usage measures the TT taken to complete all of the aforementioned steps.

4. Statistical Methods

All categorical variables are expressed as numbers (percentages), and all continuous variables are expressed as means ± standard deviations. All data analyses were conducted using NCSS 2021 software (NCSS, East Kaysville, UT, USA) with 2-sided tests and a type 1 error rate of 0.05. The learning curve was plotted according to TT and the number of procedures. The Curve Fitting-General package (which is a part of NCSS 2021) was used to fit the following mathematical model to the learning curve: $Y = A \times X^B$

where Y = TT of each procedure, A = the TT taken for the first procedure (i.e., the first case), X = the procedure index, and B = the index of learning. The estimated B value (and its 95% confidence interval) was then used to calculate the estimated learning rate (LR) as per the following mathematical formula:

$$B = \frac{\log LR}{\log 2.}$$

A general linear mixed-effect model was used to determine the effect of the fixed factors on each ROSA time interval. The fixed factors included in the model were stratified categories of clinical experience, sex, number of screws (4, 6, or 8), presence of scoliosis (yes or no), and T spine involvement (yes or no). Two interaction terms (number of screws × presence of scoliosis, T spine involvement × presence of scoliosis) were also included in the model. The age, body mass index (BMI), and BMI of each patient were measured as covariates, and the procedure index was measured as the random factor.

RESULTS

1. Case Demographics and Surgical Indications

In our cohort (Table 1), the mean age of patients was 64.7 ± 10.3 years (range, 27–88 years). Moreover, 104 (62.3%) and 63 (37.7%) were women and men, respectively. Their BMI was 25.9 ± 4.3 kg/m^2 (range, 16.2–41.1 kg/m^2), and their mean BMD T-score was -0.9 ± 1.7 (range, -4.4 to 5.4). Comorbidities comprised cancer (n = 4), osteoporosis (n = 31), obesity (n = 56), diabetes (n = 31), cardiovascular disease (n = 21), and hypertension (n = 83). Surgical indications comprised spondylolisthesis (n = 156), scolio-

Table 1. Characteristics of 167 patients who received ROSA-guided pedicle screw placement

Variable	Value
Age (yr)	64.7 ± 10.3
< 65	75
≥ 65	92
Sex, male:female	63:104
Body mass index (kg/m^2)	25.9 ± 4.3
< 27	111
≥ 27	56
Bone mineral density (T-score)	-0.9 ± 1.7
> -2.5	127/158
≤ -2.5	31/158
Comorbidity	
Hypertension	83
Type 2 diabetes mellitus	31
Coronary heart disease	21
Indication	
Spondylolisthesis	
Grade I	124
Grade II	32
Fracture	8
Vertebral body malignancies	3
Scoliosis	
Yes	46
No	121
Instrumentation level	
T spine	4
T+L spine	4
L and L+S spine	159

Values are presented as mean ± standard deviation or number.

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sis (n = 46), and fracture (n = 8) or malignancies (n = 4) of the vertebral body resulting in spinal stenosis and myelopathy. Robotic surgery was most often performed with 4 screws (n = 106), followed by 6 (n = 51) and 8 (n = 10) screws. The spinal level of screw fixation was from T2 to S1, and the lumbar spine was involved for most patients (95.2%; the thoracic spine was involved in only 8 patients).

2. Effect of Number of Screws, Thoracic Spine Involvement, Scoliosis, and Spondylolisthesis on Total ROSA Usage Time

The mean total ROSA usage time was 107.1 ± 27.3 minutes, and the most time-consuming fractioned ROSA usage component was operating theater preparation and reference device installation (S1 = 40.2 ± 16.1 minutes), followed by guide pin placement (S4 = 29.5 ± 11.0 minutes), screw planning (S3 = 15.5 ± 7.3 minutes), and image acquisition (S2 = 12.0 ± 7.3 minutes). Mean TT differed significantly ($p < 0.01$) among the subgroups stratified by number of screws, with the shortest mean TT (98.70 minutes; 95% CI, 85.10–112.30 minutes) achieved for 4-screw surgeries, followed by the mean TT for 6-screw (113.00 minutes; 95% CI, 100.90–125.09 minutes) and 8-screw (140.62 minutes; 95% CI, 120.58–160.67 minutes) surgeries. The subgroup analysis of TT was performed for patients who underwent ROSA spinal surgery, and the results revealed that thoracic spine involvement was associated with a longer mean TT ([131.11 minutes; 95% CI, 109.21–153.01 minutes] vs. [103.77 minutes; 95% CI, 96.73–110.82 minutes], $p = 0.01$). The presence of scoliosis ($p = 0.73$) or spondylolisthesis ($p = 0.70$) did not significantly influence mean TT for all patients. An analysis was further conducted to adjust for the interacting effect of number of screws, presence of spondylolisthesis, and presence of scoliosis; it did not reveal any significant difference among subgroups (Table 2).

3. Learning Curve for ROSA Usage Time

Through the application of a cumulative average model, we fitted a learning curve on the TT of all patients (Fig. 3), with an R^2 value of 0.35. The estimated LR was revealed to be 90.1% (88.3%–92.0%), and the largest slope change occurred close to time of the 20th surgery. Most enrolled patients received 4 screws; hence, we applied the same model to estimate the learning curve for each ROSA usage period in this specific group. Fig. 4 indi-

Table 2. Effect of number of screws, thoracic spine involvement, scoliosis, and spondylolisthesis on total time (TT)

Variable	Mean (95% CI)	p-value
Screw numbers		< 0.01
Group 1:4	98.70 (85.10–112.30)	0.02[†] / < 0.01[‡]
Group 2:6	113.00 (100.90–125.09)	< 0.01[§]
Group 3:8	140.62 (120.58–160.67)	
T spine involvement		0.01
No	103.77 (96.73–110.82)	
Yes	131.11 (109.21–153.01)	
Presence of scoliosis		0.73
No	118.63 (104.62–132.64)	
Yes	116.25 (101.48–131.01)	
Presence of spondylolisthesis		0.70
No	116.19 (103.78–128.61)	
Yes	118.69 (103.08–134.29)	
Presence of scoliosis × screw numbers	-	0.08
Presence of spondylolisthesis × screw numbers	-	0.08
Presence of scoliosis × presence of spondylolisthesis	-	0.30

Least square means of the TT for the levels of each fixed factor of interest when age = 65.3, body mass index = 25.8 kg/m^2, and bone mineral density = -0.90.
CI, confidence interval.
All values are adjusted for sex, clinical experience (every 20 cases), and presence of scoliosis × T spine involvement interaction.
[†]Benferroni adjusted p-value comparison between group 1 and 2. [‡]Benferroni adjusted p-value comparison between group 1 and 3. [§]Benferroni adjusted p-value comparison between groups 2 and 3.

cates that in the 4-screw group, the R^2 values of the estimated learning curve for S1, S2, S3, S4, and TT were 0.06, 0.12, 0.37, 0.03, and 0.51 respectively. These findings indicated that the observed overall learning trend for the 4-screw group can primarily be attributed to S3.

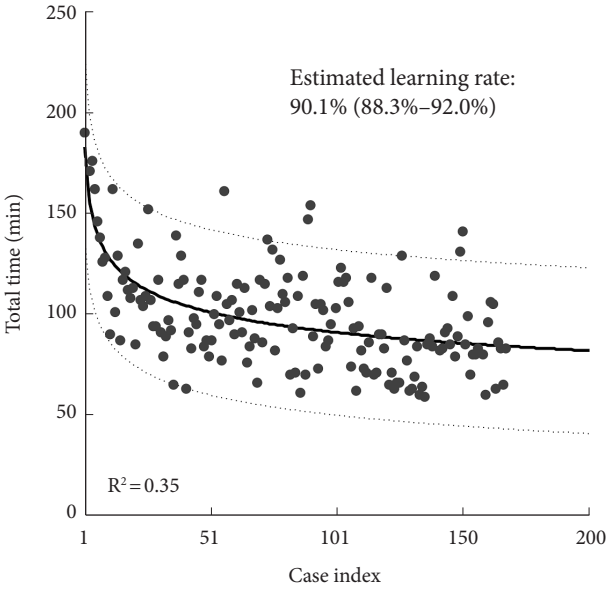

Fig. 3. Learning curve fitting when number of screws = 4.

4. Effect of Surgeon's Experience, Patients' Demographics and Comorbidities, Anatomical Variation and Deformity, and Level and Numbers of Involved Vertebrae on Fractioned ROSA Usage Period

For the conventional freehand technique, surgeon's experience, spinal level, number of screw insertions, obesity, and presence of spinal deformity (e.g., spondylolisthesis and scoliosis) were assumed to affect time usage for transpedicular screw placement. Therefore, we examined whether these measures moderated the effect of phase on fractioned ROSA usage period. Table 3 summarizes the results of the F tests for each of the fixed effects in each model, and they revealed the significant main effect of surgeon's experience (per 20 surgeries) on S2 ($F = 4.37$, $p < 0.01$), S3 ($F = 6.69$, $p < 0.01$), S4 ($F = 5.11$, $p < 0.01$), and TT ($F = 9.99$, $p < 0.01$). No significant association between surgeon's experience and S1 ($F = 1.18$, $p = 0.32$) was observed, and age

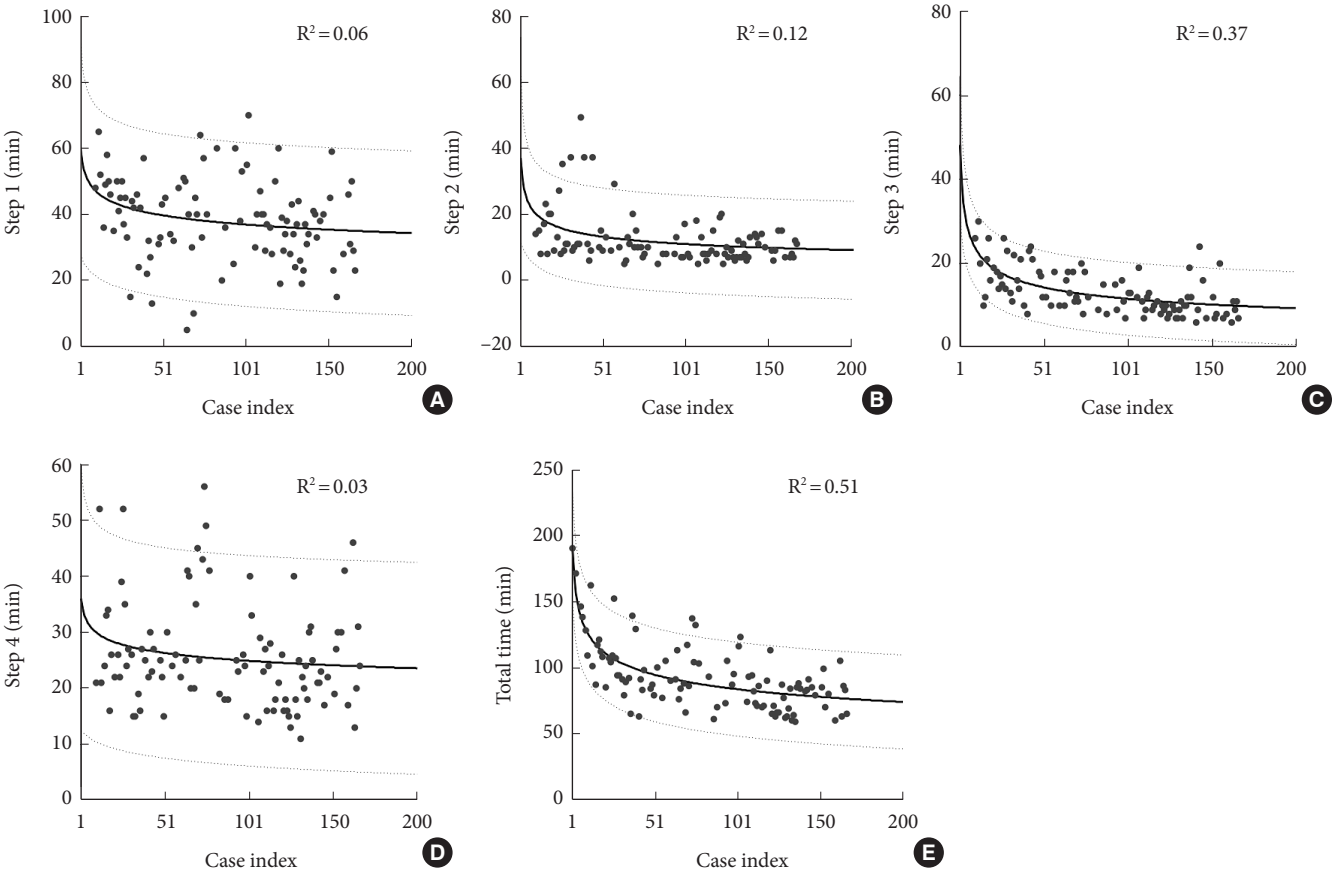

Fig. 4. Learning curve from all cases.

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Table 3. Effect of clinical experience and each factor on fractioned ROSA usage period

Fix factor	Step 1			Step 2			Step 3			Step 4			Total time		
	F-value	β-value	p-value	F-value	β-value	p-value	F-value	β-value	p-value	F-value	β-value	p-value	F-value	β-value	p-value
Clinical experience	1.18	-	0.32	4.37	-	< 0.01	6.69	-	< 0.01	5.11	-	< 0.01	9.99	-	< 0.01
Age	0.41	0.07	0.52	0.58	-0.05	0.45	0.03	-0.01	0.86	0.65	-0.06	0.42	0.01	0.02	0.91
Female sex	0.02	-0.34	0.89	0.02	-0.21	0.89	3.08	2.24	0.08	0.13	-0.62	0.72	0.32	2.23	0.57
BMI	0.11	0.09	0.74	1.68	0.20	0.20	0.38	-0.08	0.54	17.86	0.76	< 0.01	6.74	1.11	0.01
BMD	0.81	0.68	0.37	1.77	-0.58	0.19	0.46	0.25	0.50	1.57	0.64	0.21	1.03	1.15	0.31
Screw numbers	1.51	-	0.23	0.05	-	0.95	11.10	-	< 0.01	23.51	-	< 0.01	11.31	-	< 0.01
4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-4.16	0.22	-	-0.10	0.96	-	5.50	< 0.01	-	9.59	< 0.01	-	10.39	0.04
8	-	-18.46	0.07	-	4.84	0.42	-	6.55	0.21	-	23.91	< 0.01	-	17.29	0.29
T spine involvement	8.81	19.28	0.00	0.00	-0.18	0.96	0.02	0.43	0.89	4.09	8.95	0.05	7.90	28.92	0.01
Presence of scoliosis	2.84	-6.98	0.06	0.09	-1.60	0.36	0.22	0.54	0.64	3.06	-3.05	0.08	0.03	-10.69	0.86
Presence of spondylolisthesis	1.18	-3.13	0.33	0.28	2.06	0.69	0.00	-1.24	0.99	0.00	-1.67	0.98	0.50	-1.14	0.48

BMI, body mass index; BMD, bone mineral density.

and sex did not significantly influence the fractioned ROSA usage periods. BMI significantly influenced and positively predicted S4 ($F = 17.86$, $p < 0.01$) and TT ($F = 6.74$, $p = 0.01$). BMD did not significantly influence any fractioned/total ROSA usage period. Number of screws significantly influenced and positively predicted S3 ($F = 11.10$, $p < 0.01$), S4 ($F = 23.51$, $p < 0.01$), and TT ($F = 11.31$, $p < 0.01$). Also, the thoracic spine involvement significantly influenced and positively predicted S4 ($F = 4.09$, $p = 0.05$) and TT ($F = 7.90$, $p = 0.01$). When the presence of scoliosis or spondylolisthesis was added to the model, no significant main effect was observed (Table 3).

DISCUSSION

Similar to most contemporary surgical robotic devices, ROSA was designed as a shared-control system that combines the application of navigation with robotic technology.[4] Studies have demonstrated ROSA's benefits, particularly those derived from its real-time guidance feature.[6] Furthermore, the accuracy and reliability of 3D trajectory are helpful for minimally invasive surgery when exposure is limited.[4] However, surgeons who use ROSA are still affected by several major limitations, including a steep learning curve, inability to produce preoperative screw trajectories, and prolonged time taken to perform system installation and setup.[5]

Our single-institution retrospective study revealed the experience derived from performing a high number of surgeries, a large case number, and the learning curves for each crucial step of ROSA-guided pedicle screw placement. Significant, but nonlinear, increases in TT of ROSA usage, screw planning time, and guide pin implantation time were observed when more inserted guide pins were used. Notably, thoracic spine involvement and high BMI significantly prolonged TT and guide pin placement time. This finding indicates that the structural complexity and tension of the myocutaneous flap after its dissection along a screw trajectory (e.g., stiffer thoracodorsal fascia compared with lumbodorsal fascia or thicker subcutaneous fat tissue in obesity patients) can affect the difficulty of ROSA usage and, consequently, increase ROSA usage time. In addition, the presence of osteoporosis or spinal deformity (i.e., scoliosis and spondylolisthesis) did not significantly influence total/fractioned ROSA usage time, which indicates the benefits of ROSA usage relative to the freehand technique. Our data suggest that the learning curve for pedicle screw placement in terms of time taken can be shortened for an experienced surgeon. We noted a decrease in the learning curve gradient after the first 20 surger-

ies, with an LR of 90.1% (Fig. 3); this can primarily be attributed to the trajectory planning period (S3; $R^2 = 0.37$) of the 4-screw group (Fig. 4). This finding is comparable to that of Schatlo et al.[7] who reported higher misplacement rates between the 10th and 20th surgery, which limited the learning curve for robotic spine surgeries. Thus, for surgeons with no experience in using the technique, experienced supervision should be provided for the first 25 surgeries.

Due to familiar with the manipulation of the ROSA and O-arm device, and the diminishing the S3 time-consuming, the TT of ROSA usage can be reduced. In our experience, the more practice in patient positioning with the ROSA and O-arm device we did, the more S1 time-consuming we reduced. Besides, you also can put some labels on the floor to mark the position between. About the reducing the time of the S2, we believed the most importance is the intraoperative 3D image acquisition which is related to the positioning between the fiducial box and O-arm device. Moreover, there were the skills required for the pedicle drilling which might be influenced the surgical time of the S4, although the distribution of the statistic Fig. 4 in the S4 is too wide to be reliable.

Nine cases of technical error were reported for our cohort; they included delays in equipment sterilization (n = 2), repeat sterilization of equipment dropped by accident (n = 1), re-registration of ROSA (n = 1), system failure of ROSA (n = 3), system failure of O-arm system (n = 1), and hardware failure due to broken wheel of O-arm device (n = 1). Notably, major improvement was achieved after the rebuilding of the operating floor to eliminate the unnoticeable yet problematic tilting of ROSA, which hindered the successful and accurate registration of ROSA. Similar to the finding reported by BÄcker et al.[8] who investigated the use of the Renaissance robotic system, we observed that the surgical workflow may be influenced by variations in surgical teams comprising scrub nurses and residents. Therefore, to enhance the efficacy and reproducibility of the ROSA setup, several measures were implemented to correct the position of the surgical table, O-arm, and ROSA. This measure reduced the number of interpersonal errors made by scrub nurses and residents, especially with respect to the mounting of the device over the operating room table, which is crucial in the system setup step. All devices should be routinely checked and serviced to minimize the occurrence of software and hardware failure.

The present study was a retrospective study. We detected missing data points and outliers that were related to the technical errors that led to an increase in time taken and which might have had a negative effect on the results of the analysis. Nine missing data points (5.3%) and 4 cases of technical error (2.4%) were identified for S1, 9 missing data points (5.3%) were identified for S2, 9 missing data (5.3%) were identified for S3, 9 missing data points (5.3%) were identified for S4, and 1 missing data point was identified for TT (0.6%).

CONCLUSION

The present study addresses a single surgeon's learning curve and experience with respect to robot-assisted pedicle screw placement using ROSA. The indicative learning curve involved 20 surgeries, and the presence of scoliosis or spondylolisthesis did not significantly influence ROSA usage time. With the enhancement of system installation and teamwork, ROSA usage time can be reduced.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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REFERENCES

1. Kotani T, Akazawa T, Sakuma T, et al. Accuracy of pedicle screw placement in scoliosis surgery: a comparison between

conventional computed tomography-based and O-arm-based navigation techniques. Asian Spine J 2014;8:331-8.
2. Li HM, Zhang RJ, Shen CL. Accuracy of pedicle screw placement and clinical outcomes of robot-assisted technique versus conventional freehand technique in spine surgery from nine randomized controlled trials: a meta-analysis. Spine (Phila Pa 1976) 2020;45:E111-9.
3. Mason A, Paulsen R, Babuska JM, et al. The accuracy of pedicle screw placement using intraoperative image guidance systems. J Neurosurg Spine 2014;20:196-203.
4. Lefranc M, Peltier J. Evaluation of the ROSA™ Spine robot for minimally invasive surgical procedures. Expert Rev Med Devices 2016;13:899-906.
5. D'Souza M, Gendreau J, Feng A, et al. Robotic-assisted spine surgery: history, efficacy, cost, and future trends. Robot Surg 2019;6:9-23.
6. Chenin L, Peltier J, Lefranc M. Minimally invasive transforaminal lumbar interbody fusion with the ROSA(TM) Spine robot and intraoperative flat-panel CT guidance. Acta Neurochir (Wien) 2016;158:1125-8.
7. Schatlo B, Martinez R, Alaid A, et al. Unskilled unawareness and the learning curve in robotic spine surgery. Acta Neurochir (Wien) 2015;157:1819-23; discussion 1823.
8. BÄcker HC, Freibott CE, Perka C, et al. Surgeons' learning curve of renaissance robotic surgical system. Int J Spine Surg 2020;14:818-23.

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Original Article

Radiation Dose Reduction and Surgical Efficiency Improvement in Endoscopic Transforaminal Lumbar Interbody Fusion Assisted by Intraoperative O-arm Navigation: A Retrospective Observational Study

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Objective: Endoscopic transforaminal lumbar interbody fusion (Endo-TLIF) has gained increasing popularity among spine surgeons. However, with the use of fluoroscopy, intraoperative radiation exposure remains a major concern. Here, we aim to introduce Endo-TLIF assisted by O-arm-based navigation and compare the results between O-arm navigation and fluoroscopy groups.
Methods: Sixty-four patients were retrospectively analyzed from May 2019 to September 2020; the nonnavigation group comprised 34 patients, and the navigation group comprised 30 patients. Data on radiation dose, blood loss, postoperative drains, surgery time, complications, and length of hospital stay (LOS) were collected. Clinical outcomes were evaluated from postoperative data such as fusion rate, Oswestry Disability Index (ODI), and visual analogue scale (VAS). Radiation dose and surgery time were selected as primary outcomes; the others were second outcomes.
Results: All patients were followed up for at least 12 months. No significant differences were detected in intraoperative hemorrhage, postoperative drains, hospital LOS, or complications between the 2 groups. The radiation dose was significantly lower in the navigation group compared with the nonnavigation group. The time of cannula placement and pedicle screw fixation was significantly reduced in the navigation group. No significant differences were detected between the clinical outcomes in the 2 groups (VAS and ODI scores).
Conclusion: The present study demonstrates that O-arm-assisted Endo-TLIF is efficient and safe. Compared with fluoroscopy, O-arm navigation could reduce the radiation exposure and surgical time in Endo-TLIF surgery, with similar clinical outcomes. However, the higher doses exposed to patients remains a negative effect of this technology.

Keywords: Endo-TLIF surgery, O-arm device, Fluoroscopy, Surgery time, Percutaneous pathway, Radiation exposure

INTRODUCTION

As the elderly population continues to grow, an increasing number of people suffer from lumbar degenerative disease (LDD), which causes pain and disability. Spinal fusion is considered an effective technique for treating LDD, and this technique is continuously developing to achieve the goal of maximizing outcomes and minimizing morbidity. Minimally inva-

sive spinal (MIS) surgery has gained popularity among spinal surgeons because of advances that reduce intraoperative trauma, require smaller incisions, require less recovery time, and result in fewer perioperative complications.[1,2] Spinal endoscopy techniques have developed rapidly and are widely used in treating LDD. A newly emerging endoscopic spinal surgery, endoscopic transforaminal lumbar interbody fusion (Endo-TLIF), is manipulated via the transforaminal corridor with little bone removal and maximum preservation of the surrounding structures.[3,4] Many previous studies have suggested that Endo-TLIF is an effective and safe procedure for LDD.[5-7]

However, as in other MIS surgeries, fluoroscopic assistance is essential for Endo-TLIF because surgeons must reach the proper target and place the pedicle screws percutaneously. In fact, fluoroscopy is used both in the first step and throughout the procedure because it is difficult to identify the operation direction through the percutaneous pathway. In addition, further fluoroscopic checks are required for the insertion of the polyetheretherketone (PEEK) cage and fixation of the pedicle screws. Therefore, intraoperative radiation exposure for both patients and surgeons is of significant concern.

In recent years, navigation systems have been successfully applied in various surgical fields[8] including neurosurgery, endoscopy, bronchoscopy, and arthroscopy. They are also used in spinal surgery, and many studies have suggested that they can effectively reduce radiation exposure and surgical time.[9-11]

There have been very few studies on the navigation systems used in Endo-TLIF. Therefore, we aimed to introduce Endo-TLIF using the O-arm-based navigation system and compare the results between the navigation and fluoroscopy groups.

MATERIALS AND METHODS

We retrospectively analyzed 64 patients who underwent Endo-TLIF assisted by O-arm navigation or conventional 2-dimensional (2D) fluoroscopy in our center between May 2019 and September 2020. The Ethics Committee of the Second Affiliated Hospital of Army Medical University approved this study, and written informed consents were obtained from all patients. Patients who met all of the following criteria were included: (1) age ≥18 and ≤80 years, (2) diagnosis of lumbar spondylolisthesis (below Meyerding grade II), lumbar instability, or lumbar spinal nerve canal stenosis, and (3) conservative therapy for ≥3 months prior. The exclusion criteria included inoperable physical ailments or mental disease, history of lumbar spinal surgery, spinal infection or tumor, and traumatic lesions. One experienced surgeon performed all the surgeries.

Perioperative data such as radiation dose, blood loss, postoperative drains, surgery time, complications, and length of hospital stay (LOS) were collected. In addition, the time required for specified steps in the surgery was recorded, including the navigation set-up time, cannula placement time, and percutaneous pedicle screw fixation time. Clinical outcomes were evaluated from postoperative data such as Oswestry Disability Index (ODI), visual analogue scale (VAS), and modified MacNab criteria. Surgical complications were assessed, including severe nerve root injury, vascular damage, hematoma, and cauda equina injury. Additionally, patient spine fusion was assessed using computed tomography (CT) images at 12 months postoperatively. The bridging trabecular bone formation between the vertebral body was regarded as solid fusion in the CT images. Radiation dose and surgery time were selected as primary outcomes, and the others were secondary outcomes. The radiation dose was collected from the radiation generator, and the duration of radiation exposure was also collected.

1. Endo-TLIF Assisted by O-arm Navigation Surgical Procedure

Patients with general anesthesia were placed in the prone position. A nerve monitoring system monitored somatosensory-evoked potentials and free-running electromyography throughout the operation. Two K-wires (2.0-mm diameter) were used to anchor the reference frame to the iliac crest (Fig. 1A). Next, the O-arm (O-arm Surgical Imaging System and Stealth-Station; Medtronic, Minneapolis, MN, USA) was used to obtain intraoperative 3-dimensional (3D) images (Fig. 1B). Then acquired CT pictures were instantly transmitted to the computer, and multiplanar images of the lumbar spine were reconstructed using the navigation system. Subsequently, surgical instruments were registered to be traced intraoperatively in real time. In general, navigation preparation time, including reference frame fixation, O-arm scan, picture transmit, and instrument registration, is less than 10 minutes.

The entry point of pedicle screws was determined using 3D-image guidance to optimize screw length and avoid neurovascular structures. The pedicle screw was placed at a suitable depth using a navigated screwdriver (Fig. 2A, B). The image of screw trajectory and position was displayed on the monitor in real time, and the surgeon could make appropriate adjustments according to the image (Fig. 2C, D). After the screws were in place, C-arm was used to confirm the final position of the screws. Next, we use a spinal needle to reach the target point via the naviga-

Fig. 1. (A) The percutaneous iliac pin with attached reference array is fixed in place. (B) The O-arm device is in place and prepared for image capture.

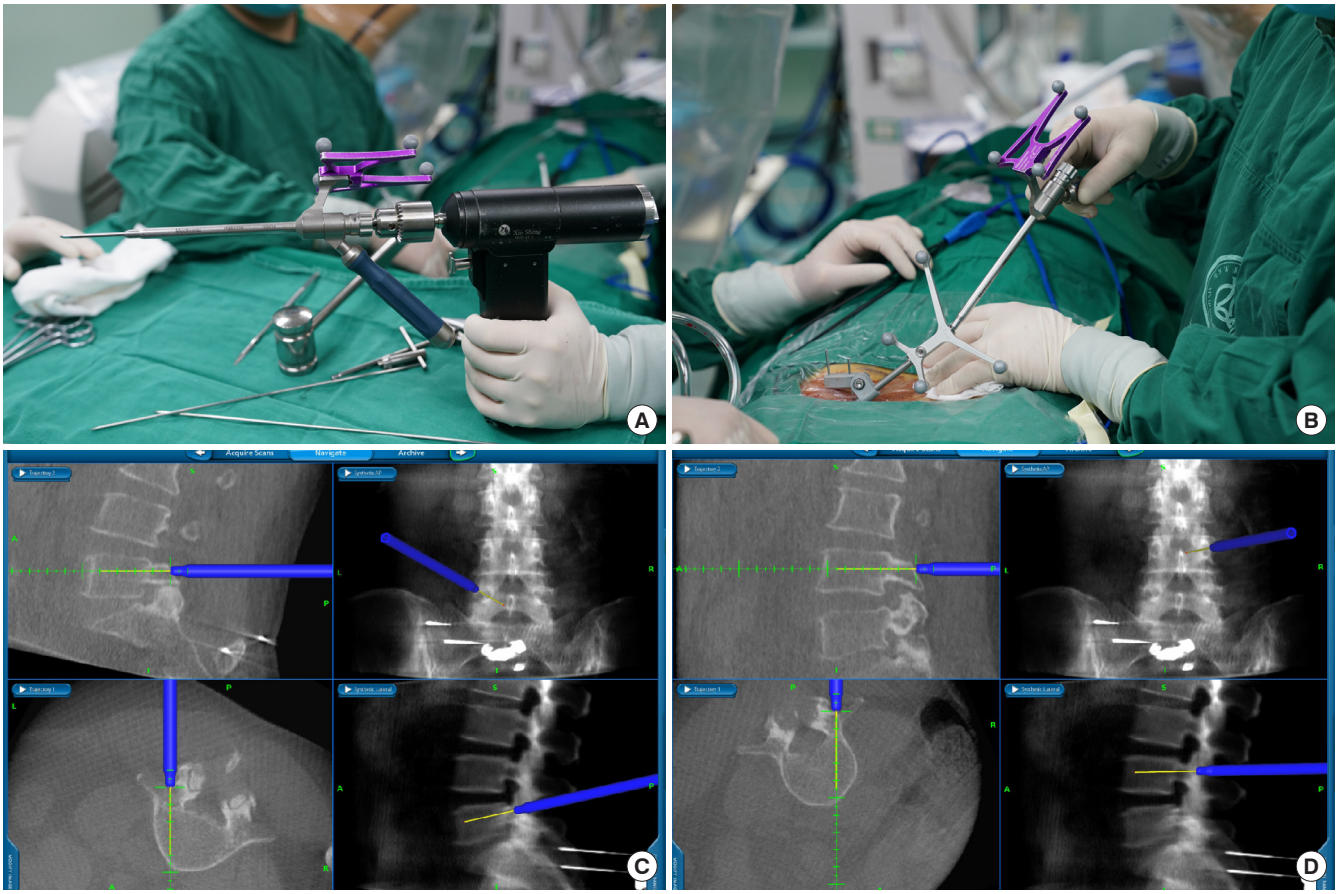

Fig. 2. (A) Image of a navigated screwdriver with an attached tracking array, and (B) it was registered intraoperatively. (C, D) The track of the Access Tracker was visible in real time and the surgeon could make appropriate adjustments.

tion system. Sequential dilation was performed to expand the soft tissue, and a double-cannula device was docked on the lateral aspect of the facet joint to perform foraminoplasty under navigation guidance. The navigation system showed the depth and pathway of the reamer or bone drill on a computer screen in real time until foraminoplasty was completed (Fig. 3). After the working cannula was advanced through the dilator and its position was confirmed using C-arm, reamers of different di-

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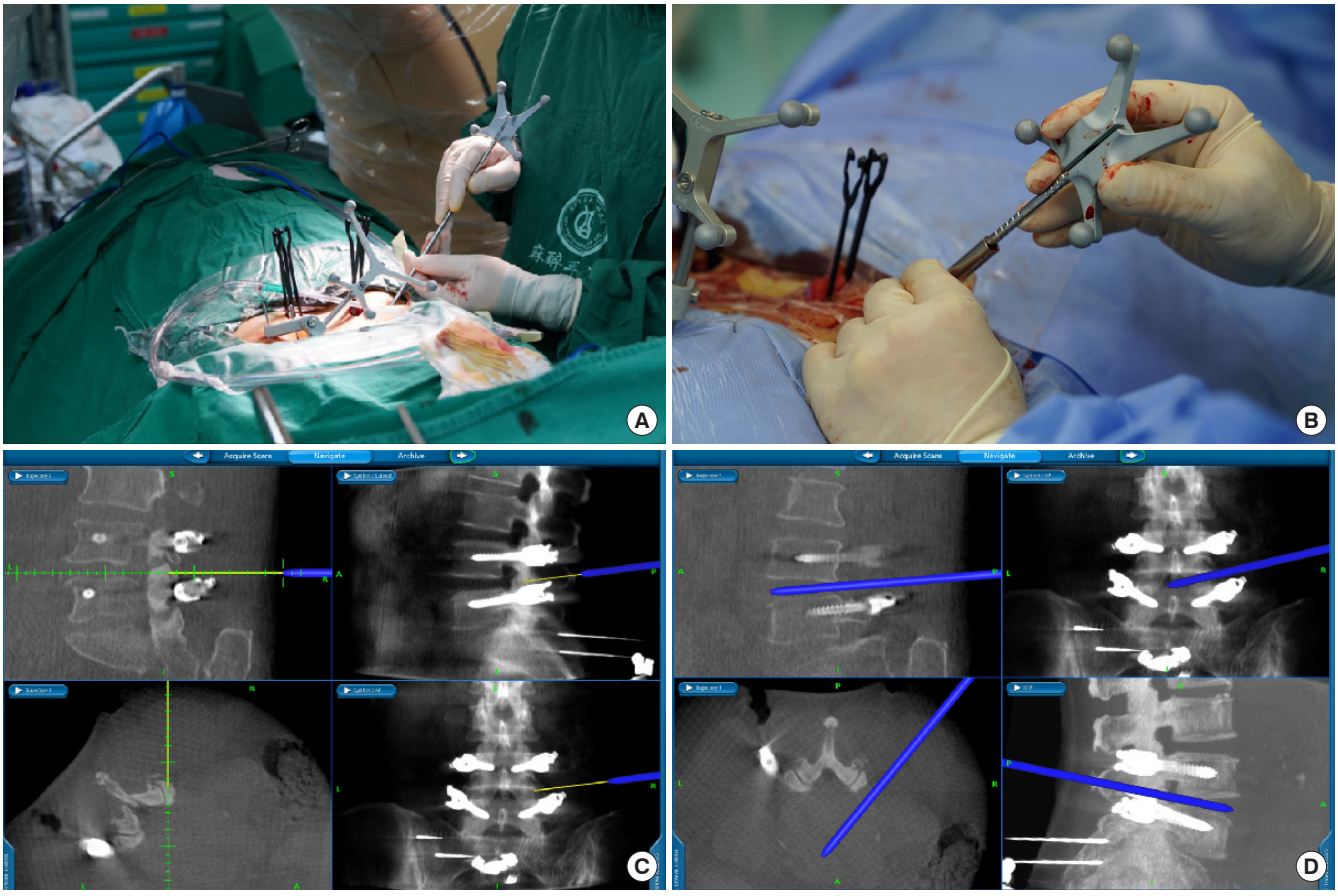

Fig. 3. (A, B) The navigated trocar-like puncture probe was used during foraminoplasty. (C) The entire puncture trajectory was designed and accurately assisted by navigation. (D) The depth of the processed intervertebral space was evaluated by the Access Tracker.

ameters were used to remove the degenerative disc tissue. Thereafter, the intervertebral disc was filled with allografts and recombinant human bone morphogenetic protein, and PEEK cages were implanted via an expandable tube (ZELIF, Sanyou, China). The final position of PEEK cages was identified using C-arm. Finally, a standard percutaneous endoscopic lumbar discectomy procedure was performed.

2. Surgical Technique of Endo-TLIF Assisted by C-arm

The operation was performed with the assistance of traditional fluoroscopy, as previously reported.[12] After surgery, analgesic and anti-inflammatory treatments were administered.

3. Statistical Analysis

The IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA) was used to analyze data, and Statistical significance was defined as p-values less than 0.05. Statistics are expressed as mean ± standard deviation or frequency. The Independent-sample t-test, chi-square test, and Mann-Whitney U-test were used to examine differences between the 2 groups, as appropriate.

RESULTS

Thirty-four patients were included in the nonnavigation group (14 men and 20 women), and 30 patients in the navigation group (13 men and 17 women). The follow-up time of all patients was at least a year. No significant differences in patient demographics were detected between the 2 groups (Table 1).

The dose of radiation administered was 7.58 ± 0.84 mGy in the navigation group; this was significantly lower than in the nonnavigation group (59.08 ± 9.77 mGy). The duration of radiation exposure was 59 seconds in the nonnavigation group and 9 seconds in the navigation group ($p < 0.001$). Intraoperative blood loss, postoperative drainage, hospital LOS, and complications were not significantly different between the 2 groups (Table 1). The navigation set-up time was 5.9 ± 0.84 minutes. Both

Table 1. Patient demographics and perioperative data

Characteristic	Nonnavigation (n = 34)	Navigation (n = 30)	p-value
Sex			0.862
Male	14	13	
Female	20	17	
Age (yr)	53.35 ± 7.52	55.60 ± 8.38	0.262
Body mass index (kg/m^2)	25.18 ± 2.90	24.74 ± 2.21	0.503
Types of lumbar degenerative disease			0.976
Degenerative spondylolisthesis	14	13	
Lumbar discogenic pain	4	3	
Lumbar spinal canal stenosis	6	7	
Recurrent lumbar disc herniation	4	3	
Segmental instability	6	4	
Surgical level			
L3–4	4	2	0.792
L4–5	27	26	
L5–S1	3	2	
Radiation dose (mGy)	59.08 ± 9.77	7.58 ± 0.84	< 0.001
Radiation exposure duration (sec)	59 (46–72)	9 (6–12)	< 0.001
Blood loss (mL)	45.24 ± 9.84	44.50 ± 17.44	0.886
Postoperative drains (mL)	38.62 ± 10.14	36.17 ± 8.48	0.512
Hospital length of stay (day)	3.79 ± 1.02	3.40 ± 0.59	0.081
Complications (n)	2	0	0.494

Values are presented as number or mean ± standard deviation.

Table 2. Comparison of surgery time between the 2 groups

Variable	Nonnavigation	Navigation	p-value
Set-up time	-	5.9 ± 0.84	
Cannula placement time	34.6 ± 3.7	22.6 ± 2.7	< 0.001
Pedicle screw fixed time	47.1 ± 2.8	37.0 ± 2.8	< 0.001
Total operation time	134.2 ± 10.2	119.8 ± 10.5	< 0.001

Values are presented as mean ± standard deviation.

cannula placement time (22.6 ± 2.7 minutes) and pedicle screw fixation time (37.0 ± 2.8 minutes) were significantly shorter in the navigation group. The total operation time was also reduced in the navigation group ($p < 0.001$) (Table 2). Compared with preoperative scores, both VAS and ODI scores significantly improved after surgery at different times in both groups (Table 3). Nevertheless, there were no significant differences between the 2 groups (Table 3). The excellent and good rates were 91.2% in the nonnavigation group and 93.3% in the navigation group. No significant difference was observed between the excellent and good rates of the 2 groups ($p = 0.682$). No major complications occurred during the surgery. Only 2 occurrences of transient ipsilateral dysesthesia were recorded, and the clinical symptoms disappeared with conservative treatment. The spine fusion was 94.1% (32 cases) and 93.3% (28 cases) respectively in the nonnavigation group and navigation group at 12 months postoperatively, and no significant difference was observed between the groups. However, all patients in the 2 groups had achieved solid spine fusion at the final follow-up, and there was no subsidence occurrence in both groups.

DISCUSSION

As a minimally invasive procedure, Endo-TLIF has been successfully manipulated to treat LDD and achieve positive clinical outcomes.[7,13] Jin et al.[13] presented a consecutive case series of Endo-TLIF, demonstrating satisfactory clinical and radiological results. It indicated that Endo-TLIF is a promising surgical alternative for treating LDD. In 2020, Wu et al.[14] compared Endo-TLIF with open-TLIF in the treatment of LDD, supporting the hypothesis that Endo-TLIF is a viable option for treating single-

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Table 3. Comparison of clinic outcomes between the 2 groups

Characteristic	Nonnavigation	Navigation	p-value
VAS scores of low back			
Preoperative	5.47 ± 0.93	5.53 ± 0.90	0.670
1 Day	2.53 ± 0.75	2.87 ± 0.97	0.140
3 Months	1.06 ± 0.55	1.00 ± 0.37	0.602
12 Months	0.62 ± 0.60	0.7 ± 0.53	0.493
VAS scores of leg			
Preoperative	4.61 ± 2.71	4.83 ± 3.14	0.276
1 Day	1.88 ± 1.17	1.97 ± 1.30	0.535
3 Months	0.68 ± 0.59	0.7 ± 0.60	0.878
12 Months	0.53 ± 0.71	0.57 ± 0.57	0.563
ODI scores			
Preoperative	49.26 ± 6.65	50.87 ± 5.91	0.154
3 Months	11.74 ± 7.89	12.7 ± 6.41	0.433
12 Months	6.99 ± 6.55	8 ± 5.52	0.272
MacNab criteria (n)			0.682
Excellent	28	26	
Good	3	2	
Fair	1	2	
Poor	2	0	
Fusion rate (%)	94.1	93.3	1.000

Values are presented as mean ± standard deviation unless otherwise indicated.
VAS, visual analogue scale; ODI, Oswestry Disability Index.

segment LDD with little trauma, rapid recovery, and inexpensive cost. These both suggest that Endo-TLIF is an effective technique with less trauma and faster recovery. Intraoperative ionization-based imaging techniques are essential for MIS surgery to expose the spine visually. Compared with open procedures, x-rays are more frequently used during the operation, which increases surgery time and causes harm to both patients and medical staff.[15,16] Therefore, the associated radiation exposure remains a major concern, especially for surgeons who are frequently exposed.[17]

Compared with open surgery, MIS techniques such as MIS-TLIF are highly dependent on fluoroscopy as the limited exposure fields and constrained working tube, which results in higher radiation exposure to both patients and the surgeon.[18] In a meta-analysis, the results indicated that mean fluoroscopy in MIS-TLIF was 94 seconds which was 2-fold of open surgery.[19] In addition, Godzik et al.[20] also reported that radiation exposure to the surgeon in the MIS-TLIF group was 408.3 ± 192.3 μSv which was significantly higher than lateral transpsoas lumbar interbody fusion (208.6 ± 146.9 μSv). A previous prospective cohort study[21] showed that Endo-TLIF had less intraoperative blood loss, less patient postoperative pain, and shorter hospital stay with similar surgical outcomes when compared with MIS-TLIF. These outcomes prove that Endo-TLIF is better than MIS-TLIF in certain diseases. However, as a less invasive surgery than MIS-TLIF, there are many other percutaneous procedures in Endo-TLIF besides percutaneous screw placement, leading to more radiation exposure. The advent and development of navigation technology have had a profound impact on spinal surgery.[22,23] Computer-assisted 3D navigation can provide high-resolution images and a more detailed view of the pedicles, improving the precision of spinal screw placement. As reported in a previous study, the nerve injury risk and clinical complications could be decreased through this technique.[24] Zhao et al.[25] compared the occurrence of postoperative hydrothorax between O-arm navigation and free-hand in spinal deformity surgery. They found that the volume of postoperative hydrothorax could be significantly reduced using the O-arm navigation, and this was ascribed to the improvement in screw implantation accuracy. Besides this, the O-arm navigation system can significantly reduce the radiation exposure of surgeons. Images can be obtained using navigation systems, with the surgeons outside the operating theater, with no additional intraoperative CT scan or fluoroscopy required to continue with the procedures. A prospective randomized study compared radiation exposure between 2D and 3D fluoroscopic techniques. The results suggested that the surgeon radiation exposure in the 2D fluoroscopy group was 9.96 times higher than that in the navigation group.[26] In the present study, the mean radiation dose in the navigation group was 7.58 ± 0.84 mGy, much lower than that in the nonnavigation group. Our results are consistent with those of a previous study.[27]

In our study, although there is an additional mean 5.9-minute navigation set-up time before surgery, the total duration of surgery in the navigation group was significantly shorter than that in the nonnavigation group (119.8 ± 10.5 minutes vs. 134.2 ± 10.2 minutes). This may be ascribed to the reduced time of cannula placement (22.6 ± 2.7 minutes vs. 34.6 ± 3.7 minutes) and pedicle screw placement (37.0 ± 2.8 minutes vs. 47.1 ± 2.8 minutes) in the navigation group. The results showed that the efficiency of Endo-TLIF was improved by navigation. In another retrospective study, the effect of navigation on surgical efficiency was explored.[28] The total operative time decreased significantly in the O-arm navigation group compared with the free-hand group. In the present study, clinical outcomes such as VAS and ODI

scores improved significantly in the 2 groups postoperatively. Differences between the nonnavigation and navigation groups were not detected significantly in the VAS and ODI scores. Also, hospital LOS and complications were not significantly different in the 2 groups. Several previous studies have assessed the impact of O-arm navigation on clinical outcomes (nerve injury and reoperation rate). These studies support the hypothesis that navigation-assisted spinal surgery could improve clinical outcomes by reducing nerve injury and reoperation rates for mispositioned screws.[29-31] All surgeries in our study were performed by senior doctors; hence, it was not difficult for them to place screws accurately in the lumbar pedicle. Therefore, we did not study the screw placement. No patients underwent reoperation in either of the 2 groups; only 2 occurrences of transient ipsilateral dysesthesia were recorded in the nonnavigation group, and the clinical symptoms disappeared with conservative treatment.

Endo-TLIF surgery assisted by O-arm navigation offers several advantages. First, the surgical efficiency could be improved, especially in some percutaneous procedures, including cannula placement and pedicle screw fixation. Second, the radiation exposure to operation staff can be reduced, having a positive effect on protecting their health. In addition, surgeons can determine the desired screw sizes and rod lengths and assess the extent of the discectomy. However, some disadvantages have also been reported. First, O-arm for intraoperative CT navigation resulted in higher radiation doses to patients compared with C-arm.[32-34] In a multicenter study, the results indicated that the mean doses for patients in the O-arm group were 4 times higher than those in the C-arm group.[35] Radiation exposure shows a positive dose effect in breast cancer mortality[36] and has been linked to various cancers.[37] Although some minimized-dose O-arm Protocols could be used to reduce negative effects for patients,[38] the impact of exposure for patients in O-arm navigation remains a problem. Moreover, O-arm-assisted Endo-TLIF surgery is comparatively expensive and may lead to an additional financial burden on patients. Although the cost of new technologies is reducing steadily over time, more research on cost-effectiveness is needed to justify the navigation technique financially.[39] There are some limitations to our study. This was a retrospective study that compared the intraoperative data and clinical outcomes between the 2 groups. The sample size was relatively small, and inherent selected bias could not be ignored. Randomized controlled trials with large sample sizes and long-term follow-up are needed in future.

CONCLUSION

We have shown that Endo-TLIF assisted by O-arm navigation is efficient and can reduce radiation exposure. O-arm navigation could reduce radiation exposure and surgical time in Endo-TLIF surgery with clinical outcomes similar to those with fluoroscopy. Navigation is a promising alternative for patients undergoing Endo-TLIF surgery. However, the higher doses exposed to patients remain a negative effect of this technology.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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REFERENCES

1. Banczerowski P, Czigléczki G, Papp Z, et al. Minimally invasive spine surgery: systematic review. Neurosurg Rev 2015; 38:11-26; discussion 26.
2. Altshuler M, Mueller K, MacConnell A, et al. Does minimally invasive spine surgery reduce the rate of perioperative medical complications? A retrospective single-center experience of 1435 degenerative lumbar spine surgeries. Eur Spine J 2021; 30:122-7.
3. Lee SH, Erken HY, Bae J. Percutaneous transforaminal endoscopic lumbar interbody fusion: clinical and radiological results of mean 46-month follow-up. Biomed Res Int 2017; 2017:3731983.
4. Ahn Y, Youn MS, Heo DH. Endoscopic transforaminal lumbar interbody fusion: a comprehensive review. Expert Rev Med Devices 2019;16:373-80.

 https://doi.org/10.14245/ns.2143324.662

5. Wagner R, Haefner M. Uniportal endoscopic lumbar interbody fusion. Neurospine 2020;17(Suppl 1):S120-8.
6. Heo DH, Hong YH, Lee DC, et al. Technique of biportal endoscopic transforaminal lumbar interbody fusion. Neurospine 2020;17(Suppl 1):S129-37.
7. Kolcun JPG, Brusko GD, Basil GW, et al. Endoscopic transforaminal lumbar interbody fusion without general anesthesia: operative and clinical outcomes in 100 consecutive patients with a minimum 1-year follow-up. Neurosurg Focus 2019;46:E14.
8. Luo X, Mori K, Peters TM. Advanced endoscopic navigation: surgical big data, methodology, and applications. Annu Rev Biomed Eng 2018;20:221-51.
9. Kim TT, Johnson JP, Pashman R, et al. Minimally invasive spinal surgery with intraoperative image-guided navigation. Biomed Res Int 2016;2016:5716235.
10. Klingler JH, Scholz C, Krüger MT, et al. Radiation exposure in minimally invasive lumbar fusion surgery: a randomized controlled trial comparing conventional fluoroscopy and 3D fluoroscopy-based navigation. Spine (Phila Pa 1976) 2021; 46:1-8.
11. Vaishnav AS, Merrill RK, Sandhu H, et al. A review of techniques, time demand, radiation exposure, and outcomes of skin-anchored intraoperative 3D navigation in minimally invasive lumbar spinal surgery. Spine (Phila Pa 1976) 2020; 45:E465-76.
12. Gong J, Huang Z, Liu H, et al. A modified endoscopic transforaminal lumbar interbody fusion technique: preliminary clinical results of 96 cases. Front Surg 2021;8:676847.
13. Jin M, Zhang J, Shao H, et al. Percutaneous transforaminal endoscopic lumbar interbody fusion for degenerative lumbar diseases: a consecutive case series with mean 2-year follow-up. Pain Physician 2020;23:165-74.
14. Wu W, Yang S, Diao W, et al. Analysis of clinical efficacy of endo-LIF in the treatment of single-segment lumbar degenerative diseases. J Clin Neurosci 2020;71:51-7.
15. Bronsard N, Boli T, Challali M, et al. Comparison between percutaneous and traditional fixation of lumbar spine fracture: intraoperative radiation exposure levels and outcomes. Orthop Traumatol Surg Res 2013;99:162-8.
16. Mariscalco MW, Yamashita T, Steinmetz MP, et al. Radiation exposure to the surgeon during open lumbar microdiscectomy and minimally invasive microdiscectomy: a prospective, controlled trial. Spine (Phila Pa 1976) 2011;36:255-60.
17. Bindal RK, Glaze S, Ognoskie M, et al. Surgeon and patient radiation exposure in minimally invasive transforaminal lumbar interbody fusion. J Neurosurg Spine 2008;9:570-3.
18. Khan NR, Clark AJ, Lee SL, et al. Surgical outcomes for minimally invasive vs open transforaminal lumbar interbody fusion: an updated systematic review and meta-analysis. Neurosurgery 2015;77:847-74; discussion 874.
19. Kim CH, Lee CH, Kim KP. How High Are Radiation-related risks in minimally invasive transforaminal lumbar interbody fusion compared with traditional open surgery? A meta-analysis and dose estimates of ionizing radiation. Clin Spine Surg 2016;29:52-9.
20. Godzik J, Mastorakos GM, Nayar G, et al. Surgeon and staff radiation exposure in minimally invasive spinal surgery: prospective series using a personal dosimeter. J Neurosurg Spine 2020 Feb 7;1-7. https://doi.org/10.3171/2019.11.SPINE19448. [Epub].
21. Ao S, Zheng W, Wu J, et al. Comparison of Preliminary clinical outcomes between percutaneous endoscopic and minimally invasive transforaminal lumbar interbody fusion for lumbar degenerative diseases in a tertiary hospital: is percutaneous endoscopic procedure superior to MIS-TLIF? A prospective cohort study. Int J Surg 2020;76:136-43.
22. Xi Z, Chou D, Mummaneni PV, et al. The navigated oblique lumbar interbody fusion: accuracy rate, effect on surgical time, and complications. Neurospine 2020;17:260-7.
23. Park P. Impact of spinal navigation on the oblique lumbar interbody fusion. Neurospine 2020;17:268-9.
24. Houten JK, Nasser R, Baxi N. Clinical assessment of percutaneous lumbar pedicle screw placement using theO-arm multidimensional surgical imaging system. Neurosurgery 2012;70:990-5.
25. Zhao Z, Liu Z, Hu Z, et al. Improved accuracy of screw implantation could decrease the incidence of post-operative hydrothorax? O-arm navigation vs. free-hand in thoracic spinal deformity correction surgery. Int Orthop 2018;42:2141-6.
26. Villard J, Ryang YM, Demetriades AK, et al. Radiation exposure to the surgeon and the patient during posterior lumbar spinal instrumentation: a prospective randomized comparison of navigated versus non-navigated freehand techniques. Spine (Phila Pa 1976) 2014;39:1004-9.
27. Chang CC, Chang HK, Wu JC, et al. Comparison of radiation exposure between O-arm navigated and C-arm guided screw placement in minimally invasive transforaminal lumbar interbody fusion. World Neurosurg 2020;139:e489-95.
28. Khanna AR, Yanamadala V, Coumans JV. Effect of intraoperative navigation on operative time in 1-level lumbar fusion surgery. J Clin Neurosci 2016;32:72-6.

29. Verma R, Krishan S, Haendlmayer K, et al. Functional outcome of computer-assisted spinal pedicle screw placement: a systematic review and meta-analysis of 23 studies including 5,992 pedicle screws. Eur Spine J 2010;19:370-5.
30. Xiao R, Miller JA, Sabharwal NC, et al. Clinical outcomes following spinal fusion using an intraoperative computed tomographic 3D imaging system. J Neurosurg Spine 2017;26:628-37.
31. Watkins RG, Gupta A, Watkins RG. Cost-effectiveness of image-guided spine surgery. Open Orthop J 2010;4:228-33.
32. Costa F, Tosi G, Attuati L, et al. Radiation exposure in spine surgery using an image-guided system based on intraoperative cone-beam computed tomography: analysis of 107 consecutive cases. J Neurosurg Spine 2016;25:654-9.
33. Mendelsohn D, Strelzow J, Dea N, et al. Patient and surgeon radiation exposure during spinal instrumentation using intraoperative computed tomography-based navigation. Spine J 2016;16:343-54.
34. Tabaraee E, Gibson AG, Karahalios DG, et al. Intraoperative cone beam-computed tomography with navigation (O-ARM) versus conventional fluoroscopy (C-ARM): a cadaveric study comparing accuracy, efficiency, and safety for spinal instrumentation. Spine (Phila Pa 1976) 2013;38:1953-8.
35. Su AW, McIntosh AL, Schueler BA, et al. How does patient radiation exposure compare with low-dose o-arm versus fluoroscopy for pedicle screw placement in idiopathic scoliosis? J Pediatr Orthop 2017;37:171-7.
36. Hoffman DA, Lonstein JE, Morin MM, et al. Breast cancer in women with scoliosis exposed to multiple diagnostic x rays. J Natl Cancer Inst 1989;81:1307-12.
37. Boice JD Jr, Morin MM, Glass AG, et al. Diagnostic x-ray procedures and risk of leukemia, lymphoma, and multiple myeloma. JAMA 1991;265:1290-4.
38. Su AW, Luo TD, McIntosh AL, et al. Switching to a pediatric dose o-arm protocol in spine surgery significantly reduced patient radiation exposure. J Pediatr Orthop 2016;36:621-6.
39. Al-Khouja L, Shweikeh F, Pashman R, et al. Economics of image guidance and navigation in spine surgery. Surg Neurol Int 2015;6(Suppl 10):S323-6.

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Biomechanical Analysis of 3-Level Anterior Cervical Discectomy and Fusion Under Physiologic Loads Using a Finite Element Model

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Objective: Pseudarthrosis and adjacent segment degeneration (ASD) are 2 common complications after multilevel anterior cervical discectomy and fusion (ACDF). We aim to identify the potential biomechanical factors contributing to pseudarthrosis and ASD following 3-level ACDF using a cervical spine finite element model (FEM).
Methods: A validated cervical spine FEM from C2 to C7 was used to study the biomechanical factors in cervical spine intervention. The FEM model was used to simulate a 3-level ACDF with intervertebral spacers and anterior cervical plating with screw fixation from C4 to C7. The model was then constrained at the inferior nodes of the T1 vertebra, and physiological loads were applied at the top vertebra. The pure moment load of 2 Nm was applied in flexion, extension, and lateral bending. A follower axial force of 75 N was applied to reproduce the weight of the cranium and muscle force, was applied using standard procedures. The motion-controlled hybrid protocol was utilized to comprehend the adjustments in the spinal biomechanics.
Results: Our cervical spine FEM demonstrated that the cranial adjacent level (C3–4) had significantly more increase in range of motion (ROM) (+90.38%) compared to the caudal adjacent level at C7–T1 (+70.18%) after C4–7 ACDF, indicating that the cranial adjacent level has more compensatory increase in ROM than the caudal adjacent level, potentially predisposing it to earlier ASD. Within the C4–7 ACDF construct, the C6–7 level had the least robust fixation during fixation compared to C4–5 and C5–6, as reflected by the smallest reduction in ROM compared to intact spine (-71.30% vs. -76.36% and -77.05%, respectively), which potentially predisposes the C6–7 level to higher risk of pseudarthrosis.
Conclusion: Biomechanical analysis of C4–7 ACDF construct using a validated cervical spine FEM indicated that the C3–4 has more compensatory increase in ROM compared to C7–T1, and C6–7 has the least robust fixation under physiological loads. These findings can help spine surgeons to predicate the areas with higher risks of pseudarthrosis and ASD, and thus developing corresponding strategies to mitigate these risks and provide appropriate preoperative counseling to patients.

Keywords: Cervical spine, Finite element, Anterior cervical discectomy and fusion, Pseudarthrosis, Adjacent segment degeneration

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) is a "workhorse" procedure widely used to treat various cervical spine pathologies. Even though the clinical outcome of ACDF is generally favorable, postoperative complications do occur. Pseudarthrosis and adjacent segment degeneration (ASD) are 2 common issues encountered by spine surgeons after multilevel ACDF.

A recent study by Wewel et al.[1] showed that patients undergoing 3-level ACDF had a pseudarthrosis rate of 42%, whereas patients with 4-level ACDF had a pseudarthrosis rate as high as 56%. Fortunately, majority of the patients with pseudarthrosis in their series were asymptomatic, and only 11% of patients had symptomatic pseudarthrosis requiring revision surgery.[1] The author also noted that the caudal level had the most risk for pseudarthrosis in their series.

The rate of symptomatic ASD after ACDF requiring surgery has been reported to be 16% after 10 years for single-level ACDF,[2] and 18% after 2-level ACDF.[3] There is not yet good long-term data on rate of symptomatic ASD requiring surgery after 3-level ACDF. However, there are some retrospective data suggesting that the radiographic rate of ASD after 3-level ACDF can be as high as 40%.[4] Given these clinical observations in the existing literature, we aim to investigate the potential biomechanical factors contributing to pseudarthrosis and ASD following 3-level ACDF using a finite element cervical spine model.

MATERIALS AND METHODS

1. Intact Spine Finite Element Model

A previously validated 3-dimensional osteoligamentous finite element model (FEM) of the human subaxial cervical spinal column was used.[5,6] The FEM of the C2–T1 spinal column was assembled using a mapping block-based hexahedral meshing technique. The mesh was generated based on the geometry segmented from computed tomography images of a midsize male spine. The soft tissues definitions included intervertebral discs (annulus fibrosus and nucleus pulposus), facet joints (articular cartilage, capsular ligaments, fluid), and ligaments (anterior longitudinal, posterior longitudinal, ligamentum flavum, and interspinous). They were represented by respective element shapes and types based on their individual roles to sustain the applied external loading. The model included the C2–T1 vertebrae, intervertebral discs, and ligaments. Each vertebral body consisted of the cortical shell, cancellous bone, and superior and inferior endplates. The cortical bone (0.5 mm thick) and endplates (0.2 mm thick) were modeled as linear isotropic materials, and the cancellous bone was also modeled as an isotropic material. Intervertebral discs composed of the nucleus pulposus, and annulus ground substance and fibers. The discs had anteroposterior asymmetry simulating the posteriorly displaced nucleus in the human spine.[7,8] Annular fibers were defined using membrane elements with tension-only directional fibers embedded in the ground substance that was simulated using the Hill strain energy function. The anterior and posterior regions of the disc consisted of 16 and 8 layers. The anterior annular fibers were defined in a crisscross manner, while the posterior fibers were defined along the vertical direction. The anterior fibers did not form a continuous ring with the posterior fibers; however, a gap was formed bilaterally at the uncovertebral anatomy. The material properties of the anterior and posterior longitudinal ligaments, and other posterior ligaments were defined using nonlinear stress-strain relationships, with data obtained experimental force-displacement curves. The material properties used in the model are given in Table 1.[8-18] A total of 11,452 finite elements were in the model with 1,392 elements at C2–3, 2,060 at C3–4, 1,970 at C4–5, 2,060 at C5–6, 2,130 at C6–7, and 1,840 at C7–T1 levels.

2. ACDF Modeling

The ACDF procedure was simulated by inserting a bone graft that was placed centrally between the vertebral bodies, and material properties of the trabecular bone were assigned to the graft. A titanium plate with variable angle screws into the vertebral bodies, were simulated. The solid model of the anterior cervical plate with variable screw system was developed using CATIA V6 software (Dassault systems Corp., Velizy-Villacoublay, Cedex, France). The size of the anterior cervical plate system and variable screws were: 18 mm in length and a mean diameter of 3 mm. The solid models of the variable screws were modeled with real screw threads. The interface between the bone graft and adjacent vertebral bodies had bonded contact. After the implantation of the anterior cervical plate and screw system, the solid models were converted into the IGES format and transferred to the ANSA software and were meshed with hexahedral elements. The material properties of the instrumentation were obtained from literature (Table 1). The surface contact between the screw and vertebra was assigned with tie constraint, and between the screw and plate was assigned with automatic surface-to-surface contact definition. The intact spine was modified to simulate C4 to C7 fusion by changing the material properties of the discs to that of the cancellous bone. Af-

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Table 1. Material properties of the spine and instrumentation

Component	Element type	Constitutive model	Parameters
Spine			
Cortical bone	Quadrilateral shell	Isotropic linear elastic	E = 16.8 GPa, μ = 0.3
Trabecular bone	Hexahedral solid	Isotropic linear elastic	E = 0.4 GPa, μ = 0.3
Endplate	Quadrilateral shell	Isotropic linear elastic	E = 5.6 GPa, μ = 0.3
Facet cartilage	Quadrilateral shell	Isotropic linear elastic	E = 0.01 GPa, μ = 0.3
Ground substance	Hexahedral solid	Hill foam	n = 2, C1 = 0.000115 GPa C2 = 0.002101 GPa, C3 = -0.000893 GPa b1 = 4, b2 = -1, b3 = -2
Annulus fibrosus	Membrane	Orthotropic nonlinear elastic	Fiber angle (45°–60°)
Nucleus	Hexahedral solid	Fluid	K = 1,720 MPa
Ligaments	Membrane	Nonlinear properties	Stress-strain curves
Instrumentation			
Plate	Hexahedral solid	Isotropic linear elastic	Titanium alloy, E = 110 GPa, μ = 0.3
Screw	Hexahedral solid	Isotropic linear elastic	Titanium alloy, E = 110 GPa, μ = 0.3

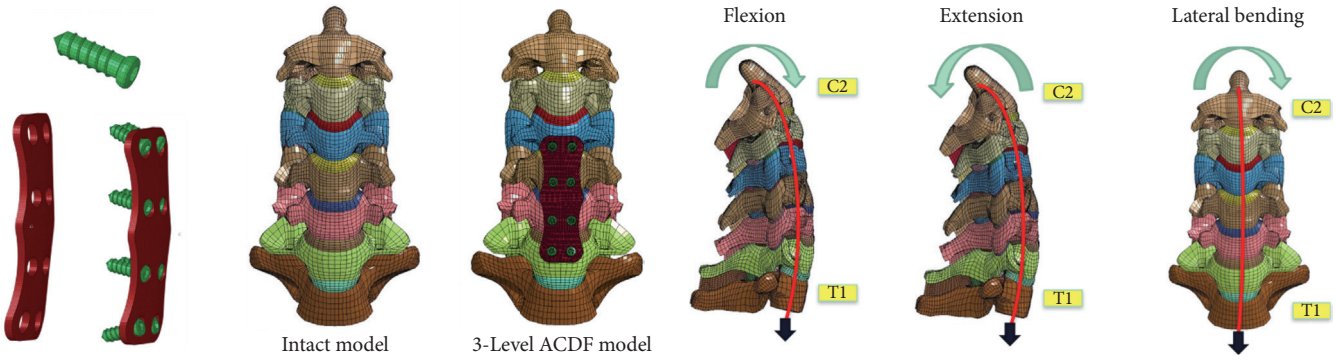

Fig. 1. Intact and 3-level anterior cervical discectomy and fusion (ACDF) finite element models.

Fig. 2. Loading modes used in the study.

ter graft placement at the 3 levels, a plate (height, 37.5 mm; width, 17 mm; and thickness, 2 mm) was placed along the anterior surfaces from C4 to the C7, and 2 titanium screws were simulated (Fig. 1).

3. Loading and Boundary Conditions

Both intact and ACDF FEMs of the spine were constrained at the inferior nodes of the T1 vertebra. Physiological bending moments (2 Nm) combined with a follower load (75 N) were applied (Fig. 2).[19] First, the intact spine was exercised under flexion and extension (sagittal loading) and lateral bending modes, and the overall range of motion (ROM) was determined under each loading mode. The next step was to determine the magnitude of the bending moments to the 3-level ACDF spine that matched the ROM obtained above for the intact spine. This was done by altering the externally applied moment, under each mode, until the overall column ROM of the spine with the ACDF matched with the magnitude of the ROM of the intact spine. This is termed in literature as the hybrid loading protocol, which is described in the following section.[5,6,20] The ranges of motion at the 3 index levels and 2 cranial and caudal adjacent levels were obtained to characterize the segmental kinematics of the intact and 3-level ACDF spines. All kinematic data were normalized with respect to the intact spine and expressed as a percentage using the following equation.

$$\text{Normalized motion} = \frac{(\text{Motion with ACDF} - \text{Motion for the intact spine})}{\text{Motion for the intact spine}}$$

Where motion represents the ROM in flexion, extension, and lateral bending, and from C2 to C7 levels.

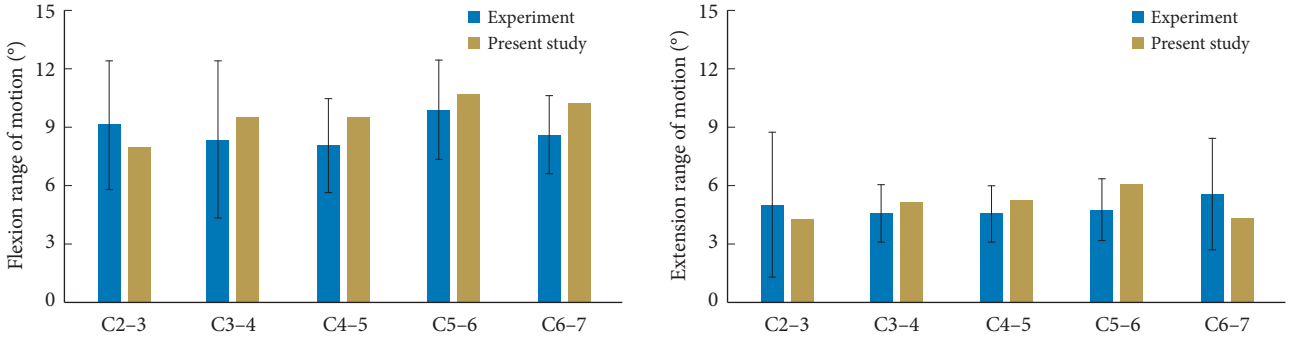

Fig. 3. Finite element model (FEM) model validation results 1.

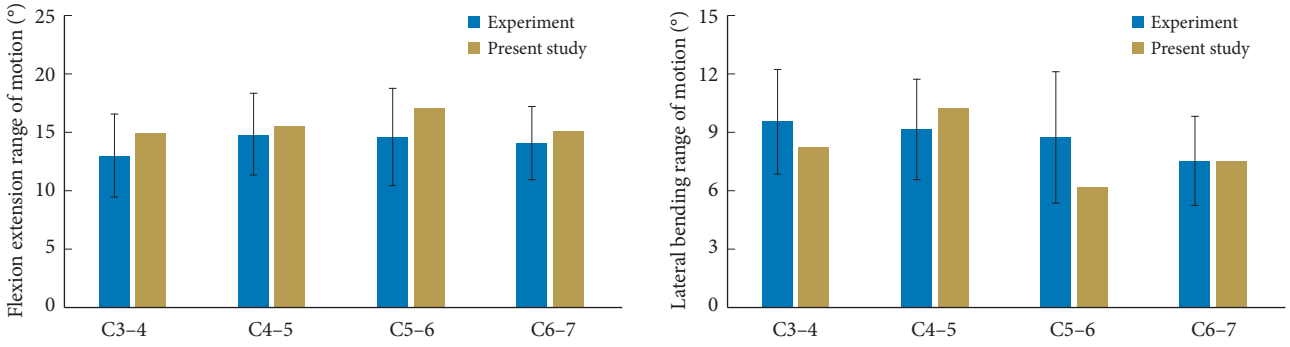

Fig. 4. Finite element model (FEM) model validation results 2.

4. Use of the Hybrid Loading Protocol

In this study, the hybrid loading protocol was used. It consisted of applying the physiological loading to the intact spine (simulating a patient's loading paradigm preop state), extracting the overall ROM of the column, in this case C2–T1 angulation, and for the 3-level ADCF spine, determining the equivalent flexion, extension, and lateral bending moments that resulted in the same C2–T1 angulations in the 3 modes. Because of the structural differences between the intact and surgically altered spines, the moment values that match the intact spine values will be different; however, determining the segmental motions that correspond to the equivalent overall motions (of the intact and ACDF spines) from a patient perspective simulates the postop condition that can be evaluated against the preop condition. This protocol is widely used in spine finite element analyses and was adopted in this study.[5,6,20]

5. Validation

The ROM of the intact model was validated under sagittal bending by comparing the flexion-extension responses from human cadaver cervical columns that were subjected to 2 Nm of pure moment loading.[21] In the cited study, 13 spinal columns with a mean age of 33 years were subjected to 2 Nm pure moments, and the model-predicted ROM at all segmental levels for both flexion and extension were within mean ±1 standard deviation data from experiments (Fig. 3).

Another human cadaver study was used to validate the present intact model under lateral bending.[22,23] The study used 12 spinal columns with a mean age of 62 years and applied moment of 2 Nm and follower load of 50 N. As before, the model-predicted ROM at all segmental levels were within mean ±1 standard deviation data (Fig. 4). Similar data from human cadaver tests are not available for the 3-level ACDF spines. From this perspective, it would be necessary to conduct experiments to further validate the ACDF model. This is a topic for future investigation.

For validating the model, experimental data were available for 2 loading cases: pure moment at 2 Nm, and combined moment and force loading of 2 Nm and 50 N. Results from the 3 level ACDF were based on a greater force of 75 N (instead of 50 N), while the moment loading remained the same. The effect of 2 Nm + 75 N versus 2 Nm + 50 N loading scenarios, as measured by the difference in the ROM between the 2 load magnitudes across all levels and modes ranged from 3.9% to 5.6%,

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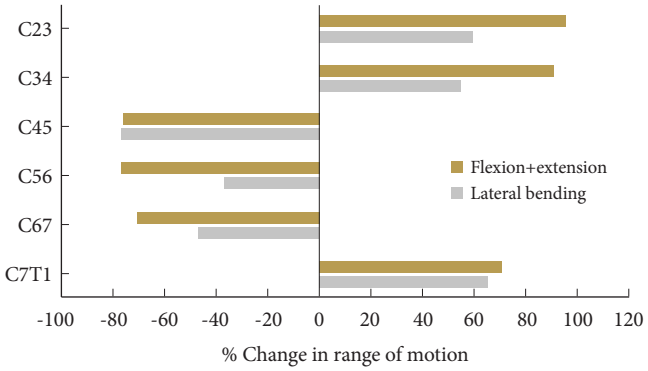

Fig. 5. Bar charts showing the change in motion at each level. Note that the motions decrease at the 3 index levels.

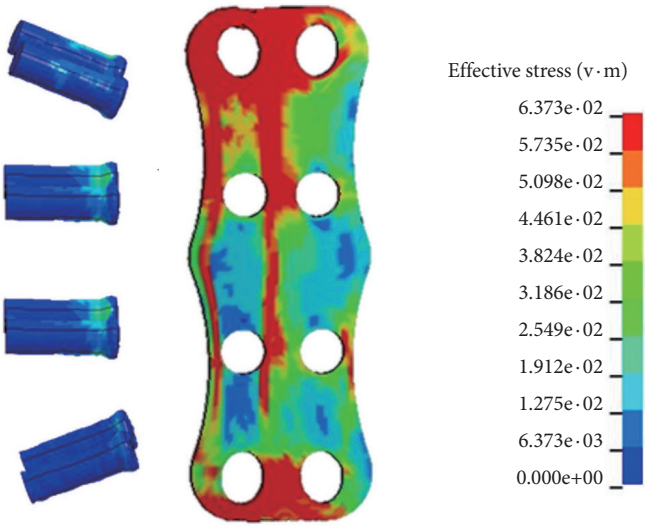

Fig. 6. Stress distribution on the plate-screw interface in the model in flexion. Red areas indicate the greatest von Mises (VM) stress in the anterior cervical discectomy and fusion plate and the light blue regions show the least VM stress. The maximum stress in the plate was 64 MPa.

with a mean of 4.9%. Because of small differences in the modeling output, results with 75 N are considered more realistic as it better simulates muscular forces and accounts for the weight of the head on the spine.

RESULTS

After C4–7 ACDF, the mean reductions in ROM across C4–7 were -79.3% ± 2.3% under flexion, -66.2% ± 6.4% under extension, and -53.8% ± 20.9% under lateral bending. The maximum ROM reductions were at C4–5 for flexion and C5–6 for extension.

Under flexion loading, the mean increase in ROM across

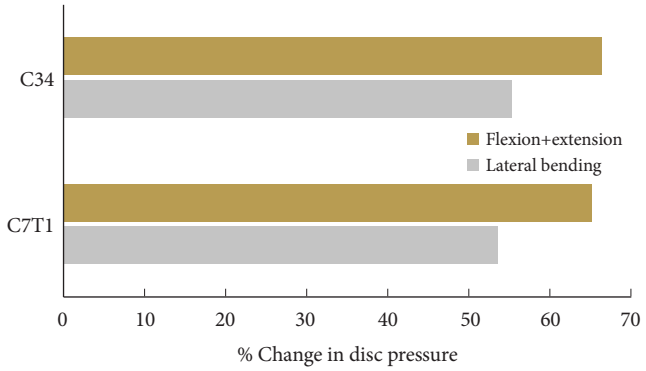

Fig. 7. Bar charts showing the change in disc pressure at adjacent level (50N load).

C2–3 and C3–4 levels were 97.0% ± 9.6%, under extension loading it was 84.1% ± 9.3%, with the maximum increase at the C2–3 in the former and C3–4 in the later mode. At the caudal level, C7–T1, under flexion, extension, and lateral bending, the increase in motion was 73.8%, 64.0%, and 65.2%, respectively. Under lateral bending the mean decrease in motion across C4–7 was 57.0% ± 3.3% (Fig. 5). Fig. 6 demonstrates the stress distribution on the plate-screw interface in flexion. Red areas indicate the greatest von Mises (VM) stress in the ACDF plate and the light blue regions show the least VM stress. The maximum stress in the plate was 64 MPa. disc pressure at C3–4 increased by over 59%, 74%, and 55% for the flexion, extension, and lateral bending in the 3-level ACDF when compared with intact spine and a similar trend was observed for C7–T1 (Fig. 7).

DISCUSSION

The objective of the study was to investigate the responses of the 3-level ACDF from a segmental ROM perspective and compare them to the intact spine under 3 physiological loading conditions: flexion, extension, representing sagittal bending, and lateral bending. As expected, angulations at the index levels changes in all modes of loading, with greater decreases in sagittal than coronal loading. As shown in the results section, among the 3 index levels, under combined sagittal bending moments, the least rigid segment was at the caudal level (decrease in motion -71.3%), and the cranial and middle levels had approximately same levels of decrease in range motion (-76.4% and -77.1%). In other words, the greatest and least motion reduction occurred at the middle and caudal levels, C5–6 and C6–7, respectively. While changes between the 3 levels were small and their clinical significance is not clearly established, the added mobility at the caudal segment may delay arthrodesis. Interestingly, this result

mirrors a recent clinical study by Nichols et al.[24] where they found that the middle level had the highest rate of fusion, and the caudal level had the lowest rate of fusion at 24 months after 3-level ACDF. Specifically, the authors analyzed the radiographic outcome of a group of 77 patients who underwent 3-level ACDF and used flexion-extension x-rays to assess fusion status at various time points. At 6 months after surgery, they found the fusion rates were 17%, 34%, and 4% for the cranial, middle, and caudal levels, respectively; at 24 months after surgery, they rates were 61%, 89%, and 28%, respectively. The segmental fusion pattern observed in their clinical series agrees with the findings from our current FEM study.

We acknowledge that the longitudinal effects of the patient's spine are not fully incorporated in the current finite element kinematic analysis. Despite this being a single cycle study, the present findings appear to offer support to the theory advanced by the authors in the cited study: pseudarthrosis occurrence at the caudal segment.[24] Additional studies are however, needed to fully explore the repeated loading paradigm, for which properties of the components such as the viscoelasticity of the discs and their degeneration status should be included. Preliminary data on such properties are available.[25,26] Furthermore, the present model was developed using mapping block morphing techniques,[27] it should be possible to simulate the actual anatomical geometry of the patient, include appropriate material properties via computed tomography and magnetic resonance imaging, and more accurately determine the cranial, middle, and caudal level ranges of motions and estimate the rates of arthrodesis in the future.

At adjacent levels, the cranial segments (C2–3, C3–4) experienced more compensatory increase in segmental motion under load compared to the caudal level (C7-T1). This suggests that the added rigidity of the 3-level ACDF induces a nonuniform shift of the kinematics to the adjacent levels. This finding may be explained by the proximity to the head mass. The rate of adjacent segment disease will be nonuniform from this perspective, a phenomenon observed in previous retrospective studies.[28,29] In addition, Lundine et al.[30] demonstrated that the cranial adjacent level is more likely to have adjacent level degeneration compared to the caudal adjacent level, which is consistent with the findings suggested by our FEM model.

Because lateral bending is also an important physiological motion of the cervical spine, the present study investigated the responses under this loading condition as well. It should be noted at the outset that the bilateral symmetry of the structure is lost in this mode as ipsilateral facet column is under a compressive phase while the contralateral column is under a tensile phase. Acknowledging the asymmetric modality, the caudal and middle index levels responded with lesser increase in angulation than the cranial index level. This implies as greater load on the ipsilateral column at the middle and cranial levels compared to the caudal index level. A similar phenomenon also occurred at the 2 most superior adjacent levels (C2–4) when compared to the inferior (C7–T1) level. Taken together, the biomechanical responses of the 3-level ACDF spine are level-specific and motion-dependent. Our FEM study appears to offer quantitative explanations and support clinical hypothesis regarding its outcomes.

CONCLUSION

Biomechanical analysis of C4–7 ACDF construct using a validated cervical spine FEM indicated that C6–7 has the least robust fixation under physiological loads, potentially predisposing it to higher rate of pseudarthrosis. The C2–3 and C3–4 have more compensatory increase in ROM compared to C7–T1, which may imply that these levels are more prone to develop ASD over time. These findings can potentially help spine surgeons to predicate the areas with higher risks of postoperative complications and thus developing corresponding strategies to mitigate these risks and provide appropriate preoperative counseling to patients.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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REFERENCES

1. Wewel JT, Kasliwal MK, Adogwa O, et al. Fusion rate following three- and four-level ACDF using allograft and segmental instrumentation: a radiographic study. J Clin Neurosci 2019;62:142-6.
2. Ghobrial GM, Lavelle WF, Florman JE, et al. Symptomatic adjacent level disease requiring surgery: analysis of 10-year results from a prospective, randomized, clinical trial comparing cervical disc arthroplasty to anterior cervical fusion. Neurosurgery 2019;84:347-54.
3. Gornet MF, Lanman TH, Burkus JK, et al. Two-level cervical disc arthroplasty versus anterior cervical discectomy and fusion: 10-year outcomes of a prospective, randomized investigational device exemption clinical trial. J Neurosurg Spine 2019 Jun 21:1-11. https://doi.org/10.3171/2019.4.SPINE19157. [Epub].
4. Shin JJ. Comparison of adjacent segment degeneration, cervical alignment, and clinical outcomes after one- and multilevel anterior cervical discectomy and fusion. Neurospine 2019;16:589-600.
5. Choi H, Purushothaman Y, Baisden J, et al. Unique biomechanical signatures of Bryan, Prodisc C, and Prestige LP cervical disc replacements: a finite element modelling study. Eur Spine J 2020;29:2631-9.
6. Purushothaman Y, Yoganandan N, Jebaseelan D, et al. External and internal responses of cervical disc arthroplasty and anterior cervical discectomy and fusion: a finite element modeling study. J Mech Behav Biomed Mater 2020;106:103735.
7. Mercer S, Bogduk N. The ligaments and annulus fibrosus of human adult cervical intervertebral discs. Spine (Phila Pa 1976) 1999;24:619-26; discussion 627-8.
8. Tonetti J, Potton L, Riboud R, et al. Morphological cervical disc analysis applied to traumatic and degenerative lesions. Surg Radiol Anat 2005;27:192-200.
9. Holzapfel GA, Schulze-Bauer CA, Feigl G, et al. Single lamellar mechanics of the human lumbar anulus fibrosus. Biomech Model Mechanobiol 2005;3:125-40.
10. Iatridis JC, Setton LA, Foster RJ, et al. Degeneration affects the anisotropic and nonlinear behaviors of human anulus fibrosus in compression. J Biomech 1998;31:535-44.
11. Cassidy JJ, Hiltner A, Baer E. Hierarchical structure of the intervertebral disc. Connect Tissue Res 1989;23:75-88.
12. Yamada H. Strength of biological materials. Baltimore: Williams & Wilkins; 1970.
13. Yoganandan N, Kumaresan S, Pintar FA. Geometric and mechanical properties of human cervical spine ligaments. J Biomech Eng 2000;122:623-9.
14. Kopperdahl DL, Keaveny TM. Yield strain behavior of trabecular bone. J Biomech 1998;31:601-8.
15. Skrzypiec DM, Pollintine P, Przybyla A, et al. The internal mechanical properties of cervical intervertebral discs as revealed by stress profilometry. Eur Spine J 2007;16:1701-9.
16. Panzer MB, Cronin DS. C4-C5 segment finite element model development, validation, and load-sharing investigation. J Biomech 2009;42:480-90.
17. Reilly DT, Burstein AH. The elastic and ultimate properties of compact bone tissue. J Biomech 1975;8:393-405.
18. Mattucci SF, Moulton JA, Chandrashekar N, et al. Strain rate dependent properties of younger human cervical spine ligaments. J Mech Behav Biomed Mater 2012;10:216-26.
19. Patwardhan AG, Havey RM, Ghanayem AJ, et al. Load-carrying capacity of the human cervical spine in compression is increased under a follower load. Spine (Phila Pa 1976) 2000;25:1548-54.
20. Panjabi MM. Hybrid multidirectional test method to evaluate spinal adjacent-level effects. Clin Biomech (Bristol, Avon) 2007;22:257-65.
21. Wheeldon JA, Pintar FA, Knowles S, et al. Experimental flexion/extension data corridors for validation of finite element models of the young, normal cervical spine. J Biomech 2006;39:375-80.
22. Barrey C, Campana S, Persohn S, et al. Cervical disc prosthesis versus arthrodesis using one-level, hybrid and two-level constructs: an in vitro investigation. Eur Spine J 2012;21:432-42.
23. Barrey C, Rousseau MA, Persohn S, et al. Relevance of using a compressive preload in the cervical spine: an experimental and numerical simulating investigation. Eur J Orthop Surg Traumatol 2015;25 Suppl 1:S155-65.
24. Nichols NM, Jamieson A, Wang M, et al. Characterizing the fusion order and level-specific rates of arthrodesis in 3-level anterior cervical discectomy and fusion: a radiographic study. J Clin Neurosci 2020;81:328-33.

25. Umale S, Yoganandan N. Mechanisms of cervical spine disc injury under cyclic loading. Asian Spine J 2018;12:910-8.
26. Yoganandan N, Umale S, Stemper B, et al. Fatigue responses of the human cervical spine intervertebral discs. J Mech Behav Biomed Mater 2017;69:30-8.
27. John JD, Arun MWJ, Yoganandan N, et al. Mapping block-based morphing for subject-specific spine finite element models. In: 54th Annual Rocky Mountain Bioengineering Symposium & 54th International ISA Biomedical Sciences Instrumentation Symposium 2017; 2017 March 31- April 1; Denver (CO), USA. Biomed Sci Instrum; 2017;53.
28. Gore DR. Roentgenographic findings in the cervical spine in asymptomatic persons: a ten-year follow-up. Spine (Phila Pa 1976) 2001;26:2463-6.
29. Rao RD, Gore DR, Tang SJ, et al. Radiographic changes in the cervical spine following anterior arthrodesis: a long-term analysis of 166 patients. J Bone Joint Surg Am 2016;98:1606-13.
30. Lundine KM, Davis G, Rogers M, et al. Prevalence of adjacent segment disc degeneration in patients undergoing anterior cervical discectomy and fusion based on pre-operative MRI findings. J Clin Neurosci 2014;21:82-5.

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Original Article

Prevalence and Clinical Impact of Cervical Facet Joint Degeneration on Degenerative Cervical Myelopathy: A Novel Computed Tomography Classification Study

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Objective: To evaluate cervical facet joint degeneration using a newly developed classification, investigate its prevalence and relationship with cervical degenerative spondylolisthesis, and clarify its clinical significance in patients with degenerative cervical myelopathy (DCM).
Methods: This study included 145 consecutive patients with DCM who underwent surgical treatment. Clinical variables and radiological findings were analyzed. A new 6-grade computed tomography (CT) classification for cervical facet joint degeneration was adapted, and its prevalence was evaluated by categorizing the joints into those at responsible and those at nonresponsible spinal segmental levels. We evaluated the association between rapidly progressive myelopathy and the presence of significant facet joint degeneration or spondylolisthesis at the responsible segmental level.
Results: Finally, 140 patients with a mean age of 64.1 ± 12.8 years were analyzed. The prevalence of grade 1, 2, 3, 4, 5A, and 5B classification in all facet joints was 72.0%, 9.5%, 10.9%, 4.3%, 2.9%, and 0.4%, respectively. There was a statistically significant difference in the distribution of CT grades between the joints at the responsible and nonresponsible segmental levels ($p < 0.001$), with a high prevalence of grade 4 or 5B degeneration at the responsible segmental level, reflecting articular irregularity. There was also a statistically significant relationship between rapidly progressive myelopathy and grade 4 or 5B degeneration at the responsible segmental level ($p < 0.001$), but not between rapidly progressive myelopathy and spondylolisthesis ($p = 0.255$).
Conclusion: This novel CT classification for facet joints deserves additional evaluation in patients with DCM. Abnormal findings on the articular surfaces might be related to the progression of myelopathy.

Keywords: Articular, Cervical myelopathy, Degenerative, Computed tomography, Facet joint, Spondylolisthesis

INTRODUCTION

Degenerative cervical myelopathy (DCM), including cervical spondylotic myelopathy, is a common age-related spinal disorder. DCM is mostly asymptomatic, but sometimes it becomes a symptomatic background pathology and reduces quality of life due to impairment of motor function.[1] It comprises osteoarthritic changes to the spine, which include facet arthropathy, spondylosis, disc herniation, ligamentous hypertrophy, calcification, and ossification.[2] These degenerations do not occur in only one type, but often results from a combination of multiple degenerations, resulting in myelopathy. The degree of degener-

ation varies in each case, and many cases cannot be clearly subdivided in daily clinical practice.

The cervical facet joint is a synovial joint located in the posterolateral spine. Degenerative facet joint pathology is associated with cervical degenerative spondylolisthesis, which can induce myelopathy.[3] However, the evaluation of cervical facet joints has not received much attention in daily clinical practice, partly because it is difficult to evaluate them without computed tomography (CT) and partly because of the diagnostic superiority of magnetic resonance imaging in spinal and spinal cord diseases. For facet joint degeneration of the lumbar spine, several CT classifications have been reported for degenerative spondylolisthesis. CT evaluation of cervical facet joints is less debated and fewer relevant reports,[4,5] so it is not clinically significant.

We recently reported a case of DCM with unilateral severe facet joint degeneration at the responsible spinal segmental level and rapid neurological deterioration without any trauma or cervical spondylolisthesis.[6] Because the relationship between facet joint degeneration and DCM remains unknown, we conducted a retrospective study to identify the prevalence of facet joint degeneration using a newly developed CT classification reflecting articular irregularities in patients with DCM and discuss its impact on the clinical setting.

MATERIALS AND METHODS

All experiments were conducted following the guidelines of the Declaration of Helsinki. All research protocols were approved by the Institutional Review Board of Nara Medical University (approval number: 2241). The need for informed consent was waived.

1. Patient Selection

We retrospectively analyzed consecutive DCM patients who underwent surgical treatment at our institution between January 2013 and December 2020. Inclusion criteria included the responsible spinal segment being at the subaxial level between C2–3 and C6–7 and preoperative CT and radiography of the cervical spine. Patient who received revision surgery within 12 months was excluded. Clinical data, including responsible segmental level and radiological findings, were gathered retrospectively from medical records, preoperative neurologic examinations, and radiographic images. Regarding the clinical evaluation, the diagnosis of cervical myelopathy was made on the basis of symptoms first, but also on the magnetic resonance imaging (MRI) findings. The responsible segmental level was defined as the level of the lesion causing myelopathy and identified in each case based on the neurologic examinations first, and referring to the MRI findings if necessary. To study radiological classification as well as its clinical implications, the clinical course, especially concerning rapid progression of cervical myelopathy, was also investigated. Rapid progression of cervical myelopathy was defined in this study as in previous reports.[7,8] In brief, patients with rapid DCM progression had difficulty maintaining a standing posture or walking without support, which corresponded to Nurick grade 4 or 5, within 4 weeks of symptom onset due to rapidly progressive neurological deterioration. To assess the clinical impact of facet joint degeneration, the study population was divided into 2 cohorts: a rapid progression group and slow progression group, depending on whether or not they met the definition.

2. CT Assessment of Cervical Facet Joint Degeneration

Preoperative CT of the cervical spine was performed on admission in each patient. Results were retrospectively reviewed

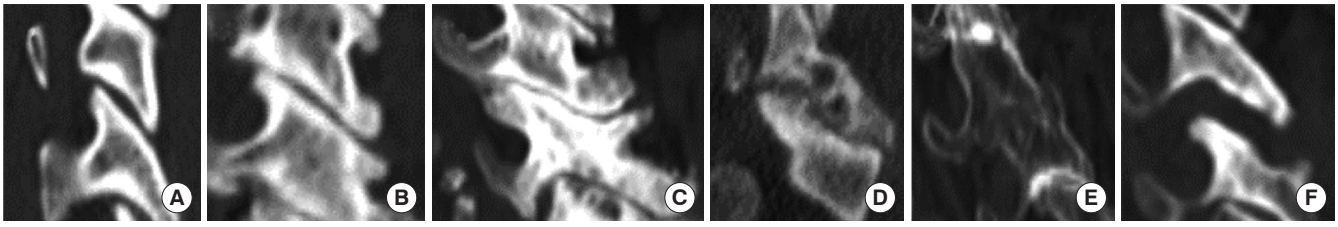

Fig. 1. Newly developed computed tomography classification for cervical facet joint degeneration. (A) Grade 1, normal facet joint with no degenerative changes. (B) Grade 2, mild degenerative changes with only osteophyte formation. (C) Grade 3, degenerative changes with osteophyte formation including joint space narrowing, microcyst (< 2 mm), or joint hypertrophy. (D) Grade 4, severe degenerative changes, including moderate to large cysts (≥ 2 mm), and articular irregularity. (E) Grade 5A, ankylosing changes with bony fusion of the facet joint. (F) Grade 5B, facet opening with articular irregularity.

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and assessed. We carefully evaluated all cervical facet joints from the C2–3 to C6–7 levels on the axial, sagittal, and coronal sections. In short, 10 facet joints for 5 intervertebral levels were evaluated separately for each case. We classified them into 6 grades according to the severity of the following degenerative findings: osteophyte formation, joint hypertrophy, joint space narrowing, cyst formation, articular irregularity, ankylosing changes, and facet joint opening with articular irregularity (Fig. 1). In this classification, the final stage of facet degeneration was defined as "grade 5." There are 2 types of facet degeneration in the final stage: stabilization due to joint fusion and destabilization due to advanced joint destruction as in rheumatoid arthritis. Since there are incompatible and cannot be ordered, "grade 5" was subdivided into 2 categories, 5A and 5B. Assessments were conducted independently by 2 neurosurgeons; any differences in assessments were finalized through discussion. To evaluate the reproducibility of the CT classification, 2 different initial assessments by 2 independent neurosurgeons were examined for concordance.

3. Radiographic Assessment of Cervical Spondylolisthesis

To evaluate cervical spondylolisthesis, all intervertebral spaces from C2–3 to C6–7 in each patient were examined using a preoperative lateral radiogram of the cervical spine in the neutral position. We measured anterior-posterior translation of the upper vertebral body relative to the lower vertebral body. In this study, we defined cervical spondylolisthesis as 2 mm or more in the forward or backward direction.

4. Clinical and Radiological Data Analysis

This clinical study consisted of the 3 evaluations. First, we investigated the prevalence of cervical facet joint degeneration in all patients with DCM using the classification mentioned above. The prevalence of each CT grade at all spinal intervertebral levels was investigated. In addition, we compared the distribution of CT grades by dividing the joints into those at responsible or nonresponsible segmental levels to assess the impact of the CT classification on clinical diagnostic aspects and identify which type of degeneration is clinically significant in DCM. Second, we assess the clinical relationship between cervical facet joint degeneration and spondylolisthesis in patients with DCM. The patients whose evaluation of the lower cervical vertebra was impossible due to overlapping shoulders were excluded, and the assessment of each intervertebral space from C2–3 to C6–7 in the remaining patients were collected and investigated. By dividing the joints and intervertebral levels into at responsible and nonresponsible segmental levels, the prevalence of clinically significant cervical facet degeneration, as evaluated during the first step, and spondylolisthesis were assessed and compared. We also investigated the relationship between the presence of significant cervical facet degeneration on either side of both facet joints and spondylolisthesis at responsible and nonresponsible segmental levels, respectively. Third, we assessed the clinical impact of these 2 variables at the responsible segmental level on rapidly progressive myelopathy in patients with DCM. The same patients as in the second assessment were also involved. After dividing the patients into 2 groups according to the presence or absence of rapidly progressive myelopathy, we evaluated the association between rapidly progressive myelopathy and the presence of significant cervical facet degeneration or spondylolisthesis at the responsible segmental level, separately.

5. Statistical Analysis

All statistical analyses were performed with IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA). Radiological variables at each spinal levels were compared using the Pearson chi-square test, and relationships between the radiological variables were assessed using the McNemar test. The reproducibility of the CT classification was evaluated using Cohen kappa coefficient. Data are presented as means ± standard deviation (SD). Statistical significance was defined as $p < 0.05$.

RESULTS

1. Clinical Characteristics

Although 145 patients were enrolled, 140 patients were finally included in this study (Fig. 2). As a result, 700 intervertebral levels and 1,400 cervical facet joints were assessed. The charac-

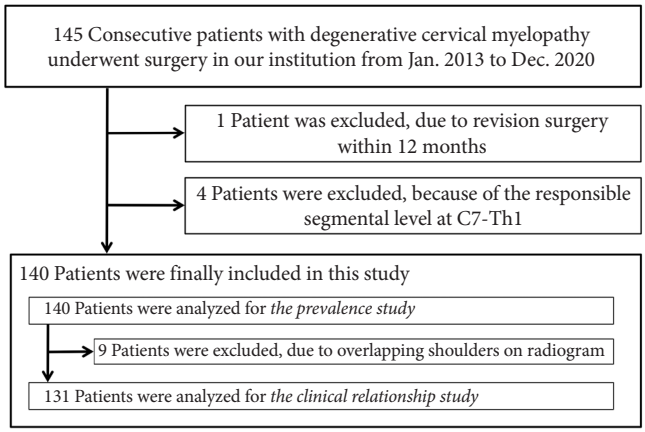

Fig. 2. Flow chart showing the patient selection process.

teristics of the study population are presented in Table 1. There were 93 men and 47 women aged 38–93 years (mean ± SD, 64.1 ± 12.8 years). Most patients had cervical canal stenosis (60.0%), followed by ossification of posterior longitudinal ligament (22.1%) and cervical disc herniation (17.9%). The most common responsible segmental level was C5–6 (37.1%), followed by C4–5 (35.0%). C2–3 was the least common (2.1%).

Table 1. Clinical characteristics of the study participants (n = 140)

Characteristic	
Age (yr)	64.1 ± 12.8
Male sex	93 (66.4)
Disease	
Cervical canal stenosis	84 (60.0)
Ossification of the posterior longitudinal ligament	31 (22.1)
Cervical disc herniation	25 (17.9)
Comorbid disorder	
Hypertension	54 (38.6)
Diabetes	31 (22.1)
Current smoking	52 (37.1)
Responsible Spinal Segmental level	
C2/3	3 (2.1)
C3/4	29 (20.7)
C4/5	49 (35.0)
C5/6	52 (37.1)
C6/7	7 (5.0)
JOA score for cervical myelopathy	
Before surgery	11.7 ± 2.8
At 1 year follow-up	14.2 ± 2.3

Values are expressed as mean ± standard deviation or the number of patients (%).
JOA, Japanese Orthopaedic Association.

2. Prevalence of Cervical Facet Joint Degeneration

The overall prevalence of cervical facet degeneration is shown in Fig. 3A. In the all facet joint survey, the prevalence of grade 1, grade 2, grade 3, grade 4, grade 5A, and grade 5B degeneration was 72.0%, 9.5%, 10.9%, 4.3%, 2.9%, and 0.4%, respectively. The Kappa coefficient was 0.822 for the first diagnosis by 2 independent neurosurgeons, which suggested almost complete agreement in the 6-grade CT classification. The grade concordance of a pair of facets at each intervertebral level was 488 out of 700 intervertebral levels (69.7%). Notably, after classifying degeneration by responsible versus nonresponsible segmental level, there was a statistically significant difference between the 2 distributions ($p < 0.001$), with grade 4 and grade 5B degeneration being more prevalent at the responsible segmental level and grade 5A degeneration being more prevalent at nonresponsible levels (Fig. 3B). Grades 4 and 5B degeneration, which reflect articular irregularities considered destructive facet joint degeneration, were grouped in further analyses.

3. Relationship Between Cervical Facet Joint Degeneration and Spondylolisthesis

Evaluation of cervical spondylolisthesis was possible in 131

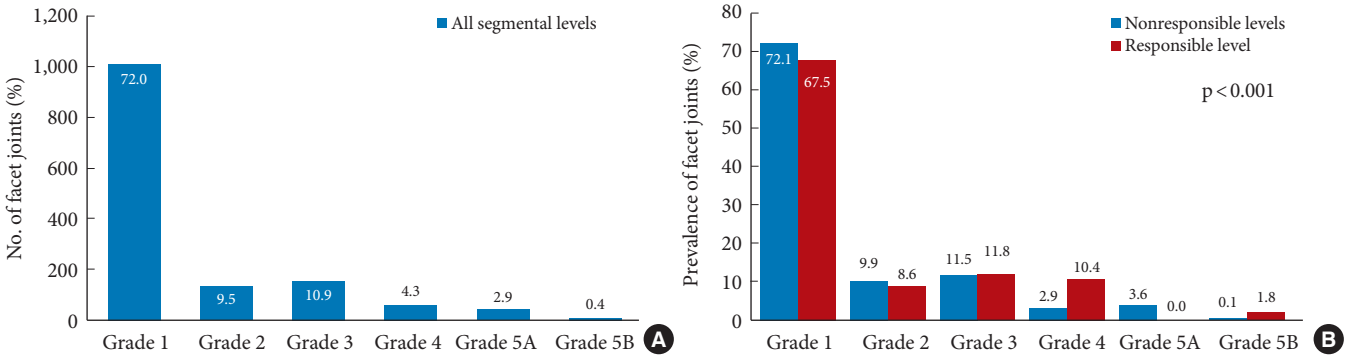

Fig. 3. Prevalence of cervical facet joint degeneration by grade. (A) Prevalence of cervical facet joint degeneration. (B) Prevalence of cervical facet joint degeneration at responsible and nonresponsible segmental levels. There was a statistically significant difference between the 2 distributions ($p < 0.001$), with grade 4 or 5B degeneration being more prevalent at the responsible segmental level and grade 5A being more prevalent at nonresponsible levels. Grade 1, normal facet joint with no degenerative changes. Grade 2, mild degenerative changes with only osteophyte formation. Grade 3, degenerative changes with osteophyte formation including joint space narrowing, microcyst (< 2 mm), or joint hypertrophy. Grade 4, severe degenerative changes including moderate to large cysts (≥ 2 mm), and articular irregularity. Grade 5A, ankylosing changes with bony fusion of the facet joint. Grade 5B, facet opening with articular irregularity.

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cases, because 9 patients were excluded for whom evaluation of the C6–7 vertebrae was impossible due to overlapping shoulders. Therefore, the following analysis was performed on 655 vertebrae. Spondylolisthesis of 2 mm or more was observed in 84 vertebrae (12.8%). Of the 131 patients with cervical myelopathy, 27 patients (20.6%) had rapid neurological deterioration before surgery. Therefore, 27 patients were classified into the rapid progression group and the remaining 104 patients into the slow progression group.

Grade 4 or 5B degeneration on either side of the cervical facet joints and spondylolisthesis were each observed with relatively high frequency at the responsible segmental level compared with nonresponsible levels. The prevalence of grade 4 or 5B degeneration in facet joints at the responsible level was 22.1% (29 out of 131 intervertebral levels), which was higher than 5.7% (30 out of 524 levels) at nonresponsible levels ($p < 0.001$). The prevalence of cervical spondylolisthesis at the responsible level was 28.2% (37 out of 131 levels), which was also higher than 8.6% (45 out of 524 levels) at nonresponsible levels ($p < 0.001$) (Fig. 4, Table 2).

Although there were similar trends for cervical facet joint degeneration and spondylolisthesis, there was no association between these 2 variables. There were no statistically significant differences between the presence of grade 4 or 5B degeneration on either side of both facet joints and the presence of spondylolisthesis at nonresponsible segmental levels ($p = 0.142$) (Table 3) or at the responsible level ($p = 0.322$) (Table 4).

Fig. 4. Prevalence of significant cervical facet degeneration and spondylolisthesis. The prevalence of grade 4 or 5B degeneration on either side of the facet joints at the responsible segmental level was 22.1%, which was higher than 5.7% at nonresponsible levels ($p < 0.001$). The prevalence of cervical spondylolisthesis at the responsible segmental level was 28.2%, higher than 8.6% at nonresponsible levels ($p < 0.001$). Grade 4, severe degenerative changes including moderate to large cysts (≥ 2 mm), and articular irregularity. Grade 5B, facet opening with articular irregularity.

Table 2. Cervical facet degeneration with articular irregularity and spondylolisthesis at each of the spinal levels

	Nonresponsible level	Responsible level	Total	p-value†
Grade 4 & 5B degeneration on either side of the facet joints				
(+)	30	29	59	-
(-)	494	102	596	-
Total	524	131	655	< 0.001
Cervical spondylolisthesis (≥ 2.0 mm)				
(+)	45	37	82	-
(-)	479	94	573	-
Total	524	131	655	< 0.001

†Pearson chi-square test.

Table 3. Relationship between cervical facet degenerations with articular irregularity and spondylolisthesis at the nonresponsible segmental level

	Cervical spondylolisthesis (≥ 2.0 mm)		Total	p-value†
	(+)	(-)		
Grade 4 & 5B degeneration on either side of the facet joints				
(+)	3	27	30	-
(-)	40	454	494	-
Total	43	481	524	0.142

†McNemar test.

Table 4. Relationship between cervical facet degenerations with articular irregularity and spondylolisthesis at the responsible segmental level

	Cervical spondylolisthesis (≥ 2.0 mm)		Total	p-value†
	(+)	(-)		
Grade 4 & 5B degeneration on either side of the facet joints				
(+)	8	21	29	-
(-)	29	73	102	-
Total	37	94	131	0.322

†McNemar test.

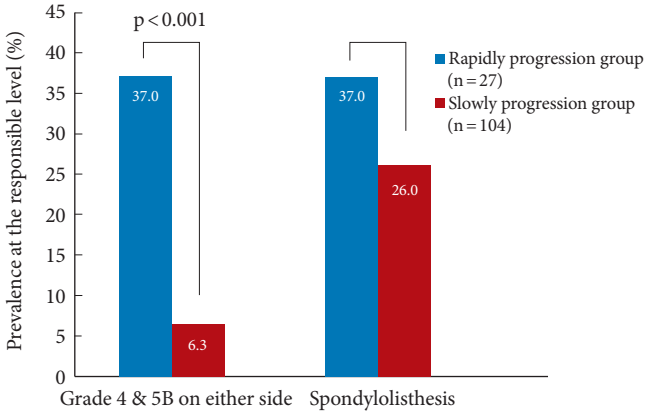

Fig. 5. Impact of cervical facet degeneration and spondylolisthesis on preoperative rapidly progressive myelopathy. The prevalence of grade 4 or 5B degeneration on either side of the facet joints at the responsible segmental level was significantly higher in the rapid progression group than in the slow progression group ($p < 0.001$). On the other hand, there were no statistically significant differences in the prevalence of cervical spondylolisthesis at the responsible level between the 2 groups ($p = 0.195$). Grade 4, severe degenerative changes including moderate to large cysts (≥ 2 mm), and articular irregularity. Grade 5B, facet opening with articular irregularity.

4. Clinical Impact of Facet Joint Degeneration and Cervical Spondylolisthesis

In the investigation of the clinical impact of facet joint degeneration and cervical spondylolisthesis in patients with DCM, the prevalence of grade 4 or 5B degeneration on either side of the facet joint at the responsible segmental level was higher in the rapid progression group compared to the slow progression group ($p < 0.001$). On the other hand, the prevalence of cervical spondylolisthesis at the responsible segmental level was higher in both the rapid and slow progression group, resulting in no statistical difference between the rapid and slow progression groups (Fig. 5) ($p = 0.255$).

DISCUSSION

The present study investigated clinical significance of facet joint degeneration in patients with DCM, by comparing the joints at responsible versus nonresponsible segmental levels. This is the first detailed comparative study of the association between facet joint degeneration and spondylolisthesis in DCM. The newly developed CT classification reflecting articular irregularity had few intraexaminer differences, and facet joint degeneration with articular irregularity and spondylolisthesis were more prevalent at the responsible segmental level. Moreover, this study showed that facet joint degeneration with articular irregularity at the responsible segmental level is significantly associated with rapid progression of myelopathy than slow progression of myelopathy. Although both articular irregularity and spondylolisthesis were significantly more prevalent at the responsible than the nonresponsible segmental levels, no such trend was observed in spondylolisthesis. We were able to clarify the clinical significance of facet joint degeneration; the impact of articular irregularity at a responsible segmental level was particularly significant in the rapid progression of DCM.

1. Evaluation of Cervical Facet Joint Degeneration

Age-related degeneration of the spine causes decreased mobility, stabilization, and bony fusion. In contrast, it can also cause increased local mobility and pathological conditions with intervertebral instability. Because the facet joints, a component of the cervical spine, play a role in static and gliding cervical motion and facilitate cervical spine mobility,[9] they are also highly susceptible to degenerative changes.[10] With increasing age, the facet joints have thinner articular cartilage and more lax capsular ligaments; there is also bone erosion.[11] Capsular ligament stiffness affects segmental mobility and spatial positioning of the vertebra. The sagittal angle of the facet joint influences the distribution of disc pressure. These effects may result in a vicious cycle of cervical spine degeneration and instability.[12] In addition, the cumulative effect of micro-injury can initiate or accelerate cervical degeneration. Significant Modic changes are a predisposing factor for facet degeneration.[13]

Facet joint degeneration of the spine also occurs not only with osteoarthritic bony changes but also with articular surface degeneration.[11] CT is more reliable than radiography or MRI in detecting facet arthrosis.[14,15] Therefore, we subdivided facet joint degeneration into 6 grades by including articular surface changes and intervertebral space opening in a new approach. Moreover, because cervical spondylosis is associated with a high incidence of asymptomatic lesions,[1] we included assessment of responsible versus nonresponsible segmental level in this study. We found for the first time that articular irregularity of the facet joints is involved in the development of myelopathy, which might indicate that motion stress concentration is occurring locally.

2. Prevalence of Facet Joint Degeneration

There have been several attempts to classify cervical facet joint degeneration and determine its prevalence.[4,14] The prevalence of facet joint degeneration varied widely in previous reports.

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Park et al.[14] evaluated the facet joints of patients who underwent CT for cervical spine-related symptoms such as neck pain, pain radiating to the arm, or difficulty walking. They found that 8.63% of all the facet joints had some kind of degeneration, including 0.5% of degeneration with bony fusion. Kim et al.[4] investigated the facet joints in patients with non-spinal pathology. They found that 33% had facet joints with degenerative changes. Although it is difficult to discuss prevalence consistently because these studies had patients with different backgrounds and used their own CT classifications, they indicate a certain amount of asymptomatic facet degeneration. In the present study, some kind of degeneration occurred in 27.9% of the facet joints at nonresponsible segmental levels that were considered clinically silent. Because of the large number of these asymptomatic lesions, it is difficult to associate facet joint degeneration alone with the pathogenesis of DCM.

There has been a report on the prevalence of cervical facet joint degeneration based on a 4-grade CT classification of facet joint degeneration in the cervical spine: grade I, normal; grade II, degenerative changes including joint space narrowing, cyst formation, and small osteophytes without joint hypertrophy; grade III, joint hypertrophy; grade IV, bony fusion of the joint.[14] Although this study was innovative in that it focused on the facet joints, it was difficult to evaluate the clinical significance of facet joint degeneration because facet joint degeneration was classified into only 2 categories, except for the evaluation of "normal" and "bony fusion." It was also difficult to detect the various changes related to facet degeneration based on only the 2 categories. In contrast, we classified joints into 6 grades in the present study. With our new classification, we found that 28.0% of facet joints had some type of degeneration, 2.9% had bony fusion (grade 5A), and 4.7% had articular irregularity (grade 4 or 5B). The presence of articular irregularity was more prevalent at the responsible segmental level than at nonresponsible levels, and the presence of bony fusion was conversely more prevalent at nonresponsible levels. In particular, the inclusion of articular irregularity in the classification provided a more detailed and clinically realistic assessment of facet joint degeneration.

We also investigated differences among evaluators, since subdivision of CT grades may cause differences in classification. In this newly proposed CT classification, the investigation of intraexaminer differences showed almost perfect agreement, despite a significant difference in the number of years of clinical experience between examiners. Therefore, this classification is a useful tool in daily clinical practice for evaluating the degree of facet joint degeneration in a comprehensive and effective manner.

3. Relationship Between Degeneration of Facet Joints and Degeneration of Other Structures

Previous studies evaluated the relationship between degeneration of facet joints and degeneration of other structures in the cervical spine. One study focused on degeneration of the vertebral disc, which is not associated with facet joint degeneration. Lee et al.[16] showed that facet joint degeneration depends on uncoveretebral joint degeneration and Modic change on MRI, but not disc or endplate degeneration, spinal stenosis, or ossification of the posterior longitudinal ligament. Moreover, there were no significant differences in disc height, segmental angle (SA), or SA range of motion based on the presence or absence of facet joint degeneration. Thus, advanced disc degeneration does not necessarily mean advanced facet joint degeneration. These results also suggest the need for the assessment of facet joint degeneration independent of the assessment of cervical disc degeneration.

On the other hand, cervical spondylolisthesis can be caused by severe facet degeneration.[16] Progressive loss of cartilage and articular remodeling as part of osteoarthritis can cause subluxation of the facet joint.[11] Therefore, facet joint degeneration can make a vertebral segment unstable and result in degenerative spondylolisthesis,[2,17,18] resulting in symptomatic DCM. Therefore, these 2 factors, facet joint degeneration and spondylolisthesis, seem to be interrelated and can together lead to the onset of DCM. However, we reported a case of rapidly progressive DCM induced by severe unilateral facet joint degeneration without any trauma or cervical spondylolisthesis.[6] This case showed that the 2 factors are not necessarily interrelated concerning the onset of DCM, as indicated in the current study. The prevalence of grade 4 or 5B degeneration, suggesting destructive changes in the facet joint, was significantly higher at the responsible level than at nonresponsible levels. There was also no relationship between the presence of grade 5 or 5B facet degeneration and spondylolisthesis at either the responsible level or nonresponsible levels. These results suggest that articular irregularity, a form of facet joint degeneration, and the occurrence of cervical spondylolisthesis are not related to the onset of DCM, but that they may be independent factors in the development of myelopathy.

4. Clinical Impact of Facet Joint Degeneration

The clinical impact of cervical facet joint degeneration on myelopathy has not been well debated, but there are few rele-

vant studies. Even in these studies, the clinical impact has not been sufficiently examined because the studies included evaluation of images from a wide range of patients, such as patients without symptoms or neck pain only,[4,14] categorized patients into only 2 groups (presence or absence of facet joint abnormalities),[19] evaluated only facet joint tropism,[20] focused on evaluating the reproducibility of the scoring system for facet degeneration,[21] or included evaluations of other characteristics such as intervertebral height loss, anterior osteophytes, and endplate sclerosis.[5] Therefore, it would be very meaningful to develop a clinically relevant and appropriate method to evaluate facet joint degeneration. The current study investigated the clinical implications of a novel classification system.

DCM occurs due to the interrelated involvement of many factors.[2,3,22,23] As cervical facet joint degeneration progresses, spondylolisthesis will occur, but if there is already spinal canal stenosis related to factors such as osteophytes, disc protrusion, or ligamentous hypertrophy, cervical myelopathy might occur before spondylolisthesis. In the present study, the prevalence of grade 4 or 5B degeneration at the responsible segmental level was significantly higher in the rapid progression group than in the slow progression group, but the prevalence of cervical spondylolisthesis was not similar. This fact may inform us about the nature of the pathology. The cervical spine contains multiple joints and is highly susceptible to movement, but cervical degeneration does not occur uniformly. As a result of stress distribution, there may be a concentration of motion stress in one area, as in the case of adjacent segmental disease after fusion surgery. The articular irregularity indicates that excessive strain has been placed on the articular surfaces. Therefore, it is speculated that articular irregularity at the responsible segmental level may be a change that could reveal motion stress concentration. It is also speculated that if spinal cord compression is present in the background, this motion stress concentration may cause the rapid progression of cervical myelopathy. Further research is warranted in this respect.

5. Limitations

This study has several limitations. First, it used a retrospective design with a small number of patients. Second, it is uncertain whether the responsible segmental level was correctly identified in all patients. Third, the evaluation of cervical spondylolisthesis was not sufficient because there is no consensus on the definition of dynamic instability, which was not assessed in this study. Considering cervical spondylolisthesis, this study compared it only with articular irregularity of facet joints. It is speculated that patients who present with cervical spondylolisthesis at the responsible segmental level often have a low grade of facet degeneration. In addition, the spondylolisthesis in this study includes both forward and backward spondylolisthesis. Further studies are required on this point. Fourth, there is a pair of facet joints at each intervertebral height, and they do not always have the same degree of degeneration. If the contralateral facet joint was classified differently, it could have reduced the proportion of joints with grade 4 or 5B degeneration despite the presence of articular irregularity, which can underestimate the impact of facet joint degeneration with articular irregularity. Therefore, the clinical effect of grade 4 or 5B degeneration might be more significant. Despite these limitations, this study demonstrated the importance and clinical usefulness of evaluating cervical facet joint degeneration in patients with DCM.

CONCLUSION

This study was the first to focus on the potential importance of facet joint degenerative pathology and demonstrate the usefulness and reliability of a newly created CT classification of cervical facet joint degeneration in patients with DCM. The novel CT classification had few intraexaminer differences and deserves additional evaluation, suggesting that abnormal findings on articular surfaces might be related to the progression of myelopathy.

NOTES

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REFERENCES

1. Bakhsheshian J, Mehta VA, Liu JC. Current diagnosis and management of cervical spondylotic myelopathy. Global Spine J 2017;7:572-86.
2. Nouri A, Tetreault L, Singh A, et al. Degenerative cervical myelopathy: epidemiology, genetics, and pathogenesis. Spine (Phila Pa 1976) 2015;40:E675-93.
3. Jiang SD, Jiang LS, Dai LY. Degenerative cervical spondylolisthesis: a systematic review. Int Orthop 2011;35:869-75.
4. Kim JH, Sharan A, Cho W, et al. The prevalence of asymptomatic cervical and lumbar facet arthropathy: a computed tomography study. Asian Spine J 2019;13:417-22.
5. Rydman E, Bankler S, Ponzer S, et al. Quantifying cervical spondylosis: reliability testing of a coherent CT-based scoring system. BMC Med Imaging 2019;19:45.
6. Takeshima Y, Okamoto A, Yokoyama S, et al. Unilateral degenerative facet joint pathology eliciting rapidly progressive cervical spondylotic myelopathy. Cureus 2021;13:e14238.
7. Morishita Y, Matsushita A, Maeda T, et al. Rapid progressive clinical deterioration of cervical spondylotic myelopathy. Spinal Cord 2015;53:408-12.
8. Takasawa E, Sorimachi Y, Iizuka Y, et al. Risk factors for rapidly progressive neurological deterioration in cervical spondylotic myelopathy. Spine (Phila Pa 1976) 2019;44:E723-30.
9. Shedid D, Benzel EC. Cervical spondylosis anatomy: pathophysiology and biomechanics. Neurosurgery 2007;60(1 Supp1 1):S7-13.
10. O'Leary SA, Link JM, Klineberg EO, et al. Characterization of facet joint cartilage properties in the human and interspecies comparisons. Acta Biomater 2017;54:367-76.
11. Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. Nat Rev Rheumatol 2013;9:216-24.
12. Wang HH, Wang K, Deng Z, et al. Effects of facet joint degeneration on stress alterations in cervical spine C5-C6: a finite element analysis. Math Biosci Eng 2019;16:7447-57.
13. Lv B, Fan X, Ding H, et al. Analysis of correlation between age and cervical facet joint degeneration and Modic changes in patients with cervical spondylotic myelopathy. Med Sci Monit 2019;25:7882-8.
14. Park MS, Lee YB, Moon SH, et al. Facet joint degeneration of the cervical spine: a computed tomographic analysis of 320 patients. Spine (Phila Pa 1976) 2014;39:E713-8.
15. Lehman RA Jr, Helgeson MD, Keeler KA, et al. Comparison of magnetic resonance imaging and computed tomography in predicting facet arthrosis in the cervical spine. Spine (Phila Pa 1976) 2009;34:65-8.
16. Lee SH, Son DW, Lee JS, et al. Relationship between endplate defects, modic change, facet joint degeneration, and disc degeneration of cervical spine. Neurospine 2020;17:443-52.
17. Pellengahr C, Pfahler M, Kuhr M, et al. Influence of facet joint angles and asymmetric disk collapse on degenerative olisthesis of the cervical spine. Orthopedics 2000;23:697-701.
18. Chaput CD, Allred JJ, Pandorf JJ, et al. The significance of facet joint cross-sectional area on magnetic resonance imaging in relationship to cervical degenerative spondylolisthesis. Spine J 2013;13:856-61.
19. Woiciechowsky C, Thomale UW, Kroppenstedt SN. Degenerative spondylolisthesis of the cervical spine--symptoms and surgical strategies depending on disease progress. Eur Spine J 2004;13:680-4.
20. Aoyama R, Shiraishi T, Kato M, et al. Characteristic findings on imaging of cervical spondylolisthesis: analysis of computed tomography and X-ray photography in 101 spondylolisthesis patients. Spine Surg Relat Res 2018;2:30-6.
21. Walraevens J, Liu B, Meersschaert J, et al. Qualitative and quantitative assessment of degeneration of cervical intervertebral discs and facet joints. Eur Spine J 2009;18:358-69.
22. Kokubun S, Sato T, Ishii Y, et al. Cervical myopathy in the Japanese, Clin Orthop Relat Res. 1996;323:129-38.
23. Aizawa T, Ozawa H, Hoshikawa T, et al. Severe facet joint arthrosis caused c7/t1 myelopathy: a case report. Case Rep Med 2009;2009:481459.

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Original Article

Analysis of Associating Radiologic Parameters With Clinical Outcomes After Posterior C1–2 Fusion

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Objective: To evaluate which radiologic parameters affect clinical outcomes in patients underwent posterior C1–2 fusion for atlantoaxial dislocation.
Methods: From January 2014 to December 2017, among 98 patients underwent C1–2 posterior fusion, patients with previous cervical surgery or extending to subaxial spine or basilar invagination were excluded. Finally, 38 patients were included. O–C2, C1–2, C1–C7, C2–C7 cobb angle (CA), T1 slope, C1–7, C2–7 sagittal vertical axis (SVA), and posterior atlantodental interval (PADI) were measured at preoperative and postoperative 1 year. The difference between postoperative and preoperative values for each parameter was designated as Δvalue. Postoperative subaxial kyphosis (PSK) was defined to decrease ≥ 10° at subaxial spine. Visual analogue scale (VAS), Japanese Orthopedic Association (JOA) score, Neck Disability Index (NDI) were used to evaluate clinical outcomes.
Results: Mean age was 54.4 ± 15.9. Male to female was 14 to 24. Of radiologic parameters, C1–7 SVA and PADI were significantly changed from 26.4 ± 12.9 mm, 17.1 ± 3.3 mm to 22.6 ± 13.0 mm, 21.6 ± 3.4 mm. ΔC1–2 CA was correlated with ΔC1–7 CA and ΔC2–7 SVA. ΔPADI correlates with ΔO–C2 CA. VAS correlates with ΔC1–7 CA ($p = 0.03$). JOA score also correlates with ΔC2–7 SVA ($p = 0.02$). NDI was associated with ΔPADI ($p < 0.01$). The incidence of PSK was 23.7%, and not significant with clinical outcomes.
Conclusion: ΔC1–2 CA was correlated with ΔC1C7 CA, ΔC2–7 SVA. ΔC1–7 CA, ΔC2–7 SVA, and ΔPADI were the key radiologic parameters to influence clinical outcomes. Postoperative C1–2 angle should be carefully determined as a factor affecting clinical outcomes and cervical sagittal alignment.

Keywords: Atlantoaxial dislocation, Correlation, Cobb angle, Posterior C1–2 fusion, Subaxial kyphosis, Sagittal vertical axis

INTRODUCTION

Atlantoaxial dislocation (AAD) can cause severe neurologic deficit which make patients disabled or neck pain results from kyphosis at upper cervical spine.[1-6] Pathologies of AAD were various such as trauma, inflammation, congenital anormaly, and iatrogenic causes.[1-10] The treatment of AAD has always been a major concern for spine surgeon. Since transarticular screw fixation and interlamina fusion was introduced by Mergel and Brook, posterior C1–2 fusion has been known as an effective treatment for AAD.[11,12] As Ham's technique emerged, cervical polyaxial screw and rod fixation system is widely used because of its simplicity of the technique and low risk of vertebral artery injury.[13]

As these surgical techniques have been popularized, some surgeons gradually interested in postoperative changes in cervical sagittal balance.[14,15] C1–2 fusion led to reciprocal changes in subaxial spine according to its angle, and it is considered to be an important factor for sagittal alignment in subaxial spine.[16] Moreover, some studies stated that these surgical techniques are

associated with complex cervical deformities such as postoperative regional kyphosis, postoperative subaxial kyphosis (PSK), or hyperlordosis.[17,18]

Previous studies focused on evaluating the relationship between postoperative C1–2 angle and subaxial sagittal alignment, but there were a few studies stated that the association between postoperative radiologic parameters related with sagittal balance and clinical outcomes.[19,20] In our study, we analyzed the correlation between radiologic parameters in cervical spine before and after posterior C1–2 fusion. Furthermore, we investigated how these changes in radiologic parameters affect clinical outcomes in patients treated posterior C1–2 fusion.

MATERIALS AND METHODS

1. Patient Selection

A retrospective analysis of medical records and radiologic data was performed on patients that had undergone posterior atlantoaxial fusion for AAD at a single center from January 2014 to June 2017. This study was approved by the Institutional Review Board of Catholic Medical Center (OC21RISI0008). Ninety-eight patients treated by posterior C1–2 fusion during this period. Patients had previous cervical surgery history or concomitant with basilar invagination were excluded. In addition, patients needed additional fusion extension to occipital or subaxial spine were also excluded. Finally, 38 patients were included in the study.

2. Surgical Techniques

The patient was placed in prone position with Mayfield head fixator under general anesthesia. The surgeon reduced C1–2 dislocation as much as possible by adjusting patient's head by flexion or extension while pulling out the Mayfield head fixator. C1–2 reduction was confirmed under the C-arm fluoroscopy. When we cannot achieve acceptable reduction by adjusting patients' position, we usually released C1–2 facet joint in order to reduce dislocation additionally by removing the capsule surrounded it during surgery. C2 roots were preserved by protecting root retractor during the releasing of C1–2 facet. All procedures were performed under intraoperative monitoring (IOM). Vascular anomalies were evaluated preoperatively to avoid neurovascular injury. Atlantoaxial fixation was accomplished using a variety of surgical constructs combined with C1 lateral mass to C2 pedicle screw, C2 pars screw, or to C2 laminar screw fixation. We controlled C1–2 angle by compressing or distracting the interspace between 2 polyaxial screws along the rods. Autograft bone harvested from the posterior superior iliac spine was inserted to the interlaminar space of C1–2 to enhance the fusion. Modified brook's Wiring technique between C1 and C2 lamina was performed to fix the autograft bone and obtain additional biomechanical strength.[11] Finally, fluoroscopy was used to confirm the reduction and lordotic angle of C1–2 (Fig. 1).

3. Radiologic Parameters

Two neurosurgeons (JTH and JHP) measured all radiologic parameters on cervical standard lateral radiographs using INFINIT PACS (INFINIT Healthcare, Seoul, Korea) using an electrical caliper on 2 occasions. The 4 sets of radiologic parameters measured were then averaged for statistical analysis. Lateral radiographs were obtained in the neutral head position. A standard distance of 1.8 m was maintained between the tube and patients. The following parameters were measured on radiograph before surgery and at 1 year after surgery.

- C2 cobb angle (CA): The angle between the line connecting McGregor line and the inferior endplate of C2 (Fig. 2A).
- C1–2 cobb angle (CA): The angle between the line connecting the middle point of the anterior and posterior arch of C1 and the inferior endplate of C2 (Fig. 2A).
- C1–7 cobb angle (CA): The angle between the line connecting the middle point of the anterior and posterior arch of C1 and the inferior endplate of C7 (Fig. 2 A).
- C2–7 cobb angle (CA): The angle between the inferior endplate of C2 and C7 (Fig. 2A).
- T1 slope: The angle between horizontal line and the T1 superior endplate. (Fig. 2A).
- C1–7 sagittal vertical axis (SVA): The distance between the plumb line from the anterior margin of C1 and posterior superior corner of C7 (Fig. 2B).
- C2–7 sagittal vertical axis (SVA): The distance between the plumb line from the center of C2 and the posterior superior corner of C7 (Fig. 2B).
- Posterior atlantodental interval (PADI): The distance between the line connecting the middle point of the anterior and posterior arch of C1 and the dens of C2 (Fig. 2B).

The difference between preoperative and postoperative values for each parameter was designated as the Δvalue.

PSK was defined as the postoperative change of ≥10° at C2–7 CA.

4. Clinical Outcomes

Clinical outcomes were assessed using visual analogue scale (VAS) for neck pain, Neck Disability Index (NDI)[21] and Japa-

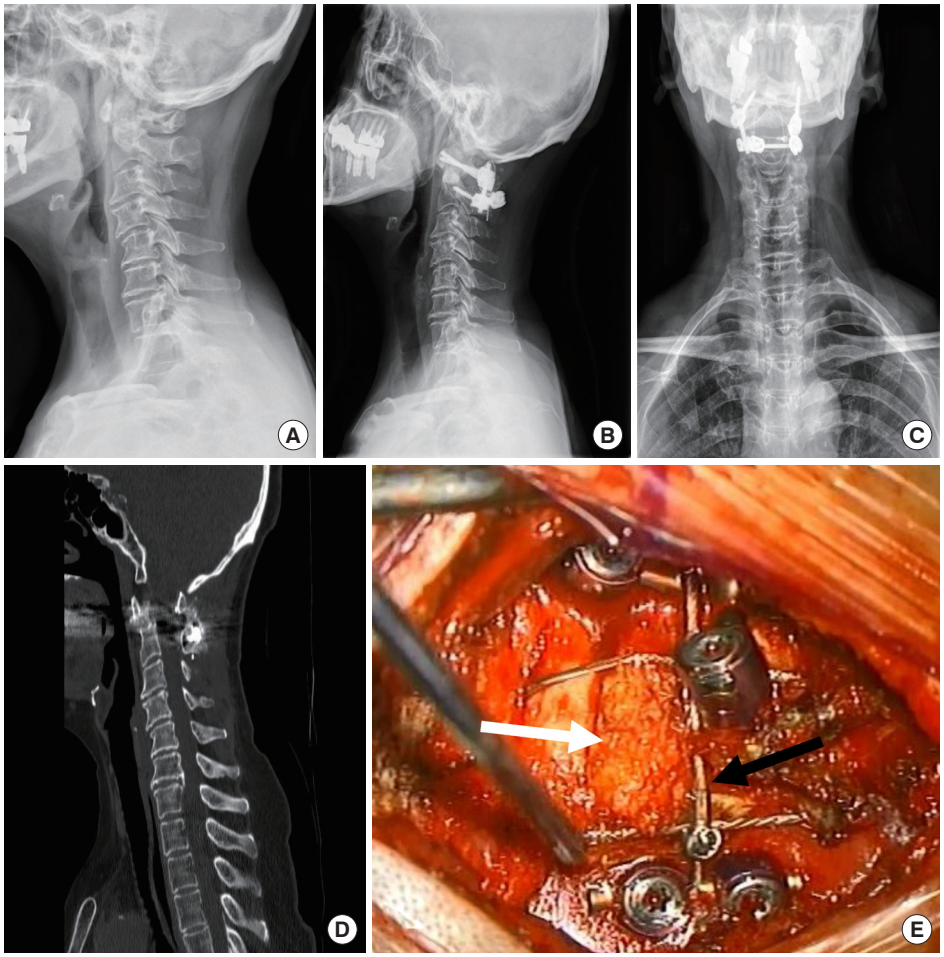

Fig. 1. Radiologic and surgical figures of the patient treated by C1 lateral mass–C2 pars and lamina screw construct wiring interlamina with autograft bone. Preoperative lateral (A) and postoperative lateral (B) and anteroposterior (C) radiographs. (D) Midsagittal image of computed tomography after surgery. (E) Intraoperative figure represents wiring interlamina (black arrow) with an autograft bone (white arrow).

nese Orthopedic Association (JOA) scores[22] at preoperative and postoperative one year. Improvements in VAS and NDI scores were also expressed as the difference between postoperative and preoperative values. The Δvalue was used for the difference between postoperative and preoperative values for each parameter.

5. Statistical Analysis

The Student t-test, the paired t-test, and Mann-Whitney U-test were used to analyze continuous and ordinal variables, as appropriate. Correlation test and a linear logistic regression model were used to evaluate the natures of correlations between the radiologic parameters and clinical outcome. p-values of <0.05 (2-tailed) were considered statistically significant, and IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) was used for the statistical analysis. The intra-inter reliabilities of radiologic parameters were calculated. Intraclass correlation coefficient values were rated as follows: 0 to 0.2 slight agreement, 0.21 to 0.4 fair agreement, 0.41 to 0.6 moderate agreement, 0.61 to 0.8 substantial agreement, and 0.81 to 1.0 excellent agreement.

RESULTS

Clinical information is summarized in Table 1. There were 14 males and 24 females of mean age 54.4±15.9 years and mean body mass index 23.3±3.6 kg/m^2. Mean height and weight were 1.6±0.1 m and 59.6±10.8 kg. Twenty patients (52.6%) had rheumatoid arthritis (RA), 11 (29%) had a congenital anomaly, and 7 (18.4%) had degenerative spondylosis as pathologies for AAD. Fourteen patients were fixed with C1 lateral mass –C2 pedicle screw construct, 4 with C1 lateral mass –C2 hybrid construct, and 20 with C1 lateral mass –C2 pars con-

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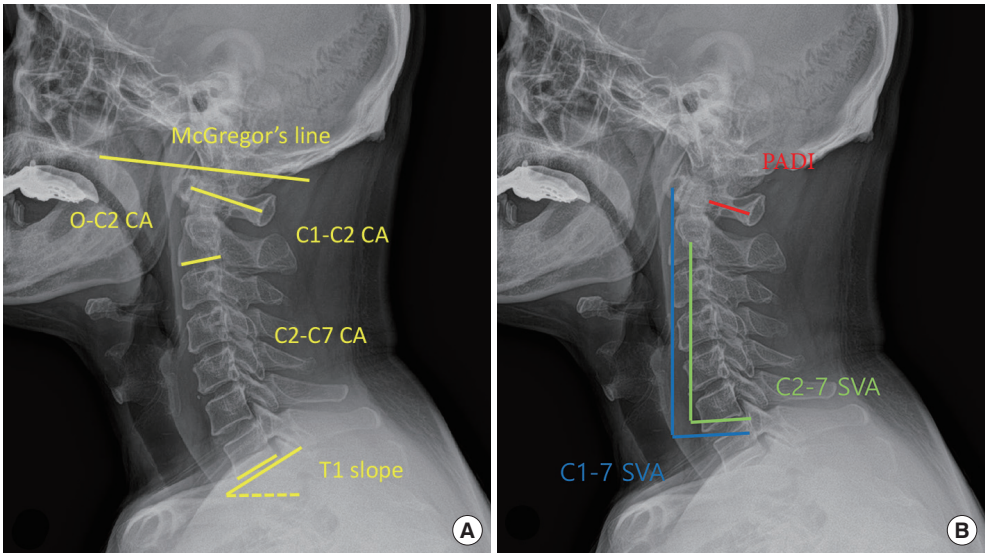

Fig. 2. Radiologic parameters on a cervical lateral plain radiograph in patient with atlantoaxial dislocation. (A) O–C2, C1–2, C1–7, C2–7, T1 slope are measured between the lines on cervical lateral plain radiograph. (B) C1–7 (blue line), C2–C7 sagittal vertical axis (SVA; green line), and posterior atlantodental interval (PADI; red line) are measured on cervical lateral plain radiograph. CA, cobb angle.

Table 1. Clinical information of the 38 patients with atlantoaxial dislocation

Characteristic	Value
Sex	
Male	14 (36.8)
Female	24 (63.2)
Age (yr)	54.4 ± 15.9
Body mass index (kg/m^2)	23.3 ± 3.6
Height (m)	1.6 ± 0.1
Weight (kg)	59.6 ± 10.8
Pathology (%)	
Spondylosis	7 (18.4)
Rheumatoid arthritis	20 (52.6)
Congenital anomaly	11 (29)
C1–2 constructs (%)	
Lateral mass-pedicle screws	14 (36.8)
Lateral mass-hybrid screws	4 (10.5)
Lateral mass-pars screws	20 (52.6)
Reducibility	
Irreducible AAD	2 (5.3)
Reducible AAD	36 (94.7)
Decompression	
Direct	2 (5.3)
Indirect	36 (94.7)

Values are presented as number (%) or mean ± standard deviation.
Hybrid screws, C2 pedicle–pars or translaminar screws; AAD, atlantoaxial dislocation.

Table 2. Comparison of preoperative and postoperative radiologic parameters

Radiologic measurement	Preoperative	Postoperative	p-value
O–C2 CA (°)	11.3 ± 8.6	12.8 ± 6.9	0.175
C1–2 CA (°)	18 ± 11.2	19.5 ± 6.2	0.402
C1–7 CA (°)	35 ± 11.1	33.4 ± 10.6	0.471
C2–7 CA (°)	16.9 ± 10.3	14.0 ± 10.2	0.087
T1 slope (°)	19.9 ± 8.7	19.2 ± 7.2	0.523
C1–7 SVA (mm)	26.4 ± 12.9	22.6 ± 13	0.032*
C2–7 SVA (mm)	11.8 ± 12.1	14.4 ± 10.6	0.141
PADI (mm)	17.1 ± 3.3	21.6 ± 3.4	< 0.001*

CA, cobb angle; SVA, sagittal vertical axis; PADI, posterior atlantoaxial interval.
*$p < 0.05$, statistical significance.

struct. Two patients were irreducible AAD, then we performed to release of C1–2 facet joint during surgery. There were no patients need anterior approaches for additional decompression. Thirty-six patients were reducible AAD and obtained sufficient reduction of C1–2 dislocation by pushing down the spinous of C2 during connecting the rod. Two patients needed C1 laminectomy for decompression, we usually inserted autograft bone chip into released C1–2 facet joint for using fusion-bed. The remaining 36 patients, only indirect decompression obtained the reduction of atlantoaxial joint was enough.

Table 3. Reciprocal relationship of the difference between preoperative and postoperative radiologic measurements

Radiologic measurements	ΔO–C2 CA	ΔC1–2 CA	ΔC1–7 CA	ΔC2–7 CA	ΔT1 slope	ΔC1–7 SVA	ΔC2–7 SVA	ΔPADI
ΔO–C2 CA	1.000	0.561*	0.128	-0.403*	-0.102	0.065	0.225	0.561*
ΔC1–2 CA	0.561*	1.000	0.624*	-0.225	0.058	0.241	0.384*	0.001
ΔC1–7 CA	0.128	0.624*	1.000	0.621*	0.357*	-0.239	-0.141	-0.203
ΔC2–7 CA	-0.403*	-0.225	0.621*	1.000	0.387*	-0.540*	-0.561*	-0.253
ΔT1 slope	-0.102	0.058	0.357*	0.387*	1.000	0.171	0.197	-0.069
ΔC1–7 SVA	0.065	0.241	-0.239	-0.540*	0.171	1.000	0.953*	0.054
ΔC2–7 SVA	0.225	0.384*	-0.141	-0.561*	0.197	0.953*	1.000	0.099
ΔPADI	0.561*	0.001	-0.203	-0.253	-0.069	0.054	0.099	1.000

CA, cobb angle; SVA, sagittal vertical axis; PADI, posterior atlantodental interval.
*$p < 0.05$, statistical significance.

1. Radiologic Parameters

Radiologic parameters obtained at preoperative and postoperative are summarized in Table 2. The difference between preoperative and postoperative each CA except C1–7 SVA and PADI was not significant because the values of each CA in some patients were counteracted for each other when analyzing all of the values together. This feature may contribute to small difference between preoperative and postoperative each CA, and it was not significant. T1 slope seemed unchanged statistically at postoperative for the same reason. C1–7 SVA showed a tendency to decrease from 26.4 ± 12.9 to 22.6 ± 13 at postoperative ($p = 0.03$). C2–7 SVA showed slight increase at postoperative, but it was not significant. PADI dramatically increased about 4.5 mm comparing to preoperative value ($p < 0.01$). The intra- and intercorrelations of radiologic parameters were 0.94 and 0.88, respectively. Measurements of radiologic parameters showed excellent degree of agreement.

Correlations between radiologic parameters are presented in Table 3. ΔO–C2 CA correlated positively with ΔC1–2 CA and ΔPADI, and negatively with ΔC2–7 CA. ΔC1–2 CA correlated positively with ΔC1–7 CA and ΔC2–7 SVA. ΔC1–7 CA correlated positively with ΔC2–7 CA and ΔT1 slope. ΔC2–7 CA correlated positively with ΔT1 slope and negatively with ΔC1–7 SVA and ΔC2–7 SVA. ΔC1–7 SVA correlated positively with ΔC2–7 SVA.

2. Clinical Outcomes

VAS, NDI, and JOA score improved significantly at postoperative. Mean VAS decreased from 5.1 ± 2.9 to 1.7 ± 1.6 ($p < 0.01$). Mean JOA scores increase from 13.2 ± 2.7 to 15.3 ± 2.6 ($p = 0.02$). Mean NDI decreased form 22.2 ± 11.0 to 6.7 ± 5.8 ($p < 0.01$). However, 3 patients deteriorated neck pain at postoperative. One patient suffered severe neck pain at VAS 9. The patient showed that reciprocal kyphotic change from 34° to 1.5° in subaxial spine after surgery. The other presented neck pain at VAS 4. The patient represented slight change of ΔC2–7 CA from 32.5° to 34.4°, but we failed to make lordotic C1–2 angle (from 4.5° to 4.8°) intraoperatively. Another complained neck pain VAS 5. The patient also showed that reciprocal kyphotic change from 10.9° to 2.2° in subaxial spine even though we made kyphotic C1–2 angle from 22.2° to 13.1°. This patient complained neck pain and developed subaxial kyphosis although we tried to underreduce C1–2 angle.

3. Relationship Between Radiologic Parameters and Clinical Outcomes

VAS, NDI, JOA score were associated with several radiologic parameters. Δ VAS correlated with ΔC1–7 CA, ΔT1S negatively ($r = -0.357$, $p = 0.03$, $r = -0.341$, $p = 0.04$). ΔNDI correlated with ΔPADI negatively ($r = -0.499$, $p = 0.01$). ΔJOA score correlated with ΔC2–7 SVA positively ($r = 0.354$, $p = 0.03$). In linear logistic regression, ΔC1–7 CA represented negatively linear correlation with ΔVAS, ΔPADI also showed negatively linear correlation with ΔNDI, ΔC2–7 SVA represented positively linear correlation with ΔJOA score, respectively (Fig. 3).

The incidence of PSK was 23.7%, it was not significantly associated with VAS ($p = 0.26$), NDI ($p = 0.32$), JOA score ($p = 0.97$).

DISCUSSION

Atlantoaxial fusion is frequently associated with sagittal realignment in subaxial spine, and many authors stated the negative correlation between ΔC1–2 CA and ΔC2–7 CA after sur-

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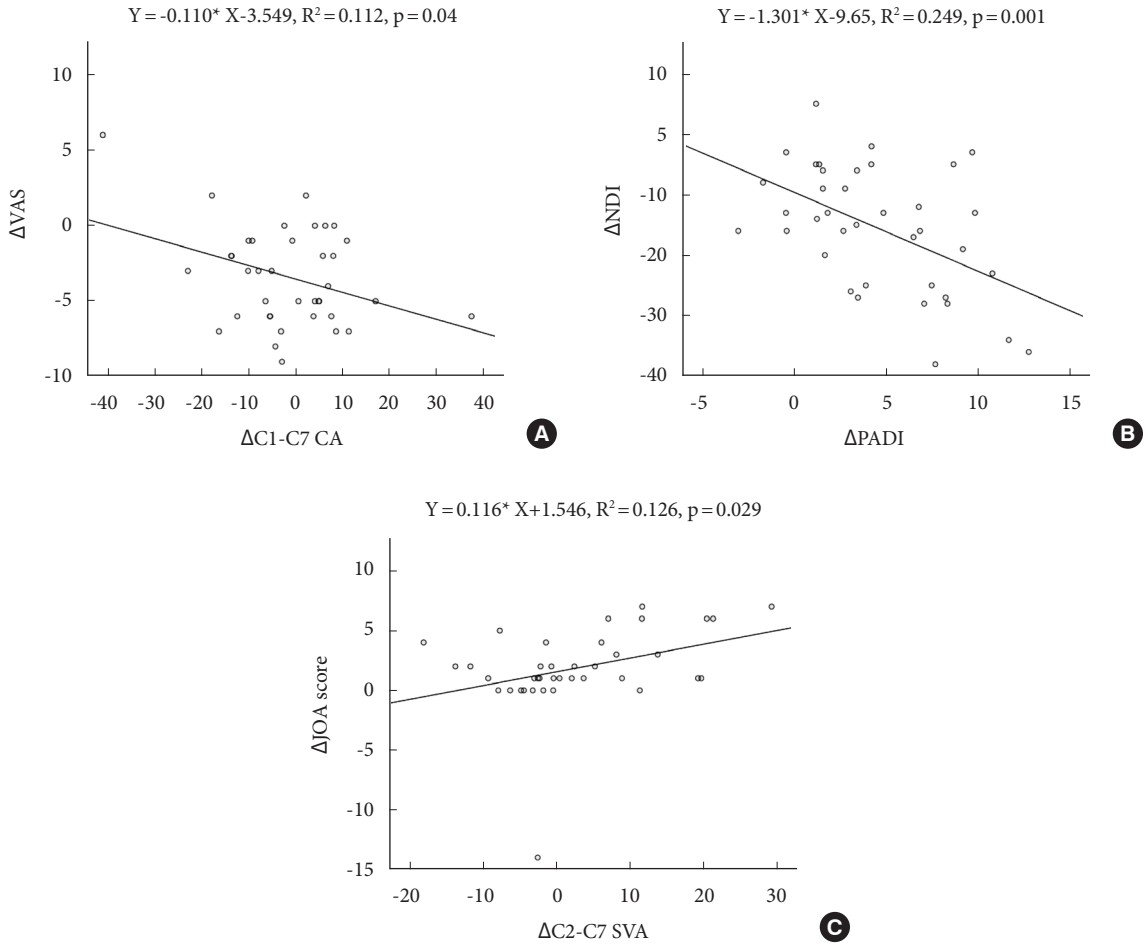

Fig. 3. Linear logistic regression plots between radiologic parameters and clinical outcomes. A linear correlation with ΔC1–7 CA (A), ΔVAS a linear correlation with ΔPADI (B) and ΔNDI a linear correlation with ΔC2–C7 SVA and ΔJOA score (C). CA, cobb angle; VAS, visual analogue scale; PADI, posterior atlantodental interval; NDI, Neck Disability Index; SVA, sagittal vertical axis; JOA, Japanese Orthopedic Association. Asterisk (*) means multiple.

gery.[14,15,17,18] However, we observed different results of correlation between ΔC1–2 CA and ΔC2–7 CA. Postoperative sagittal realignment in subaxial spine was occurred in our study. However, the reciprocally negative correlation between ΔC1–2 and ΔC2–7 CA wasn't found although preoperative C1–2 and C2–7 CA represented the negative correlation each other. We found that the reciprocally negative correlation between ΔO–C2 and ΔC2–7 CA, instead of ΔC1–2 CA. We studied why this phenomenon happened in our study unlike other studies. First, ΔC1–2 CA was compensated by ΔC2–7 CA as well as ΔO–C1 CA to maintain the horizontal gaze. The preoperative range of motion (ROM) of C1–2 angle in normal people has about 6° when flexion and extension,[23] and compensate for the change of subaxial spine in available ROM. However, postoperative C1–2 angle is fixed after surgery, and it plays the constant no room to change. It seems that the O–C1 angle plays as a buffer angle to maintain the horizontal gaze. ΔC2–7 CA was compensated by ΔO–C1 CA instead of the constant C1–2 angle. It seems that postoperative C1–2 CA as the constant does not work on cervical sagittal realignment. ΔO–C2 CA was actually the parameter obtained by adding a constant to ΔO–C1 CA. Therefore, ΔO–C2 CA was correlated with ΔC2–7 CA negatively, not ΔC1–2 CA excluding ΔO–C1 CA. Second, we observed a radiologic feature of patients in this study. The ratio of C1–2 CA and C2–7 CA was different to normal ranged patients. Some authors stated that normal values of C1–2 angle ranged from 25.6° to 28.9° and it accounted for 75%–80% of cervical standing lordosis.[24,25] However, our patients showed the proportion of cervical lordosis of C1–2 CA was about 52.5%, suggesting that C1–2 CA constitutes a relatively small proportion of cervical lordosis, and the proportion of C2-7 CA is predominant in cervical lordosis compared with others. Therefore,

ΔC2–7 CA is increased relatively compared to other studies. There is the possibility that this feature might contribute that the reciprocal correlation between ΔC1–2 and ΔC2–7 CA was not significant.

The correlation of each radiologic parameter was summarized in Table 3. The important findings of this correlation test is described to 3 things. One thing is that the change of upper cervical spine (ΔO-C2 CA) is correlated with the change of subaxial cervical spine (ΔC2-C7 CA) and this relationship does not be affected before and after surgery. Second thing is that ΔC1–2 CA is associated with cervical kyphosis and flattening of cervical curvature. Third thing is that ΔC2–7 CA is a subjective radiologic parameter affected by various radiologic parameters.

ΔC1–2 CA was associated with ΔO–C2, ΔC1–7 CA, and ΔC2–7 SVA. Moreover, ΔC1–7 CA was negatively correlated with ΔVAS (Fig. 3A). Therefore, it can be expected if ΔC1–7 CA decreased after surgery, neck pain would be unchanged or worse. In addition, ΔC2–7 SVA had a positive correlation with ΔJOA score (Fig. 3C). Therefore, cervical sagittal alignment is significantly related to neck pain as well as cervical myelopathy. Some studies supported our results. Shimizu et al.[26] found that a significant correlation between the degree of cervical kyphosis and the amount of cord flattening leading to decreased vascular supply. Cervical sagittal malalignment is strongly related with neck pain. Tang et al.[27] also reported that C2–7 SVA directly correlated with NDI and cervical myelopathy. As a result, intraoperative C1–2 angle determined by surgeon was an important factor to affect not only cervical sagittal realignment but also VAS and JOA score.

ΔC1–7 CA was associated with ΔC1–2 CA, ΔC2–7 CA, ΔT1 slope. This correlation is taken for granted that C1–7 CA was the parameter including C1–2 and C2–7 CA. ΔT1 slope was changed according to ΔC1–7 CA.

ΔC2–7 CA also correlated with ΔO–C2 CA, ΔC1–7 CA, ΔT1 slope, ΔC1–7 SVA, and ΔC2–7 SVA. It was the most subjective radiologic parameter that was correlated with various others and also associated with VAS and JOA score such like ΔC1–2 CA. Nevertheless, surgeons can adjust ΔC1–2 CA as determining intraoperative C1–2 CA under C-arm fluoroscopy, but ΔC2–7 CA cannot be controlled intraoperatively and be predicted during follow-up. Therefore, surgeons should carefully observe the change of C2–7 CA in the patient after posterior C1–2 fusion.

ΔT1 slope was relative with ΔC1–7 CA, ΔC2–7 CA. This change in T1 slope explains that ΔT1 slope was complementary to the change of cervical spine.

ΔC2–7 SVA was correlated with ΔC1–2 CA, ΔC2–7 CA, ΔC1–7 SVA, JOA score. ΔC2–7 SVA was affected simply not only ΔC2–7 CA, but also ΔC1–2 CA. ΔC1–7 SVA was correlated with ΔC2–7 SVA each other. However, ΔC1–7 SVA showed the difference to ΔC2–7 SVA in that there was not correlated with ΔC1–2 CA. This different point interestingly affected that ΔC1–7 SVA was not significant with JOA score.

ΔPADI correlates with ΔO–C2 CA, and it was a factor associated with ΔNDI. ΔPADI increased significantly after surgery, it pointed out that most patients obtained enough reduction of AAD intraoperatively. This point explained why the reduction of AAD is important in the improvement of quality of life. Several Authors emphasized the importance of enough reduction of AAD, but this was still controversial. Jun et al.[28] suggested that complete reduction of AAD could obviate the need for direct decompression. Goel and Shah[29] introduced that facet manipulation and fixation in irreducible AAD facilitated reduction of AAD. Otherwise, Wang et al.[30] stated that sufficient decompression by laminectomy and solid fusion for AAD is more important than complete reduction for treatment of AAD. Lang et al.[31] also reported that incompletely reduced AAD had comparable clinical outcomes with those with complete reduction. Nevertheless, complete reduction of AAD without laminectomy can provide patients with sufficient fusion-bed for bone graft. Because of this advantage, we removed the capsule of C1–2 facet joint and distracted the facet joint by osteotome to release sufficiently in case of irreducible AAD. Finally, we obtained sufficient reduction of AAD in 94.7% of patients except 2 cases performed C1 laminectomy.

The PSK that occurred 23.7% of patients was not correlated with clinical outcomes. There are some studies that PSK was one of causes for postoperative neck pain.[32] We also agree that neck pain was associated with PSK. In the present study, patients with PSK showed the tendency to complain of severe neck pain. However, deterioration of neck pain was also observed in patients without PSK in our study. This point resulted in the failure to prove the statistical significance that PSK is related with neck pain. Yoshimoto et al.[18] also observed similar results of ours. The author stated that 12 patients among 44 patients without any progression of PSK complained neck pain aggravated after surgery. For this reason, there was no significance found between PSK and clinical outcomes.

Several studies reported the PSK between the changes in subaxial alignment and intraoperative C1–2 angle.[17,18,33] Toyama[34] investigated 75 cases of interlaminar bone grafting with wiring

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and reported that straight, kyphotic, and swan neck deformities occurred after surgery and recommended that the optimum postoperative C1–2 CA is 20°. Kato et al.[35] also recommended that the optimum postoperative C1–2 CA should be 20° in patients with the preoperative C1–2 angle of 0°–20° or < 0°, but perform an in situ angle in patients with a C1–2 angle of ≥ 20°. Some authors stated that surgical overreduction of C1–2 CA would be associated with PSK instead of optimal C1–2 angle.[34-36] These statements will be useful to recover the lordosis of subaxial spine and decrease the kyphosis of subaxial spine postoperatively. However, there is no consensus for optimal C1–2 fusion angle because physiological cervical sagittal alignment is different individually. The understanding of postoperative sagittal alignment is still insufficient. PSK is the result from multiple factors associative with cervical sagittal realignment such as age, postoperative C1–2 angle, the extent of surgical dissection, compensation of adjacent segmental angle. Therefore, it is careful to define the optimal postoperative C1–2 CA. Nevertheless, there are several things that spine surgeon should pay attention to obtain better clinical outcomes during surgery. At first, most patients with AAD have kyphotic C1–2 angle, and it is important that kyphotic C1–2 angle change to physiological lordotic angle. It is because a decrease in the C1–2 and C0–2 angle may likely induce a reduction in the pharyngeal space and can be a predictor of postoperative dysphagia, which is not compensated by the middle or lower cervical spine. At second, it is difficult to adjust C1–2 angle to target angle intraoperatively. We tried to fix postoperative C1–2 CA to 20° under C-arm fluoroscopy, but in some patients C1–2 CA were fixed more or less than 20°. Therefore, the greatest care must be taken to determine C1–2 fixation angle during surgery. Finally, C1 slope should be posteriorly slanted. It is not only because posteriorly slanted C1 slope is important to maintain the C1–2 segment lordosis, but also because the posteriorly slanted C1 slope and kyphotic angulation of the C0–1 segment allows some degree of freedom for neck extension as the space between the occiput and C1 posterior arch and allows some rooms for upper cervical extension to prevent the collision of occiput and implant.

The weaknesses of this study are its retrospective design and small sample size. In addition, patients had various pathologies, which included RA, congenital anomalies, and osteoarthritis. This study included 2 irreducible AAD patients. We performed the releasing of C1–2 facet in these patients, but we could not obtain sufficient reduction of AAD, which may have made a different sagittal realignment comparing to other patients. Moreover, C1–2 constructs for posterior fusion was not monotonous, it composed of hybrid structures such like C2 pedicle, lamina, and pars screws. Although we compressed or distracted the rod under C-arm fluoroscopy to control appropriate C1–2 CA, some patients obtained postoperative C1–2 CA showed a large deviation around 20°. Patient numbers 6 and 36 obtained kyphotic C1–2 angle of 4.8° and 9.4°. Patient numbers 12 and 38 obtained lordotic C1–2 angle of 34.3° and 36°. It is difficult for us to adjust intraoperative C1–2 CA closely as looking images in C-arm fluoroscopy. Finally, the long-term radiographic and clinical outcomes more than one year were not evaluated in the present study.

CONCLUSION

ΔC1–7 CA, ΔC2–7 SVA, and ΔPADI were the key radiologic parameters to influence clinical outcomes. Postoperative C1–2 angle relative to ΔC1–7 CA and ΔC2–7 SVA should be carefully determined as improving individual's pain and neurologic improvement. Indirect decompression obtained by reduction of AAD is also important to increase ΔPADI and then decrease NDI.

NOTES

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REFERENCES

1. Hong JT, Jang WY, Kim IS, et al. Posterior C1 stabilization using superior lateral mass as an entry point in a case with vertebral artery anomaly: technical case report. Neurosurgery 2011;68:246-9; discussion 249.
2. Hong JT, Takigawa T, Udayakunmar R, et al. Biomechanical effect of the C2 laminar decortication on the stability of C2 intralaminar screw construct and biomechanical compari-

son of C2 intralaminar screw and C2 pars screw. Neurosurgery 2011;69:ons1-6; discussion ons6-7.
3. Jo KW, Park IS, Hong JT. Motion-preserving reduction and fixation of C1 Jefferson fracture using a C1 lateral mass screw construct. J Clin Neurosci 2011;18:695-8.
4. Kim IS, Hong JT, Jang WY, et al. Surgical treatment of os odontoideum. J Clin Neurosci 2011;18:481-4.
5. Hong JT, Kim IS, Kim JY, et al. Risk factor analysis and decision-making of surgical strategy for V3 segment anomaly: significance of preoperative CT angiography for posterior C1 instrumentation. Spine J 2016;16:1055-61.
6. Kim MS, Kim JY, Kim IS, et al. The effect of C1 bursting fracture on comparative anatomical relationship between the internal carotid artery and the atlas. Eur Spine J 2016;25:103-9.
7. Takigawa T, Simon P, Espinoza Orías AA, et al. Biomechanical comparison of occiput-C1-C2 fixation techniques: C0-C1 transarticular screw and direct occiput condyle screw. Spine (Phila Pa 1976) 2012;37:E696-701.
8. Lee HJ, Hong JT, Kim IS, et al. Analysis of measurement accuracy for craniovertebral junction pathology : most reliable method for cephalometric analysis. J Korean Neurosurg Soc 2013;54:275-9.
9. Kim IS, Hong JT, Kim MS, et al. Occipitocervical collision after C1-C2 fusion. Spine J 2014;14:1798-9.
10. Hong JT. human craniovertebral alignment as a "tertiary curvature". Neurospine 2019;16:251-4.
11. Brooks AL, Jenkins EB. Atlanto-axial arthrodesis by the wedge compression method. J Bone Joint Surg Am 1978;60:279-84.
12. Suchomel P, Stulík J, Klézl Z, et al. Transarticular fixation of C1-C2: a multicenter retrospective study. Acta Chir Orthop Traumatol Cech 2004;71:6-12.
13. Harms J, Melcher RP. Posterior C1-C2 fusion with polyaxial screw and rod fixation. Spine (Phila Pa 1976) 2001;26:2467-71.
14. Toyama Y, Matsumoto M, Chiba K, et al. Realignment of postoperative cervical kyphosis in children by vertebral remodeling. Spine (Phila Pa 1976) 1994;19:2565-70.
15. Mukai Y, Hosono N, Sakaura H, et al. Sagittal alignment of the subaxial cervical spine after C1-C2 transarticular screw fixation in rheumatoid arthritis. J Spinal Disord Tech 2007;20:436-41.
16. Nojiri K, Matsumoto M, Chiba K, et al. Relationship between alignment of upper and lower cervical spine in asymptomatic individuals. J Neurosurg 2003;99(1 Suppl):80-3.
17. Oshima S, Sudo H, Ito M, et al. Subaxial sagittal alignment after atlantoaxial fixation techniques. J Spinal Disord Tech 2015;28:E49-55.
18. Yoshimoto H, Ito M, Abumi K, et al. A retrospective radiographic analysis of subaxial sagittal alignment after posterior C1-C2 fusion. Spine (Phila Pa 1976) 2004;29:175-81.
19. Zhong J, Pan Z, Chen Y, et al. Postoperative cervical sagittal realignment improves patient-reported outcomes in chronic atlantoaxial anterior dislocation. Oper Neurosurg (Hagerstown) 2018;15:643-50.
20. Choi DH, Lee SG, Yoo CJ, et al. Sagittal alignment correlates with the C1-C2 fixation angle and functional outcome after posterior atlantoaxial fixation for traumatic atlantoaxial instability. J Clin Neurosci 2019;66:19-25.
21. Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. J Manipulative Physiol Ther 1991;14:409-15.
22. Association JO. Scoring system for cervical myelopathy. Nippon Seikeigeka Gakkai Zasshi 1994;68:490-503.
23. Kang J, Chen G, Zhai X, et al. In vivo three-dimensional kinematics of the cervical spine during maximal active head rotation. PLoS One 2019;14:e0215357.
24. Sherekar SK, Yadav YR, Basoor AS, et al. Clinical implications of alignment of upper and lower cervical spine. Neurol India 2006;54:264-7.
25. Hardacker JW, Shuford RF, Capicotto PN, et al. Radiographic standing cervical segmental alignment in adult volunteers without neck symptoms. Spine (Phila Pa 1976) 1997;22:1472-80; discussion 1480.
26. Shimizu K, Nakamura M, Nishikawa Y, et al. Spinal kyphosis causes demyelination and neuronal loss in the spinal cord: a new model of kyphotic deformity using juvenile Japanese small game fowls. Spine (Phila Pa 1976) 2005;30:2388-92.
27. Tang JA, Scheer JK, Smith JS, et al. The impact of standing regional cervical sagittal alignment on outcomes in posterior cervical fusion surgery. Neurosurgery 2012;71:662-9; discussion 669.
28. Jun BY. Complete reduction of retro-odontoid soft tissue mass in os odontoideum following the posterior C1-C2 tranarticular screw fixation. Spine (Phila Pa 1976) 1999;24:1961-4.
29. Goel A, Shah A. Atlantoaxial facet locking: treatment by facet manipulation and fixation. Experience in 14 cases. J Neurosurg Spine 2011;14:3-9.
30. Wang L, Gu Y, Chen L, et al. Surgery for chronic traumatic atlantoaxial dislocation associated with myelopathy. Clin

 https://doi.org/10.14245/ns.2143312.656

Spine Surg 2017;30:E640-7.
31. Lang Z, Tian W, Liu B, et al. Posterior C1-C2 transarticular screw fixation for atlantoaxial instability assisted by intraoperative 3-dimensional fluoroscopy-based navigation. Zhonghua Yi Xue Za Zhi 2013;93:2296-300.
32. Villavicencio AT, Babuska JM, Ashton A, et al. Prospective, randomized, double-blind clinical study evaluating the correlation of clinical outcomes and cervical sagittal alignment. Neurosurgery 2011;68:1309-16; discussion 1316.
33. Matsumoto M, Chiba K, Nakamura M, et al. Impact of interlaminar graft materials on the fusion status in atlantoaxial transarticular screw fixation. J Neurosurg Spine 2005;2:23-6.
34. Toyama Y. The optimum position of fusion in atlanto-axial arthrodesis. Cerv Spine Res Soc 1992;59:134-5.
35. Kato Y, Itoh T, Kanaya K, et al. Relation between atlantoaxial (C1/2) and cervical alignment (C2-C7) angles with Magerl and Brooks techniques for atlantoaxial subluxation in rheumatoid arthritis. J Orthop Sci 2006;11:347-52.
36. Huang JC, Qian BP, Qiu Y, et al. Surgical overreduction and hyperlordotic fusion of C1-C2 joint are associated with cervical sagittal malalignment. Arch Orthop Trauma Surg 2017;137:1631-9.

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Original Article

What Type of Incision for Anterior Cervical Spine Surgery Involving Long Segments Can Bring Better Cosmetic and Functional Outcomes?

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Objective: To determine whether double transverse incisions could provide superior cosmetic and functional outcomes, including rates of dysphagia and dysphonia, compared with longitudinal incisions in patients undergoing anterior cervical spine surgery (ACSS) involving ≥3 levels.
Methods: A total of 62 consecutive patients who underwent ACSS involving ≥3 levels were included in this study. They consist of 33 with longitudinal incisions (L group) and 29 with double transverse incisions (DT group). We recorded functional outcome measures including the Bazaz score for postoperative dysphagia and the Voice Handicap Index-10 (VHI-10) for postoperative dysphonia. The Vancouver Scar Scale (VSS) and the patient and observer scar assessment scale (POSAS) were used to evaluate postoperative skin scarring.
Results: Cosmetic results, as assessed using the VSS and POSAS, were significantly better in the DT than in the L group at most follow-up time points ($p < 0.01$ each). Dysphagia rates were significantly lower in the DT group than in the L group during the late postoperative period from 6 months until final 2 years of follow-up ($p < 0.01$ each). There were no significant different results between the 2 groups in terms of dysphonia.
Conclusion: A double transverse incision can be a feasible option when performing ACSS involving ≥3 levels, providing better cosmesis and lower rates of persistent dysphagia than with a longitudinal incision.

Keywords: Anterior cervical spine surgery, Double transverse incision, Dysphagia, Dysphonia, Skin scarring

INTRODUCTION

Although the Smith-Robinson approach using a single transverse incision is the most widely applied approach for anterior cervical spine surgery (ACSS), operations involving ≥3 levels often require longitudinal incisions for better exposure.[1,2] However, longitudinal incisions with long segments of ACSS may result in higher rates of postoperative complications,[3-6] including dysphagia[7] and dysphonia,[8] with unsatisfied wound problems. Higher rates of complications with multilevel ACSS might be related to the type of incision. Previous studies evaluating rates of dysphagia and dysphonia after ACSS have been limited by the lack of validated, quantitative outcomes. Therefore, it is necessary to evaluate functional outcomes as a validated value. Postoperative scarring can directly affect patient satisfaction because ACSS is the surgery in spine practice for which the wound cannot be concealed by clothing or hair. Longitudinal incisions are perpendicular to the minimal skin tension line, creating more tension than transverse incisions and possibly leading to inferior cosmetic results.[9] Moreover, to our knowl-

edge, no study has compared the cosmetic results among different incisions in multilevel ACSS involving ≥3 levels.

The purpose of this study was to determine whether double transverse incisions could provide superior cosmetic and functional outcomes, including rates of dysphagia and dysphonia, when compared with longitudinal incisions in patients undergoing ACSS involving ≥3 levels.

MATERIALS AND METHODS

1. Inclusion Criteria

This study enrolled 62 consecutive patients who underwent ACSS involving ≥3 levels between March 2013 and February 2019. The study was approved by the institutional review board of our institution. The indications of surgery were cervical spondylosis with or without disc herniation with refractory radiculopathy or progressive myelopathy. Patients were excluded if they had (1) prior anterior cervical surgery; (2) congenital CNS disease; (3) conditions other than degenerative disease, such as trauma, infection, or tumor; or (4) a single transverse incision using the Smith-Robinson approach.

2. Surgical Procedures

All surgical procedures were performed by a single orthopedic spine surgeon, and all patients were followed up for a minimum of 24 months. Two types of surgery, anterior cervical discectomy and fusion (ACDF) and vertebral body sliding osteotomy (VBSO), were performed. VBSO is a surgical technique reported as a substitute for corpectomy.[10] In VBSO, the vertebral body is translated anteriorly to widen the spinal canal, minimizing the need for direct removal of the pathology such as ossified mass and bony spurs.[11-13] For double transverse incision, 2 transverse incisions were made parallel to Langer's skin line, with the bridge of the minimum 3-cm flap secured between the 2 incisions (Fig. 1). To secure all cervical levels from C2 to T1, the upper incision was made at the C3–4 level and the lower incision at the C6–7 level. Platysma cutting is made parallel to the incision line in the L group, and slightly transverse in the DT group. An anterior cervical plate could be inserted into one incision, and screws could be inserted through both the upper and lower incisions (Fig. 2).

3. Clinical Evaluation

Patients' demographic characteristics, including gender, age, and comorbidities, such as diabetes and hypertension, as well as surgical characteristics, including type of incision, type of surgery, level of surgery, lower level of surgery (C6, C7, T1), upper level of surgery (C3, C4), duration of surgery, and estimated blood loss, were obtained from electronic medical records. Recorded postoperative adverse events included dural tear, infection, pseudarthrosis, and skin problems.

Swallowing difficulty was assessed by contrast esophagography on postoperative day 3. Abnormal findings, including aspiration, stricture, achalasia, and spasm, were recorded. If necessary, rehabilitation and Otorhinolaryngology doctors were consulted to evaluate and manage dysphagia and dysphonia. A vid-

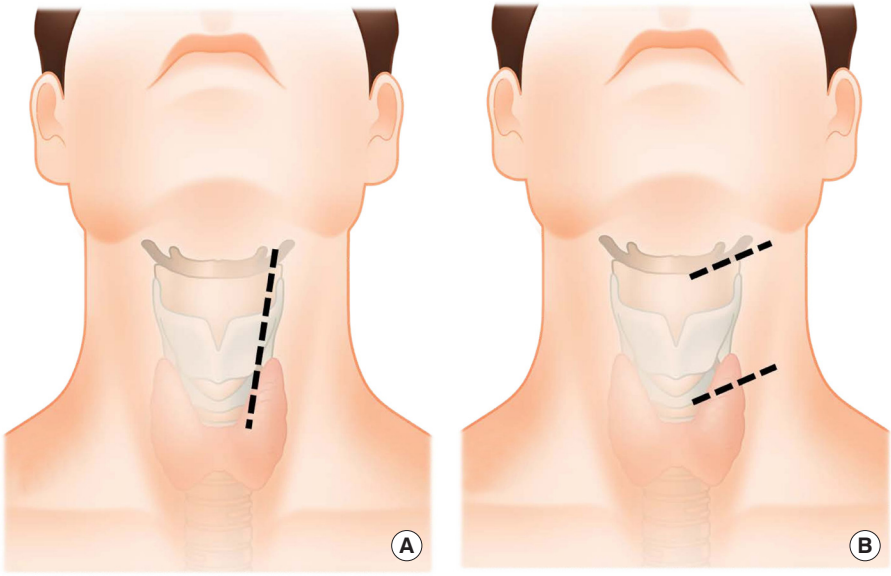

Fig. 1. Incision lines for anterior cervical spine surgery. (A) Longitudinal incision. (B) Double transverse incision.

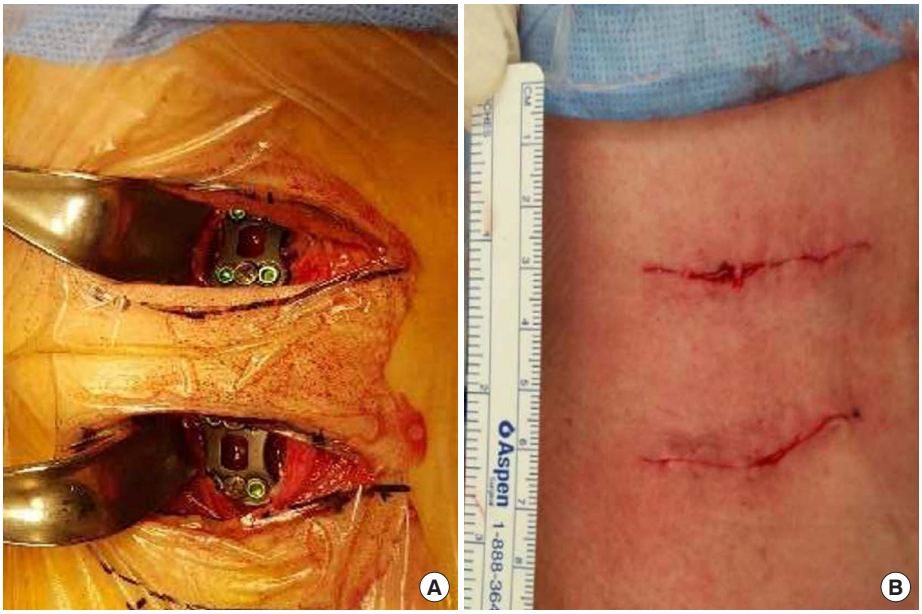

Fig. 2. Intraoperative (A) and immediate postoperative (B) medical photos of a double transverse incision, showing a 3-cm bridge flap between the 2 incisions.

eo fluoroscopic swallowing study (VFSS) was performed if esophagography showed abnormal results or if dysphagia persisted, with abnormal VFSS results recorded using the penetration aspiration scale (PAS).

4. Functional and Cosmetic Outcome Measures

Dysphagia and dysphonia were assessed using patient-reported outcome measures at 1, 3, 6, 12, and 24 months postoperatively. Postoperative dysphagia was determined according to the Bazaz classification, and postoperative dysphonia according to the Voice Handicap Index-10 (VHI-10). The Bazaz score graded dysphagia as none, mild, moderate, and severe.[3,14] None indicated that the patient experienced no episodes of swallowing difficulty with either liquids or solids. Mild indicated no difficulty in swallowing liquids and only some difficulty with solids. Moderate indicated no (or rare) difficulty in swallowing liquids and occasional difficulty with specific solids. Severe indicated no (or rare) difficulty in swallowing liquids and frequent difficulty with most solids. The VHI-10 is a shortened, 10-item version of the VHI, with the 2 showing a high degree of correlation ($r > 0.90$, $p = 0.01$).[15,16] The VHI-10 contains 10 questions that subjectively assess dysphonia (Table 1). Scores on the VHI-10 ranged from 0 to 40.[15-17]

Skin scarring was evaluated at 3, 6, 12, and 24 months postoperatively. Medical photographs were taken of each patient's skin scar at each postoperative visit. Cosmetic results were evaluated using the Vancouver Scar Scale (VSS) and the patient and observer scar assessment scale (POSAS).[18,19] The VSS rated scars according to 4 parameters: vascularity, pigmentation, pliability, and height. Each parameter contained ranked subscales, with total scores ranging from 0 to 13. Patients and observers rated scars on the POSAS blindly on the same day. The observer component of the POSAS consisted of 6 parameters: vascularity, pigmentation, thickness, relief, pliability, and surface area, with each parameter consisting of several categories. The patient component of the POSAS also consisted of 6 parameters: pain, itchiness, color, stiffness, thickness, and irregularity. Each parameter was rated on a 10-point scale, with 1 representing near-normal skin and 10 representing the worst scar imaginable. Patients with unsatisfactory cosmetic results after ACSS were referred to a plastic surgeon for scar revision.

5. Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). Time-dependent data were analyzed by repeated-measures analysis of variance, followed by *post hoc* comparisons of patients with longitudinal (L group) and double transverse (DT group) incisions. Bonferroni adjustments, including all pairwise comparisons within a specific model, were applied to p-values to account for multiple testing. *Post hoc* comparisons were performed between the main effects of all pairs of time points. The multiple imputa-

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Table 1. VHI-10 questionnaire

VHI-10 questionnaire	Score				
1. My voice makes it difficult for people to hear me.	0	1	2	3	4
2. I run out of air when I talk.	0	1	2	3	4
3. People have difficulty understanding me in a noisy room.	0	1	2	3	4
4. The sound of my voice varies throughout the day.	0	1	2	3	4
5. My family has difficulty hearing me when I call them throughout the house.	0	1	2	3	4
6. I use the phone less often than I would like to.	0	1	2	3	4
7. I'm tense when talking to others because of my voice.	0	1	2	3	4
8. I tend to avoid groups of people because of my voice.	0	1	2	3	4
9. People seem irritated with my voice.	0	1	2	3	4
10. People ask, "What's wrong with your voice?"	0	1	2	3	4

VHI-10, Voice Handicap Index-10; 0, never; 1, almost never; 2, sometimes; 3, almost always; 4, always.

Table 2. Demographic and clinical characteristics of study patients

Characteristic	Incision type		p-value
	L (n = 33)	DT (n = 29)	
Sex, male:female	21:12	16:13	0.49
Age (yr)	59.1 ± 13.3	62.7 ± 11.6	0.41
DM	9 (27.2)	6 (20.7)	0.54
HTN	10 (30.3)	6 (20.7)	0.38
No. of involved levels			0.07
3	21	12	
4	12	16	
5	-	1	
Upper cervical level			0.01*
C3	18	24	
C4	15	5	
Lower cervical level			0.78
C6	7	7	
C7	25	21	
T1	1	1	
Operation			0.07
ACDF	12	18	
VBSO	20	11	
ACDF+VBSO	1	-	
Duration of surgery (min)	209.5 ± 27.7	222.6 ± 35.4	0.74
EBL (mL)	142.7 ± 106.5	150.3 ± 114.2	0.91

Values are presented as number, mean ± standard deviation, or number (%).
L, longitudinal; DT, double transverse; DM, diabetes mellitus; HTN, hypertension; ACDF, anterior cervical discectomy and fusion; VBSO, vertebral body sliding osteotomy; EBL, estimated blood loss.
*$p < 0.05$, statistical significance.

tions method with regression model was used for missing data. Statistical significance was set at $p < 0.05$.

RESULTS

Sixty-two patients were evaluated in the present study, including 33 with longitudinal incisions (L group) and 29 with double transverse incisions (DT group). All patients were followed for ≥ 24 months, with mean follow-up of patients in the L and DT groups being 38.3 ± 16.40 and 37.7 ± 13.79 months, respectively, during which their functional and cosmetic outcomes were evaluated. The demographic characteristics, medical comorbidities, and surgical variables of the 2 groups are presented in Table 2. These 2 groups differed significantly in upper cervical level ($p = 0.01$). Of these 62 patients, 30 underwent ACDF, 31 underwent VBSO, and 1 underwent VBSO with ACDF. Barium esophagography on postoperative day 3 showed aspiration in 5 of 33 patients in the L group, with VFSS in 3 of these 5 patients

Table 3. Frequency of adverse events

Adverse events	L (n = 33)	DT (n = 29)	p-value
Abnormal esophagogram	5 (15.2)	2 (6.9)	0.351
Scar revision	3 (9.1)	0 (0)	0.09
Skin tenting sign	7 (21.2)	0 (0)	< 0.01*
Skin necrosis	0 (0)	0 (0)	-
Infection	0 (0)	0 (0)	-
Dural tear	1 (3)	0 (0)	0.34
Pseudarthrosis	6 (18.2)	4 (13.8)	0.577

Values are presented as number (%).
L, longitudinal; DT, double transverse.
*$p < 0.05$, statistical significance.

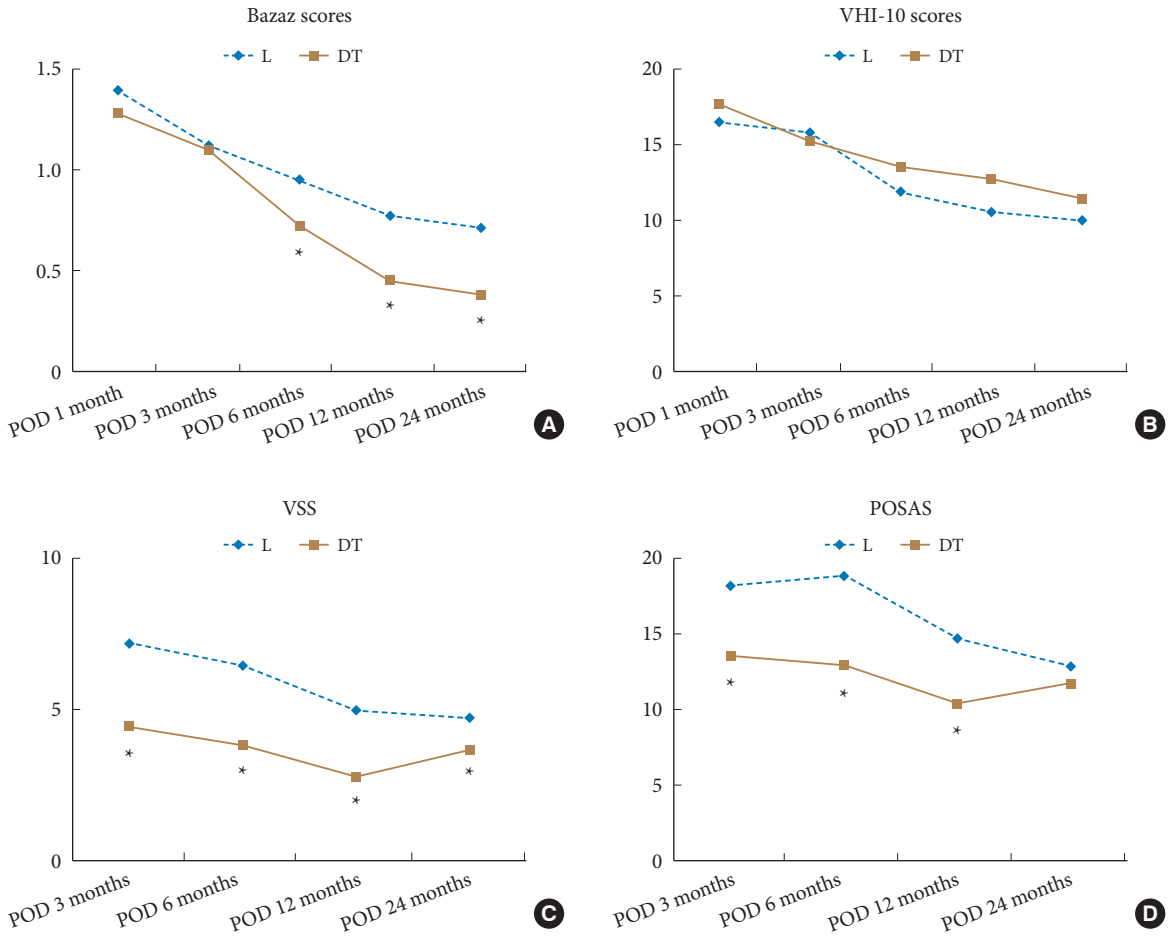

Fig. 3. Functional results of dysphagia and dysphonia and cosmetic outcomes after anterior cervical spine surgery using patient-reported outcome. Bazaz scores (A), VHI-10 scores (B), Vancouver Scar Scale (VSS) (C), and patient and observer scar assessment scale (POSAS) (D). ACSS, anterior cervical spine surgery; VHI-10, Voice Handicap Index-10. L, longitudinal; DT, double transverse; POD, postoperative day. *Statistically significant difference at each time point ($p < 0.01$).

showing PAS scores of 6, and only 1 confirmed as having vocal cord palsy. Barium esophagography showed aspiration in 2 of the 29 patients in the DT group, with 1 patient having a PAS score of 6 and none being diagnosed with vocal cord palsy. Rates of complications, including dural tears, infections, and pseudarthrosis, did not differ between the 2 groups (Table 3).

Dysphagia was assessed using the Bazaz score, and significantly improved over time in both the DT and L groups ($p < 0.01$ each). The Bazaz scores were significantly lower in the DT than in the L group at 6, 12, and 24 months postoperatively ($p < 0.01$ each). However, the differences were insignificant at 1 and 3 months (Fig. 3A, Table 4). Dysphonia assessed using the VHI-10 also improved significantly over time in the DT ($p < 0.01$) and L ($p < 0.01$) groups, but the difference between the groups was not statistically significant (Fig. 3B, Table 4). Cosmetic results, as assessed using the VSS, showed that cosmesis was significantly better in the DT than in the L group at all follow-up time points ($p < 0.01$ each). Similarly, cosmetic results assessed using the POSAS showed significantly superior results in the DT compared with the L group at all time points except at 24 months ($p < 0.01$ for 3, 6, and 12 months) (Fig. 3C, D; Table 4). In addition, 7 patients in the L group (21.2%) showed severe longitudinal skin tenting along the scar, whereas none of the patients in the DT group showed a tenting sign along the scar (Table 3, Fig. 4). Moreover, patients with tenting scars complained of restricted neck extension motion. Three patients in the L group (9.1%) needed scar revision due to unsatisfactory cosmetic results after ACSS. There was no skin necrosis in DT group. Although we did not separately investigate the sensory change of the flap area, no patient complained of numbness when the medical chart was reviewed.

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Table 4. Patient-reported outcomes

Variable	Incision type		p-value
	L (n = 33)	DT (n = 29)	
Bazaz scores			
POD 1 month	1.41 ± 0.83	1.27 ± 0.87	0.575
POD 3 months	1.13 ± 0.80	1.09 ± 0.84	0.939
POD 6 months	0.96 ± 0.69	0.72 ± 0.87	0.018*
POD 12 months	0.75 ± 0.50	0.47 ± 0.60	0.007*
POD 24 months	0.69 ± 0.50	0.39 ± 0.63	0.005*
VHI-10 scores			
POD 1 month	16.02 ± 9.32	17.61 ± 10.43	0.615
POD 3 months	13.42 ± 9.00	17.05 ± 11.27	0.265
POD 6 months	11.52 ± 9.05	13.57 ± 10.97	0.521
POD 12 months	9.59 ± 8.57	12.75 ± 10.23	0.295
POD 24 months	8.86 ± 7.50	11.46 ± 9.52	0.339
VSS			
POD 3 months	7.20 ± 2.64	4.44 ± 1.94	< 0.0001*
POD 6 months	6.45 ± 2.92	3.82 ± 3.11	< 0.0001*
POD 12 months	4.96 ± 2.71	2.74 ± 2.81	< 0.0001*
POD 24 months	4.73 ± 2.77	3.67 ± 2.88	0.009*
POSAS			
POD 3 months	18.17 ± 7.10	13.52 ± 4.34	< 0.0001*
POD 6 months	18.81 ± 8.11	12.94 ± 5.27	< 0.0001*
POD 12 months	14.74 ± 6.85	10.40 ± 3.92	< 0.0001*
POD 24 months	12.88 ± 6.89	11.72 ± 7.01	0.247

Values are presented as mean ± standard deviation.
L, longitudinal; DT, double transverse; POD, postoperative day; VHI-10, Voice Handicap Index-10; VSS, Vancouver Scar Scale; POSAS, Patient and Observer Scar Assessment Scale.
*p < 0.05, statistical significance.

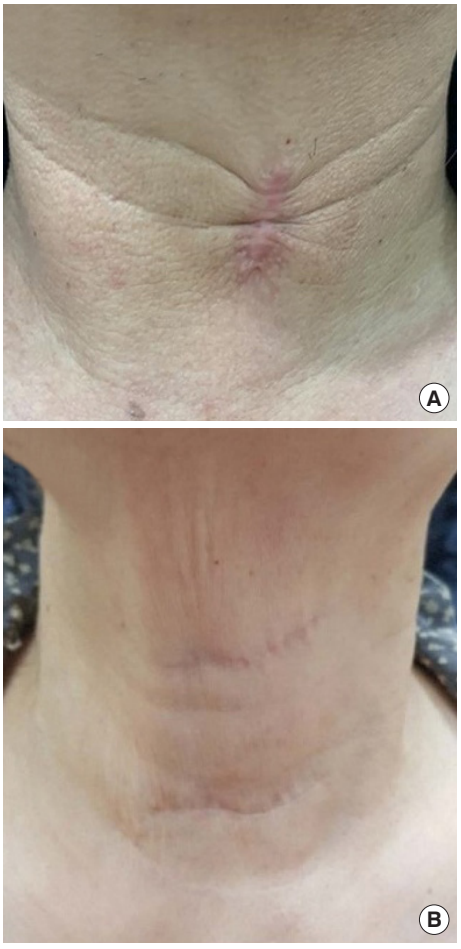

Fig. 4. Skin scarring 24 months after anterior cervical spine surgery using a longitudinal incision (A) and a double transverse incision (B).

DISCUSSION

This study demonstrated that DT incision was better than longitudinal incision for ACSS of more than 3 levels in terms of dysphagia and cosmetic results. Proper incisions for multilevel ACSS are crucial for appropriate exposure and better functional and cosmetic outcomes. For long segments ACSS, the surgeon might choose between longitudinal and double transverse incisions.

As more patients return to the workforce and social activities after ACSS, cosmetic results may affect their quality of life.[20,21] Inferior skin scarring at the anterior neck negatively affects self-esteem and can lead to anxiety and depression.[22] However, few studies to date have assessed cosmetic outcomes after ACSS. To our knowledge, this is the first study to compare cosmetic results of double transverse incisions with longitudinal incisions for multilevel ACSS (≥ 3 levels). The VSS was the first validated and remained one of the most widely used scar scales.[18,19] The POSAS is a reliable and validated scar assessment scale and includes subjective evaluations by patients.[18,23] The VSS may be susceptible to observer bias, underestimating skin scarring after surgery. In addition to surgeon's bias, patients may be subject to a social desirability bias, as they may not want to disappoint the surgeon.[20] To control for these biases, skin scarring after multilevel ACSS was evaluated by the VSS and POSAS in this study. On both scales, the DT group showed better results than the L group. The lack of significant difference between the 2 groups on the POSAS only at 24 months may be due to improvements in patient opinions of their scars.[24] These cosmetic results agree with previous studies of postoperative linear scars. In a double transverse incision, the skin is incised parallel to the tension line, minimizing wound contraction and providing better cosmetic outcomes than longitudinal incisions.[9] The skin is maxi-

mally extensible perpendicular to the tension line, minimizing tension when incisions are made along the tension line.[25] Parallel cutting to the platysma muscle fiber has superior cosmetic results with lower rates of puckering.[26] Beyond scoring results, most patients in the DT group were satisfied with their cosmetic results. On the other hand, complications including wound revision surgery and restricted motion of neck extension in L group decreased patient quality of life after ACSS.

Higher rates of dysphagia and dysphonia have been reported in patients undergoing ≥3-level ACSS than single or 2-level ACSS.[3,4,27,28] This study hypothesized that the DT group would show better outcomes than the L group in dysphagia and dysphonia after multilevel ACSS. Dysphagia rates were significantly lower in the DT than in the L group from 6 months postoperatively to 24 months of final follow-up. These findings indicated that DT group showed a better outcome in chronic postoperative dysphagia than L group. We examined the possible reasons for the low rates of dysphagia after long segments of ACSS using a double transverse incision as follows. Dysphagia can be classified according to time and by various causes, and it can also be caused by extrinsic compression in the chronic stage.[3,14,29] In the DT group, skin tenting with fibrosis and platysma puckering[26] occur less than in the L group because the direction of the incision is parallel to the skin crease and the muscle fiber in the platysma.[9,21,30] The effect of extrinsic compression due to this fibrotic tissue formation may affect the difference in the incidence of dysphagia.

DT incision may also be advantageous over L incision for deeper level dissection. For deep cervical fascia dissection, blunt dissection is commonly used to prevent unwanted nerve injury due to sharp dissection.[1] However, in surgical approach exposure process for long segments more than 3 levels, it would be difficult to complete the exposure simply by blunt dissection; under this situation, sharp separation is inevitable.[31] Therefore, excessive blunt dissection cannot be performed in the upper and lower ends, and sharp dissection is necessary. Because the recurrent laryngeal nerve, internal branch of superior laryngeal nerve (SLN), superior thyroid artery, and superior laryngeal artery run between the middle layer of deep cervical fascia (strap muscle fascia) and the carotid sheath, the probability of an injury causing permanent dysphagia is increased during sharp dissection of the deep cervical fascia.[31-34] On the other hand, with DT incision, less than 2 levels at upper and lower incisions are to be exposed, so sharp dissection is rarely required and most cases are resolved with blunt dissection. These differences seem to be related to differences in the incidence of permanent dysphagia. Parallel incision with nerve pathway may also explain the advantages of double transverse incisions over longitudinal incisions in reducing nerve injuries that result in dysphagia. In the upper cervical level, hypoglossal nerve travels transversally at the level of C2–3, and the SLN travels transversally and the internal branch of the SLN travels similarly from the investing fascia surrounding the carotid sheath to the thyrohyoid membrane at the C3–4 level.[32,35-37] Compared to the longitudinal incision, a double transverse incision can provide transverse visibility and field space of the upper cervical level. Previous studies have reported that thorough dissection parallel to the nerve pathway could lower the possibility of nerve injuries in excessive retraction and unintentional ligation.[35,36]

In addition, using DT incision has the advantage that it is not necessary to dissect all levels of deep cervical fascia to reach the prevertebral level. There is a surgical method for fracture called minimally invasive plate osteosynthesis (MIPO).[38] MIPO is an advantageous method making an incision only in the upper and lower parts without opening all parts during the plating process to increase vascularity of the fracture site, thus improving functional outcome and cosmesis. Using DT incision, the middle part can be spared since it is possible to reach the prevertebral level using the space of the upper and lower incision levels (Fig. 5). At the level between C3–4 and C6–7, the path of the external SLN is variable, suggesting that a direct longitudinal dissection may increase the risk of unintentional damage to its branches because perpendicular direction of incision to nerve pathway. Without bridge flap invasion, double transverse incision could avoid incidental injury to superficial branches of SLN. Considering that most nerve injuries that cause dysphagia occur during the dissection of the deep cervical fascia,[1,31,33,34] sparing the middle part of cervical level can be advantageous by using DT incision. Whereas, rates of dysphonia, as measured by VHI-10 scores, did not differ significantly between the 2 groups, perhaps due to the relatively low rates of dysphonia after ACSS. This result suggested that the incidence of dysphonia after multilevel ACSS might be more affected by number of levels or duration of surgery than type of incision.

This study had several limitations. First, it was a non-randomized and retrospective analysis involving relatively few patients, making it underpowered. Second, dysphagia and dysphonia were not measured preoperatively, preventing determination of improvements over baseline. Third, the surgeons determined the incision, which may have caused a selection bias. Moreover, the VBSO is known to have a lower complication rate than corpectomy, but it is not yet familiar to all surgeons. Therefore, it

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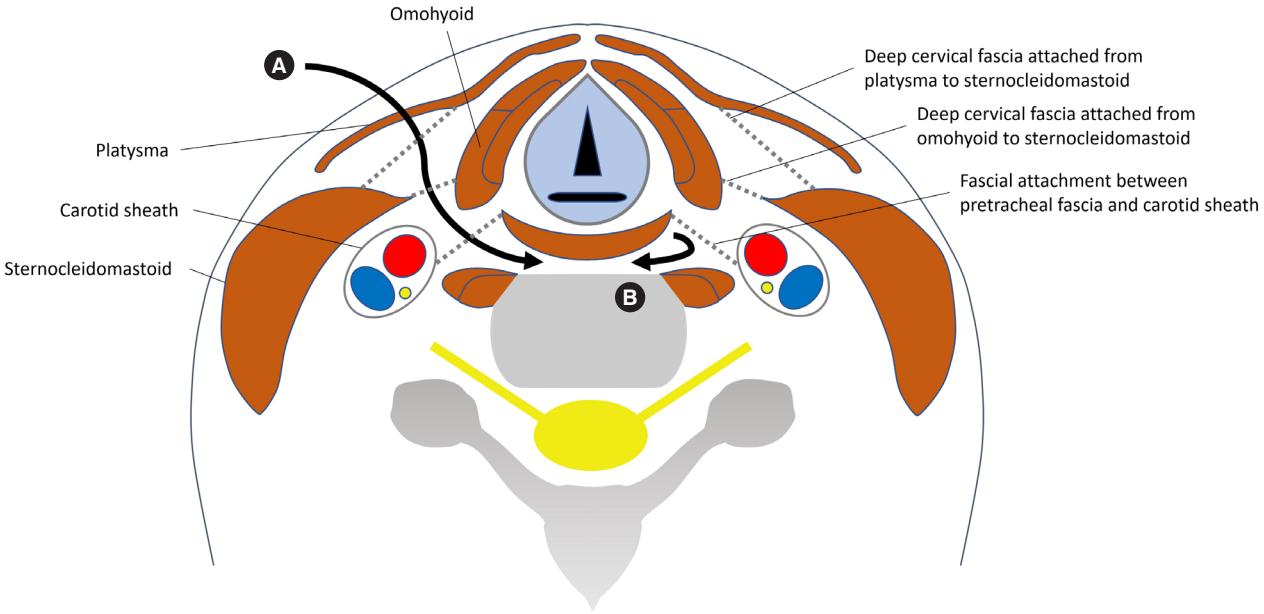

Fig. 5. Illustration of axial cut in midsection spared in double transverse incision. Surgical routes are expressed with longitudinal incision (A) and double transverse incision (B). Skin incision, platysma cutting, and dissection of deep cervical fascial layers are performed in midsection using longitudinal incision. In double transverse incision, the dissection process described above can be omitted to reach the prevertebral fascia using the space at the upper and lower cervical levels.

may be helpful to consider a double transverse incision while preparing a long-level ACDF, but for VBSO, we recommend to try a double transverse incision after gaining sufficient surgical experience with its technique. Finally, the different surgical types (VBSO versus ACDF) may have affected the results of postoperative dysphagia more significantly than the incision type. Comparing 2 incisions within both types of surgery can be too heterogenous. However, surgery types between 2 groups did not differ significantly. Therefore, we concluded that the incision type may have a considerable effect on the results of postoperative dysphagia after long level ACSS.

CONCLUSION

In conclusion, present study focused on ACSS involving ≥3 levels, and analyzed the association of incision type with dysphagia, dysphonia, and skin cosmesis. A double transverse incision can be used when performing ACSS involving ≥3 levels, possibly providing better cosmesis and lower rates of persistent dysphagia than a longitudinal incision.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: HRL, DL; Data curation: SYS; Methodology: HRL; Visualization: HRL, JHC; Writing - original draft: HRL; Writing - review & editing: SP, JHC, CJH, CSL.

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REFERENCES

1. Sherk HH, Pratt L. Anterior approaches to the cervical spine. Laryngoscope 1983;93:168-71.
2. Choi SH, Kang CN. Degenerative cervical myelopathy: pathophysiology and current treatment strategies. Asian Spine J 2020;14:710-20.

3. Bazaz R, Lee MJ, Yoo JU. Incidence of dysphagia after anterior cervical spine surgery: a prospective study. Spine (Phila Pa 1976) 2002;27:2453-8.
4. Cho SK, Lu Y, Lee DH. Dysphagia following anterior cervical spinal surgery: a systematic review. Bone Joint J 2013;95-B:868-73.
5. Tervonen H, Niemelä M, Lauri ER, et al. Dysphonia and dysphagia after anterior cervical decompression. J Neurosurg Spine 2007;7:124-30.
6. Louie PK, Sexton AC, Bohl DD, et al. Rigid-plating and cortico-cancellous allograft are effective for 3-level anterior cervical discectomy and fusion: radiographic and clinical outcomes. Neurospine 2020;17:146-55.
7. Perez-Roman RJ, Luther EM, McCarthy D, et al. National trends and correlates of dysphagia after anterior cervical discectomy and fusion surgery. Neurospine 2021;18:147-54.
8. Mehra S, Heineman TE, Cammisa FP Jr, et al. Factors predictive of voice and swallowing outcomes after anterior approaches to the cervical spine. Otolaryngol Head Neck Surg 2014;150:259-65.
9. Wilhelmi BJ, Blackwell SJ, Phillips LG. Langer's lines: to use or not to use. Plast Reconstr Surg 1999;104:208-14.
10. Lee DH, Cho JH, Lee CS, et al. A novel anterior decompression technique (vertebral body sliding osteotomy) for ossification of posterior longitudinal ligament of the cervical spine. Spine J 2018;18:1099-105.
11. Lee DH, Park S, Hong CG, et al. Significance of vertebral body sliding osteotomy as a surgical strategy for the treatment of cervical ossification of the posterior longitudinal ligament. Global Spine J 2022;12:1074-83.
12. Lee DH, Park S, Lee WS, et al. Vertebral body sliding osteotomy for cervical myelopathy with rigid kyphosis. Neurospine 2020;17:640-7.
13. Lee DH, Riew KD, Choi SH, et al. Safety and efficacy of a novel anterior decompression technique for ossification of posterior longitudinal ligament of the cervical spine. J Am Acad Orthop Surg 2020;28:332-41.
14. Shriver MF, Lewis DJ, Kshettry VR, et al. Dysphagia rates after anterior cervical diskectomy and fusion: a systematic review and meta-analysis. Global Spine J 2017;7:95-103.
15. Forti S, Amico M, Zambarbieri A, et al. Validation of the Italian Voice Handicap Index-10. J Voice 2014;28:263.e17-263.e22.
16. Arffa RE, Krishna P, Gartner-Schmidt J, et al. Normative values for the Voice Handicap Index-10. J Voice 2012;26:462-5.
17. Behlau M, Madazio G, Moreti F, et al. Efficiency and cutoff values of self-assessment instruments on the impact of a voice problem. J Voice 2016;30:506.e9-506.e18.
18. Truong PT, Lee JC, Soer B, et al. Reliability and validity testing of the Patient and Observer Scar Assessment Scale in evaluating linear scars after breast cancer surgery. Plast Reconstr Surg 2007;119:487-94.
19. Draaijers LJ, Tempelman FR, Botman YA, et al. The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation. Plast Reconstr Surg 2004;113:1960-5; discussion 1966-7.
20. Vila PM, Ramsey T, Yaeger LH, et al. Reporting of cosmesis in head and neck reconstruction: a systematic review. Otolaryngol Head Neck Surg 2019;160:573-9.
21. Cheung KM, Mak KC, Luk KD. Anterior approach to cervical spine. Spine (Phila Pa 1976) 2012;37:E297-302.
22. Bronheim H, Strain JJ, Biller HF. Psychiatric aspects of head and neck surgery. Part II: Body image and psychiatric intervention. Gen Hosp Psychiatry 1991;13:225-32.
23. Vercelli S, Ferriero G, Bravini E, et al. Cross-cultural adaptation, reproducibility and validation of the Italian version of the Patient and Observer Scar Assessment Scale (POSAS). Int Wound J 2017;14:1262-8.
24. Martin D, Umraw N, Gomez M, et al. Changes in subjective vs objective burn scar assessment over time: does the patient agree with what we think? J Burn Care Rehabil 2003;24:239-44; discussion 238.
25. Son D, Harijan A. Overview of surgical scar prevention and management. J Korean Med Sci 2014;29:751-7.
26. Agrawal A, Rao M. Transverse cervical skin incision and vertical platysma splitting approach for anterior cervical vertebral column exposure. Rom Neurosurg 2014;21:89-93.
27. Tasiou A, Giannis T, Brotis AG, et al. Anterior cervical spine surgery-associated complications in a retrospective case-control study. J Spine Surg 2017;3:444-59.
28. Teo SJ, Yeo W, Ling MZ, et al. The effect of body mass index on long-term patient-reported outcome scores after anterior cervical discectomy and fusion in an Asian population: a 2-year study. Asian Spine J 2021;15:512-22.
29. Olsson EC, Jobson M, Lim MR. Risk factors for persistent dysphagia after anterior cervical spine surgery. Orthopedics 2015;38:e319-23.
30. Chandler JR, Ponzoli VA. The use of double transverse incisions in major head and neck surgery. Ann Otol Rhinol Laryngol 1969;78:757-70.
31. Shan J, Jiang H, Ren D, et al. Anatomic relationship between right recurrent laryngeal nerve and cervical fascia and its

 https://doi.org/10.14245/ns.2143260.630

application significance in anterior cervical spine surgical approach. Spine (Phila Pa 1976) 2017;42:E443-7.
32. Haller JM, Iwanik M, Shen FH. Clinically relevant anatomy of high anterior cervical approach. Spine (Phila Pa 1976) 2011; 36:2116-21.
33. Haller JM, Iwanik M, Shen FH. Clinically relevant anatomy of recurrent laryngeal nerve. Spine (Phila Pa 1976) 2012;37: 97-100.
34. Rajabian A, Walsh M, Quraishi NA. Berry's Ligament and the Inferior Thyroid Artery as reliable anatomical landmarks for the Recurrent Laryngeal Nerve (RLN): a fresh-cadaveric study of the cervical spine. The RLN relevant to spine. Spine J 2017;17:S33-9.
35. Okamoto N, Azuma S. Upper cervical anterior fusion with a particular focus on superior laryngeal nerve and hypoglossal nerve. Spine Surg Relat Res 2018;2:121-6.
36. Park SH, Sung JK, Lee SH, et al. High anterior cervical approach to the upper cervical spine. Surg Neurol 2007;68:519-24; discussion 524.
37. Sengupta DK, Grevitt MP, Mehdian SM. Hypoglossal nerve injury as a complication of anterior surgery to the upper cervical spine. Eur Spine J 1999;8:78-80.
38. Toogood P, Huang A, Siebuhr K, et al. Minimally invasive plate osteosynthesis versus conventional open insertion techniques for osteosynthesis. Injury 2018;49 Suppl 1:S19-23.

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Original Article

Psychometric Properties of the Scoliosis Research Society Questionnaire (Version 22r) Domains Among Adults With Spinal Deformity: A Rasch Measurement Theory Analysis

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Objective: Adult spinal deformity (ASD) have lower health-related quality of life (HRQoL) compared to the general population. Applying Rasch measurement theory (RMT), this study tested the revised Scoliosis Research Society-22 (SRS-22r) HRQoL instrument among symptomatic adult patients with degenerative spinal disorders and varying degrees of ASD.
Methods: SRS-22r data from 637 outpatient spine clinic patients with degenerative spine conditions were investigated for unidimensionality, item/scale fit, differential item functioning (DIF), scale coverage/targeting, and person separation index (PSI) using RMT.
Results: Unidimensionality of the SRS-22r was not supported for either the total score or for 3 of its 5 domains. Item fit was acceptable for 11/22 items. The individual domains showed good coverage despite the degree of structural disorders. Ordered thresholds were achieved by merging response categories in some of the items. DIF towards age or sex was found in 11/22 items and in some domain items. The PSI exceeded 0.7 for the SRS-22r total score.
Conclusion: The individual domain scores of the SRS-22r perform better than the total score providing good coverage and targeting among patients with ASD. Refinements of items and domains may improve the structural validity of the instrument to meet the criteria for measuring ASD patients, even when multidimensionality persists.

Keywords: Spinal diseases, Rasch measurement theory, Latent trait theory, Revised Scoliosis Research Society-22, Outcomes research, Health-related quality of life

INTRODUCTION

Adult spinal deformity (ASD) is a common problem, with a reported prevalence of 32%, increasing with age.[1] In the population over age 60, a prevalence of degenerative scoliosis as high 68% has been reported.[2] The prevalence of spinal deformities is expected to rise further with increased life expectancy and population aging.[1] ASD patients have been reported to have lower health-related quality of life (HRQoL) when compared to the unaffected population standardized by age.[3] Patients with symptomatic spinal structural disorders have pain and limitations in functional abilities as well as problems with self-image and mental health issues.[3] Compared to other prevalent chronic diseases, such as arthritis, congestive heart failure, chronic lung

disease and diabetes, impaired HRQoL has been found to be even more prominent in patients with ASD.[4]

Spinal structural disorders in adults develop gradually over the years due to multiple etiologies, such as spinal degeneration, idiopathic scoliosis, neuromuscular or congenital origin, and obliquity of the pelvis.[5] Low back pain and sciatica are usually the main symptoms in the early phases of ASD.[6] Patients' HRQoL is affected in the early phases of sagittal malalignment long before the visible loss of sagittal or coronal balance.[7,8] Thus, it is essential to monitor the HRQoL of the patients with spinal disorders and detect problems associated with their spinal structural changes.

The Scoliosis Research Society questionnaire is a deformity-specific patient-reported outcome (PRO) instrument used to measure HRQoL outcomes of patients with spinal deformity.[3,8-10] Thus far the SRS questionnaire is the only disease-specific instrument available to measure HRQoL in patients of all ages with spinal deformity.

The revised Scoliosis Research Society-22 (SRS-22r) has 22 items[11,12] which are based on a 5-point symmetrical agree-disagree Likert scale. The response options are "very good, good, fair, poor, very poor", "none, mild, moderate, moderate to severe, severe," or "very often, often, sometimes, rarely, never." The items are scored from 1 to 5, with 1 being the worst and 5 the best result. The SRS questionnaire and the scoring guide are available free on the patient outcomes webpage: www.srs.org/professionals. The questionnaire can be scored as subtotals for individual domains (function/activity, pain, self-image/appearance, mental health) or as a total score (subtotal + satisfaction with management domain) (Table 1).

Since 1999 the SRS questionnaires have had different versions: 22, 22r (revised), 23, 24, and 30. In 2021, the SRS removed all but the revised version of SRS-22 from their webpage (www.srs.com) and recommends that all practitioners should utilize the SRS-22r, and its various translations. A translation code from all versions to the SRS-22r has been published by the developers of the questionnaires.[12] Thus far the SRS-22r has been more widely translated, validated, and revised among adolescent scoliosis population[11] rather than adults with degenerative spinal deformity.[3,13-15] Both the measurement properties of different translations[14,16] and structural validity of the SRS-22r total score[17-19] have been debated.

The SRS questionnaire has previously been found to be culturally and linguistically valid among adult patients with degenerative spinal complaints in Finland.[10] However, the structural validity of the SRS-22r domains has not been investigated using a partial credit model based on the Rasch measurement theory (RMT) model. Shortcomings in an instrument's structure may lead to bias when comparing large patient cohorts with different ages, diagnoses, cultures, and languages between centers or

Table 1. Domains, item numbers and content of the SRS-22r questionnaire domains

Domain	Items	Content of the domain
Function/activity	5, 9, 12, 15, 18	Level of ambulatory, professional and household activity
		Financial and social functioning
		Change in daily performance and leisure activity
Pain	1, 2, 8, 11, 17	Pain over the last 6 months, past month
		Pain at rest
		Level of pain medication
		Sick days due to pain
Self-image	4, 6, 10, 14, 19	Looks, outwards appearance
		Happiness with current body shape
		Attractivity among other people
		Personal relationships
Mental health	3, 7, 13, 16, 20	During last 6 months:
		Calm and peaceful or nervousness
		Downhearted and blue, feeling down
		Happiness
Satisfaction/dissatisfaction with management	21, 22	Are you satisfied with the results of your back management?
		Would you have the same maganement again if you had the same condition?

during follow-ups.[17] The RMT provides a tool to investigate the ability of the SRS-22r to measure a latent trait such as function, pain, self-image, mental health, or satisfaction with management. A scale measuring one latent trait can be considered unidimensional and linear, which is essential when measuring longitudinal changes in scores. Item and scale fit in the predefined model as well as construct validity can be tested using the RMT. Furthermore, response bias in each of the scale items can be tested for different degrees of structural disorders using differential item functioning (DIF). Currently, the RMT analysis can be considered one of the gold standard statistical techniques for instrument development and psychometric validation research.[20]

This study aimed to evaluate the applicability of the SRS-22r domains in clinical practice among all patients with subacute and chronic spinal degenerative conditions, with special emphasis on the level of structural disorders. Unidimensionality, item and scale fit, residual correlation, DIF, scale coverage/targeting, and person separation were investigated using RMT based on predefined hypotheses.

MATERIALS AND METHODS

A total of 991 consecutive patients with prolonged degenerative thoracolumbar disorder referred for specialist consultation to the spine clinic during 12 months in 2013 and 2014 were recruited to the study. Inclusion criteria were age over 18 years, ability to communicate in the official language and having full spine radiographs. Patients with specific health conditions, including malignancy, pregnancy, neuromuscular disease, or acute fracture were excluded. Altogether 874 patients met the inclusion criteria and 670 gave their written informed consent to participate in the study.

The patients completed the SRS-22r version of the questionnaire. Based on the spinal radiographs, the patients were classified into 3 categories of sagittal structural disorders severity (none or mild, moderate, and severe) according to the SRS-Schwab simplified classification as previously described.[8] All radiographic parameters were measured by a senior spine deformity surgeon. The study protocol was approved by the Central Finland Healthcare District Research Ethical Committee, Jyväskylä Finland (17U/2012).

RMT is a mathematical model designed to evaluate the properties of measurement instruments.[21] RMT analysis calculates the extent to which the observed responses fit the predefined measurement model responses and assesses the unidimensionality of the scale and the precision of measurement.[22,23] The model is based on latent trait theory and the application of additive conjoint measurement.[24] For Rasch analysis, sample sizes of ≥200 subjects can be considered very good with, sizes of 100–199 adequate, sizes of <50–100 doubtful, and sizes of <50 subjects inadequate.[25]

The study applied the RMT using Rumm2030 software to measure construct validity, model and individual item fit, and reliability. The polytomous partial credit model[26] was chosen. The RMT mathematic model describes the process and pertinent psychometric criteria for fit statistics and reliability.[26-29] Person estimation was conducted with the weighted maximum likelihood method. Analyses were conducted using statistical and illustrative tests in the software. Unidimensionality is one of the main assumptions of the RMT and refers to whether the items in a PRO instrument measure a single construct or a specific latent trait, such as pain or function.

The unidimensionality of the SRS-22r total score and its domains was examined. Principal component analysis (PCA) was conducted to define the "Rasch factor," i.e., the first factor identified with the highest eigenvalue. After identifying the Rasch factor, the existence of residual factors was examined by dividing the SRS-22r items into 2 groups according to their correlation coefficients with the second factor identified in the PCA. The items with correlation coefficients over +0.3 and those with correlation coefficients below -0.3 formed the 2 sets of items. The person estimates for each item for each patient were calculated in both sets of items. Conducting a series of independent-samples t-tests patient by patient, the estimates were compared between the 2 item sets. Less than 5% of significant t-tests at a 0.05 probability were used as the criterion for unidimensionality. Further, calculating residual correlations between each item pairs was used to identify item dependency. We used a value equal to or over 0.2 to recognize residual correlations.[30] Higher values are generally considered to indicate similarity between items and hence, either item redundancy or the existence of another latent trait after controlling for the influence of the primary factor. If unidimensionality was violated, testlets based on residual correlation between items were formed.

Testlest is formed by summing the response categories of suitable items into one item. Thus, testlets are item bundles that share a common content. To alleviate the influence of item dependency, each bundle is considered as a single polytomous item. The resulting polytomous RMT model is then applied to analyze the testlets. Items with residual correlations over 0.2 were combined to form testlests. Next, another set of independent-samples t-tests was conducted to investigate if the violation of

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unidimensionality had been corrected. The authors hypothesized that the SRS-22r instrument and its 5 separate domains would exhibit a unidimensional structure.

To investigate the fit of the SRS-22r to the RMT, overall goodness-of-fit and item fit statistics were calculated. Chi-square (χ^2) values (item-trait interaction) and standardized fit residuals (item–person interaction) were investigated to identify item fit. χ^2-values can be used to investigate how well the difficulty in performing of the item meets the ability of the respondent and hence correctly discriminates between different states of the trait being measured. The standardized fit statistics provide information on how much a response differs from the model expectation. The outcome may be interpreted with very low standardized fit statistics indicating redundancy and high values indicating poor fit (Supplementary material 1). The authors hypothesized that the p-values of the chi-square test statistics after Bonferroni adjustment would be nonsignificant, indicating good fit.

The fit residual calculation (item–person interaction score) shows the level of divergence of the item for the persons who fit the model. The divergence calculation yields a residual score that estimates a standard normal distribution where the expected mean is 0 and standard deviation ± 1. In the RMT model, fit residuals between -2.5 and +2.5 are generally considered to indicate acceptable fit. Values below or over this range indicate over- or underdiscrimination in relation to average discrimination ability and thus poor fit of the item to the RMT model and measurement disturbances. A high residual fit can provide information on the redundancy of the given item, as the item may not contribute any new information to the scale.

The targeting ability of each item was examined by investigating the order of the thresholds of the response categories. A threshold indicates the point at which a 50% probability exists for the response to fall into either 1 of the 2 adjacent categories. Disordered thresholds indicate that the response categories resemble each other too closely to detect which category the answer should fall into. The authors hypothesized that the thresholds of the SRS-22r would be ordered.

The targeting and coverage of the SRS-22r scale were examined to investigate whether the questionnaire captures the whole spectrum of the subject matter in the sample as well as to obtain information about the range in which a questionnaire best functions in a distinct patient group. Person and item locations were then examined to determine whether the distribution of items matched the patient distribution on the scale. Differences in person-item distribution in subgroups by age, sex, and degree of spinal deformity were examined. Differences in person-item distribution and the functioning of the SRS-22r total score and of individual domains in the aforementioned subgroups were examined. Analysis of variance (ANOVA) was used to test the statistical significance between different groups. Differences in the mean score of those with different degrees of spinal structural disorders were tested. The authors hypothesized that no significant differences would be observed when the type I error rate (alpha) was set to 0.05. The person separation index (PSI) value was calculated to investigate the sensitivity of the instru-

Table 2. Patients' sociodemographic and clinical background details

Variable	Value
Age (yr)	54.8 ± 15.3
Female sex	358 ± 56.2
Body mass index (kg/m^2)	27.6 (4.8)
Marriage/live-in relation	452 (70.8)
Years of education	12 ± 3.6
Available for work	379 (59.4)
Smokers	153 (24.0)
Daily users of painkillers	338 (53.1)
Duration of current back pain (mo), median (IQR)	18 (7–60)
Diagnoses	
Scoliosis or kyphosis	34 (5.3)
Spondylolisthesis	98 (15.4)
Neural compression	307 (48.2)
Spondylosis without neural compression	198 (31.1)
Previous lumbar spine surgery	34 (5.3)
Severity of spinal structural disorders*	
None or mild	407 (64)
Moderate	159 (25)
Severe	71 (11)
SRS scores, maximum 5 points	
SRS total score	2,88 ± 0.56
SRS function/activity	2.82 ± 0.75
SRS pain	2.40 ± 0.76
SRS mental health	3.4 ± 0.88
SRS self-image/appearance	2.86 ± 0.67
SRS satisfaction with management	3.12 ± 0.75
SRS subtotal	2.88 ± 0.61

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
IQR, interquartile range; SRS, Scoliosis Research Society.
*Spinal structural disorders were classified with the SRS-Schwab classification of adult spinal deformity.

ment to discriminate between patients of varying health status.[31] The PSI ranges between 0 and 1, with a higher value indicating better sensitivity. Values exceeding 0.7 are generally considered acceptable. The authors hypothesized a minimum PSI value of 0.80. DIF was used to test for possible response bias between subgroups in each item. DIF occurs when, for example, men and women within the same sample respond differently to an individual item. Uniform DIF means that the difference in probability remains constant at different levels of measurement. Nonuniform DIF, in turn, means that probabilities differ between groups at different levels of measurement. If the response distribution is similar between the subgroups under examination, then no DIF exists between the groups. If the distribution is similar in shape but follows different logit values, a uniform DIF (UD) is confirmed. If the shape of distribution is different, a nonuniform DIF (NUD) is confirmed. DIF was analyzed for age and sex. The authors hypothesized that there would not be DIF in any of the item towards age or sex. Bonferroni-adjusted ANOVA was used to identify potential item DIF.

RESULTS

A total of 637 patients with complete data and a signed informed consent (mean ± SD, aged 54.8 ± 15.3 years; 56.2% female) were included in the final analysis (effective response rate: 64.3%). Overall, 407 patients (64%) had none or mild, 159 moderate (25%) and 71 severe spinal structural disorders (11%). Patient characteristics are presented in Table 2.

1. SRS-22r Total Score

The unidimensionality of the SRS-22 items was not supported, as 20.57% of t-tests were significant at 0.05 probability (Table 3). A residual correlation over 0.2 was found between 38 item pairs (residual correlation matrix; see Supplementary material 2). Creating testlets using residual correlations or clinical and logically associations between relevant items did not produce unidimensional scale.

The item fit statistics calculated for each SRS-22r item revealed significant chi-square values after Bonferroni adjustment in 12 items (items 3, 7–8, 11, 13–14, 16–18, 20–22). Further, fit residuals falling outside the range of -2.5 to +2.5 were found in 11 items (items 7–8, 10–11, 13–17, 21–22).

When the 22 items of the SRS-22r were investigated as one scale, 16 of the 22 items had ordered thresholds. The remaining 6 items (11, 15, 17, 18, 19, and 22) had disordered thresholds.

Patients scored within the range set for the coverage of the scale. No statistically significant differences were observed for age ($p = 0.68$) or sex ($p = 0.06$) in the person and item distribution (Supplementary material 3). However, a moderate statistically significant difference ($p = 0.01$) was found for the person-item threshold distribution after grouping the patients by degree of structural spinal disorders but not after Bonferroni adjustment (Supplementary material 4). The PSI for the 22 items was 0.89 (Table 3). The PSI 0.89 indicated good degree to which patients can be differentiated into groups of person separation. Cronbach alpha was 0.89 for the SRS-22r. Five items (5, 6, 9, 10, 19) showed DIF for age and one item (12) DIF for sex (Table 4). As unidimensionality was not found for the total score with reasonable adjustments, the subsequent adjustment analyses are reported only for the domains of the SRS-22r.

2. Function/activity (F/A) domain

Table 3. Analysis monitoring statistics

SRS-22 score	Items		Persons		χ^2	df	p-value	PSI (extrems/no extrems)	Percentage of significant t-tests
	Location	Fit residual	Location	Fit residual					
Total score	0.0 ± 0.7	0.6 ± 3.6	-0.2 ± 0.8	-0.2 ± 1.4	918.7	198	0.000000	0.89/0.89	20.6
Function/activity	0.0 ± 0.9	0.7 ± 1.3	-0.3 ± 1.4	-0.3 ± 1.0	110.8	45	0.000000	0.77/0.77	4.9
Pain	0.0 ± 0.6	1.1 ± 1.3	-0.9 ± 1.1	-0.3 ± 1.0	67.3	45	0.02	0.67/0.60	6.6
Testlet 1	0.0 ± 0.9	-0.1 ± 4.7	-0.9 ± 1.2	-0.3 ± 1.0	57.0	45	0.11	0.85/0.85	1.4
Self-image	0.0 ± 0.9	0.3 ± 1.9	-0.2 ± 1.1	-0.3 ± 1.0	104.0	54	0.00005	0.76/0.76	11.1
Testlet 1	0.0 ± 1.5	-2.2 ± 7.8	-0.2 ± 1.3	-0.5 ± 0.8	16.5	18	0.56	0.76/0.77	3.1
Mental health	0.0 ± 0.7	-0.3 ± 2.0	-1.1 ± 2.6	-0.6 ± 1.1	49.1	45	0.31	0.90/0.89	6.3
Satisfaction with management	0.0 ± 1.2	-0.4 ± 0.3	-0.0 ± 1.2	-0.7 ± 1.1	11.0	11	0.45	0.33/0.23	1.9

Values are presented as mean ± standard deviation.
SRS-22, Scoliosis Research Society-22; df, degrees of freedom; PSI, person separating index.

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Table 4. Fit statistics and DIF for the items in the SRS-22r and its subscales

SRS-22r	Item	Missing	FR	χ^2	df	p-value	DIF age	DIF gender
Total score	1	0	0.09	9.84	9	0.364	-	-
	2	0	-0.37	9.04	9	0.4335	-	-
	3	1	-2.1	27.93	9	0.0009*	-	-
	4	0	0.14	7.80	9	0.5542	-	-
	5	3	-0.28	17.42	9	0.0426	UD*	-
	6	6	1.09	14.04	9	0.0426	UD*	-
	7	0	-3.12	28.40	9	0.0008*	-	-
	8	1	5.42	53.06	9	<0.0001*	-	-
	9	58	-1.19	10.95	9	0.2789	NUD*	-
	10	3	2.57	16.89	9	0.0504	UD*	-
	11	1	6.15	64.41	9	<0.0001*	-	-
	12	0	-1.98	23.76	9	0.0045	-	NUD*
	13	0	-2.87	50.69	9	<0.0001*	-	-
	14	0	-4.71	45.79	9	<0.0001*	-	-
	15	2	3.88	21.31	9	0.0113	-	-
	16	0	-3.9	50.74	9	<0.0001*	-	-
	17	204	5.09	122.73	9	<0.0001*	-	-
	18	5	-1.7	34.03	9	<0.0001*	-	-
	19	7	0.65	10.50	9	0.3118	UD*	-
	20	1	-2.47	40.76	9	<0.0001*	-	-
	21	9	3.33	31.98	9	0.0002*	-	-
	22	46	8.65	226.60	9	<0.0001*	-	-
Function	5	3	0.07	23.87	9	0.0045	UD*	-
	9	58	-1.15	17.16	9	0.0463	UD*	-
	12	0	0.04	18.29	9	0.0319	UD*	UD*
	15	2	2.15	18.74	9	0.0274	-	UD*
	18	5	1.79	32.23	9	<0.0002	-	-
Pain	1	0	-0.07	18.23	9	0.0062	-	-
	2	0	0.01	18.14	9	0.0095	-	-
	8	1	3.17	12.60	9	0.2561	-	-
	11	1	1.23	6.87	9	0.5856	-	-
	17	204	0.96	11.48	9	0.5541	-	-
Self-image	4	0	2.15	26.07	9	0.0019*	UD*	-
	6	6	-0.38	9.91	9	0.3577	UD*	-
	10	3	0.85	12.71	9	0.1761	-	NUD*
	14	0	-0.4	14.81	9	0.0964	-	-
	19	7	-2.47	26.54	9	0.0016	UD*	-
Mental health	3	1	1.04	3.652	9	0.9328	-	-
	7	0	-1.84	18.44	9	0.0305	-	-
	13	0	-0.71	9.95	9	0.3543	-	-
	16	0	-2.41	9.49	9	0.3932	-	UD*
	20	1	2.45	7.57	9	0.5778	NUD*	-
Satisfaction with management	21	9	0.58	4.23	9	0.6451	-	-
	22	46	0.21	6.73	9	0.2417	-	-

DIF, differential item functioning; SRS-22r, revised Scoliosis Research Society-22; FR, fit residual; df, degrees of freedom; UD, uniform DIF; NUD, nonuniform.
*Probabilities below Bonferroni adjustment.

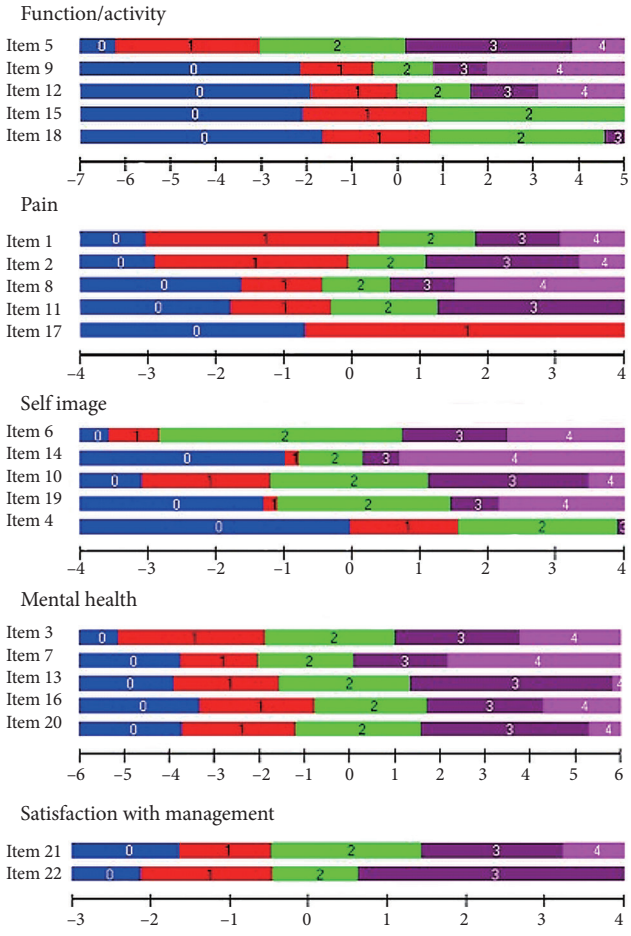

Fig. 1. Item response category thresholds (IRCTs) of the function/activity domain after merging response categories 1, 2, and 3 in item 1 and 2 and 3 in item 5. IRCTs of the pain domain after merging response categories 1 and 2 in item 4 and 0–2 and 3–4 in item 17. IRCTs of the self-image domain after merging response categories 1 and 2 in item 4 and 0–2 and 3–4 in item 17. IRCTs of the satisfaction with management domain after merging response categories 3 'probably not' and 4 'definitely not' in item 2. No merging to achieve ordered thresholds was required for the mental health domain.

In the function/activity domain, 4.9% of the t-tests were significant ($p < 0.05$), thereby supporting its unidimensionality (Table 3). Residual correlations over 0.2 were noted in 5 of the 10 item pairs (residual correlation matrix shown in Supplementary material 2). The item fit statistics in the function domain indicated good fit of the items to the RMT model (Table 3). The PSI for the domain was 0.77 and thus was below the hypothesized value of 0.8 (Table 3). Items 15 and 18 had disordered thresholds. Merging item response categories that score 1 to 3 in item 15 and 3 and 4 in item 18 led to ordered response category thresholds in each of the 5 function domain items (Fig. 1). The person-item threshold distribution showed only minor exceptions in the coverage of the function domain in the lower extremity of the scale (Supplementary material 5A). Subgroup analysis revealed significant differences between the severity classes in the person-item distribution of the Function domain, with higher severity patients having lower mean logit values ($p < 0.001$) (Fig. 2A). Uniform DIF for age and/or sex was observed in all the function domain items except item 18 (Table 4).

3. Pain Domain

In the original version of the pain domain, 6.6% of the t-tests were significant, indicating violation of the unidimensionality assumption (Table 3). Rescoring the items did not lead to a unidimensional scale structure, as the percentage of significant t-tests was unchanged. Nine out of 10 item pairs showed residual correlations over 0.2 (residual correlation matrix Supplementary material 2). The formation of a testlet by combining items 1 ('Which one of the following best describes the amount of pain you have experienced during the past 6 months?'), 2 ('Which one of the following best describes the amount of pain you have experienced over the last month?'), and 17 ('In the last 3 months have you taken any days off of work, including household work, or school because of back pain?') according to their residual correlations and contents led to a unidimensional scale, as 1.2% of the t-tests were significant (Table 3). All the pain domain items except item 8 showed acceptable fit residuals whereas, according to the Bonferroni-corrected chi-square tests, the item-trait interactions showed no significant distortions (Table 3). The PSI for the pain domain was 0.67 (Table 2). After testlet formation, the PSI increased to 0.85 (Table 3). In the pain domain, items 11 and 17 had disordered thresholds. Merging item response categories "nonnarcotics daily or less" in item 11 and categories "0–2 days absence" and "over 3 days absence" in item 17 led to ordered thresholds (Fig. 1). Overall, the patients scores indicated that coverage of the pain domain was good (Supplementary material 5B). The patients' logit values did not differ between the deformity severity subgroups ($p = 0.9$) (Fig. 2B). Age ($p = 0.0018$) was associated with the item location distribution. No DIF was observed in any of the pain domain items (Table 4).

4. Self-Image Domain

In the self-image domain, 9.91% of the t-tests were significant, indicating violation of the unidimensionality assumption (Table 3). A residual correlation of over 0.2 was found in 7 out of 10 item pairs. To achieve unidimensionality, items 4, 6, 10,

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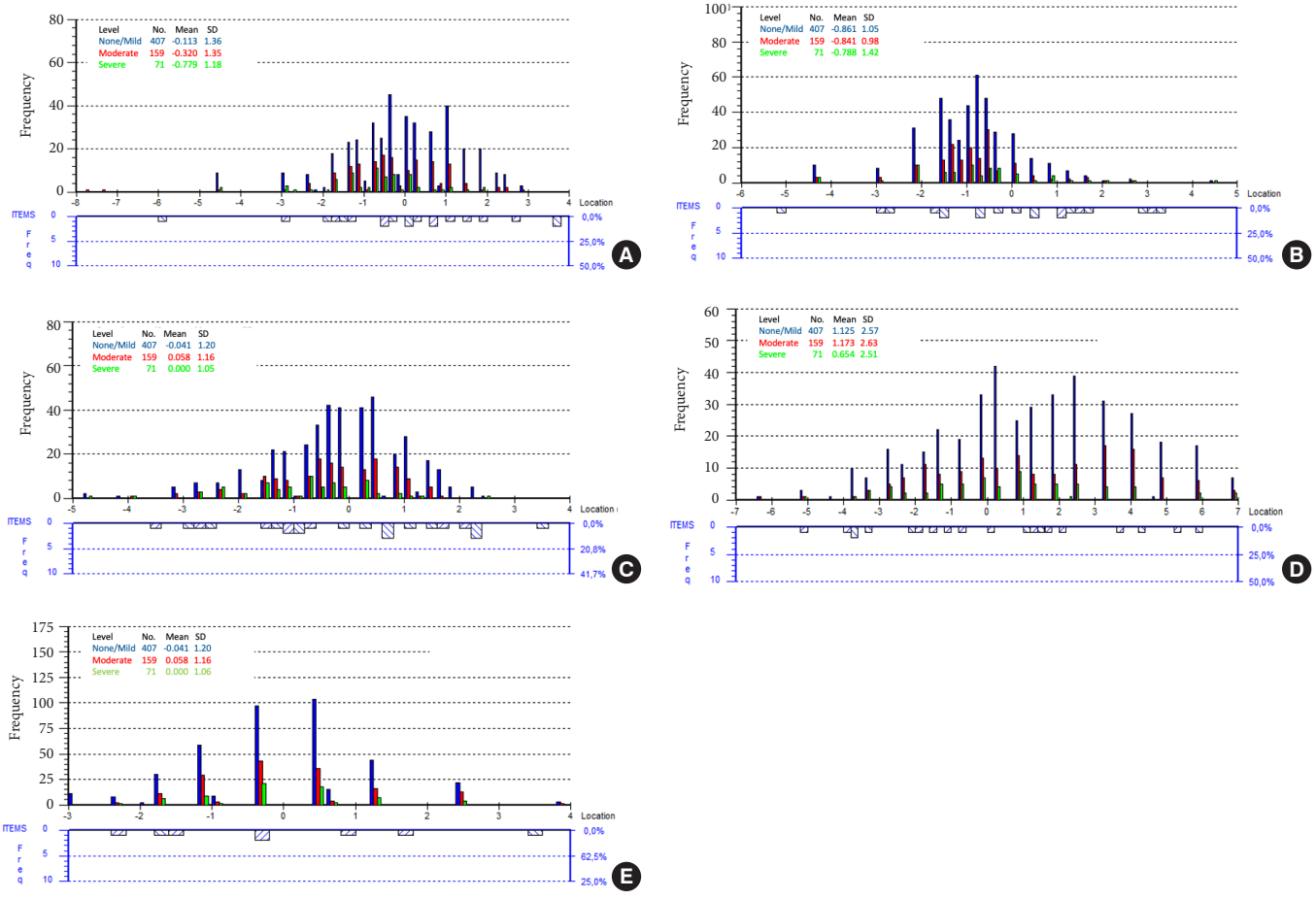

Fig. 2. Illustrations showing the person-item threshold distribution difference between groups of degree of spinal deformity in the distribution of person scores and items of the SRS-22r. Person-Item threshold distribution and degree of deformity. Mild or moderate deformity (blue), moderate (red), and marked structural disorder (green). Function/activity (A), pain (B), self-image (C), mental health (D), satisfaction with management (E). SRS-22r, revised Scoliosis Research Society-22; SD, standard deviation.

14, and 19 were pooled to form a testlet based on item content. The testlet reduced the proportion of significant t-tests to 3.1% (Table 3). All the self-image items except item 4 showed good fit to the RMT model (Table 3). Both the fit residual and Bonferroni-corrected chi-square statistic for item 4 indicated poor fit to the RMT model (Table 3). The PSI of the self-image domain was 0.76 (Table 3). To achieve ordered thresholds, response categories "somewhat happy" and "neither happy nor unhappy" in item 4 were merged (Fig. 1). Coverage of the self-image domain was good with minor discrepancy as 4 patients scored beyond the range of which the scale provided (Supplementary material 5C). There was a statistically significant difference in person-item distribution in age ($p < 0.001$), sex ($p = 0.01$), and degree of deformity ($p < 0.001$). Uniform DIF was observed across the age groups in items 4, 6, and 19, and nonuniform DIF was observed between sexes in item 10 (Table 4).

5. Mental Health Domain

In the mental health domain, the proportion of significant t-tests was 6.3%, and hence the domain was not unidimensional (Table 3). Residual correlations over 0.2 were found in 6 of the 10 item pairs. No clear testlet solution that would achieve unidensionality was available. All the items in the domain showed ordered thresholds as well as good fit to the RMT model (Fig. 1, Table 3). The PSI of the domain was 0.90. The domain covered the patients well, as only a few outliers were found at both extremities of the range (Supplementary material 5D). Coverage was equal in terms of degree of spine deformity ($p = 0.32$), age ($p = 0.64$), or sex ($p = 0.70$). DIF was detected in 2 out of 5 items (Table 4).

6. Satisfaction With Management Domain

The satisfaction with management domain met the criterion

Table 5. Results of the SRS-22r total score and it's domains

Reference value	Item fit	Ordered thresholds	Item DIF
	Nonsignificant after Bonferroni-correction		Nonsignificant after Bonferroni-correction
Total score	11/22	16/22	16/22
Function	4/5	3/5	1/5
Pain	5/5	3/5	5/5
Self-image	4/5	4/5	4/5
Mental well-being	5/5	5/5	3/6
Satisfaction with management	2/2	1/2	2/2

SRS-22r, revised Scoliosis Research Society-22; DIF, differential item functioning.

for unidimensionality, as 1.9% of the t-tests were significant (Table 3). No residual correlation was found between the 2 items. The item fit statistics indicated good fit to the RMT model of the 2 items (Table 3). Item 22 had disordered threshold categories. Merging response categories 'probably not' and 'definitely not' in item 22 produced ordered thresholds. The PSI value of the treatment satisfaction domain was 0.33 (Table 3). The patients' satisfaction with management scores showed that the domain covered the sample well (Supplementary material 5E). There was no discrepancy in the person-item distribution for age ($p = 0.21$), sex ($p = 0.26$), or degree of deformity ($p = 0.66$). No DIF was observed in either item (Table 4).

An overall summary of the RMT statistics for the SRS-22r domains is presented in Table 5.

DISCUSSION

The performance and structural validity of the SRS-22r questionnaire differed according to whether it was analyzed as the total score or as the individual domains. The SRS-22r total score showed poor structural validity when inserted into the RMT model. It seems that the construct validity of the SRS-22r improves when it is divided into distinct subscales. Nonetheless, the total score and its 5 domains provided sufficient coverage and targeting in all the spinal deformity severity categories.

In the present study on adults with degenerative spine conditions, the unidimensionality of the SRS-22r total score was not supported. The present findings are in line with previous findings of multidimensionality of the SRS questionnaires.[17,32] Jain et al.[18] and Caronni et al.[19] introduced a reduced, unidimensional and linear 7-item version (SRS-7) of the SRS-22 that met the Rasch criteria among adolescents with scoliosis. Jain et al.[33] validated the SRS-7 version on adults but the fit for RMT was not separately tested. Four of the pooled items in the SRS-7 were from the self-image and one each from the pain, function/activity, and mental health domains. The short version of the SRS instrument was found to be a good for assessing global changes but lacking the individual aspects of spinal deformity.[17,33] Mannion et al.[17] performed structural factor analysis on different linguistic versions of the SRS-22. They suggested that removing the worst fitting items (3, 14, 15, 17), one from each nonmanagement domains, would improve the multidimensional instrument together with standardization and validation of the items across language versions.[17] In the early revisions, items 17 and 18 were rephrased for the present SRS-22r after further adaptations among adolescents and adults.[11,13]

The concept of HRQoL is multidimensional,[34] and thus it is plausible that RMT analysis does not support the unidimensionality of the SRS questionnaires. Our findings indicate that the structural validity of the SRS-22r could be enhanced by re-evaluating its content and removing the afore mentioned potentially mis-fitting items. Moreover, the fact that the individual SRS-22r domains showed better structural validity leads us to recommend that the individual domain scores rather than the total score are used in clinical work and research. This might provide more accurate patient-reported outcome measure (PROM) data.

To the best of the authors' knowledge, the performance of no SRS instrument has previously been evaluated in participants with different degrees of ASD severity. The domains of the SRS-22r seem to work well irrespective of the degree of spinal structural disorders. The sample used in the present analysis presents the population visiting an orthopedic spine center due to prolonged degenerative thoracolumbar disorders. In adolescents, the SRS-22 was found to be inferior to the specific Spinal Appearance Questionnaire (SAQ) in detecting patients who required surgery and had greater curve magnitude.[35] In ASD, pain, disability, and sagittal structural changes cause deterioration in HRQoL and are the main drivers for seeking surgical treatment[36] instead of the deformity magnitude. Adults also comprise a very heterogenous group of people as to their spinal disorders and medical conditions compared to adolescents with idiopathic scoliosis. The degree of spinal deformity may affect the completion of the total score so that more respondents have for example higher scores from harder items affecting the person-item distribution. Further studies could focus on performing the RMT analysis for different stages of spinal deformity, a task that

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was beyond the scope of this study. Also, the previously studied HRQoL instruments failed to account sufficiently for neurogenic injury or impairment.[37] The SRS version 30 total score has been structurally evaluated in relation to radicular symptoms,[9] but further studies are required to evaluate the validity of the SRS-22r for measuring neurogenic impairment. Structural validity of the SRS or other deformity-specific HRQoL instruments has not been mathematically analyzed in large patient cohorts or with RMT. The SRS-22r domains are reported separately in several studies, but to the author's best knowledge few studies report results in comparison between the individual SRS domains.[14,38]

Compared to the SRS-22r total score or other domains, Function/activity most optimally met the RMT model criteria. It was found to be unidimensional with both good item fit and coverage and an acceptable PSI level. The domain achieved ordered thresholds in all items after merging the response categories in items asking about current level of activity and the frequency of going out compared to friends. Potential item response bias, compromising fit to the RMT model, was noted when patients were divided into subgroups by age or sex. Majority of the function/activity domain items showed DIF with at least one tested age or sex group. Patients with high degree of sagittal deformity also had lower logit values and hence a different person-item distribution in the function/activity domain. This may indicate that physical functioning and the capability to perform and daily activities depend on the degree of spinal deformity and that this difference is detected by the SRS-22r Function/activity domain.[3,4]

The pain domain showed good item fit and sensitivity, and no DIF was found. The domain items ask about pain during the last 6 months, during the past month and during rest, the use of pain medication, and the frequency of absence from work or school (item 17). The last 2 items may also measure other traits that patients cannot clearly differentiate from their spinal condition when filling in the questionnaire. Item 17 showed misfit to the RMT rating scale structure parameters (Andrich thresholds), indicating that the response categories did not match the item's intended meaning. Altogether 40% of the participants were not available for employment or school, which could explain the confusion over the response categories in this older population. Adapting item 17 to better serve ASD patients who may be students, in employment or retired, can be recommended. Pain was the only SRS-22r domain that showed no response bias between the age or sex groups. The domain functioned well across all degrees of spinal deformity. However, the pain scale differed between the age groups in its coverage and targeting.

Although the self-image/appearance domain did not show unidimensionality, it showed good item fit in 4/5 of the items, sensitivity and coverage. Item 4 ("If you had to spend the rest of your life with your back shape as it is right now, how would you feel about it?") showed potential misfit to the RMT model. The sensitivity of the domain was acceptable. It was also multidimensional; however, removing or modifying item 4 might improve the fit of the domain to the RMT model. This domain might also improve the value of the SRS instrument in measuring HRQoL in all degrees of ASD, as the other spine questionnaires do not place similar emphasis on the emotional and psychological functions.[39]

The mental health domain items were taken with permission from the Rand Corporation's SF-36 instrument. All the mental health items are good measures of mental well-being problems, as demonstrated by their ordered thresholds, good sensitivity, coverage and fit to the RMT model. However, in this study, the mental health domain was not unidimensional. In another patient cohort with prolonged back pain and associated depression and distress, the SRS-22r has also shown a multidimensional structure.[40] Potential age-related response bias was found for item 20, which asks how often the respondent has been a happy person, and sex-related bias for item 16, which asks whether the respondent has felt downhearted and blue. Such bias may be explained by the multidimensionality of the measured trait and respondents' interpretation of the positive vs negative tone of the item (happy vs. blue).

Satisfaction with management is rarely covered in the PROMs used for spinal problems. This 2-item unidimensional domain showed good coverage and fit to the RMT model and no DIF. Merging 2 response categories (probably not and definitely not) in item 22 resulted in ordered thresholds. The domain is simple and short, has good structural and psychometric validity, and can be recommended in clinical use.

The strength of this study was the consecutive-sample cohort of symptomatic adult patients with a wide range of different degrees of spinal deformities. The dropout rate of the recruitment was low, and thus the result can be generalized to real-life studies of this patient population. RMT was applied in a sufficient sample size to provide reliable information on the psychometric and structural properties of the SRS-22r. Furthermore, to our best knowledge, the individual SRS-22r domains have not been evaluated with the RM among adults. Chi-square statistics can be sensitive to large sample sizes. As our sample size was ample, it could potentially result in significant chi-square statistics, even for a well-fitting measure. The limitations of the current study

are that analysis only included mostly preoperative patients and that the study was as a single-center study conducted in one spine clinic. Furthermore, the SRS-22r and its domains scores could be structurally investigated and developed among adult patients who have undergone surgery due to spinal deformity.

CONCLUSION

The results of the present RMT analysis show that, among ASD patients, the individual domain scores of the SRS-22r perform better than the total score. Refining items and domains may improve the validity of the instrument for use with adult patients with spinal deformities, even when multidimensionality between domains persists. The questionnaire largely performed equally across age and sexes. The SRS-22r domains were able to differentiate between degrees of spinal deformity.

SUPPLEMENTARY MATERIALS

Supplementary materials 1-5 can be found via https://doi.org/10.14245/ns.2143354.677.

NOTES

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REFERENCES

1. Ames CP, Scheer JK, Lafage V, et al. Adult spinal deformity: epidemiology, health impact, evaluation, and management. Spine Deform 2016;4:310-22.
2. Schwab F, Dubey A, Gamez L, et al. Adult scoliosis: prevalence, SF-36, and nutritional parameters in an elderly volunteer population. Spine (Phila Pa 1976) 2005;30:1082-5.
3. Berven S, Deviren V, Demir-Deviren S, et al. Studies in the Modified Scoliosis Research Society outcomes instrument in adults: validation, reliability, and discriminatory capacity. Spine (Phila Pa 1976) 2003;28:2164-9; discussion 2169.
4. Pellisé F, Vila-Casademunt A, Ferrer M, et al. Impact on health related quality of life of adult spinal deformity (ASD) compared with other chronic conditions. Eur Spine J 2015;24:3-11.
5. Aebi M. The adult scoliosis. Eur Spine J 2005;14:925-48.
6. Mendoza-Lattes S, Ries Z, Gao Y, et al. Natural history of spinopelvic alignment differs from symptomatic deformity of the spine. Spine (Phila Pa 1976) 2010;35:E792-8.
7. Buckland AJ, Vira S, Oren JH, et al. When is compensation for lumbar spinal stenosis a clinical sagittal plane deformity? Spine J 2016;16:971-81.
8. Kyrölä K, Repo J, Mecklin JP, et al. Spinopelvic changes based on the simplified SRS-Schwab adult spinal deformity classification: relationships with disability and health-related quality of life in adult patients with prolonged degenerative spinal disorders. Spine (Phila Pa 1976) 2018;43:497-502.
9. Kyrölä K, Häkkinen AH, Ylinen J, et al. Further validation of the Scoliosis Research Society (SRS-30) questionnaire among adult patients with degenerative spinal disorder. Disabil Rehabil 2021;43:98-103.
10. Kyrölä K, Järvenpää S, Ylinen J, et al. Reliability and validity study of the finnish adaptation of Scoliosis Research Society questionnaire version SRS-30. Spine (Phila Pa 1976) 2017;42:943-9.
11. Asher MA, Lai SM, Glattes RC, et al. Refinement of the SRS-22 health-related quality of life questionnaire function domain. Spine (Phila Pa 1976) 2006;31:593-7.
12. Lai SM, Burton DC, Asher MA, et al. Converting SRS-24, SRS-23, and SRS-22 to SRS-22r: establishing conversion equations using regression modeling. Spine (Phila Pa 1976) 2011;36:E1525-33.
13. Bridwell KH, Cats-Baril W, Harrast J, et al. The validity of the SRS-22 instrument in an adult spinal deformity population compared with the Oswestry and SF-12: a study of response distribution, concurrent validity, internal consistency, and reliability. Spine (Phila Pa 1976) 2005;30:455-61.
14. Arima H, Carreon LY, Glassman SD, et al. Cultural variations in the minimum clinically important difference thresholds

for SRS-22R after surgery for adult spinal deformity. Spine Deform 2019;7:627-32.
15. Mannion AF, Impellizzeri FM, Leunig M, et al. EUROSPINE 2017 FULL PAPER AWARD: Time to remove our rose-tinted spectacles: a candid appraisal of the relative success of surgery in over 4500 patients with degenerative disorders of the lumbar spine, hip or knee. Eur Spine J 2018;27:778-88.
16. Monticone M, Nava C, Leggero V, et al. Measurement properties of translated versions of the Scoliosis Research Society-22 Patient Questionnaire, SRS-22: a systematic review. Qual Life Res 2015;24:1981-98.
17. Mannion AF, Elfering A, Bago J, et al. Factor analysis of the SRS-22 outcome assessment instrument in patients with adult spinal deformity. Eur Spine J 2018;27:685-99.
18. Jain A, Sponseller PD, Negrini S, et al. SRS-7: A valid, responsive, linear, and unidimensional functional outcome measure for operatively treated patients with AIS. Spine (Phila Pa 1976) 2015;40:650-5.
19. Caronni A, Zaina F, Negrini S. Improving the measurement of health-related quality of life in adolescent with idiopathic scoliosis: the SRS-7, a Rasch-developed short form of the SRS-22 questionnaire. Res Dev Disabil 2014;35:784-99.
20. Cano S, Barrett L, Zajicek J, et al. Beyond the reach of traditional analyses: using Rasch to evaluate the DASH in people with multiple sclerosis. Mult Scler 2011;17:214-22.
21. Pallant J, Tennant A. An introduction to the Rasch measurement model: an example using the Hospital Anxiety and Depression Scale (HADS). Br J Clin Psychol 2007;46:1-18.
22. Andrich D. Rating scales and Rasch measurement. Expert Rev Pharmacoecon Outcomes Res 2011;11:571-85.
23. Bond TG, Yan Z, Heene M, et al. Applying the Rasch model. 4th ed. Fourth edition. New York (NY): Routledge; 2020.
24. Tennant A, McKenna SP, Hagell P, et al. Application of Rasch analysis in the development and application of quality of life instruments. Value Health 2004;7 Suppl 1:S22-6.
25. Mokkink LB, Terwee CB, Knol DL, et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. BMC Med Res Methodol 2010;10:22.
26. Andrich D. Rasch models for measurement. Newbury Park (CA): Sage Publications; 2002.
27. Tennant A, Conaghan PG. The Rasch measurement model in rheumatology: what is it and why use it? When should it be applied, and what should one look for in a Rasch paper? Arthritis Rheum 2007;57:1358-62.
28. Tesio L. Measuring behaviours and perceptions: Rasch analysis as a tool for rehabilitation research. J Rehabil Med 2003; 35:105-15.
29. Hobart JC, Cano SJ, Zajicek JP, et al. Rating scales as outcome measures for clinical trials in neurology: problems, solutions, and recommendations. Lancet Neurol 2007;6:1094-105.
30. Christensen KB, Makransky G, Horton M. Critical values for Yen's Q3: identification of local dependence in the Rasch model using residual correlations. Appl Psychol Meas 2017; 41:178-94.
31. Wright B, Stone M. Reliability in Rasch measurement. In: Wright BD, Stone MH. Measurement essentials. 2nd ed. Wilmington (DE): Wide Range Inc.; 1994. p. 157-65.
32. Rothenfluh DA, Neubauer G, Klasen J, et al. Analysis of internal construct validity of the SRS-24 questionnaire. Eur Spine J 2012;21:1590-5.
33. Jain A, Lafage V, Kelly MP, et al. Validity, reliability, and responsiveness of SRS-7 as an outcomes assessment instrument for operatively treated patients with adult spinal deformity. Spine (Phila Pa 1976) 2016;41:1463-8.
34. Sajid MS, Tonsi A, Baig MK, et al. Health-related quality of life measurement. Int J Health Care Qual Assur 2008;21:365-73.
35. Bernstein DN, Papuga MO, Sanders JO, et al. Evaluating the correlation and performance of PROMIS to SRS questionnaires in adult and pediatric spinal deformity patients. Spine Deform 2019;7:118-24.
36. Diebo BG, Varghese JJ, Lafage R, et al. Sagittal alignment of the spine: what do you need to know? Clin Neurol Neurosurg 2015;139:295-301.
37. Stienen MN, Maldaner N, Sosnova M, et al. Lower extremity motor deficits are underappreciated in patient-reported outcome measures: added value of objective outcome measures. Neurospine 2020;17:270-80.
38. Bourghli A, Boissière L, Kieser D, et al. Multiple-rod constructs do not reduce pseudarthrosis and rod fracture after pedicle subtraction osteotomy for adult spinal deformity correction but improve quality of life. Neurospine 2021;18:816-23.
39. Repo JP, Ponkilainen VT, Häkkinen AH, et al. Assessment of construct validity of the Oswestry Disability Index and the Scoliosis Research Society-30 Questionnaire (SRS-30) in patients with degenerative spinal disease. Spine Deform 2019; 7:929-36.
40. Leino P, Magni G. Depressive and distress symptoms as predictors of low back pain, neck-shoulder pain, and other musculoskeletal morbidity: a 10-year follow-up of metal industry employees. Pain 1993;53:89-94.

Supplementary material 1. Item-trait interaction formulae in Rasch measurement theory.

Müller and Kreiner describe the formulae behind the RUMM2030 analysis as follows: "The item-trait interaction is calculated using group residuals for item chi-square fit statistics as the sum of squared group residuals." Persons are grouped into classes (g) depending on the individual scores (Formula 1).

$$X_i^2 = \sum_{g} Z_{gi}^2 = \sum_{g} \left[\frac{\sum_{v \in g} X_{vi} - \sum_{v \in g} E(X_{vi})}{\sqrt{\sum_{v \in g} Var(X_{vi})}} \right]^2$$

The total "item-trait interaction" chi-square test statistic is the sum of item chi-square test statistic, as shown below in Formula 2.

$$X^2 = \sum_{i} X^2{}_i \, , df = k \cdot df_i$$

Adapted from: Müller M, Kreiner S. Item fit statistics in common software for rasch analysis. Copenhagen; 2015. Available from: https://ifsv.sund.ku.dk/biostat/annualreport/images/2/2f/Research_Report_15-06.pdf.

Supplementary material 2. Residual correlation matrix SRS-22 domains. SRS-22r, revised Scoliosis Research Society-22.

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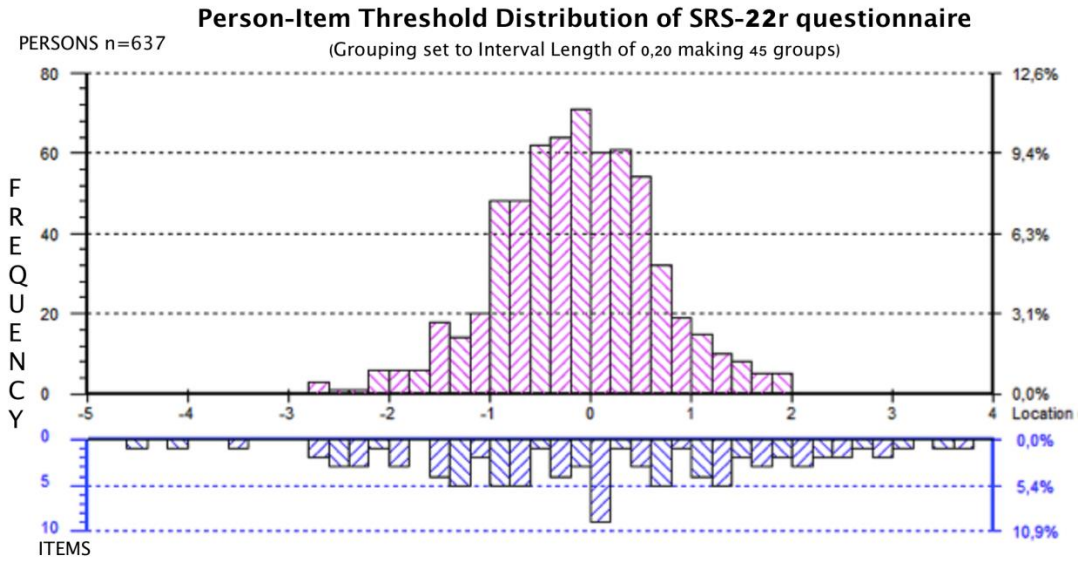
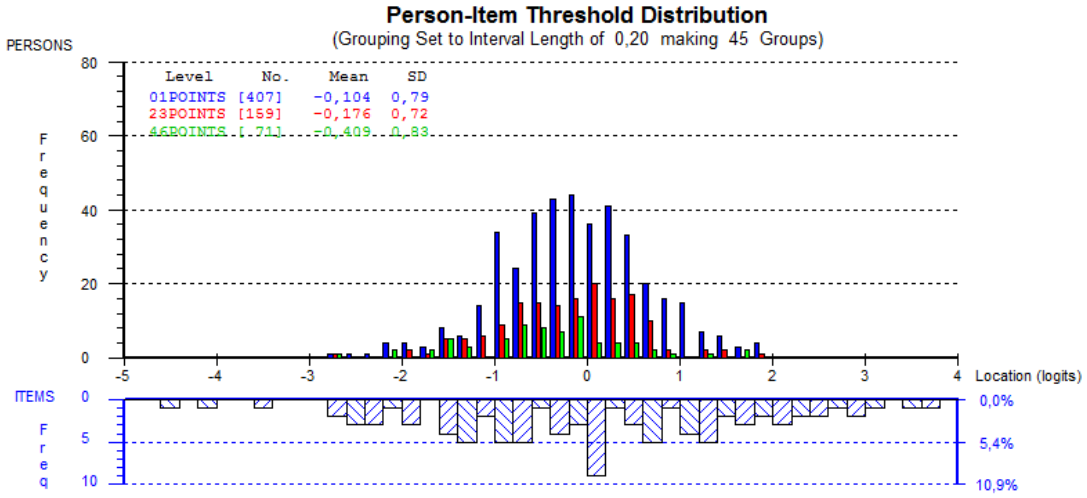


Supplementary material 3. Person-Item threshold distribution of the SRS-22r questionnaire total score. SRS-22r, revised Scoliosis Research Society-22.



Supplementary material 4. Person-Item threshold distribution of the SRS-22r total score according to different stages of deformity. The scale provided coverage for patients locating between -4.5 and 4 logits. All patients were inside the range where the scale provided coverage. Mild or no deformity (blue), moderate (red), and marked deformity (green). SRS-22r, revised Scoliosis Research Society-22.

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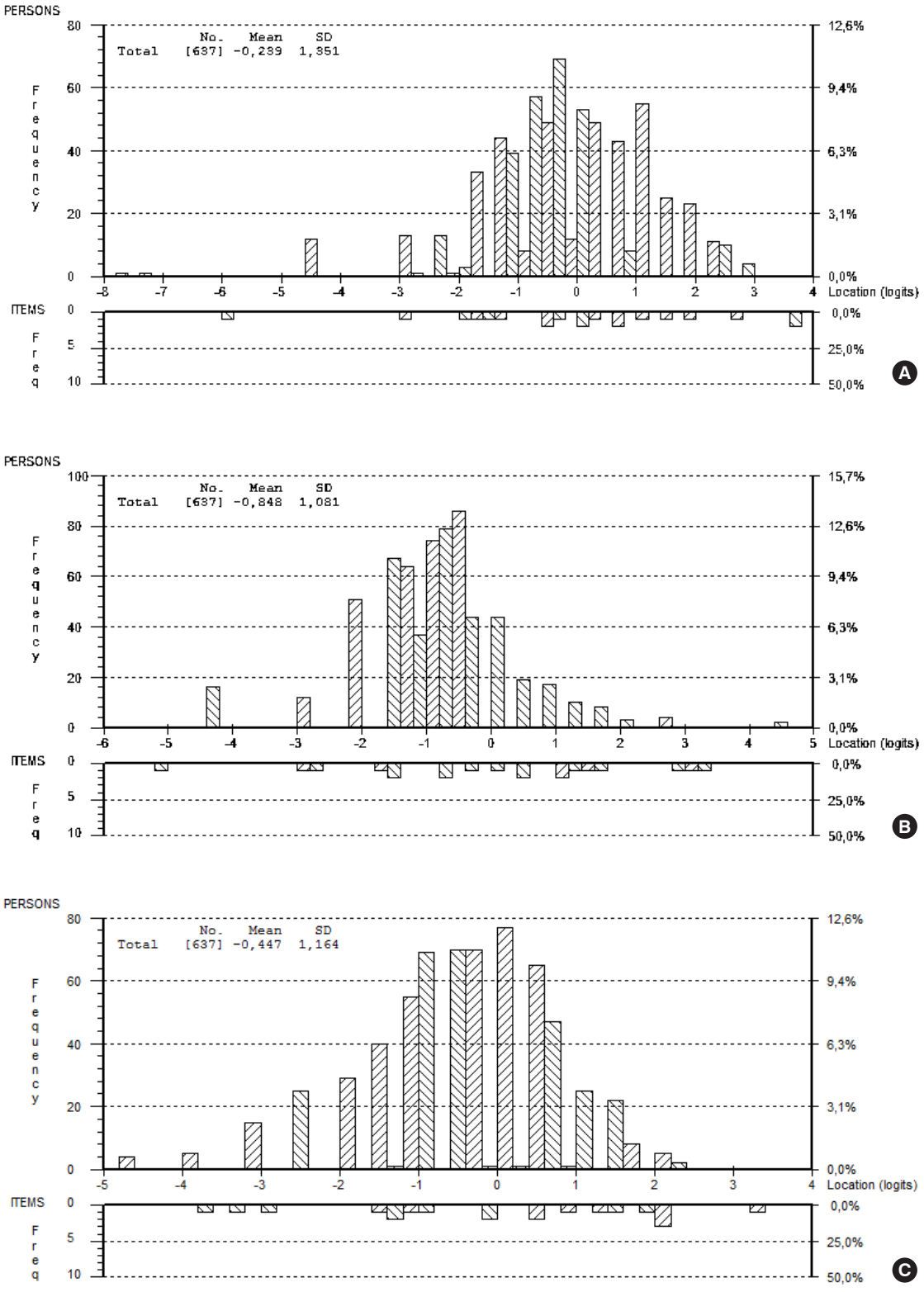
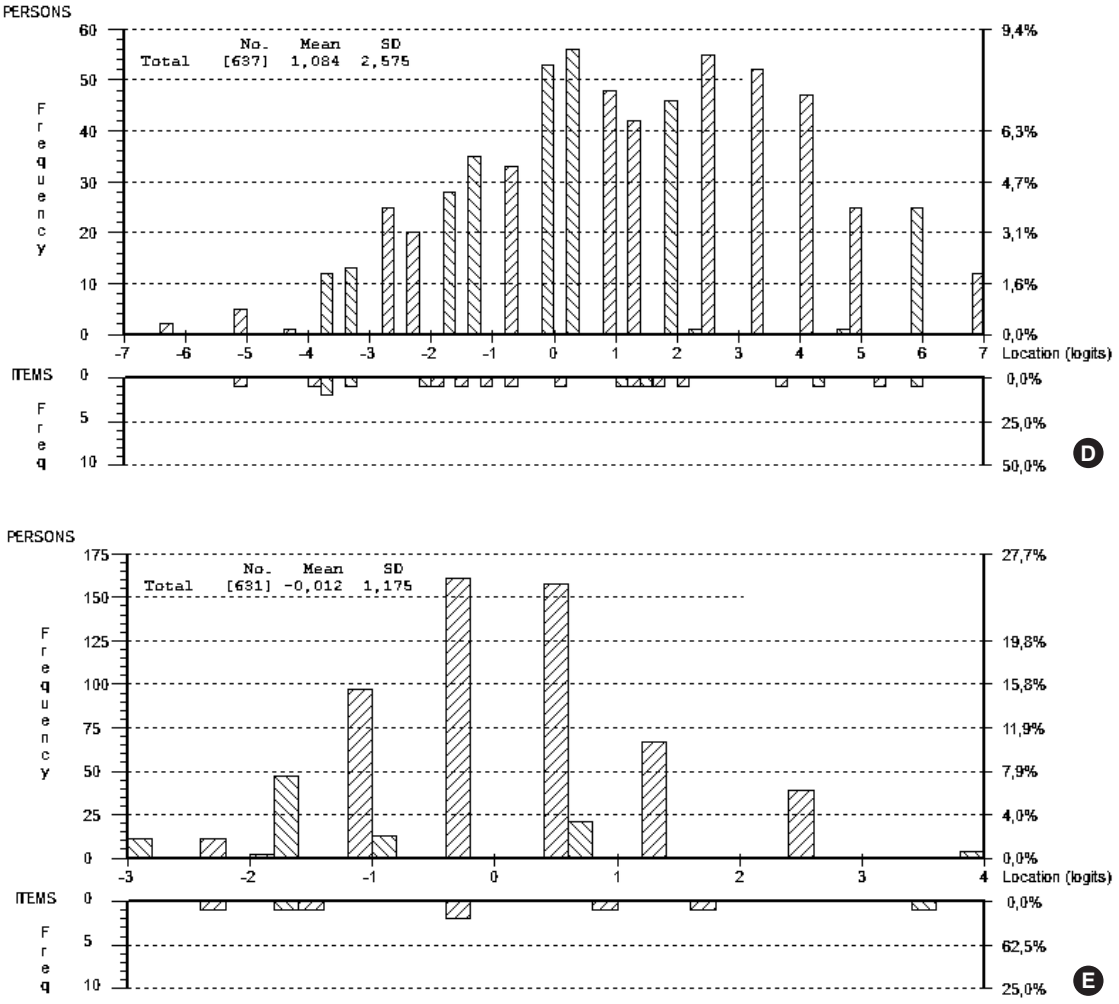


Supplementary material 5. Person-Item threshold distribution of the SRS-22r domains, grouping set to interval length of 0.20 making 55 groups. Function/activity (A), pain (B), self-image (C), mental health (D), satisfaction with management (E). SRS-22r, revised Scoliosis Research Society-22. (*continued*)



Supplementary material 5. Person-Item threshold distribution of the SRS-22r domains, grouping set to interval length of 0.20 making 55 groups. Function/activity (A), pain (B), self-image (C), mental health (D), satisfaction with management (E). SRS-22r, revised Scoliosis Research Society-22. (continued)

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Original Article

Impact of Radiation Therapy on Outcomes After Spinal Instrumentation for Craniocervical Junction Malignancies

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Objective: Spinal reconstruction after resection of invasive craniocervical junction malignancies is fraught with technical and management considerations as well as a paucity of data in the existing literature. In this study, we describe our experience with craniocervical junction malignancies, especially the influence of radiation on the need for revision spinal instrumentation.
Methods: We performed a retrospective chart review of all patients who underwent occipitocervical fixation between 2011 and 2019 at The University of Texas MD Anderson Cancer Center.
Results: Twenty-five patients had primary malignancies and 12 (30%) had metastatic tumors. Thirteen (33%) underwent a staged resection in multiple operations during their hospital stay. Tumor resection was performed in 19 patients (48%), while only stabilization was performed in 21 patients (52%). Nine patients (23%) underwent expanded endoscopic transclival approaches for tumor resection, 10 patients (25%) an extreme lateral approach, and 2 patients (5%) an anterior open approach. Eleven patients underwent early postoperative radiation therapy (within 3 months) and 8 underwent delayed radiation therapy (between 3 months and 1 year in 7 patients). The revision rate was 8%, with a median time to revision surgery of 42 months. The administration and timing of adjuvant radiation therapy relative to surgery had no significant effect on the need for instrumentation revision on log-rank and Cox regression analyses ($p < 0.05$).
Conclusion: Revision surgery was needed infrequently in our patients. Postoperative radiation therapy was not associated with hardware failure, indicating that the timing of radiation therapy should be dictated by the diagnosis and can be initiated postoperatively without delay.

Keywords: Craniocervical junction, Instrumentation, Cancer, Radiation

INTRODUCTION

The craniocervical junction (CCJ) is a complex anatomic region that encompasses the lower clivus, foramen magnum, occipital condyles, and vertebrae of the atlas and axis, with all of their associated ligaments and vascular and neural structures.[1] Primary or metastatic tumors that affect the CCJ can affect the stability of this region, resulting in pain, lower cranial nerve dysfunction, cerebral vascular insufficiency, and myelopathy. It is estimated that only 0.5% of all spinal metastases occur in the CCJ, with the most common histologies being breast, renal, lung, and prostate cancer.[2] The most common primary tumors of the CCJ are chordomas, chondrosarcomas, giant cell tumors, and nasopharyngeal carcinomas.[2]

The surgical approach to tumor resection in the CCJ varies according to the underlying pathology, patients' symptoms, and extent of the disease. Modern endoscopic techniques that are associated with improvements in intraoperative navigation are

frequently used to resect ventrally located tumors that extend from the level of the soft palate to the anterior arch of C1.[3] A transoral extension allows an approach from the lower clivus to up to the C3–4 disc. The far lateral transcondylar approach, with or without mobilization of the vertebral artery, is used to resect dorsal and lateral lesions, as well as tumors located from the mid portion of the dens to the lower body of C2.[4] These approaches are associated with significant disruption of the ligaments and bony structures, requiring CCJ fixation.

Craniocervical reconstruction is mandatory in the setting of the CCJ malignant disease and extensive adjuvant therapy often is required. Additionally, there are concerns regarding the impact of adjuvant therapy on the achievement of mature arthrodesis, which drives the wide variability in the spectrum of reconstruction strategies reported.[5] It is also unclear whether radiation therapy should be delayed to allow the development of arthrodesis, especially in slow-growing low-grade chondrosarcomas, where the time to the initiation of radiation therapy does not clearly impact long-term outcomes. In addition to possible hindrance of the fusion process, high dose radiation therapy required for local control of chordomas can induce muscle atrophy and subcutaneous scars as well as reducing the blood supply to discs and cartilage. These pathophysiological processes can accelerate degenerative changes within the radiation field. Additionally, there are few outcome data on whether the need for and timing of radiation therapy affect the need for revision spinal instrumentation in CCJ reconstruction patients.

In this study, we evaluated the effect of postoperative radiation therapy on the durability of occipitocervical stabilization in a retrospective review of patients who underwent stabilization for malignant disease involving the CCJ at a large tertiary cancer center. We also describe our experience with CCJ malignanices, especially the influence of radiation on the need for revision spinal instrumentation.

MATERIALS AND METHODS

1. Patient Selection

A retrospective review was performed with the following inclusion criteria: all patients who underwent occipitocervical stabilization at The University of Texas MD Anderson Cancer Center (Houston, TX, USA) for a CCJ malignancy between 2011 and 2019 with a greater than 6-month follow-up. The study was approved by the Institutional Review Board (IRB) of The University of Texas MD Anderson Cancer Center (IRB No. PA17-0906), in compliance with regulations set by our institution for the study of human subjects, and it met all Health Insurance Portability and Accountability Act standards. A waiver of informed consent was granted. Patients were identified via a search of a prospectively collected departmental registry. Their clinical charts were reviewed to collect baseline characteristics, imaging and pathology findings, radiation treatments, and chemotherapy regimens. Preoperative imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) results were assessed to determine the extent of tumor invasion of the bony and ligamentous structures of the CCJ.

2. Decision Making and Surgical Technique

Decisions pertaining to tumor resection were made in a histology-specific fashion in which radical resection was attempted for primary malignancies. In cases of metastatic disease, the decision to pursue resection versus limited debulking or stabilization was tailored on the basis of the feasibility of adequate tumor control with adjuvant conventional external-beam radiation therapy or spinal stereotactic radiation surgery.[6] The decision to perform occipitocervical fixation was based on the following factors: intractable neck pain, mechanical instability, and resection of critical bony and ligamentous structures because of tumor involvement or as part of the surgical approach. In transcondylar approaches (lateral open, ventral open, or endoscopic), >70% resection of a single condyle or >50% of both condyles were the thresholds for fusion. In staged surgical strategies in which the fusion was performed separately from the resection, patients were kept in a halo vest in the interim.

The occipitocervical fixation technique has been well described.[5,6] The construct length was decided based on bone quality, osteoporosis, and additional sites of subaxial disease with the intent of performing the shortest segment fixation feasible. All spinal instrumentation was performed with a midline buttress plate on the occiput, pedicle, or pars screws at C2 and lateral mass screws in the subaxial spine. Arthrodesis was performed with decortication and the use of demineralized bone matrix and local autologous bone when available. Complex plastics closure with rotational flaps was performed in reoperative cases with previous irradiation or a need for extensive soft tissue dissection.

3. Outcome Analysis

The primary outcome was time to hardware revision, defined as the time from occipitocervical fixation to instrumentation failure requiring revision surgery, stratified by a binary measure of radiation therapy status (received/did not receive) as well as

a binary measure of radiation therapy timing (early > 3 months and delayed < 3 months). Reasons for delayed radiation therapy include worry of hurting the durability of spinal instrumentation, wound complications such as dehiscence or infection, or lack of need due to complete tumor resection. Instrumentation failure was identified on the basis of imaging findings (CT or MRI) that demonstrated hardware failure and clinical notes that confirmed the need for revision surgery. We also analyzed the overall survival period of enrolled patients.

4. Statistical Analysis

The frequency distribution and summary statistics were calculated for all variables. Kaplan-Meier estimates of the primary outcome were calculated, and survival curves, stratified by radiation therapy status, were compared using the log-rank test at a maximum significance of $p < 0.05$. A Cox regression analysis was used to generate the hazard ratio between the radiation therapy and no radiation therapy cohorts, and chi-square was used to evaluate the statistical significance of the model at a significance level of $p < 0.05$. All statistical analysis were performed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA).

Table 1. Baseline characteristics of study cohort

Characteristic	No. of patients (%)
Sex	
Male	22 (55)
Female	18 (45)
Age range (yr)	
0–18	3 (8)
18–35	6 (15)
35–65	20 (50)
> 65	11 (28)
Breakdown by histologic diagnosis	
Primary tumor	
Chordoma	16 (40)
Giant cell tumor	2 (5)
Pleomorphic sarcoma	3 (8)
Medulloblastoma	1 (3)
Neurofibromatosis	1 (3)
Multiple myeloma	2 (5)
Metastatic tumor	
Colon cancer	2 (5)
Renal cell carcinoma	5 (13)
Breast cancer metastasis	4 (10)
Thyroid cancer	1 (3)
Osteoradionecrosis	3 (8)
Previous cancer-related treatments directed at the craniocervical junction	
Radiation therapy	18 (45)
Chemotherapy	9 (23)
Surgery	11 (28)
Spinal instrumentation	2 (5)

RESULTS

1. Study Cohort and Descriptive Data

Forty patients who had undergone instrumented occipitocervical fusion at our institution were included. The baseline characteristics of the study cohort are shown in Table 1. Twenty-five patients (63%) had primary malignancies, and 12 (30%) had metastatic tumors; the remaining 3 patients (8%) had osteoradionecrosis. Eighteen patients (45%) had undergone previous radiation therapy, 9 (23%) had undergone previous chemotherapy, 11 (28%) had undergone previous surgery for the same lesion, and 2 (5%) had undergone previous spinal instrumentation. Median follow-up was 18.8 months.

The degrees of preoperative disease involvement of the bony and ligamentous structures of the CCJ are shown in Table 2. The most common bony site affected by tumor was the C1 lateral

Table 2. Degree of bony and ligamentous involvement

Variable	No. of patients (%)
Severity of bony involvement	
Occipital condyles	21 (53)
Unilateral	17 (43)
Bilateral	4 (10)
C1	22 (55)
Partial	22 (55)
Complete	0 (0)
C2	21 (53)
Dens	9 (23)
Body	11 (28)
Pars	1 (3)
Clivus	12 (30)
Ligamentous involvement	
All ligaments	12 (30)
Apical	6 (15)
Transverse	14 (35)
Alar	11 (28)
None	8 (20)

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masses/anterior arch in 22 patients (55%), followed by the occipital condyles 21 (53%) and the C2 body/dens in 21 individuals (53%). Twelve patients (30%) had integrity of all CCJ ligaments compromised by the tumor invasion. Individual CCJ ligament involvement occurred as follows: apical ligament, 6 (15%); transverse ligament, 14 (35%); alar ligament, 11 (28%), 8 (20%) had no significant ligamentous insufficiency suspected. Baseline characteristics were not significantly different between the postoperative radiation and nonpostoperative radiation groups using binary logistic regression analysis, shown in Table 3.

Table 3. Overview of surgical outcomes

Variable	No. of patients (%)
Staged surgical resection	13 (33)
Surgical approach for resection	
Endoscopic endonasal	9 (23)
Extreme lateral	10 (25)
Anterior open	2 (5)
No resection	21 (43)
Halo vest placement	11 (28)
Levels fused with occipitocervical fixation	
Less than 3 levels	5 (13)
3–6 Levels	32 (80)
More than 7 levels	3 (8)
PEG placement	12 (30)
Tracheostomy placement	12 (30)
30-Day complications	
Medical complications	5 (13)
Swelling and emergent tracheostomy	2 (5)
Wound dehiscence	2 (5)
CSF leak	1 (3)
Adjuvant radiation therapy	17 (38)
Time to initiation of radiation therapy	
0–3 Months	11 (25)
>3 Months–1 year	8 (18)

PEG, percutaneous endoscopic gastrostomy; CSF, cerebrospinal fluid.

Table 4. Association of baseline characteristics with postoperative radiation using binary logistic regression

Variable	Odds ratio	p-value
Previous chemo	0.4	0.43
Previous radiation	0.23	0.29
Previous resection	5.1	0.23
Recurrent tumor	4.7	0.28
Metastasis	1.6	0.67

2. Surgical Outcomes

Table 4 shows patients' surgical details and postoperative data. Tumor resection was performed in 19 patients (48%), while stabilization alone was performed in 21 (52%). Thirteen patients (33%) underwent a staged resection in multiple operations during their hospital stay. Nine patients (23%) underwent an expanded endoscopic transclival approach for tumor resection, 10 (25%) an extreme lateral approach, and 2 (5%) an anterior open approach. Eleven patients (28%) had a halo vest placed between surgical stages. Thirty-two patients (80%) had 3 to 6 levels fused. Seven patients (18%) had significant swallowing dysfunction requiring a percutaneous endoscopic gastrostomy (PEG) before surgery, while 5 (13%) had developed postoperative dysphagia requiring placement of PEG tubes for postoperative nutritional support. Twelve patients (30%) experienced a complication within 30 days after surgery. Postoperative radiation therapy was given as early (within 3 months) after surgery to 19 patients (48%), and in delayed fashion (between 3 to 12 months) in 8 patients. The most common radiation therapy modalities were proton therapy and stereotactic radiation therapy, with average doses of 70 GyRBE (radiation biological equivalents) and 27 Gy to the clinical target volume, respectively.

3. Primary Outcome Analysis

The median overall survival was 20.3 months. The revision rate was 8% (3 patients), with a median time to revision surgery of 42 months. Fig. 1 shows the Kaplan-Meier curve when using

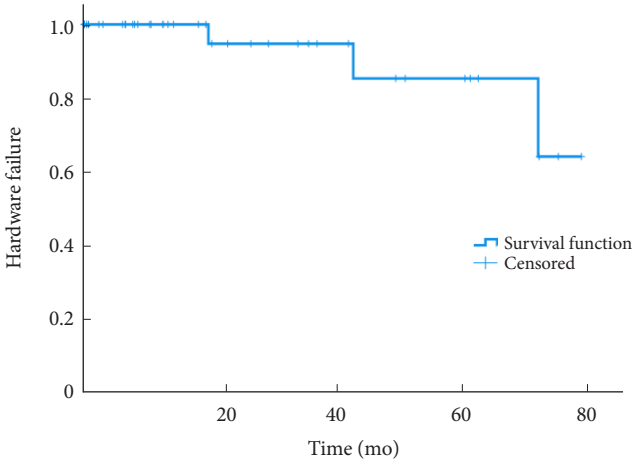

Fig. 1. Kaplan-Meier curve of overall need for revision surgery in patients undergoing occipitocervical fixation for malignant disease.

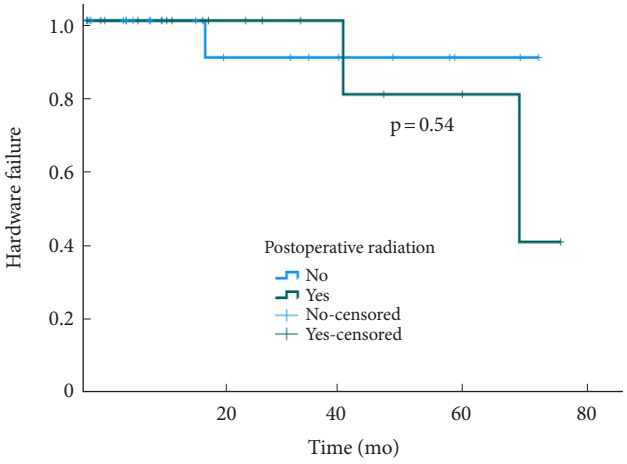

Fig. 2. Kaplan-Meier curve demonstrating impact of adjuvant radiation therapy on the need for revision surgery after occipitocervical fixation.

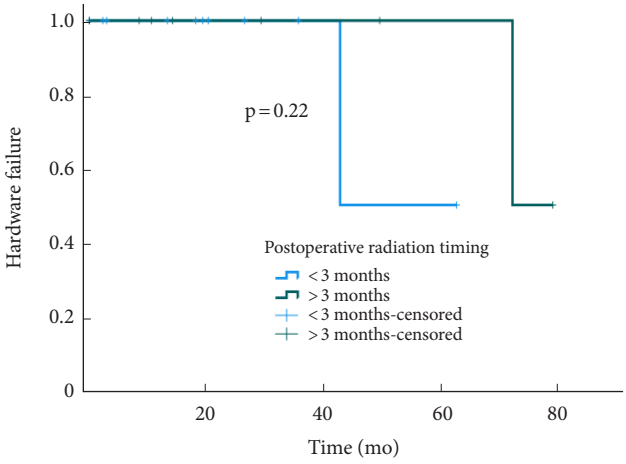

Fig. 3. Kaplan-Meier curve demonstrating impact of adjuvant radiation therapy timing on the need for revision surgery after occipitocervical fixation.

hardware failure and revision surgery as the primary outcome. The Kaplan-Meier analysis stratified by postoperative radiation therapy did not show statistically significant difference of survival rate (Fig. 2, $p = 0.54$). No statistically significant difference was found between the 2 cohorts ($p = 0.54$). Similarly, no statistically significant difference was found ($p = 0.55$) in a Cox regression analysis (Fig. 2). In the Kaplan-Meier analysis of revisions surgery in the postoperative radiation therapy cohort, stratified by the timing of adjuvant radiation therapy, no statistically significant difference of survival was noted between patients undergoing early (less than 3 months postoperatively) versus delayed (greater than 3 months) adjuvant radiation therapy (Fig. 3).

We could not find a correlation between presence and timing of adjuvant radiation therapy influencing the occurrence of revision surgery. The patient who received early radiation had a fall 5 years after surgery and developed traumatic disconnection of the spinal hardware. The patient who received delayed radiation experienced tumor recurrence 3 years after surgery leading to a pathologic fracture of C2 and bilateral rod breakage. The patient who had undergone no postoperative radiation therapy experienced loosening of the lateral mass screws approximately 2 years after surgery.

DISCUSSION

CCJ malignancies pose unique surgical and management challenges. Given the unique biomechanical function of this region and the contributing bony and ligamentous structures, the indications for and technique of occipitocervical fixation require special consideration. A critical management decision is the need for and ideal timing of postoperative radiation therapy to minimize its negative impact on the wound healing and durability of instrumented spinal stabilization. The results of our study indicate that in general, independent of the timing of radiation therapy, revision surgery after occipitocervical instrumentation was extremely infrequent. The administration and timing of adjuvant radiation therapy did not significantly impact instrumentation outcomes.

The stability of the CCJ stems from its cup-shaped configuration and its ligamentous structures that connect the clivus, dens, and atlas. Instability can be induced by tumor invasion of these critical structures or the surgical approach employed. Table 2 describes the severity of bony and ligamentous involvement in our patient cohort, which are key variables used to guide surgical planning. Any disruption involving the transverse ligament of the atlas, anterior arch of the atlas, or bilateral disruption of the alar ligaments was considered high risk for craniocervical instability and we performed occipitocervical fusion in these cases. The only cases that we did not consider high risk for instability was resection of the lower clivus with isolated disruption of the apical ligament.

For example, the far lateral transcondylar approach has been shown to result in instability, with 50%–75% condylar resection, that is compounded by disruption of the posterior atlantooccipital membrane, along with the alar ligaments.[7,8] Beyond bony and ligamentous resection, the resection of the adjacent muscular structures that are responsible for CCJ mobility and stability also contributes to postresection instability as a result of the extensive extracompartmental resection outside of the CCJ. These surgical considerations factor into determining the indi-

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cations for postoperative fixation. Champagne et al.[9] recognized that there are indeterminate situations in the need for fixation; in an effort to avoid the consequences of instrumentation on radiation therapy fields, they reported a protocol in which instrumentation can be delayed until the need for fixation is clearly demonstrated on radiographic follow-up in patients with CCJ chordomas.

Spinal reconstruction in the setting of cancer surgery and the need for adjuvant therapy is fraught with the obstacles highlighted above. Because of the rarity of malignancies in this CCJ, the data regarding reconstruction strategies across all spinal sites are limited to retrospective studies; the data regarding CCJ instrumented fixation are even more limited. To this effect, Glennie et al.[10] performed a systematic review to identify optimal strategies in the cancer setting. Regardless of the location along the spine, instrumentation revision rates of 7.7%–10% were reported. Arthrodesis techniques included the use of vascularized autograft, morcelized allograft, and bone graft substitutes. The reported spectrum of techniques highlights the lack of a consensus approach to fixation strategies after cancer ablative surgery. Despite the unique challenges of the CCJ, our revision rate compares well to the results of Glennie et al.[10] and supports the techniques used in our cohort.

Anterior reconstruction was not attempted in any of our cases. We believe that modern spinal instrumentation is adequate for the stabilization of the CCJ junction, if there is at least 50% of one occipital condyle left. As most of our patients require immediate postoperative radiation therapy or chemotherapy, we do not perform harvesting of iliac crest, as the viability of this autograft may be compromised by adjuvant therapy. As we observed a low incidence of hardware failure, we prefer to have an iliac crest autograft available for eventual hardware revision, where radiation therapy will have less chance to negatively affect the newly implanted iliac crest graft. All hardware failures in our study occurred at the distal end of the construct or with rod breakage.

We did not observe the presence of a solid bony fusion that bridged the occipital bone to the subaxial spine in any of our patients. A longer follow-up period than 18.8 months is needed to clarify whether a lack of arthrodesis affects functional outcomes. We did not observe increased hardware failure or wound-related complications in patients treated with adjuvant radiation therapy. We attribute the lack of wound-related complications to our frequent collaboration with plastic surgeons to perform muscle advancement flaps or complex free flap reconstructions in cases that were considered high risk, which included prior radiation therapy, prior extensive surgery, severe malnutrition, and skin-related trophic changes.

The patients in our series underwent occipitocervical instrumented fusion for the treatment of craniocervical instability due to malignant disease. Patients with primary tumors underwent attempted maximal cytoreduction, which required a staged anterior and posterior approach. It is our practice to perform the anterior operation first, in which the patient's head is positioned in extension and rotation. Upon the completion of this stage, we place the patient in a halo vest if there is disruption of the transverse and alar ligaments, resection of the anterior arch of C1 or odontoid process, or compromise of more than 50% of the occipital condyle. Upon completion of the posterior approach, spinal instrumentation is applied. We do not use cervical braces in the postoperative period. All 12 patients in our series with metastatic disease were treated with a single-stage posterior approach. In radiation-resistant histologies, the goal was tumor resection to allow adequate spinal cord decompression and delivery of tumoricidal doses of postoperative spinal stereotactic radiation therapy. In radiation-sensitive tumors, we performed posterior instrumented fusion and subsequent external-beam radiation therapy.

The incidence of dysphagia requiring PEG placement highlights the importance of achieving optimal craniocervical alignment. As expected with extensive CCJ malignancies, all patients in this cohort who required percutaneous gastrostomy had preexisting dysphagia due to tumor involvement of the lower cranial nerves. However, swallowing difficulty as a result of suboptimal alignment of the CCJ is well-documented in the medical literature, with rates of up to 24% in patients even without tumor pathology.[11] Several techniques have been reported that use preoperative radiographic parameters to assist in optimizing cervical alignment.[12,13] Consistent with Bagley et al.[14] we found that it is easier to achieve a functionally comfortable alignment in patients undergoing staged surgical strategies with postresection halo vests. The technique allows patients to report their comfort level and be evaluated by speech pathologists in the halo prior to being fused permanently into that position. As a result, in patients with lower cranial nerve deficits, optimal alignment can be used to maintain the ideal function of the muscles responsible for deglutition.

We recognize several limitations of this study, including its retrospective nature, the relatively short follow-up, the small sample size, the lack of standardization in postoperative radiation therapy regimens, the different surgical approaches, the heterogeneous tumor histology, and the variability in the num-

ber of levels instrumented. However, we believe that this series represents a real-world sample of rare cases that were managed in a tertiary cancer center. Our data suggest that radiation therapy administered in a short interval following instrumented occipitocervical stabilization does not affect the durability of spinal reconstruction. Longer follow-up and additional studies are needed to clarify the durability of spinal constructs in the absence of documented solid arthrodesis between the occiput and the axial spine.

CONCLUSION

We report a retrospective series of CCJ malignancies treated with occipitocervical fixation; we found a low incidence of hardware failure and need for revision surgery. Postoperative radiation therapy did not impact long-term fixation outcomes, providing evidence that radiation therapy can be postoperatively administered without delay.

NOTES

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REFERENCES

1. Rhoton AL Jr. The foramen magnum. Neurosurgery 2000;47(3 Suppl):S155-93.
2. O'Sullivan MD, Lyons F, Morris S, et al. Metastasis affecting craniocervical junction: current concepts and an update on surgical management. Global Spine J 2018;8:866-71.
3. Baird CJ, Conway JE, Sciubba DM, et al. Radiographic and anatomic basis of endoscopic anterior craniocervical decompression: a comparison of endonasal, transoral, and transcervical approaches. Neurosurgery 2009;65(6 Suppl):158-63; discussion 63-4.
4. Kawashima M, Tanriover N, Rhoton AL Jr, et al. Comparison of the far lateral and extreme lateral variants of the atlanto-occipital transarticular approach to anterior extradural lesions of the craniovertebral junction. Neurosurgery 2003;53:662-74; discussion 674-5.
5. Zuckerman SL, Kreines F, Powers A, et al. Stabilization of tumor-associated craniovertebral junction instability: indications, operative variables, and outcomes. Neurosurgery 2017;81:251-8.
6. Fourney DR, York JE, Cohen ZR, et al. Management of atlantoaxial metastases with posterior occipitocervical stabilization. J Neurosur 2003;98(2 Suppl):165-70.
7. Bejjani GK, Sekhar LN, Riedel CJ. Occipitocervical fusion following the extreme lateral transcondylar approach. Surg Neurol 2000;54:109-15; discussion 115-6.
8. Vishteh AG, Crawford NR, Melton MS, et al. Stability of the craniovertebral junction after unilateral occipital condyle resection: a biomechanical study. J Neurosurg 1999;90(1 Suppl):91-8.
9. Champagne PO, Voormolen EH, Mammar H, et al. Delayed instrumentation following removal of cranio-vertebral junction chordomas: a technical note. J Neurol Surg B Skull Base 2020;81:694-700.
10. Glennie RA, Rampersaud YR, Boriani S, et al. A systematic review with consensus expert opinion of best reconstructive techniques after osseous en bloc spinal column tumor resection. Spine (Phila Pa 1976) 2016;41 Suppl 20:S205-11.
11. Wang X, Chou D, Jian F. Influence of postoperative O-C2 angle on the development of dysphagia after occipitocervical fusion surgery: results from a retrospective analysis and prospective validation. World Neurosurg 2018;116:e595-601.
12. Kaneyama S, Sumi M, Takabatake M, et al. The prediction and prevention of dysphagia after occipitospinal fusion by use of the S-line (Swallowing Line). Spine (Phila Pa 1976) 2017;42:718-25.
13. Takami T, Ichinose T, Ishibashi K, et al. Importance of fixation angle in posterior instrumented occipitocervical fusion. Neurol Med Chir (Tokyo) 2008;48:279-82; discussion 282.
14. Bagley CA, Witham TF, Pindrik JA, et al. Assuring optimal physiologic craniocervical alignment and avoidance of swallowing-related complications after occipitocervical fusion by preoperative halo vest placement. J Spinal Disord Tech 2009;22:170-6.

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Original Article

Current Trends in the Surgical Management of Intramedullary Tumors: A Multicenter Study of 1,033 Patients by the Neurospinal Society of Japan

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Objective: We performed a retrospective observational study to demonstrate the surgical risks and long-term prognoses of intramedullary tumors in Japan using a multicenter registry authorized by the Neurospinal Society of Japan.
Methods: Data from 1,033 consecutive patients with intramedullary tumors, treated between 2009 and 2020, were collected from 58 centers. Patients with spinal lipomas or myxopapillary ependymomas were excluded. Patient characteristics, clinical presentations, imaging characteristics, treatments, and outcomes were analyzed. The modified McCormick scale was used to classify functional status. Survival was described using Kaplan-Meier curves, and multivariable logistic regression analyses were performed.
Results: The mean age of the patients was 48.4 years. Data of 361 ependymomas, 196 hemangioblastomas, 168 astrocytic tumors, 160 cavernous malformations, and the remaining 126 cases including subependymomas, metastases, schwannomas, capillary hemangiomas, and intravascular B-cell lymphomas were analyzed. Twenty-two patients were undiagnosed. The mean follow-up duration was 46.1 ± 38.5 months. Gross total tumor removal was achieved in 672 tumors (65.1%). On the modified McCormick scale, 234 patients (22.7%) had worse postoperative grades at the time of discharge. However, neurological status gradually improved. At 6 months postoperatively, 251 (27.5%), 500 (54.9%), and 160 patients (17.6%) had improved, unchanged, and worsened grades, respectively. Preoperative functional status, gross total tumor removal, and histopathological type were significantly associated with mortality and functional outcomes.
Conclusion: Our findings demonstrate better postoperative functional outcomes in patients with fewer preoperative neurological deficits. Degree of resection, postoperative treatments, and prognoses are closely related to the histology of intramedullary tumors.

Keywords: Intramedullary tumors, Astrocytoma, Ependymoma, Cavernous angioma, Hemangioblastoma

INTRODUCTION

Intramedullary spinal cord tumors are rare. However, they significantly affect patients' daily life by causing neurological dysfunction and mortality.[1-3] When treating patients with intramedullary tumors, referring to standardized treatment protocols would be ideal in order to decide when and how to perform surgical interventions. However, such protocols are available but scarce,[4,5] as planning prospective randomized studies have been difficult because of the rarity and varied clinical courses of these tumors.

Thus, this study aimed to present the clinical course and surgical outcomes of intramedullary tumors by analyzing the available data from Japanese neurosurgical centers. Here, we developed a multicenter registry of intramedullary tumors authorized by the Neurospinal Society of Japan. In addition to the epidemiological and clinical characteristics, we determined the factors associated with improved survival and functional outcomes.

MATERIALS AND METHODS

1. Ethics

This was a multicenter cohort study authorized by the Neurospinal Society of Japan. The study protocol was approved by the Institutional Review Board of Tohoku University Hospital (2021-1-130) and the participating centers. As this was a retrospective and noninvasive study, the requirement for written informed consent from patients was waived. Instead, a public notice that provided information on this study was given on individual center websites.

2. Patient Selection

The inclusion criterion was consecutive patients with intramedullary spinal cord tumors treated surgically at 58 centers between 2009 and 2020. The exclusion criteria were patients with the spinal lipoma or the myxopapillary ependymoma. Patients who underwent their first surgery at different hospitals or before 2008 were also excluded.

3. Baseline Characteristics

Clinical characteristics including age, sex, height, weight, past medical history (including neurofibromatosis, von Hippel-Lindau disease, and brain tumors), clinical presentations, and duration of the disease were anonymously extracted from the patients' medical records. Modified McCormick scales[6] (grade I, normal gait; grade II, mild gait disturbance not requiring support; grade III, gait with support; grade IV, assistance required; and grade V, wheelchair needed) were periodically analyzed, allowing comparisons between the preoperative and postoperative status. Specifically, the grades at discharge and 6 months postoperatively were compared to those before surgery. Radiological data were collected from preoperative and postoperative images, including lesion level, lesion length, magnetic resonance imaging (MRI), and computed tomography findings. From the surgical records, surgical approaches, degree of excision, operative time, blood loss, and complications were assessed. The surgeons' years of experience and certification status in the Neurospinal Society of Japan were also reported from each facility. Pathological diagnoses and immunohistochemical markers were extracted from the pathological records. Information was also recorded on the postoperative clinical course, including adjuvant radiochemotherapy, presence of recurrence and dissemination, and treatment modalities for recurrence.

4. Functional and Performance Grades

Using the modified McCormick scale, when a patient remained at the same grade, we termed the pattern "stable." Changes of at least one level when compared to the preoperative status were described as "improved" or "worsened" as appropriate.

5. Statistical Analysis

All data were analyzed for completeness and accuracy, and anonymized prior to being scrutinized. The survival period, defined as the number of months from surgery to death, was censored at the last available follow-up or cutoff study date (December 31, 2020) for those who were still alive. Kaplan-Meier curves were created to estimate overall survival for the entire cohort as well as survival in subgroups classified based on histological diagnosis. Risk factors for mortality and factors indicating better functional outcomes were identified using multivariable logistic regression analyses across different demographic characteristics, tumor types, and surgical interventions after controlling for potential confounders. The effects are presented as odds ratios with associated 95% confidence intervals. The multivariable models were adjusted for all included factors. Each preliminary model was then entered into the final logistic regression model. Goodness of fit was assessed using the Hosmer-Lemeshow test. Statistical analyses were performed using IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA).

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RESULTS

1. Patient Demographics

In total, 1,033 individual cases were identified. The mean age of the patients at the time of surgery was 48.4 years (range, 0–88 years). Patient demographics are summarized in Table 1. Of the cases, 560 were men (54.2%), and 473 were women (45.8%), indicating a slight male predominance. A clinical diagnosis of neurofibromatosis type 1 was present in 6 cases (0.6%), and neurofibromatosis type 2 was present in 16 cases (1.6%). Seventy-four patients (7.1%) were diagnosed with von Hippel-Lindau disease. The mean duration of symptoms was 22.8 months, with limb paresthesia being the most common presenting symptom (85.1%), followed by weakness (66.2%), and gait disturbance (57.2%). The patients also presented with head, neck, or back pain (41.2%), limb pain (40.9%), or bladder and/or bowel disturbances (33.0%).

The tumors were distributed across the following spinal levels (Table 2): 465 cervical (44.9%), cervical and thoracic (127% and 12.4%, respectively), 333 thoracic (32.2%), and thoracic and lumbar (108% and 10.5%, respectively). Based on MRI findings, the tumors were classified as cystic (8.2%), solid (50.1%), mixed (25.6%), or hemorrhagic (15.1%). The tumor size was measured based on sagittal images. The average tumor length was 39.1 mm. Concomitant brain tumors were observed in 130 cases (12.5%).

Table 1. Summary of patient demographics among 1,033 cases of the intramedullary spinal cord tumors

Variable	Value
Age on admission (yr)	48.4 (0–88)
Sex	
Men	560 (54.2)
Women	473 (45.8)
Cases with hereditary disease	
Neurofibromatosis, type 1	6 (0.6)
Neurofibromatosis, type 2	16 (1.6)
von Hippel-Lindau disease	74 (7.1)
Mean duration of the symptoms (mo)	22.8
Clinical presentations	
Head, neck or back pain	426 (41.2)
Limb pain	424 (40.9)
Limb paresthesia	882 (85.1)
Limb weakness	686 (66.2)
Gait disturbance	593 (57.2)
Bladder/bowel disturbance	342 (33.0)

Values are presented as mean (range) or number (%) unless otherwise indicated.

2. Histopathology and Tumor Characteristics

Among the 1,033 intramedullary spinal cord tumor cases, 361 were ependymomas, 196 were hemangioblastomas, 168 were astrocytic tumors, and 160 were cavernous malformations. The remaining 126 cases comprised subependymomas, metastases, capillary hemangiomas, lymphomas, and schwannomas (Table 3). Twenty-two cases remained undiagnosed, even after histological evaluation.

3. Surgical Treatment

As demonstrated in Table 4, surgery was performed via the posterior approach in almost all cases (1,023 operations, 99.0%). Ten surgeries (1.0%) were performed anteriorly. Most surgeons (94.5%) had > 10 years of experience. In 88.3% of the cases, the main operators were certified spine surgeons of the Neurospinal Society of Japan. The mean operative time was 399.9 ± 173.2 minutes. The mean blood loss was 186.0 ± 247.0 mL. Overall, 65.1% of the cases were treated with gross total resection, while 13.0% and 14.1% of the lesions received subtotal and partial removal, respectively. Biopsy was performed in 7.8% of the cases to confirm the histological diagnosis. The frequency of total resection varied among different histological subtypes. For example, 91.8% of hemangioblastomas were completely removed,

Table 2. Tumor characteristics of the 1,033 cases of the intramedullary spinal cord tumors

Characteristic	Value
Tumor levels	
Cervical	465 (44.9)
Cervical and thoracic	127 (12.4)
Thoracic	333 (32.2)
Thoracic and lumbar	108 (10.5)
Tumor characteristics	
Cystic	85 (8.2)
Solid	518 (50.1)
Mixed	265 (25.6)
Hemorrhagic	156 (15.1)
Unclassified	9 (0.9)
Tumor length	39.1 (3–500)
Intracranial tumors, concomitant	130 cases

Values are presented as number (%) or mean (range) unless otherwise indicated.

Table 3. Histopathological types of the 1,033 intramedullary tumors in Japan, data arranged in decreasing order of frequency

Type	No. of cases (%)
Ependymoma	361 (35.0)
Hemangioblastoma	196 (18.9)
Astrocytoma	168 (16.2)
Cavernous malformations	160 (15.4)
Subependymoma	22 (2.1)
Metastasis	21 (2.0)
Capillary hemangioma	16 (1.5)
Lymphoma	13 (1.3)
Schwannoma	12 (1.2)
Embryonal tumors (medulloblastoma, PNET, ATRT)	8 (0.8)
Solitary fibrous tumor	5 (0.5)
Germ Cell tumors (germinoma, mature teratoma, yolk sac tumor)	5 (0.5)
Gangliocytoma, Ganglioglioma	5 (0.5)
Neurenteric cyst	4 (0.4)
Rosette-forming glioneuronal tumor	3 (0.3)
Malignant peripheral nerve sheath tumor	2 (0.2)
Neurofibroma	1 (0.1)
Pineoblastoma	1 (0.1)
Paraganglioma	1 (0.1)
Glioependymal cyst	1 (0.1)
Meningioma	1 (0.1)
Granuloma	2 (0.2)
Sclerosing epithelioid fibrosarcoma	1 (0.1)
Dermoid cyst	1 (0.1)
Central neurocytoma	1 (0.1)
Undiagnosed	22 (2.1)

PNET, primitive neuroectodermal tumor; ATRT, atypical teratoid/rhabdoid tumor.

whereas total resection was performed in 88.8% and 74.8% of cavernous malformations and ependymomas, respectively. However, only 10.7% of astrocytomas underwent total resection. Postoperative radiation therapy was performed in 130 cases (12.6%), including 13 cases (1.3%) with whole-spinal irradiation. Chemotherapy was administered using temozolomide alone in 57 patients and temozolomide and bevacizumab in 24 cases. Methotrexate, monoclonal antibodies, and other chemotherapeutic agents have been used to treat metastatic tumors, lymphomas, and embryonal and germ cell tumors.

Table 4. Surgical details and the results of the 1,033 intramedullary tumor cases

Characteristic	Value
Surgical approaches	
Posterior	1,023 (99.0)
Anterior	10 (1.0)
Surgeons' experience	
> 10 years	976 (94.5)
< 10 years	57 (5.5)
Main operator	
Board-certified spine surgeons	912 (88.3)
Operation time (min)	399.9 ± 173.2
Blood loss (mL)	186.0 ± 247.0
Degrees of removal	
Total	672 (65.1)
Subtotal	134 (13.0)
Partial	146 (14.1)
Biopsy	81 (7.8)
Total removals	
Ependymoma	270/361 (74.8)
Hemangioblastoma	180/196 (91.8)
Cavernous malformations	142/160 (88.8)
Astrocytoma	18/168 (10.7)
Others	54/126 (42.9)
Postoperative radiation	
Local	117 (11.3)
Whole spine	13 (1.3)
Chemotherapy	
Temozolomide only	57 (5.5)
Temozolomide and bevacizumab	24 (2.3)

Values are presented as number (%) or mean ± standard deviation.

4. Postoperative Course

Immediately postoperatively, 286 patients (27.7%) experienced symptom improvement, 333 (32.2%) remained stable, and 414 (40.1%) experienced worsening of their symptoms (Table 5). On the modified McCormick scale, 153 (14.8%), 646 (62.5%), and 234 patients (22.7%) had improved, unchanged, and worsened grades postoperatively (at discharge), respectively. In the same scale at 6 months postoperatively, 251 (27.6%), 500 (54.9%), and 160 patients (17.6%) had improved, unchanged, and worsened grades, respectively.

Postoperative complications included cerebrospinal fluid (CSF) leakage in 28 patients, hematoma in 8, infection in 9, and pulmonary embolism in 2. Sixty-nine patients experienced local

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Table 5. Postoperative course and the complications

Characteristic	No. (%)
Symptoms at discharge	
Improved	286 (27.7)
Unchanged	333 (32.2)
Worsened	414 (40.1)
Modified McCormick Scales at discharge (comparison with the preoperative status)	
Improved	153 (14.8)
Unchanged	646 (62.5)
Worsened	234 (22.7)
Modified McCormick Scales 6 months after the operations (comparison with the preoperative status)	
Improved	251 (27.6)
Unchanged	500 (54.9)
Worsened	160 (17.6)
Complications	
CSF leak	28 (2.7)
Postoperative hematoma	8 (0.8)
Infection	9 (0.9)
DVT, pulmonary embolism	2 (0.2)
Relapse of the tumors	
Local recurrence	42 (4.1)
CSF dissemination	10 (1.0)
Local recurrence and CSF disseminations at the same time	27 (2.6)

CSF, cerebrospinal fluid; DVT, deep venous thrombosis.

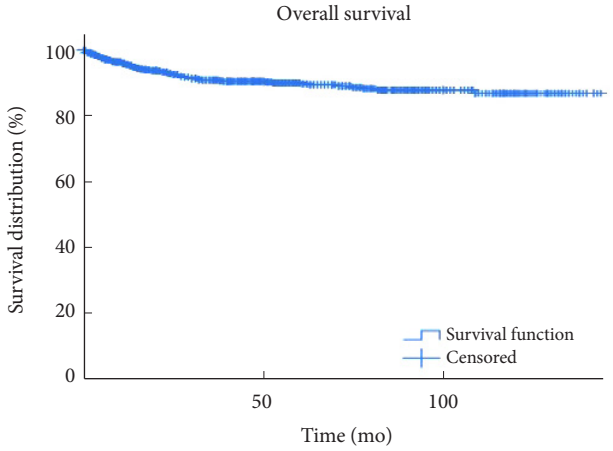

Fig. 1. Overall survival is demonstrated using Kaplan-Meier curves of those who underwent surgical interventions for intramedullary tumors.

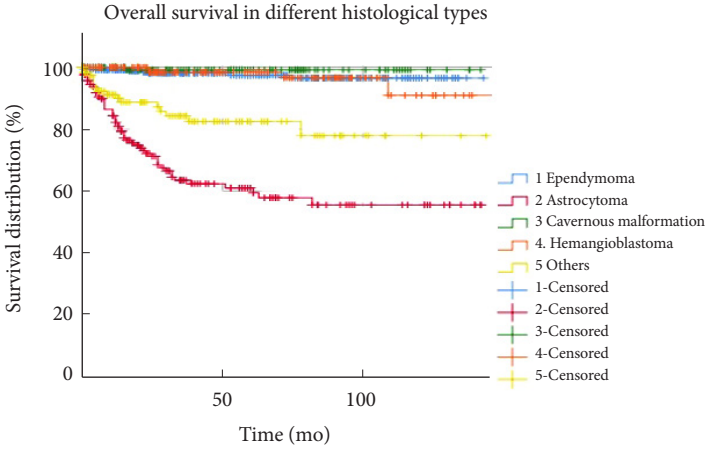

Fig. 2. Overall survival is demonstrated using Kaplan-Meier curves for tumors with different histological diagnoses. Astrocytomas had worse survival than the other histological types.

recurrence, which included 42 astrocytomas, 12 ependymomas, 6 cavernous malformations, and 4 hemangioblastomas. Among them, 27 patients also had evidence of CSF dissemination at the time of recurrence, while 10 patients experienced only CSF dissemination. Of the 37 patients who experienced CSF disseminations, 29 and 5 patients were originally diagnosed as astrocytoma and ependymoma, respectively. The mean time interval before recurrence and/or dissemination postoperatively was 23.8 ± 28.2 months. As treatment, 24 patients including 11 astrocytomas, 5 ependymomas, 4 cavernomas, and 2 hemangioblastomas underwent reoperations. Thirteen and 21 patients received radiation therapy and chemotherapy, respectively. Among them, 27 and 5 patients were originally diagnosed as astrocytoma and ependymoma, respectively.

5. Mortality and Risk Factors

From the 1,033 patients, we excluded 55 patients due to loss of follow-up. Among the 978 patients, 871 (89.1%), and 841 (86.0%) survived longer than 5 and 10 years, respectively. Overall survival is depicted in the Kaplan-Meier curves (Fig. 1). Survival varied according to histological type, as illustrated in Fig. 2. Five-year survival rates of patients with ependymomas, hemangioblastomas, astrocytomas, and cavernous malformations were 96.5%, 96.6%, 59.4%, and 99.1%, respectively. Patients with astrocytoma had worse survival than those in the other histological groups. The multivariable analyses indicated that lesser degrees of tumor removal, worse preoperative modified McCormick scales, and histopathological types of the tumors were associated with mortality (Table 6). Younger age was also a risk factor, although the statistical significance was marginal.

Table 6. Multiple logistic regression modeling with clinical factors indicating mortality (n = 978, 55 cases were lost of follow up)

Variable	Multivariable analysis		
	OR	95% CI	p-value
Age	0.99	0.97–0.99	0.046
Male sex†	1.29	0.75–2.22	0.36
Surgery			
Biopsy	Reference		
Partial removal	0.64	0.32–1.28	0.21
Subtotal removal	0.56	0.24–1.31	0.18
Total removal	0.12	0.04–0.33	< 0.001
Modified McCormick Scales (III, IV, V)‡	4.82	2.62–8.88	< 0.001
Histopathology			
Ependymoma	Reference		
Astrocytoma	6.20	2.53–15.20	< 0.001
Cavernous malformations	0.30	0.04–2.44	0.26
Hemangioblastoma	1.59	0.44–5.72	0.48
Others	3.31	1.29–8.49	0.01
Locations	0.89	0.72–1.11	0.30
Hosmer and Lemeshow goodness of fit test		0.146	

OR, odds ratio; CI, confidence interval.
†OR was calculated with Female as reference. ‡OR was calculated with modified McCormick Scales I and II as reference.

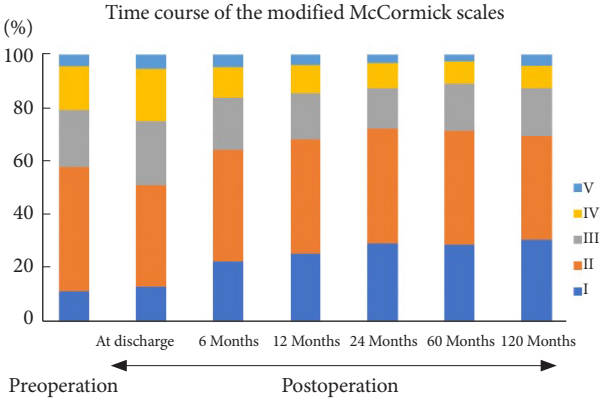

Fig. 3. Time course of neurological function expressed using the modified McCormick scale. The proportions of patients with McCormick grades I and II decreased immediately postoperatively (at discharge). However, the proportions increased at 6 months postoperatively. The surgical results were better than the preoperative status. The improved functional status was maintained thereafter.

Table 7. Multiple logistic regression modeling with clinical factors indicating the better functional outcomes (n = 896 with 6-month follow-up)

Variables	Multivariable analysis		
	OR	95% CI	p-value
Age	0.98	0.97–0.99	0.046
Male sex†	1.02	0.73–1.44	0.90
Surgery			
Biopsy	Reference		
Partial removal	1.04	0.47–2.31	0.92
Subtotal removal	1.78	0.76–4.19	0.19
Total removal	3.66	1.62–8.23	0.002
Modified McCormick Scales (I, II)‡	14.26	10.03–20.29	< 0.001
Histopathology			
Ependymoma	Reference		
Astrocytoma	0.41	0.22–0.77	0.006
Cavernous malformations	1.20	0.72–1.98	0.49
Hemangioblastoma	0.60	0.35–1.05	0.08
Others	0.60	0.35–1.05	0.08
Locations	0.91	0.79–1.05	0.21
Hosmer and Lemeshow goodness of fit test		0.469	

OR, odds ratio; CI, confidence interval.
†OR was calculated with Female as reference. ‡OR was calculated with Modified McCormick scales III, IV, V as reference.

6. Functional Outcomes and Associated Factors

The patients' grades on the McCormick scale preoperatively and postoperatively are depicted in Fig. 3. The proportion of patients with McCormick grades I and II decreased at discharge. However, this proportion increased again, indicating improvement compared to the preoperative status 6 months postoperatively. Functional status further improved at 12 months and was maintained thereafter. Further analyses were performed on 896 patients who were followed up for > 6 months or died 6 months postoperatively. Total tumor removal, better preoperative modified McCormick grades, and histopathologic type of the tumor were also associated with better functional outcomes at 6 months postoperatively (Table 7). Younger age is also associated with better functional outcomes. However, statistical significance was marginal.

DISCUSSION

In this study, where we successfully collected real clinical data

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of 1,033 intramedullary tumor cases from 58 certified facilities authorized by the Neurospinal Society of Japan, the main operators were board-certified spine surgeons of the society in 88.3% of the cases.[4,7] To the best of our knowledge, this is the first multicenter collaborative study on surgically treated intramedullary spinal cord tumors in Japanese neurosurgical centers authorized by the Neurospinal Society of Japan. Moreover, our report is one of the largest studies to present details of surgically treated intramedullary tumors, including 361 ependymomas, 196 hemangioblastomas, 168 astrocytic tumors, and 160 cavernous malformations.

The overall incidence of intramedullary spinal cord tumors was reported as 0.31 or 0.35 per 100,000 persons in the United States.[1,2] If we apply this number to the Japanese population (125,000,000), we could expect approximately 340 new cases of intramedullary tumors annually in Japan. In fact, the Japanese Neurosurgical Registry has reported 266 surgical cases of intramedullary tumors annually, accounting for 27.3% and 1.29% of all spinal and intracranial tumors, respectively.[3]

Because of the rarity of these tumors, information regarding standard treatment protocols has been sparse.[5] When relevant studies in the literature were reviewed, almost all the reports were retrospective in nature and were classified as providing low-quality evidence.[7-9] Under these circumstances, we still believe that retrospective case reviews could play a meaningful role, especially since we included a large number of cases exceeding those of previous reports.

1. Long-term Results

In this study, the 5-year and 10-year survival rates were 89.1% and 86.0%, respectively. Furthermore, 71.5% and 69.4% of the patients had grade I or II on the modified McCormick scale and were functionally fully independent at 5 and 10 years postoperatively, respectively. Our results were better than those of other reports.[10,11] This could be because the majority of our cases (75.1%) were low-grade lesions, including ependymomas, hemangioblastomas, cavernous malformations, subependymomas, capillary hemangiomas, and schwannomas. Furthermore, the proportion of the astrocytoma was important, which was low at 16.2% in our study. Constantini et al.[10] have reported the long-term clinical results of intramedullary tumors, especially in children and young adults. They had 164 intramedullary tumors, of which 79.3% and 46.3% of the tumors were low-grade lesions and astrocytic tumors, respectively. In their study, 76.8% of patients underwent total tumor removal. The mean follow-up time was 85.1 ± 4.4 months, with 5- and 10-year survival rates of 76% and 70%, respectively. As an example of an adult case series, Raco et al.[11] have reported 202 patients whose mean age was 42.3 years old. In their follow-up, 61.8% of the patients had a stable or improved neurological status. The 5- and 10-year survival rates were 73% and 42%, respectively. They had astrocytomas in 42.6% of cases, which might have influenced the results and led to worse prognoses.

2. Preoperative Neurological Status

Among the various factors, we identified the preoperative modified McCormick scale, the degree of surgical resection of the tumor, and tumor histology as strong indicators of the functional status at 6 months and mortality in the multivariable analyses. The surgical results of intramedullary tumors have been published in the literature (Table 8). However, simply comparing different studies would not be ideal because they included different types of tumors in various proportions. However, across all previous studies, the authors have agreed that preoperative neurological status was a strong predictor of postoperative morbidity.[9,11-18] Here, the preoperative McCormick grade had a significant impact on both postoperative (6 months) functional status and mortality. When patients underwent surgical removal of intramedullary tumors while they were functionally independent, surgery was more likely to provide a better clinical course. These observations support early surgical interventions for intramedullary tumors.[11,16,19] Early recognition of symptoms and prompt MRI evaluation are important for the proper management of intramedullary tumors.

3. Surgical Resections of the Intramedullary Tumors

The degree of surgical removal of intramedullary tumors also had a positive impact on clinical results. Following complete tumor resection, patients had better prognoses and functional outcomes in our analyses. Several other studies support the importance of achieving higher degrees of removal of intramedullary tumors (Table 8).[11,12,15,16,18] These results are encouraging for neurosurgeons aiming for total resection as the primary goal of treatment for intramedullary tumors.

However, recognizing that complete resection is not always possible is important. Gross total resection was only possible in 65.1% of the cases in our study. Our data clearly indicated that the proportion of total resection varied among different histological subtypes. In cases of hemangioblastomas, cavernous malformations, and ependymomas, 91.8%, 88.8%, and 74.8% of the tumors, respectively, were completely removed. However, total resection could only be performed in 10.7% of the astrocyto-

Table 8. Previous studies demonstrating surgical results for the intramedullary tumors

Study	Intramedullary tumor cases	Complete resection	Postoperative deterioration	Prognostic factors
Cooper and Epstein,[12] 1985	29 Cases -14 Ependymomas -11 Astrocytomas	72%	28%	Satisfactory neurological status before surgery Histological type Complete removal
Cristante and Herrmann,[17] 1994	69 Cases -34 Ependymomas -28 Astrocytomas	55.1%	29.4%–31.5%	Preoperative neurologic deficit
Constantini et al.,[10] 2000	164 Cases -19 Ependymomas -76 Astrocytomas	76.8%	23.%	Histological type Preoperative functions Patients with shunts
Sandalcioglu et al.,[13] 2005	78 Cases -32 Ependymomas -15 Astrocytomas	83.3%	34.6%	Preoperative neurological condition Histological differentiation
Raco et al.,[11] 2005	202 Cases -86 Astrocytomas -68 Ependymomas	57.8%	38.2%	Functional status at surgery Histological type Extent of surgical removal
Woodworth et al.,[14] 2007	78 Cases -27 Ependymomas -23 Astrocytomas	Not addressed	19.2%	Serum glucose levels Preoperative ambulatory status Preoperative radiation therapy
Matsuyama et al.,[15] 2009	106 Cases -46 Ependymomas -12 Astrocytomas -16 Hemangioblastomas -17 Cavernous malformations	56.0%	31.5%	Good preoperative neurological status Total resections
Klekamp,[19] 2013	250 Cases -99 Ependymomas -76 Astrocytomas -28 Hemangioblastomas -13 Cavernous malformations	61.2%	19.5%	Surgical experience Preoperative status Thoracic tumors Tumor hemorrhage Recurrent tumors
Kumar and Banerjee,[9] 2014	43 Cases -21 Ependymomas -12 Astrocytomas -5 Hemangioblastomas	69.8%	23.3%	Preoperative neurological grade Gross tumor resections High histological grades
Boström et al.,[16] 2014	70 Cases -39 Ependymomas -11 Astrocytomas -5 Hemangioblastomas -3 Cavernous Malformations	64.3%	14.3%	Degree of resection Preoperative status
Hongo et al.,[18] 2019	49 Cases -32 Ependymomas -17 Astrocytomas	49.0%	Not addressed	Histological type Gross total resection for ependymoma

mas (Table 4). In ependymomas, cavernous malformations, and hemangioblastomas, we could expect dissecting margins between the lesions and the normal spinal cord, making radical resection a reasonable approach.[20-23] Instead, astrocytomas tend to be more infiltrative, lacking a good plane of dissection.[15,24] A recent study has indicated that surgical removal of intramedullary astrocytomas could be associated with higher rates of neurological complications.[25]

During each surgery, surgeons must decide whether to continue or stop resection. As neurosurgeons, we should know the microanatomy of the spinal cord and train in microsurgical techniques so that we can remove tumors without damaging the spinal cord function when there is a surgical dissection plane.[26] If there is no plane, making the difficult decision to discontinue the surgical resection is crucial. Currently, spinal cord monitoring is mandatory when performing intramedullary tumor sur-

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gery.[27] The recordings of motor and sensory evoked potentials provide useful information regarding the functional integrity of the spinal cord tracts.[28] Rijs et al.[29] have recently performed a meta-analysis that included 1266 intramedullary spinal cord tumor patients who underwent surgery with intraoperative monitoring. These included 727 ependymomas, 173 astrocytomas, 129 hemangioblastomas, and 20 cavernous malformations. Altogether, 855 (72%) and 242 patients (21%) underwent gross total and subtotal resection, respectively. According to the criteria defined by the respective studies, the motor and sensory evoked potentials predicted the emergence of new postoperative neurologic morbidities in 83.8% and 80.8% of the cases, respectively.[29] Nonetheless, judgments based on spinal cord monitoring may have false-positives and false-negatives in predicting postoperative neurological function.[30,31] Especially, rates of the false-positives were reported as high as 50% and 59% in the 2 recent studies from Japan analyzing intraoperative motor evoked potential recordings.[30,31] Since the critical points in the neuromonitoring in predicting new postoperative deficits were different among studies and have not been established, neurosurgeons should still take responsibility for deciding the degree of surgical resection in each case.

4. Surgical Morbidity

Early and radical surgical interventions are associated with better postoperative outcomes after intramedullary tumor surgery. However, at the same time, our study indicated that surgical resection of intramedullary tumors can be challenging. Among the 1,033 patients, 414 (40.1%) experienced worsening of symptoms immediately postoperatively. An analysis based on the modified McCormick scale indicated that 234 patients (22.7%) demonstrated deterioration at discharge. Previous studies have reported consistent results for the risk of postoperative neurological deterioration, ranging from 14.8% to 38.2% (Table 8).[9,11-17,19]

Over the last century, substantial advances have been made in microsurgical techniques, including operating microscopes and intraoperative spinal cord monitoring.[30,32,33] These accomplishments have led to increased safety and effectiveness in intramedullary tumor resection. Several studies have reported that surgical results have improved over time. Klekamp[19] reviewed 278 intramedullary tumors operated on from 1990 to 2012. They divided the study periods into 3 categories: prior to 1990 (n=67), from 1991 to 2000 (n=92), and from 2001 to 2012 (n=87). In these periods, permanent morbidity occurred in 27.9%, 19.8%, and 11.9% of the patients, respectively. In a series of 164 intramedullary tumors over 15 years, Constantini et al.[10] have reported a surgical morbidity rate of 23.8%. However, in the latter half of the study period, the incidence of deterioration by more than one grade on the modified McCormick scale was 5.6%.

Importantly, our data indicate that we could expect gradual recovery and improvement of functional outcomes, despite deterioration immediately postoperatively. These findings are encouraging for surgeons and patients. Although 22.7% of the patients had worse grades immediately postoperatively, this rate improved to 17.6% at 6 months postoperatively. Klekamp[19] have reported worsening of neurological status in 61.5% of patients postoperatively. However, the deficits were transient in 41.5% of the patients. The permanent surgical morbidity rate was 19.5%. Cristante and Herrmann[17] also presented detailed information on postoperative neurological deterioration and delayed recovery in 86 cases of intramedullary tumors, including 34 ependymomas and 28 astrocytomas. Overall, postoperative functional deterioration of the upper and lower extremities was observed in 65.4% and 55.1% of patients, respectively. After a mean follow-up period of 54 months, significant neurological improvements were evident, while 31.5% and 29.4% of the patients continued to have worse upper and lower extremity function, respectively, compared to the preoperative status. Although neurological recovery could be expected over time postoperatively, intramedullary tumor resection poses a potential risk of damaging the neural circuits. The risk of surgery and the expected time course of neurological recovery presented in this study constitute important information for both surgeons and patients.

5. Limitations

This study had some limitations. First, this study was retrospective in nature, and only surgically treated cases were sampled. Therefore, we were unable to include all intramedullary spinal cord tumors treated in Japan. In particular, we could not assess the clinical course of tumors that were treated conservatively. Second, a discussion on the individual histological types of tumors was beyond the scope of this study. For example, we were unable to discuss the roles of adjuvant radiation therapy and chemotherapy in the functional outcomes and survival of malignant astrocytic tumors. Last, our study included 22 cases of intramedullary subependymomas, and we were unable to analyze the clinical characteristics of these intramedullary tumors separately. Consequently, each histological tumor subtype, including these rare lesions, will be further investigated and reported in different studies.

CONCLUSION

These are the first results of a multicenter collaborative study on surgically treated intramedullary spinal cord tumors authorized by the Neurospinal Society of Japan. The degree of resection and postoperative functional outcomes were closely related to the histology of intramedullary tumors. Early surgical interventions aimed at higher degrees of tumor resection, while the patients were functionally independent, were considered a reasonable approach. Simultaneously, the risks associated with intramedullary surgery should be reaffirmed.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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REFERENCES

1. Schellinger KA, Propp JM, Villano JL, et al. Descriptive epidemiology of primary spinal cord tumors. J Neurooncol 2008;87:173-9.
2. Duong LM, McCarthy BJ, McLendon RE, et al. Descriptive epidemiology of malignant and nonmalignant primary spinal cord, spinal meninges, and cauda equina tumors, United States, 2004-2007. Cancer 2012;118:4220-7.
3. Report of Japan Neurosurgery Registry (2015 - 2017). Neurol Med Chir (Tokyo) 2019;59(Spec):13-81.
4. Tobin MK, Geraghty JR, Engelhard HH, et al. Intramedullary spinal cord tumors: a review of current and future treatment strategies. Neurosurg Focus 2015;39:E14.
5. Juthani RG, Bilsky MH, Vogelbaum MA. Current management and treatment modalities for intramedullary spinal cord tumors. Curr Treat Options Oncol 2015;16:39.
6. McCormick PC, Torres R, Post KD, et al. Intramedullary ependymoma of the spinal cord. J Neurosurg 1990;72:523-32.
7. Harrop JS, Ganju A, Groff M, et al. Primary intramedullary tumors of the spinal cord. Spine (Phila Pa 1976) 2009;34(22 Suppl):S69-77.
8. Chamberlain MC, Tredway TL. Adult primary intradural spinal cord tumors: a review. Curr Neurol Neurosci Rep 2011;11:320-8.
9. Kumar R, Banerjee S. Management and functional outcome of intramedullary spinal cord tumors: a prospective clinical study. Asian J Neurosurg 2014;9:177-81.
10. Constantini S, Miller DC, Allen JC, et al. Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. J Neurosurg 2000;93(2 Suppl):183-93.
11. Raco A, Esposito V, Lenzi J, et al. Long-term follow-up of intramedullary spinal cord tumors: a series of 202 cases. Neurosurgery 2005;56:972-81.
12. Cooper PR, Epstein F. Radical resection of intramedullary spinal cord tumors in adults. Recent experience in 29 patients. J Neurosurg 1985;63:492-9.
13. Sandalcioglu IE, Gasser T, Asgari S, et al. Functional outcome after surgical treatment of intramedullary spinal cord tumors: experience with 78 patients. Spinal Cord 2005;43:34-41.
14. Woodworth GF, Chaichana KL, McGirt MJ, et al. Predictors of ambulatory function after surgical resection of intramedullary spinal cord tumors. Neurosurgery 2007;61:99-105; discussion 105-6.
15. Matsuyama Y, Sakai Y, Katayama Y, et al. Surgical results of intramedullary spinal cord tumor with spinal cord monitoring to guide extent of resection. J Neurosurg Spine 2009;10:404-13.
16. Boström A, Kanther NC, Grote A, et al. Management and outcome in adult intramedullary spinal cord tumours: a 20-year single institution experience. BMC Res Notes 2014;7:908.
17. Cristante L, Herrmann HD. Surgical management of intramedullary spinal cord tumors: functional outcome and sources of morbidity. Neurosurgery 1994;35:69-76.
18. Hongo H, Takai K, Komori T, et al. Intramedullary spinal cord ependymoma and astrocytoma: intraoperative frozen-section diagnosis, extent of resection, and outcomes. J Neurosurg Spine 2018;30:133-9.
19. Klekamp J. Treatment of intramedullary tumors: analysis of surgical morbidity and long-term results. J Neurosurg Spine 2013;19:12-26.
20. Karikari IO, Nimjee SM, Hodges TR, et al. Impact of tumor histology on resectability and neurological outcome in primary intramedullary spinal cord tumors: a single-center experience with 102 patients. Neurosurgery 2011;68:188-97.
21. Hoshimaru M, Koyama T, Hashimoto N, et al. Results of microsurgical treatment for intramedullary spinal cord ependymomas: analysis of 36 cases. Neurosurgery 1999;44:264-9.
22. Mehta GU, Asthagiri AR, Bakhtian KD, et al. Functional outcome after resection of spinal cord hemangioblastomas associated with von Hippel-Lindau disease. J Neurosurg Spine 2010;12:233-42.
23. Ren J, Hong T, He C, et al. Surgical approaches and long-term outcomes of intramedullary spinal cord cavernous malformations: a single-center consecutive series of 219 patients. J Neurosurg Spine 2019;31:123-32.
24. Epstein FJ, Farmer JP, Freed D. Adult intramedullary spinal

cord ependymomas: the result of surgery in 38 patients. J Neurosurg 1993;79:204-9.
25. Babu R, Karikari IO, Owens TR, et al. Spinal cord astrocytomas: a modern 20-year experience at a single institution. Spine (Phila Pa 1976) 2014;39:533-40.
26. Takami T, Naito K, Yamagata T, et al. Surgical management of spinal intramedullary tumors: radical and safe strategy for benign tumors. Neurol Med Chir (Tokyo) 2015;55:317-27.
27. Kothbauer KF. Intraoperative neurophysiologic monitoring for intramedullary spinal-cord tumor surgery. Neurophysiol Clin 2007;37:407-14.
28. Sala F, Palandri G, Basso E, et al. Motor evoked potential monitoring improves outcome after surgery for intramedullary spinal cord tumors: a historical control study. Neurosurgery 2006;58:1129-43.
29. Rijs K, Klimek M, Scheltens-de Boer M, et al. Intraoperative neuromonitoring in patients with intramedullary spinal cord tumor: a systematic review, meta-analysis, and case series. World Neurosurg 2019;125:498-510.e2.
30. Kurokawa R, Kim P, Itoki K, et al. False-positive and false-negative results of motor evoked potential monitoring during surgery for intramedullary spinal cord tumors. Oper Neurosurg (Hagerstown) 2018;14:279-87.
31. Takahashi M, Imagama S, Kobayashi K, et al. Validity of the alarm point in intraoperative neurophysiological monitoring of the spinal cord by the monitoring working group of the Japanese Society for Spine Surgery and related research: a prospective multicenter cohort study of 1934 cases. Spine (Phila Pa 1976) 2021;46:E1069-76.
32. Sciubba DM, Liang D, Kothbauer KF, et al. The evolution of intramedullary spinal cord tumor surgery 2009;65(6 Suppl):84-91; discussion 91-2.
33. Abe H. History of spinal surgery in Japan - from the pioneering period to the progressive era (1911-2017). Neurospine 2019;16:155-83.

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Impact of Surgical Timing on Neurological Outcomes for Spinal Arachnoid Cyst: A Single Institution Series

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Objective: Spinal arachnoid cysts (SACs) are rare lesions that often present with back pain and myelopathy. There is a paucity of literature evaluating the impact of surgical timing on neurological outcomes for primary SAC management. To compare long-term neurological outcomes in patients who were managed differently and to understand natural progression of SAC.
Methods: We conducted a retrospective analysis of adult patients treated for SAC at our institution from 2010 to 2021, stratified into 3 groups (conservative management only, surgical management, or conservative followed by surgical management). Study outcome measures were neurological outcomes as measured by modified McCormick Neurologic Scale (MNS), postoperative complications, and cyst recurrence. Nonparametric analysis was performed to evaluate differences between groups for selected endpoints.
Results: Thirty-six patients with SAC were identified. Eighteen patients were managed surgically. The remaining 18 patients were managed conservatively with outpatient serial imaging, 7 of whom (38.9%) ultimately underwent surgical treatment due to neurological decline. Most common presenting symptoms included back pain (50.0%), extremity weakness (36.1%), and numbness/paresthesia (36.1%). Initial/preoperative ($p = 0.017$) and 1-year postoperative ($p = 0.006$) MNS were significantly different between the 3 groups, but not at 6 weeks or 6 months postoperatively ($p > 0.05$). Additionally, at 1 year, there was no difference in MNS between patients managed surgically and those managed conservatively but ultimately underwent surgery ($p > 0.99$).
Conclusion: Delayed surgical intervention in minimally symptomatic patients does not seem to result in worse long-term neurofunctional outcomes. At 1 year, postoperative MNS were significantly higher in both surgical groups, when compared to the conservative group highlighting worsening clinical picture regardless of preoperative observational status.

Keywords: Spinal arachnoid cyst, Microsurgical resection, McCormick Neurologic Scale, Functional outcome, Case series

INTRODUCTION

Spinal arachnoid cysts (SACs) are rare lesions that often present with back pain and myelopathy.[1-4] The majority of these cysts are thoracic in nature and are more common in men with a peak incidence in the second decade of life.[1-3,5,6] SAC are classified into 3 subtypes. Type 1 cysts are extradural (EACs) without nerve root involvement, type 2 cysts are EACs with nerve root involvement, and type III cysts are intradural meningeal cysts.[7] While the etiology of SAC is unclear, they are generally thought

to arise due to congenital defects such as vertebral anomalies, neural tube defects, and syringomyelia.[5] Secondary causes of cyst formation such as infection, trauma and surgical procedures including lumbar myelography and laminectomy have been reported, but are less common.[1,2,5,8-10] The mechanism of cyst formation is poorly understood and multiple theories have been proposed including osmotic gradients resulting in fluid shifts, and active fluid secretion from the cyst itself.[3,5] Additionally, inflammatory adhesions of the arachnoid layer are known to form arachnoid webs.[11] Such arachnoid granulations have been postulated to create a one-way valve mechanism entrapping circulating cerebrospinal fluid (CSF), ultimately leading to the formation of SAC.[12,13]

The current dogma for management of SAC is to treat symptomatic patients with surgery and to use observational management for asymptomatic patients or those with minimal symptoms.[1,2,4,5] Surgical management includes exploration and decompression through cyst excision, marsupialization, fenestration, shunting or a combination of these techniques.[2,4,14] Whether an observational method of treatment is the optimal therapy or potentially harmful for minimally symptomatic cases remains unknown as the natural progression of this rare pathology is understudied. Moreover, there is a paucity of literature pertaining to the long-term outcomes of patients who are managed conservatively first, but ultimately undergo surgery following neurological decline. It is unclear whether this group benefits from a period of surveillance and whether their long-term neurological outcome is different when compared to patients who undergo surgery at symptom presentation. The aim of this study is to compare long-term neurological outcomes in patients with SAC who were managed both conservatively and surgically, including a subset of patients who were managed conservatively first but ultimately underwent surgery secondary to neurological demise. This case series aims bring a better understanding of the natural course of SAC with a focus on long-term neurological outcomes.

MATERIALS AND METHODS

1. Study Design/Eligibility Criteria

We conducted a single-institution retrospective review of all adult patients (>18 years) with SAC over a 10-year period from January 2010 to August 2020. Data was collected via medical record review. Formal radiological reports were individually reviewed by 3 study authors (KS, SS, RW) and all patients with other cystic disorders of the spine including syrinx and hydromyelia were excluded. Demographics variables and clinical presentation including presenting symptoms, examination findings, and duration of symptoms were extracted. Patients were stratified into 3 groups based on their treatment: conservative

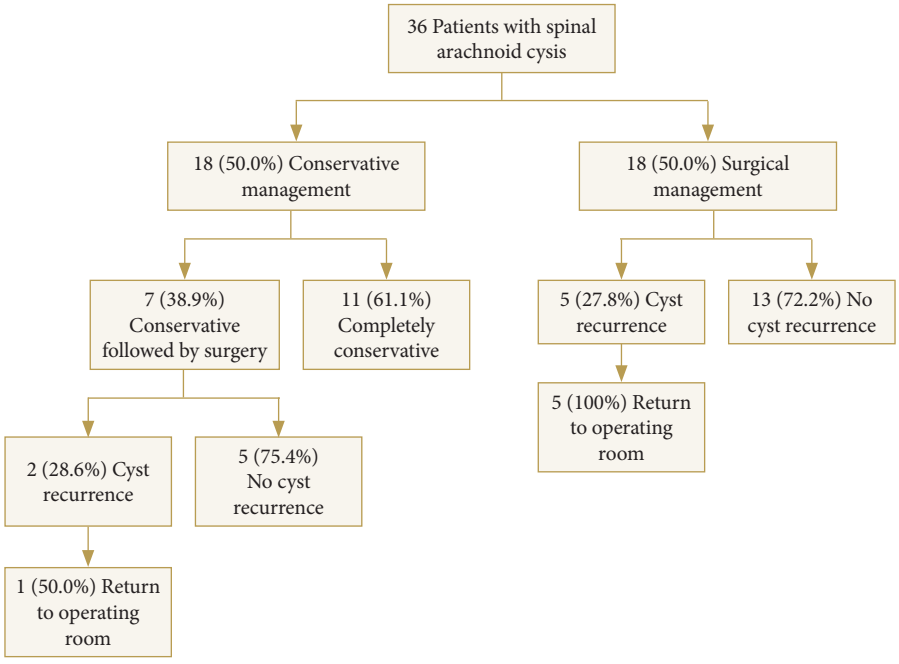

Fig. 1. Flow diagram illustrating the different treatment avenues for patients with spinal arachnoid cysts. Rates of cyst recurrence and return to the operating room are included.

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management only (i.e., "conservative-only"), surgery at presentation (i.e., "initial-surgery"), and conservative management followed by surgery due to symptomatic progression (i.e., "conservative+surgery") (Fig. 1). For patients who underwent surgical management, operative reports were reviewed to confirm surgical technique and other relevant intraoperative findings. Histopathologic reports of resected tissue were also evaluated to confirm SAC diagnosis. The study was evaluated by the independent Colorado Multiple Institutional Review Board (IRB) and found to be exempt from IRB review (No. 20-2783). Patient consent was not required.

2. Surgical Protocol

Surgical candidacy in both the conservative and nonconservative cohorts were determined by both imaging findings and severity of clinical symptoms at the discretion of the attending neurosurgeon (Fig. 2). In all surgical cases, the cyst was exposed via a posterior approach using laminectomies spanning the length of the lesion and tailored to patient's individual anatomy. For intradural cysts, ultrasound (US) imaging was used in most patients prior to the durotomy. Midline dural openings were performed followed by tack-up sutures to achieve satisfactory exposure (Fig. 3A). The cyst wall was carefully dissected away from the surrounding dura and spinal cord using blunt dissection (Fig. 3B). In most cases, the cyst wall was thickened and milky white allowing for clear identification. Meticulous surgical technique ensured that the cyst was visualized in its entirety. Patients either underwent complete cyst resection when able, marsupialization and/or fenestration at time of operation. In cases of extradural cysts, surgical exploration for a transdural conduit connecting the cyst and the subarachnoid space was carried out. When such communication was identified, it was ligated intraoperatively. Tissue specimens obtained from surgery were formalin fixed and stained with hematoxylin and eosin for pathological analysis.

3. Outcomes

The primary endpoint was neurologic functional status as determined by the modified McCormick Neurologic Scale (MNS) postoperatively at 6-week, 6-month, and 1-year. MNS values

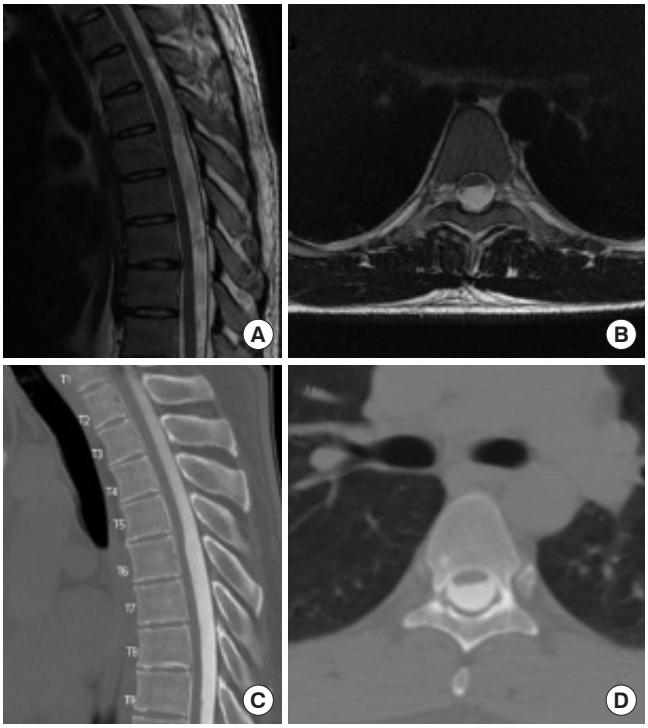

Fig. 2. Case of a 26-year-old male who presented with a 2-year history of midback pain with no other symptoms. Sagittal (A) and axial (B) T2-weighted magnetic resonance images demonstrate ventral displacements of thoracic spinal cord. Sagittal (C) and axial (D) images of computed tomography myelogram revealed flattening of spinal cord greatest at the T6 level. Surgical exploration revealed intradural dorsal arachnoid cyst which was resected.

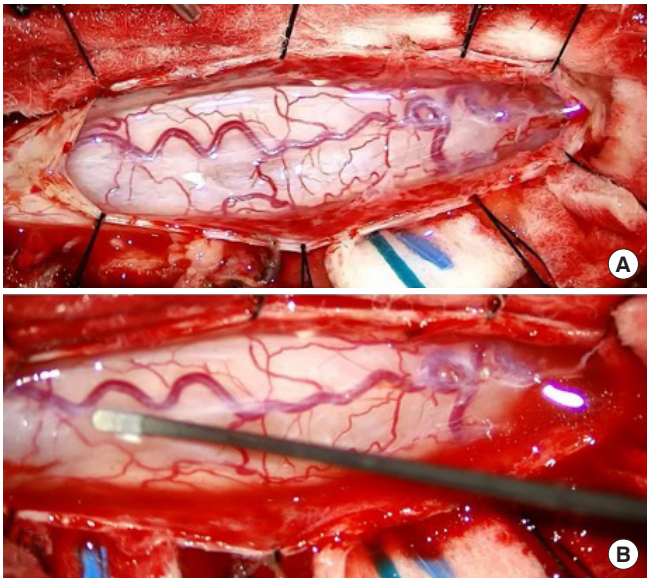

Fig. 3. Intraoperative pictures showing surgical exploration of intradural arachnoid cyst. (A) A midline dural opening followed by tack-up sutures were performed to achieve satisfactory exposure. In most cases, the cyst wall is thickened and is milky white allowing it clear identification. (B) Cyst wall is then carefully dissected away from the surrounding dura and spinal cord using blunt dissection. Meticulous surgical technique ensures that the cyst is visualized in its entirety.

were independently confirmed by 2 authors (KS, SS) who were blinded to preoperative MNS. MNS was analyzed as a discrete variable counted 1–5 and, categorically with a value of 3 (neurofunctional independence) as the cutoff point for qualitative comparisons. Additionally, classification of treatment strategies (conservative management only, initial surgical treatment, and conservative followed by surgery), cyst recurrence, and the use of preoperative imaging and intraoperative US were also of particular interest.

4. Statistical Analysis

Data analysis and storage were performed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). Descriptive data are reported as simple means or proportions with standard deviations where applicable. For categorical variables, contingency tables were constructed and then analyzed using the chi-square test or Fisher exact test for counts less than 5. To query the difference in MNS between the 3 groups (conservative-only, initial-surgery, and conservative followed by surgery,), a nonparametric one-way analysis of variance on ranks Kruskal-Wallis test was conducted at initial/preoperative evaluation and at 6 weeks, 6 months and 1 year postoperatively along with Dunn multiple comparisons. Three- and 5-year data were too scarce for adequate comparison. A p-value of 0.05 determined significance.

RESULTS

1. Cohort Demographics and Characteristics

In total, 36 patients with SAC were identified. The average age at diagnosis was 49.4 ± 16.7 years (range, 22–81 years) and 20 (55.6%) were female and 16 (44.4%) were male (Table 1). Most cysts were thoracic (61.1%) followed by lumbar (13.9%), sacral (8.3%), cervical (5.6%), thoracolumbar (5.6%), and lumbar-sacral (5.6%) in nature (Fig. 4). Eighteen patients (50.0%) were managed surgically (initial-surgery) whilst the remaining 18 patients (50.0%) were managed conservatively with serial imaging and outpatient follow-up. Seven patients (38.9%) in the conservative group eventually underwent surgery secondary to neurological decline (conservative+surgery group) (Fig. 1) with an average preoperative observational period of 38.04 months (range, 2.17–171.57 months) (Table 1).

The most common initial symptoms in both cohorts included back pain (50.0%), extremity weakness (36.1%), extremity

Table 1. Patient demographics between groups included in this series

Variable	All patients	Initial-surgery	Conservative-only	Conservative followed by surgery
No. of patients	36	18 (50.0)	11 (30.6)	7 (19.4)
Sex				
Male	16 (44.4)	8 (44.4)	5 (45.5)	3 (42.9)
Female	20 (55.6)	10 (55.6)	6 (54.5)	4 (57.1)
Age at diagnosis (yr)				
Mean ± SD	49.4 ± 16.7	51.4 ± 16.3	47.2 ± 20.0	47.7 ± 13.7
Range	22–81	24–79	22–81	26–64
Location				
Intradural	29 (80.6)	17 (58.6)	6 (20.7)	6 (20.7)
Extradural	7 (19.4)	1 (14.3)	5 (71.4)	1 (14.3)
Duration of symptoms (mo)†				
Mean ± SD	30.35 ± 38.02	13.64 ± 23.63	55.04 ± 27.58	38.04 ± 56.28
Range	1.14–171.57	1.14–79.43	14.77–89.94	2.17–171.57
Preoperative MNS	2.26 ± 0.95	2.67 ± 1.03	1.60 ± 0.70	2.14 ± 0.38
Postoperative MNS at 1 year	2.46 ± 1.32	2.75 ± 1.14	1.17 ± 0.41	2.80 ± 1.30
Length of stay (day)	6.10 ± 4.44	5.82 ± 4.98	N/A	6.58 ± 3.10

Values are presented as number (%) unless otherwise indicated.
SD, standard deviation; MNS, McCormick Neurologic Scale.
†Duration of symptoms calculated as the difference between the date of diagnosis (via imaging) and the date of most recent surgery or present time for patients managed conservatively.

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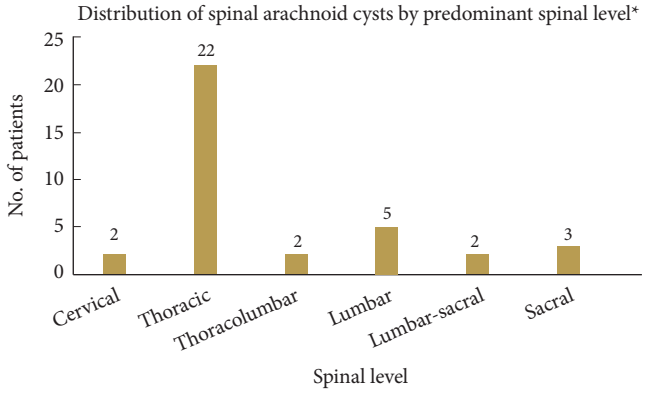

Fig. 4. Spinal arachnoid cyst distribution by predominant spinal level. Thoracic was the most common spinal arachnoid cyst level followed by lumbar, sacral, cervical/thoracolumbar, and lumbar-sacral. *In patients with cysts which spanned multiple levels, spinal level predominance was determined by the number of vertebral levels involved. If patients had cysts that equally involved 2 levels, they were classified as either thoracolumbar or lumbar-sacral predominant.

numbness (36.1%), and extremity pain (33.4%). Less common symptoms included bladder and bowel dysfunction (22.2% and 8.4%, respectively), allodynia (11.1%), difficulties with coordination (8.4%), and truncal numbness (5.6%). Duration of symptoms varied between cohorts with the conservative group having the greatest symptom duration (55.0 ± 27.6 months), followed by the conservative followed by surgery group (38.0 ± 56.3 months), and surgical group (13.6 ± 23.6 months) (Table 1).

Twenty-nine patients (80.6%) had intradural cysts. Seven patients (19.4%) had extradural cysts, 5 of which were managed completely conservatively and diagnosed via imaging. Two patients with extradural cysts were managed surgically and were found to have transdural conduits connecting the cyst to the subarachnoid space intraoperatively (Table 1).

2. Neurological Outcomes

Mean preoperative/initial examination MNS was highest for the initial-surgery group (2.67 ± 1.03), followed by the conserva-

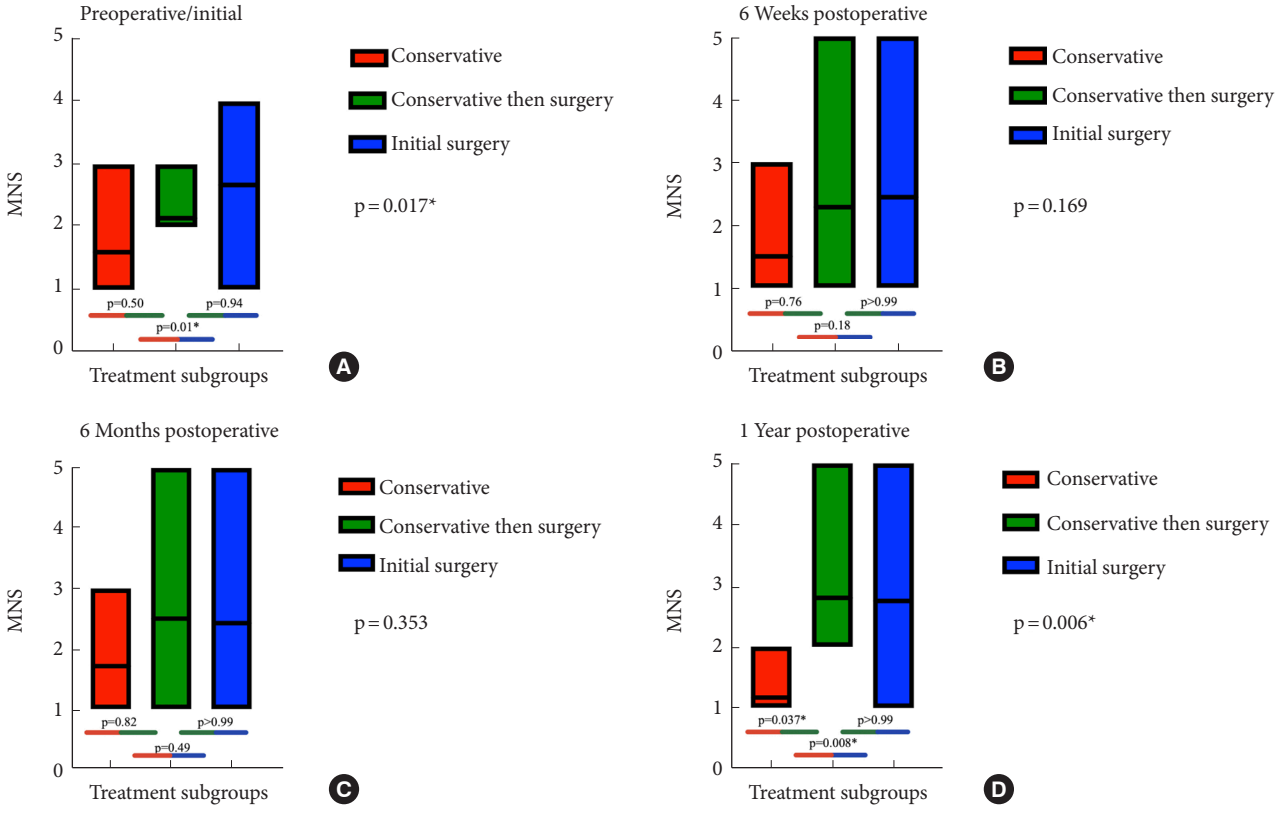

Fig. 5. Box plot showing average preoperative/initial and postoperative McCormick Neurologic Scale (MNS) scores at 6 weeks, 6 months, and 1 year. Red color represents the group of patients who were managed solely conservatively. The green represents the group of patients who were initially managed conservatively but who ultimately underwent surgical management secondary to neurological decline. The blue represents the group of patients who underwent surgery at symptoms presentation. *$p < 0.05$, statistically significant differences.

Table 2. Results of literature review

Study	No of patients	Female sex (%)	Mean age (yr)	Presenting symptoms (% pts)	Diagnostic imaging	Spinal level	Location	Treatment type (% pts)	Mean follow-up (mo)	Outcome % pts
Fam et al.,[2] 2018	16	75%	57	Pain (63%), falls (31%), paresthesia (6%), weakness (44%), gait ataxia (50%), sphincter dysfunction (25%)	MRI, CT myelogram (n=5)	10 Dorsal thoracic, 2 ventral thoracic, 1 ventral cervical, 1 dorsal lumbar, 1 ventral lumbar	Intradural (n=11, 50%), extradural (n=6, 27%) ventral spinal cord herniation (n=2, 9%)	Total cyst excision (79%), fenestration/marsupialization (14%), fenestration & ligation (8%)	8.2	Complete radiographic resolution in 14 of 16 patients, improved patient reported outcomes (SF-36 parameters) across all quality-of-life parameters
Sadek et al.,[3] 2019	17	35.3%	58	Paresthesia (76%), neuropathic pain (76%), weakness (47%), unsteadiness (53%)	MRI with CSF flow studies	17 Thoracic	Intradural (n=17, 100%)	Marsupialization	17	All patients experienced improvement in at least one of their presenting symptoms and or clinical signs
Eroglu et al.,[1] 2018	13	62%	42	Pain (80%), sensory changes (70%), extremity weakness (62%), gait disturbance (15%), bowel/bladder dysfunction (23%)	CT, MRI, CSF flow analysis	2 Cervical, 7 thoracic, 4 lumbar	Intradural (n=7, 54%), extradural (n=5, 38%)	Total cyst excision (38%), f enestration (54%)	55	Most patients with improvement or complete resolution of symptoms
Viswanathan et al.,[20] 2017	14	35.7%	52.1	Myelopathy with combination of extremity weakness (78.6%), gait disturbance (100%), paresthesias (85.7%), urinary incontinence (28.6%), upper motor neuron signs (71.4%)	MRI	1 Cervicothoracic, 12 thoracic, 1 thoracolumbar	Intradural (n=14, 100%)	Cyst fenestration and partial wall resection	22	Stable or improved neurologic symptoms in all patients starting at 6-week postoperative follow-up
Moses et al.,[21] 2018	21	42.9%	55.1	Weakness (67%), sensory disturbances (67%), pain (57%), gait changes (52%), bowel and/or bladder dysfunction (24%)	MRI, CT Myelogram (n=12)	15 Thoracic, 4 cervicothoracic, 2 lumbosacral	Intradural (n=21, 100%)	Laminectomy (86%), laminoplasty (14.3%), duraplasty (38%)	18	60%–70% of patients experienced postoperative improvement in symptoms. Those who underwent duroplasty were more likely to have relief of pain symptoms.
Schmutzer et al.,[4] 2020	72	66.7%	53.1	Gait disturbance (80%), dysesthesia (64%), paresis (80%)	MRI, myelography (n=17)	10 Cervical, 45 thoracic, 17 lumbosacral	Intradural (n=72, 100%)	Complete resection (25%), fenestration (66.7%), cystoperitoneal shunt (5.5%), marsupialization (2.8%)	44.8	For cysts without internal septations, both fenestration and resection resulted in significant clinical improvement and reduction in cyst size.
Garg et al.,[22] 2017	11	26.4%	32.9	Weakness (73%), pain (64%), quadriparesis (11%)	MRI	9 Thoracic	Intradural (n=1, 9%), extradural (n=10, 91%)	Cyst excision (82%), marsupialization (9%), fenestration (9%)	56.4	Complete resolution of symptoms in 2 patients and substantial improvement in 5.

(*continued*)

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Table 2. Results of literature review (continued)

Study	No of patients	Female sex (%)	Mean age (yr)	Presenting symptoms (% pts)	Diagnostic imaging	Spinal level	Location	Treatment type (% pts)	Mean follow-up (mo)	Outcome % pts
French et al.,[23] 2017	10	75%	57	Gait ataxia (90%), lower limb sensory disturbance (60%), radicular pain (30%), lower limb weakness (10%), urinary incontinence (10%), sphincter disturbance (10%), thoracic back pain (10%)	MRI (bSSFP MRI in 3 patients)	10 Thoracic	Intradural (n = 10, 100%)	Cyst excision (40%), fenestration (60%)	4.4	The majority of patients experienced resolution of pain and improvement in neurologic function. However, recovery of gait ataxia and myelopathy were less consistent.
Shi et al.,[6] 2021	41	59%	41.1	Lumbar back pain (85.4%), radicular lower limb pain (46.3%), buttock and perineum pain (4.8%)	MRI+CT	12 Thoracic, 26 thoracolumbar, 3 lumbar	Extradural (n = 41, 100%)	Cyst excision (95%), dural defect repairs (88%)	52.3	The majority of patients had positive outcomes according to Odom's criteria.
Cai et al.,[24] 2021	34	44%	45	Back pain (53%), sensory deficits (41%), weakness (12%), gait ataxia (12%)	MRI	4 Cervical, 6 thoracic, 10 thoracolumbar, 14 lumbar	Extradural (n = 34, 100%)	Laminoplasty (71%), laminectomy with pedicle screw fixation (29%), fistula ligation 68%)	80	Improvement in patients' symptoms and complete resections achieved confirmed with imaging.

pts, patients; MRI, magnetic resonance imaging; CT, computed tomography; SF-36, 36-item Short Form health survey; CSF, cerebrospinal fluid; bSSFP, balanced steady-state free precession.

tive+surgery (2.14 ± 0.38) and the conservative-only (1.60 ± 0.70) groups, which was significantly different on analysis of variance (p = 0.017) (Fig. 5A). For multiple comparisons, mean preoperative/initial MNS was significantly lower in the conservative-only group compared to the initial-surgery group (p = 0.01). No significant differences in preoperative/initial MNS were found between the conservative-only and conservative+surgery groups (p = 0.50) or between the initial-surgery and conservative+surgery groups (p = 0.94).

At 6 weeks postoperatively, mean MNS was 1.50 ± 0.84 for the conservative-only group, 2.29 ± 1.50 for the conservative+surgery group, and 2.44 ± 1.10 for the initial-surgery group, which was not significant on analysis of variance between the 3 groups (p = 0.17) (Fig. 5B). When looking at multiple comparisons, no significant differences in MNS were found between the conservative-only and initial-surgery groups (p = 0.18) suggesting improvement in neurological status. Similarly, no differences were noted between the conservative-only and conservative+surgery groups (p = 0.76) or when comparing patients in the surgery versus the conservative+surgery groups (p > 0.99).

At 6 months postoperatively, mean MNS was 1.71 ± 0.95 for the conservative-only group, 2.50 ± 1.52 for the conservative+surgery group, and 2.43 ± 1.09 for the initial-surgery group, which was not significant on analysis of variance between the 3 groups (p = 0.35) (Fig. 5C). For multiple comparisons, there were no significant differences in MNS found between the conservative-only and initial-surgery groups (p = 0.49). Likewise, no significant differences were found between the conservative-only and conservative + surgery groups (p = 0.82) or when comparing the initial-surgery and the conservative + surgery groups (p > 0.99).

At 1 year postoperatively, mean MNS was 1.17 ± 0.41 for the conservative-only group, 2.80 ± 1.30 for the conservative+surgery group, and 2.75 ± 1.14 for the initial-surgery group, which was significantly different on analysis of variance between the 3 groups (p = 0.006) (Fig. 5D). Significant differences for multiple comparisons were observed in postoperative MNS scores when comparing both the conservative-only and initial-surgery groups (p = 0.008) and conservative-only and conservative+surgery groups (p = 0.037) indicating worsening neurological outcome. No significant differences were observed between the initial-surgery and conservative+surgery groups (p > 0.99).

3. Imaging Modalities

Preoperative computed tomography (CT) myelogram was obtained in 13 of 25 patients (52.0%), 7 of whom also had an MRI performed. Postoperative cyst recurrence rates were not

significantly different in patients who underwent preoperative MRI alone versus MRI+CT myelogram ($p > 0.99$). Similarly, the use of intraoperative US did not significantly decrease postoperative cyst recurrence rates ($p = 0.73$).

4. Surgical Treatment

Out of the 25 patients who underwent surgical intervention, 12 were treated with complete cyst resection and 13 were treated with fenestration, marsupialization, or shunting. Rates of cyst recurrence were similar between these 2 surgical groups ($p = 0.57$).

5. Postoperative Complications

Of 38 surgeries completed for 25 patients, complications ranged from spinal cord tethering (10.5%), postoperative infection (7.9%), CSF leak (7.9%), new or worsening neurological deficit (7.9%), and arachnoiditis (5.3%). In the initial-surgery cohort, 5 patients (27.78%) experienced cyst recurrence and returned to the operating room (OR) for further management of their arachnoid cysts (mean return to OR lead-time of 455.5 days). One patient returned to the OR 5 times due to multiple episodes of cyst recurrence. In the conservative followed by surgery cohort, 2 patients (28.6%) experienced cyst recurrence; 1 patient (50.0%) returned to the OR 5 separate times for cyst recurrence (mean return to OR lead-time of 230.2 days) (Fig. 1).

DISCUSSION

1. Treatment and Long-term Neurological Outcomes

Management of SACs is challenging as their natural history and pathophysiologic progression remains unclear. Although there are no guidelines for SAC treatment, it is accepted that if a patient develops neurological symptoms due to spinal cord compression, surgical intervention is most likely necessary. A comprehensive summary of the current literature is provided (Table 2). As anticipated, patients in the conservative group had significantly lower MNS scores when compared to patients who underwent surgery at presentation (Fig. 5A). This was not the case for the conservative+surgery groups as their initial/preoperative MNS scores were similar to the conservative group (Fig. 5A).

It is hypothesized that postoperative functional outcomes often depend on multiple factors such as preoperative neurological status, cyst size, and duration of symptoms.[15] Because of these factors, the potential benefits of surgical intervention must be weighed against the possibility of poor surgical outcomes and potential for complications. Interestingly, nearly 40% of patients who were initially managed conservatively ultimately underwent surgical intervention secondary to neurological decline. For patients who present with minimal symptoms and radiographical evidence of arachnoid cyst, it remains debatable whether a period of observation can be theoretically harmful if the SAC were to enlarge and/or patient's symptoms worsen significantly. When assessing their long-term neurological outcomes, at one year, there was no difference in McCormick scores between patients who were managed surgically and those who were initially managed conservatively and then ultimately underwent surgery (Fig. 5D). Based on this data, it does not seem that delayed surgical intervention in minimally symptomatic patients results in worse neurofunctional outcomes compared to patients who are initially treated surgically (Fig. 5B–D). Even-though a large proportion of our patients who were managed observationally eventually underwent surgical intervention with an average preoperative observational period of 38.04 months, it seems that an initial observation period for patients who are clinically stable remains beneficial. Specifically, if a patient has minimal symptoms or symptoms that are unlikely to be relieved by surgical intervention, conservative management of the arachnoid cyst in the form of serial imaging and monitoring of symptom progression should be considered. Although this may seem intuitive, exact comparison between surgical groups (initial-surgery vs. conservative+surgery) and their respective neurological outcomes in patients with SAC had not been published.

At 1 year, postoperative MNS were noted to be significantly higher in both surgical groups, when compared to the conservative group, a trend that was not observed at their 6-week or 6-month follow-up (Fig. 5B–D). This data highlights the potential long-term worsening neurological symptoms of patients who undergo surgical intervention regardless of preoperative observational status. We hypothesize that this worsening in neurological function can be attributed to more severe disease and natural progression of the cyst itself compared to patients with less severe disease who were managed completely conservatively.

2. Radiological Diagnosis

MRI is considered the gold standard diagnostic tool with a high sensitivity and specificity for correctly diagnosing CSF containing lesions and its ability to demonstrate anatomical location, relationship between the spinal cord and arachnoid cyst, and cyst laterality which has been shown to correlate with fistula level in extradural SAC.[2,3,16] The scalpel sign is often mentioned as a useful radiographical manifestation of the abrupt buckling of the spinal cord most commonly seen with SAC.[17] MRI can

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also demonstrate intrinsic cord signal which may be helpful in predicting neurological outcome. Additional imaging modalities, such as the more invasive CT myelogram, are useful tools which allow for identification of communicating tracts between the cyst wall and the main subarachnoid space. However, cyst communication may be missed on myelogram due to factors such as patient positioning in relation to CSF flow dynamics and variable location of communicating tracts.[18] Literature is lacking on whether CT myelogram confers additional clinical benefits in treatment of patients. Our data suggests that postoperative cyst recurrence rates were similar in patients who underwent preoperative MRI alone versus MRI+CT myelogram ($p > 0.99$). CT myelogram should therefore be reserved for those with inconclusive MRI findings as its usefulness as an adjunct tool from a surgical outcome perspective remains questionable.

Intraoperative US is an increasingly popular and useful tool that has been shown to reduce spinal incision length, laminectomy levels, and positively change intraoperative course. In a previous study by Harel and Knoller[19] intraoperative US changed the surgical course in 49 out of 78 cases (63%) without any related complications. In the present study, intraoperative US was utilized in 57% of cases to help identify cyst location prior to dural opening and to confirm the extent of cyst resection. While intraoperative US has been shown to have benefits, our data suggests that the use of intraoperative US does not seem to have an influence on cyst recurrence rates in patients who underwent intraoperative US versus those who did not.

3. Limitations

Our study has limitations. Its retrospective nature likely led to sampling and design biases. Additionally, although MNS is a validated measure to assess neurofunctional status, it requires a subjective investigator determination, risking selection, confirmation, measurement, and historical bias. This study was also limited by its small sample size, homogenous patient population, and single institution nature.

CONCLUSION

Although a significant proportion of patients who were initially managed conservatively ultimately underwent surgery secondary to symptom progression and/or neurological decline, delayed surgical intervention in minimally symptomatic patients does not seem to result in worse long-term neurofunctional outcomes. At 1 year, postoperative MNS were noted to be significantly higher in both surgical groups, when compared to the conservative group. This data highlights the potential long-term worsening neurological symptoms of patients who undergo surgical intervention regardless of preoperative observational status. Treatment of SACs remains controversial and dependent on surgical attending preference as the natural history of SAC progression is still poorly defined.

NOTES

Conflict of Interest: Michael Finn is a consultant for K2M/Stryker. The other authors have nothing to disclose.

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REFERENCES

1. Eroglu U, Bozkurt M, Kahilogullari G, et al. Surgical management of spinal arachnoid cysts in adults. World Neurosurg 2019;122:e1146-52.
2. Fam MD, Woodroffe RW, Helland L, et al. Spinal arachnoid cysts in adults: diagnosis and management. A single-center experience. J Neurosurg Spine 2018;29:711-9.
3. Sadek AR, Nader-Sepahi A. Spinal arachnoid cysts: presentation, management and pathophysiology. Clin Neurol Neurosurg 2019;180:87-96.
4. Schmutzer M, Tonn JC, Zausinger S. Spinal intradural extramedullary arachnoid cysts in adults-operative therapy and clinical outcome. Acta Neurochir (Wien) 2020;162:691-702.

5. McNutt SE, Mrowczynski OD, Lane J, et al. Congenital spinal cysts: an update and review of the literature. World Neurosurg 2021;145:480-91.e9.
6. Shi L, Su Y, Yan T, et al. Early microsurgery on thoracolumbar spinal extradural arachnoid cysts: Analysis of a series of 41 patients. J Clin Neurosci 2021;94:257-65.
7. Nabors MW, Pait TG, Byrd EB, et al. Updated assessment and current classification of spinal meningeal cysts. J Neurosurg 1988;68:366-77.
8. Wang MY, Levi ADO, Green BA. Intradural spinal arachnoid cysts in adults. Surg Neurol 2003;60:49-55.
9. Nath PC, Mishra SS, Deo RC, et al. Intradural spinal arachnoid cyst: a long-term postlaminectomy complication: a case report and review of the literature. World Neurosurg 2016;85:367.e1-4.
10. Kriss TC, Kriss VM. Symptomatic spinal intradural arachnoid cyst development after lumbar myelography. Case report and review of the literature. Spine (Phila Pa 1976) 1997; 22:568-72.
11. Paramore CG. Dorsal arachnoid web with spinal cord compression: variant of an arachnoid cyst? Report of two cases. J Neurosurg 2000;93(2 Suppl):287-90.
12. Rohrer DC, Burchiel KJ, Gruber DP. Intraspinal extradural meningeal cyst demonstrating ball-valve mechanism of formation. Case report. J Neurosurg 1993;78:122-5.
13. Morizane K, Fujibayashi S, Otsuki B, et al. Clinical and radiological features of spinal extradural arachnoid cysts: valve-like mechanism involving the nerve root fiber as a possible cause of cyst expansion. J Orthop Sci 2018;23:464-9.
14. Baig Mirza A, Bartram J, Vastani A, et al. Systematic review of surgical management of spinal intradural arachnoid cysts. World Neurosurg October 2021 Oct 30;S1878-8750(21)01683-1. https://doi.org/10.1016/j.wneu.2021.10.173. [Epub].
15. Maenhoudt W, Rasschaert R, Bontinck H, et al. Postarachnoiditis anterior spinal arachnoid cyst formation with compressive myelopathy: report of 2 cases. World Neurosurg 2018;118:59-62.
16. Jian Q, Song G, Liu Z, et al. Location distribution of fistulas and surgical strategies for spinal extradural meningeal cysts: a retrospective analysis of 30 cases at a single center. Neurospine 2022;19:188-201.
17. Reardon MA, Raghavan P, Carpenter-Bailey K, et al. Dorsal thoracic arachnoid web and the "scalpel sign": a distinct clinical-radiologic entity. AJNR Am J Neuroradiol 2013;34:1104-10.
18. Kulkarni AG, Goel A, Thiruppathy SP, et al. Extradural arachnoid cysts: a study of seven cases. Br J Neurosurg 2004;18:484-8.
19. Harel R, Knoller N. Intraoperative spine ultrasound: application and benefits. Eur Spine J 2016;25:865-9.
20. Viswanathan VK, Manoharan SR, Do H, et al. Clinical and radiologic outcomes after fenestration and partial wall excision of idiopathic intradural spinal arachnoid cysts presenting with myelopathy. World Neurosurg 2017;105:213-22.
21. Moses ZB, Friedman GN, Penn DL, et al. Intradural spinal arachnoid cyst resection: implications of duraplasty in a large case series. J Neurosurg Spine 2018;28:548-54.
22. Garg K, Borkar SA, Kale SS, et al. Spinal arachnoid cysts - our experience and review of literature. Br J Neurosurg 2017; 31:172-8.
23. French H, Somasundaram A, Biggs M, et al. Idiopathic intradural dorsal thoracic arachnoid cysts: A case series and review of the literature. J Clin Neurosci 2017;40:147-52.
24. Cai Z, Hong X, Huang J, et al. Microsurgical treatment of symptomatic spinal extradural arachnoid cyst: a consecutive case series of 34 patients and literature review. Clin Neurol Neurosurg 2021;210:107000.

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Original Article

Odontoid Incidence: A Novel Cervical Parameter Influencing Cervical Alignment From Top to Bottom

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Objective: By using angulation of the axis itself, this study aims to define and analyze odontoid incidence (OI) and odontoid tilt (OT) as novel cervical alignment parameters and investigate their correlations with cervical alignment.
Methods: Novel and existing parameters were measured with whole-spine lateral plain radiographs and EOS images of 42 adults without cervical symptoms. The correlations of OI, OT, C2 slope (C2S), and T1 slope (T1S) were calculated.
Results: The OI, OT, and C2S showed significant correlations with C2–7 angle ($r = 0.43$, $r = -0.42$, $r = 0.62$, respectively) and C0–2 angle ($r = -0.33$, $r = 0.48$, $r = -0.61$, respectively). OI, OT, T1S were independent predictors of the C2–7 angle in univariate regression analysis (adjusted-$R^2 = 0.17$, $R^2 = 0.15$, $R^2 = 0.28$, respectively). OI, OT, and T1S were independent predictors in the multivariable regression analysis with estimated standardized coefficients of 0.36, -0.67, -0.69, respectively (adjusted- $R^2 = 0.80$, $p < 0.001$). Regarding the C0–2 angle, OI and OT were independent predictors in the univariate regression analysis (adjusted-$R^2 = 0.08$, $R^2 = 0.21$, respectively).
Conclusion: OI, OT, and C2S had significant correlations with cervical alignment. As the pelvic incidence, the OI is the only anatomical and constant parameter that could be used as a reference point related to the cervical spine from the rostral end. The study results may serve as baseline data for further studies on the alignment and balance of the cervical spine.

Keywords: Cervical spine, Parameter, Odontoid, Lordosis, C2 slope, Sagittal alignment, T1 slope

INTRODUCTION

The cervical spine is dynamic in nature. Recent investigations have shown that the cervical alignment is affected by global sagittal alignment through compensatory mechanisms that maintain an upright posture and horizontal gaze.[1-5] Accordingly, the cervical parameters currently used are mostly positional variables, not constant parameters.[6,7]

The compensatory mechanisms within the cervical spine are well established and have been proven by numerous studies. Kyphotic alignment of the subaxial cervical spine (C2–7) is compensated by a lordotic upper cervical spine (C0–2) and *vice versa*.[6,8-10] The C2 endplate (C2EP) is the border dividing the subaxial and upper cervical spine. It has long been speculated that the morphology of the odontoid process is somehow related to the sagittal alignment of the cervical spine.[11-13] However, no studies have been able to show a significant correlation.[11,12] On the basis of these studies, we postulated that the axis (C2 vertebra) acts as the base of the subaxial and upper cervical spine, and physiological sagittal alignment is based on its orientation and structural geometry.

A novel cervical parameter termed odontoid incidence (OI), which is a constant parameter, is proposed in this study as a critical factor regulating the sagittal alignment of the cervical spine. To the best of our knowledge, no studies have reported correlations between the structural geometry of the C2EP, the odon-

toid process, and the sagittal alignment of the cervical spine. The study aimed to analyze the relationship between the structural geometry of the odontoid process and the sagittal alignment of the cervical spine and to present these parameters from a different perspective that would aid in predicting physiological cervical lordosis (CL) in asymptomatic populations.

MATERIALS AND METHODS

1. Materials

A retrospective analysis of clinical and radiographic data was performed after obtaining Institutional Review Board approval of Seoul National University Bundang Hospital, Seoul National University College of Medicine for the study (B-2111-723-102). From 2016 to 2020, 42 asymptomatic subjects (aged between 15 and 68 years old) without cervical symptoms including neck pain or radiculopathy were enrolled. Subjects were asymptomatic spinal subjects whom underwent spinal work up during a comprehensive health screening. We excluded individuals with diagnosed conditions, degenerative changes including decreased disc height or osteophyte formation, and treatment related to the cervical spine; a history of spinal surgery; and abnormal global sagittal alignment. Whole-spine lateral plain radiographs and EOS images were obtained with the subject in a comfortable upright position and an acceptable range of chin-brow vertical angle between -1.5° and 5.8°.[14] The scan was performed in a relaxed posture and the subjects were asked to look straight ahead.

2. Analysis of Radiographic Images

1) Odontoid parameters

OI was defined as the angle between the line perpendicular to the C2EP at its midpoint and the line connecting this point to the center of the odontoid process (the center of a circle with an anterior/posterior border and the apex of the dens as a tangent). Odontoid tilt (OT) was defined as the angle created by a line running from the C2EP midpoint to the center of the odontoid process and the vertical axis. C2 slope (C2S) was defined as the angle between the C2EP and a horizontal line (Fig. 1A). A geometric construction using complementary angles showed that OI is the algebraic sum of OT and C2S, similar to the formula stating that pelvic incidence (PI) = pelvic tilt (PT) + sacral slope (SS) (Fig. 1B, C).[15]

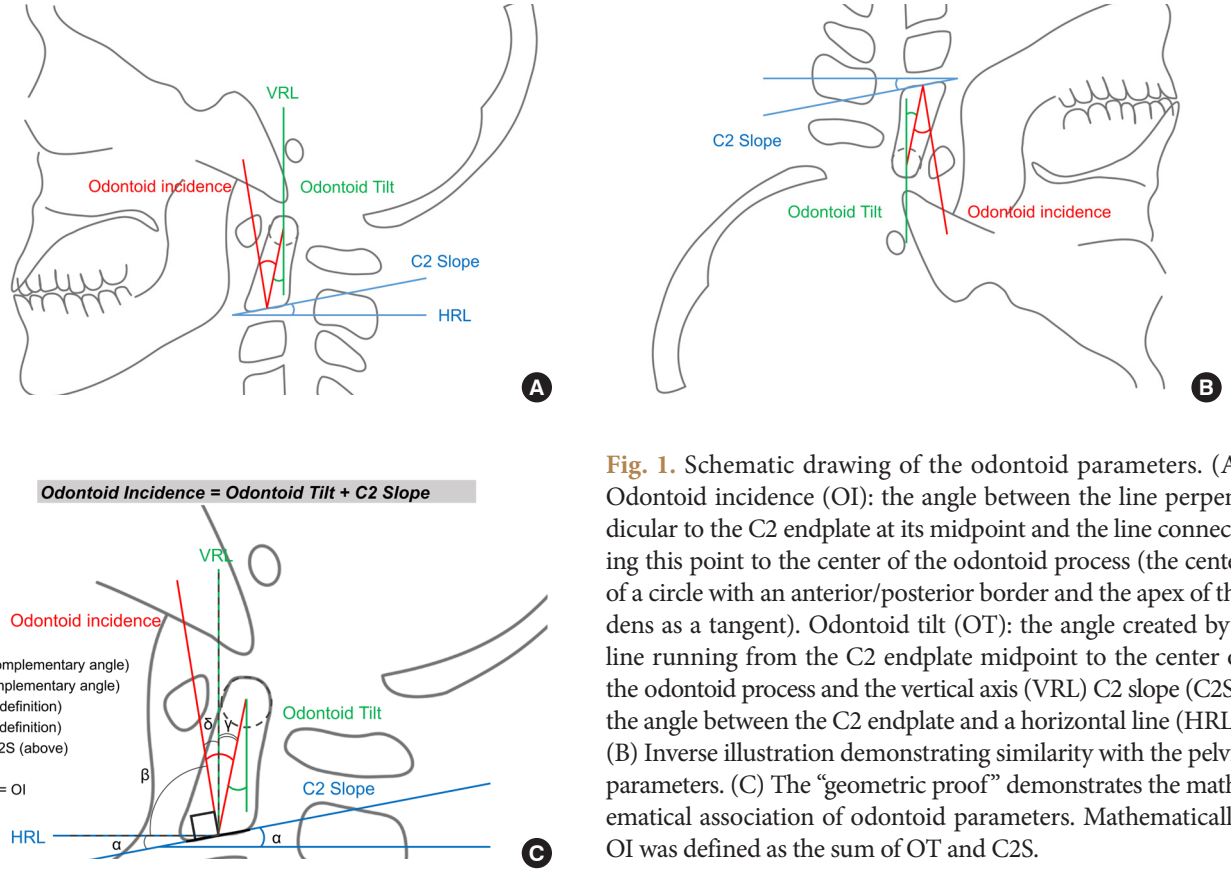

Fig. 1. Schematic drawing of the odontoid parameters. (A) Odontoid incidence (OI): the angle between the line perpendicular to the C2 endplate at its midpoint and the line connecting this point to the center of the odontoid process (the center of a circle with an anterior/posterior border and the apex of the dens as a tangent). Odontoid tilt (OT): the angle created by a line running from the C2 endplate midpoint to the center of the odontoid process and the vertical axis (VRL) C2 slope (C2S): the angle between the C2 endplate and a horizontal line (HRL). (B) Inverse illustration demonstrating similarity with the pelvic parameters. (C) The "geometric proof" demonstrates the mathematical association of odontoid parameters. Mathematically, OI was defined as the sum of OT and C2S.

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2) Cervical spine parameters

The Cobb angle at C0–2, C2–3, C2–4, C2–5, C2–6 C2–7, T1 slope (T1S), C2–7 sagittal vertical axis (cSVA), and T1S minus CL (C2–7) were measured. For the C0–2 angle, an angle between the C2EP and the McRae line was measured. T1S was defined as an angle formed between the T1 upper endplate and the horizontal plane. cSVA was defined as the distance between a plumb line from the centroid of C2 and the posterosuperior aspect of C7 (Fig. 2).

3) Global spine parameters

The C5–T3 angle, thoracic kyphosis (TK; T4–12), lumbar lordosis (LL; L1–S1), PT, SS, PI, and C7 SVA (the distance between the C7 plumb line and the posterosuperior corner of the S1 endplate) were measured.

3. Statistical Analysis

A picture archiving and communication system (p view, Infinitt, Seoul, Korea) was used for measurements. Test for nor-

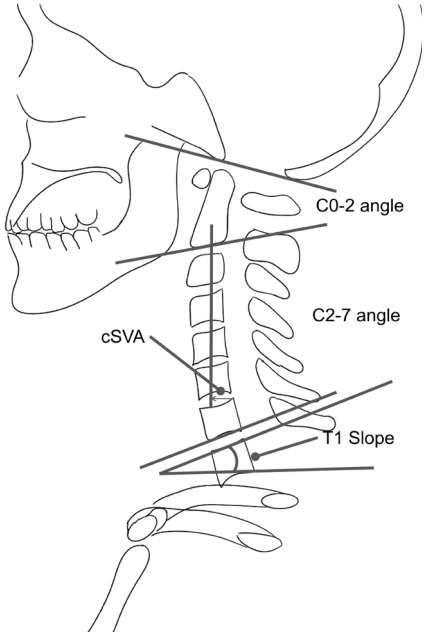

Fig. 2. Schematic drawing of cervical parameters. cSVA, cervical sagittal vertical axis.

Table 1. Mean sagittal parameters and demographics

Variable	Total (n = 42)	Male (n = 15)	Female (n = 27)	p-value
Age (yr)	49.4 (15–68)†	44.5 ± 16.2	52.2 ± 11.0	0.11
Odontoid parameters				
Odontoid incidence (°)	17.7 ± 3.7	17.5 ± 4.3	17.7 ± 3.4	0.84
Odontoid tilt (°)	6.7 ± 5.3	4.7 ± 4.5	7.8 ± 5.4	0.06
C2 slope (°)	10.9 ± 6.2	12.8 ± 5.1	9.9 ± 6.6	0.15
Cervical sagittal parameters				
C0–2 angle (°)	-25.6 ± 8.8	-27.4 ± 8.9	-24.6 ± 8.7	0.31
C2–3 angle (°)	-0.4 ± 3.8	-1.5 ± 3.7	0.1 ± 3.8	0.21
C2–4 angle (°)	-3.1 ± 5.1	-3.9 ± 4.0	-2.6 ± 5.6	0.41
C2–5 angle (°)	-4.3 ± 6.6	-4.5 ± 4.5	-4.2 ± 7.6	0.92
C2–6 angle (°)	-6.2 ± 6.2	-5.4 ± 5.2	-6.7 ± 6.8	0.53
C2–7 angle (°)	-10.4 ± 7.3	-9.5 ± 6.7	-11.0 ± 7.7	0.54
C2–7 SVA (mm)	17.8 ± 6.8	20.8 ± 6.2	16.1 ± 6.6	0.03*
T1 slope (°)	23.1 ± 6.3	24.1 ± 5.7	22.6 ± 6.6	0.45
T1 slope – C2–7 angle (°)	12.7 ± 6.5	14.6 ± 6.0	11.6 ± 6.6	0.15
Global sagittal parameters				
C5–T3 angle (°)	-0.3 ± 6.3	-0.5 ± 5.4	-0.2 ± 6.8	0.88
Thoracic kyphosis (°)	29.6 ± 10.4	27.6 ± 8.7	30.8 ± 11.2	0.37
Lumbar lordosis (°)	-48.1 ± 10.3	-44.8 ± 8.7	-50.0 ± 1.8	0.12
Pelvic tilt (°)	13.4 ± 7.2	11.2 ± 7.8	14.6 ± 6.6	0.14
Sacral slope (°)	33.2 ± 6.9	31.6 ± 7.7	34.1 ± 6.3	0.27
Pelvic incidence (°)	46.6 ± 8.6	42.9 ± 9.1	48.7 ± 7.7	0.03*
C7–S1 SVA (mm)	4.4 ± 28.2	7.1 ± 26.5	2.8 ± 29.5	0.65

Values are presented as mean ± standard deviation.
*$p < 0.05$, statistically significant differences. †Median (range).

mality was done using Shapiro-Wilk test. The correlations between the parameters were analyzed using Pearson correlation coefficients and univariable/multivariable linear regression analysis. The statistical analysis was conducted using the R&R Studio software (ver. 1.4.1717), and a p-value <0.05 was considered to indicate statistical significance.

RESULTS

The mean values and the standard deviations for the studied parameters and subject demographics are reported in Table 1. No significant difference between male and female groups except cSVA and PI were noted. The odontoid parameters showed significant correlations with the established cervical parameters (Table 2). The OI showed significant correlations with the C0–2 angle ($r=-0.33$) and C2–7 angle ($r=0.43$), but not with cSVA or T1S. The OI had a significant correlation with C2S ($r=0.52$), but not OT. However, OT was significantly correlated with all cervical parameters: C0–2 angle ($r=0.48$, $p<0.001$), C2–7 angle ($r=-0.42$, $p<0.01$), cSVA ($r=-0.57$, $p<0.001$), T1S ($r=-0.32$, $p<0.05$), and T1S-CL ($r=-0.78$, $p<0.001$). Strong correlations were found between pelvic parameters, but the odontoid parameters did not show significant correlations with global sagittal parameters (Table 2).

Using linear regression, the odontoid parameters were matched to established cervical parameters (Table 3). OT and C2S matched all cervical parameters. OI matched the C0-2 angle ($r^2=0.08$) and C2–7 angle ($r^2=0.17$). T1S matched C2–7 ($r^2=0.28$), T1S–CL ($r^2=0.10$), and cSVA ($r^2=0.19$).

Multivariable analysis was used to identify predictive variables for each cervical parameter (Table 4). The predictive formulas of the C2–7 angle, C0–2 angle, T1S–CL, and cSVA were

Table 3. Adjusted r^2 between parameters matched with established cervical alignment parameters using a linear regression model

Variable	OI	OT	C2S	T1S
C0–2 angle	0.08*	0.21**	0.35**	-0.01
C2–7 angle	0.17**	0.15**	0.36**	0.28**
T1S–CL	0.06	0.59**	0.70**	0.10*
cSVA	-0.01	0.30**	0.30**	0.19**

OI, odontoid incidence; OT, odontoid tilt; C2S, C2 slope; cSVA, cervical sagittal vertical axis; T1S, T1 slope; CL, cervical lordosis.
*$p<0.05$. **$p<0.01$.

Table 2. Pearson correlation coefficients of the odontoid and cervical, and global parameters

Variable	Odontoid parameter			Cervical parameter				
	OI	OT	C2S	C0–2	C2–7	cSVA	T1S	T1S–CL
OI	X							
OT	0.09	X						
C2S	0.52***	-0.8***	X					
C0–2	-0.33*	0.48***	-0.61***	X				
C2–7	0.43**	-0.42***	0.62***	-0.28	X			
cSVA	0.14	-0.57***	0.57***	-0.24	0	X		
T1S	-0.2	-0.32*	0.16	-0.15	-0.55***	0.46**	X	
T1S–CL	0.3	-0.78***	0.84***	-0.46***	0.59***	0.44**	0.35*	X
C5–T3	0.26	-0.08	0.22	-0.04	0.16	0.33*	-0.21	-0.02
TK	0.1	-0.29	0.31*	-0.19	-0.33*	0.48**	0.69**	0.3
TL	-0.3	-0.43**	0.19	-0.21	0.04	0.25	0.21	0.25
LL	-0.09	0.2	-0.23	0.13	0.07	-0.26	-0.36*	-0.27
PT	-0.25	0.16	-0.28	-0.08	-0.17	-0.09	-0.03	-0.22
SS	-0.07	-0.03	-0.01	0.02	-0.08	0.01	0.15	0.06
PI	-0.26	0.11	-0.25	-0.05	-0.2	-0.06	0.09	-0.14
SVA	-0.33*	0.02	-0.21	0.14	-0.34*	0.03	0.22	-0.17

OI, odontoid incidence; OT, odontoid tilt; C2S, C2 slope; SVA, sagittal vertical axis; T1S, T1 slope; CL, cervical lordosis; TK, thoracic kyphosis; TL, thoracolumbar junction: LL, lumbar lordosis; PT, pelvic tilt; SS, sacral slope; PI, pelvic incidence.
*$p<0.05$. **$p<0.01$. ***$p<0.001$.

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Table 4. Parameter estimates of multivariable linear regression models

Variable	Standardized coefficient	SE	p-value	F-value	95% CI
C2–7 angle					
Odontoid incidence	0.36	0.14	< 0.001	38.22	0.07–0.64
Odontoid tilt	-0.67	0.10	< 0.001	42.25	-0.88 to -0.47
T1 slope	-0.69	0.09	< 0.001	84.80	-0.87 to -0.52
Adjusted R^2			0.80		
F-statistic: 55.09 on 3 and 38 df			p < 0.001		
C0–2 angle					
Odontoid incidence	-0.45	0.30	< 0.001	7.23	0.07–0.64
Odontoid tilt	0.57	0.21	< 0.001	17.81	-0.88 to -0.46
Pelvic tilt	-0.28	0.16	< 0.05	4.72	-0.87 to -0.52
Adjusted R^2			0.40		
F-statistic: 9.92 on 3 and 38 df			p < 0.001		
T1S–Cervical lordosis					
Odontoid incidence	0.42	0.14	< 0.001	14.42	0.13–0.70
Odontoid tilt	-0.83	0.10	< 0.001	107.39	-1.02 to -0.63
C5–T3 angle	-0.19	0.08	< 0.05	5.75	-0.36 to -0.02
Adjusted R^2			0.75		
F-statistic: 42.52 on 3 and 38 df			p < 0.001		
Cervical sagittal vertical axis					
Odontoid tilt	-0.43	0.15	< 0.001	26.57	-0.72 to -0.13
C5–T3 angle	0.34	0.12	< 0.001	6.70	0.10–0.59
Thoracic kyphosis	0.40	0.08	< 0.001	11.60	0.24–0.55
Adjusted R-squared			0.51		
F-statistic: 14.96 on 3 and 38 df			p < 0.001		

SE, standard error; CI, confidence interval; df, degrees of freedom.

established with stepwise regression analysis. OI, OT, and T1S were identified as 3 important predictive variables for the C2–7 angle: CL = 0.36 × OI − 0.67 × OT − 0.69 × T1S (r^2 = 0.79). OI, OT, and PT were important predictors of C0–2 angle: C0–2 = -0.45 × OI+0.57 × OT − 0.28 × PT (r^2 = 0.40). OI, OT, and the C5–T3 angle were important factors for T1S-CL: T1S–CL = 0.42 × OI − 0.83 × OT − 0.19 × C5–T3 angle (r^2 = 0.75). OT, C5–T3 angle, and TK were key factors for cSVA: cSVA = -0.43 × OT + 0.34 × C5-T3 angle+0.40 × TK (r^2 = 0.51).

DISCUSSION

Since the first introduction of pelvic parameters, the sequential correlations of PI, PT, LL, and TK have been well documented.[16] Likewise, attempts have been made to discover novel measurement parameters correlating with cervical alignment over the last decade. Since the advent of thoracic inlet measurements, including T1S,[17] multiple innovative radiographic parameters have been described. Despite these efforts, however, only T1S, T1S–CL, cSVA, and C2S have shown correlations with health-related quality of life (HRQoL).[6,18-22]

T1S has been suggested as the key to understanding CL.[23] It is an important factor influencing spinal alignment, and an increase in T1S leads to larger CL in order to maintain head balance.[17,23-25] Staub et al.[26] proposed that as PI can be used to determine the optimal LL, T1S can also be used to predict CL. Previous research has shown that patients with greater T1S are likely to have underlying thoracolumbar deformity.[27] However, T1S is not a constant parameter and can be influenced by aging or posture.[17] As cervical alignment is well known to be affected by global sagittal alignment through compensatory mechanisms,[1-5,28] the positional variance of a patient makes it troublesome to determine the adequate CL.

Nevertheless, the T1S-CL has been proposed as a parameter

analogous to PI–LL to better define cervical alignment.[29,30] As with PI and LL, the greater the T1S, the larger CL is necessary in order to balance the head for harmonious alignment.[17,23,24,31] Therefore, T1S–CL describes the compensation between the cervical alignment and upper thoracic alignment.[19] If there is insufficient CL to match a given T1S in a patient, C2 will tilt forward to increase C2S.[19] Additionally, C2S has been shown to correlate with patient-reported outcomes and with T1S–CL, C0–2 angle, cSVA, CL, and T1S.[19,31]

Cervical alignment is influenced by global sagittal alignment through compensatory mechanisms.[1-5,28] But what limits the alignment in the rostral end? If the foundation is identical, is the ceiling predetermined? In the present study, we evaluated associations between odontoid and cervical parameters. The close relationship between the odontoid and cervical parameters is evident from the regression coefficients. All odontoid parameters showed significant correlations with the C0–2 and C2–7 angles (OI, r = 0.43; OT, r = -0.42; C2S, r = 0.62). The C0–2 and C2–7 angles are both closely related to the structural geometry and orientation of the axis, as the axis is at the base of the upper CL. OT showed a significant correlation with all cervical parameters, including T1S and T1S–CL (r = -0.32, r = -0.78, respectively). C2S did not show a correlation with T1S, unlike a previous study.[19] Significant interdependence was also noted between the odontoid parameters. The C2S, like the SS, is a horizontal parameter. OT, like the PT, denotes the spatial orientation of the dens, which may vary according to the balance of the cranium and horizontal gaze. Adding OT into the picture could aid in a 2-dimensional analysis of the cervical alignment and balance, with the OI as a fixed reference point.

Through multivariable regression analysis, predictive variables for CL based on odontoid parameters were postulated. Linear regression showed a significant correlation of CL with OI, OT, and T1S ($r^2 = 0.80$). Since the T1S regulates physiological CL, it can be assumed that the odontoid parameters determine CL from the top, modulating the ideal head position. T1S is a reflection of underlying thoracolumbar alignment, and T1S–CL is a result of the balance between cervical and thoracolumbar alignment.[19] C5–T3 has been proposed as an ideal parameter assessing the cervicothoracic junction.[32] The regression models demonstrated that T1S–CL ($r^2 = 0.75$) and cSVA ($r^2 = 0.51$) were strongly correlated not only with the odontoid parameters, but also with cervicothoracic alignment (C5–T3, cervicothoracic) as previously reported.[19,32]

T1S–CL shows whether a patient has a harmonious cervical alignment regarding upper thoracic alignment, and C2S is a mathematical approximation of T1S–CL.[19] If the CL is insufficient to match a given T1S, the axis tilts forward, increasing C2S.[19] As C2S increases, the vertical axis from the center of the odontoid is placed anterior to C2EP, resulting in a negative OT value (Fig. 3). C2S increases, thereby causing a decrease in OT. Similarly, in adult spinal deformity patients, individuals attempt to compensate through pelvic retroversion, which causes an increase in PT and subsequent decrease in SS.[33] Protopsaltis et al.[19] showed that cervical deformity is present if T1S–CL exceeds 17°, similar to the average OI shown in the present study (17.7°). Although the authors did not report OI values in the study, the predicted OT value in cervical deformity patients is assumed to be below zero. In addition, modified cervical deformity classification concerning T1S–CL has been proposed.[21] Some tolerate a larger T1S–CL than others. 16 out of 42 subjects in the present study showed T1S–CL exceeding 15°. As OI is the sum of OT and C2S, and OI correlates with C2S, OI could be interpreted as a compensatory reservoir of each individual. Regarding these facts, we anticipate that the value of OT might somehow be related to cervical deformity.

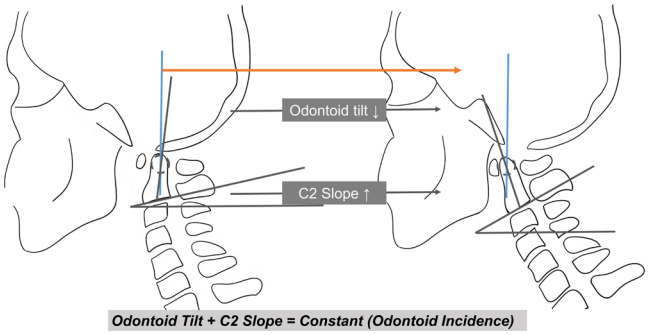

Fig. 3. Schematic illustration showing that an increase in C2 slope leads to a decrement in the odontoid tilt and anterior shifting of the vertical axis from the center of the odontoid process. The sum of C2 slope and the odontoid tilt is a constant.

The utilization of the odontoid parameters has some advantages. OI, as proposed in this study, is an independent and individual parameter not affected by any external factors. By measuring an angle within a single bony structure, we were able to define an angle devoid of muscles or other factors of mobility. We hypothesized that OI is an important parameter influencing cervical alignment from the rostral portion and can be used as a fixed reference point in understanding the physiological alignment of the cervical spine. The relationship between the odontoid parameters is also similar to that between the pelvic parameters,[15] which provides a better understanding of the concept and more straightforward clinical discussions. Though

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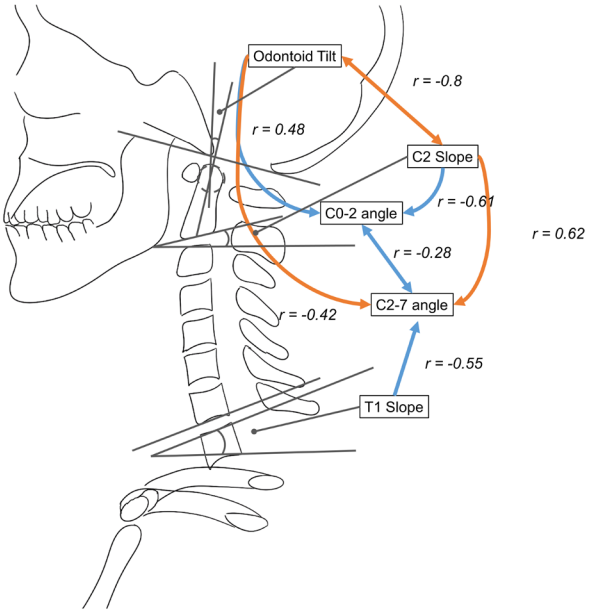

Fig. 4. Schematic illustration of the chain of correlation of cervical and odontoid parameters. The correlation from the caudal end to the rostral end (blue arrow) and from the rostral to caudal end (orange arrow) is illustrated.

the correlation shown in the regression analysis is not strong, a significant chain of correlation is observed between previously reported cervical parameters and the odontoid parameters (Fig. 4). Although the correlation coefficients between established sagittal parameters are similar to previous report,[23] the correlation cannot be said strong to say the parameters are interconnected. However, as most parameters show, the more cranial the parameter is, they tend to show less correlation coefficients.[16] The global spinal and thoracic sagittal alignment strongly influence cervical parameters.[34] In addition, regarding the cone of economy, the cervical spine show larger zone of balance. Thus, other factors may contribute to the overall alignment of the cervical spine more compared with the most cranial odontoid parameters, resulting in moderate correlation coefficients. Larger capacity to compensate cause weaker correlation, which also makes the cervical spine harder to analyze. Using both established and odontoid parameters will aid in providing a more detailed analysis of the cervical alignment.

Though the parameters cannot explain all clinical findings, the pelvic parameters are currently widely used. Due to a small number, subgroup analysis based on global sagittal alignment was note performed. However, multivariable regression analysis indicated that T1S with OI and OT were significant predictors of CL. Moreover, the axis is always visible on plain lateral radiographs, unlike either C7 or T1, which may provide more reliability.[35]

This study has several limitations. First, it is a retrospective study; therefore, there were minor variations in subjects' positions in radiographic images, leading to a possibility of selection bias. Secondly, there was an uneven distribution of sex and there is a wide age range of the examined subjects. Third, the number of cases is small for an anatomical study, and a clinical and prognostic postoperative correlation was not demonstrated. Subgroup analysis regarding global alignment, age, and sex was not performed due to a small number of patients.

Despite the small number of subjects and limitations, this study provides a comprehensive review of the global sagittal alignment using whole-spine radiographs. As the cervical alignment is strongly influenced by the global thoracic and spinal sagittal alignment, the study may provide the bases of utmost importance in future research. The wide age range, not limited to a particular generation, and normal age distribution show the sample's representativeness of the population. The results of the present study demonstrated that the odontoid parameters influence the alignment subaxial CL from the rostral end and serve as the foundation of upper CL. The structural characteristics of the axis represented by the OI could serve as a reference point assessing cervical spine as it is a fixed value. Despite the limitations, the present study may outline the possible role of the odontoid parameters and provide a fresh perspective of the spinal alignment. It will lead to future research regarding the relationship between the odontoid parameters and clinical outcomes. Further studies should ensue to define the relationship between the odontoid parameters and the global alignment, HRQoL, and its contribution to the cervical sagittal balance with a larger number of cases. The present study results may serve as baseline data for further studies on the alignment and balance of the cervical spine in clinical conditions.

CONCLUSION

The evidence of this study implies that OI is an essential factor in regulating the physiological sagittal alignment of the cervical spine from the top. OI, OT, and C2S had significant correlations with cervical alignment. Like PI, OI could be a promising parameter since it is the only anatomical and constant parameter related to the cervical spine, and therefore, OI could be a reliable parameter to evaluate interindividual variations of cervical alignment. The pelvic parameters provide a firm foundation from the caudal end, the odontoid parameters might be

the cherry on top. Altogether, OI, OT, C2S, and T1S can be used to assess normal cervical alignment, and the results of the study may serve as baseline data for further studies on the alignment and balance of the cervical spine.

NOTES

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REFERENCES

1. Le Huec JC, Saddiki R, Franke J, et al. Equilibrium of the human body and the gravity line: the basics. Eur Spine J 2011; 20 Suppl 5(Suppl 5):558-63.
2. Ha Y, Schwab F, Lafage V, et al. Reciprocal changes in cervical spine alignment after corrective thoracolumbar deformity surgery. Eur Spine J 2014;23:552-9.
3. Diebo BG, Challier V, Henry JK, et al. Predicting cervical alignment required to maintain horizontal gaze based on global spinal alignment. Spine (Phila Pa 1976) 2016;41:1795-800.
4. Hyun SJ, Kim KJ, Jahng TA. The differential effect of cervical kyphosis correction surgery on global sagittal alignment and health-related quality of life according to head- and trunk-balanced subtype. J Neurosurg Spine 2021 Apr 2;1-10. https://doi.org/10.3171/2020.9.SPINE201309. [Epub].
5. Lafage R, Challier V, Liabaud B, et al. Natural head posture in the setting of sagittal spinal deformity: validation of chin-brow vertical angle, slope of line of sight, and McGregor's slope with health-related quality of life. Neurosurgery 2016; 79:108-15.
6. Lee SH, Hyun SJ, Jain A. Cervical sagittal alignment: literature review and future directions. Neurospine 2020;17:478-96.
7. Scheer JK, Lau D, Smith JS, et al. Alignment, classification, clinical evaluation, and surgical treatment for adult cervical deformity: a complete guide. Neurosurgery 2021;88:864-83.
8. Yoshimoto H, Ito M, Abumi K, et al. A retrospective radiographic analysis of subaxial sagittal alignment after posterior C1-C2 fusion. Spine (Phila Pa 1976) 2004;29:175-81.
9. Kim JT, Lee HJ, Choi DY, et al. Sequential alignment change of the cervical spine after anterior cervical discectomy and fusion in the lower cervical spine. Eur Spine J 2016;25:2223-32.
10. Protopsaltis TS, Lafage R, Vira S, et al. Novel angular measures of cervical deformity account for upper cervical compensation and sagittal alignment. Clin Spine Surg 2017;30: E959-67.
11. Harrison DE, Harrison DD, Haas JW, et al. Do sagittal plane anatomical variations (angulation) of the cervical facets and C2 odontoid affect the geometrical configuration of the cervical lordosis? Clin Anat 2005;18:104-11.
12. Johnson GM. The correlation between surface measurement of head and neck posture and the anatomic position of the upper cervical vertebrae. Spine (Phila Pa 1976) 1998;23:921-7.
13. Koebke J. Morphological and functional studies on the odontoid process of the human axis. Anat Embryol (Berl) 1979; 155:197-208.
14. Yan YZ, Shao ZX, Pan XX, et al. Acceptable chin-brow vertical angle for neutral position radiography: preliminary analyses based on parameters of the whole sagittal spine of an asymptomatic chinese population. World Neurosurg 2018;120:e488-96.
15. Legaye J, Duval-Beaupere G, et al. Pelvic incidence: a fundamental pelvic parameter for three-dimensional regulation of spinal sagittal curves. Eur Spine J 1998;7:99-103.
16. Ames CP, Blondel B, Scheer JK, et al. Cervical radiographical alignment: comprehensive assessment techniques and potential importance in cervical myelopathy. Spine (Phila Pa 1976) 2013;38:S149-60.
17. Lee SH, Kim KT, Seo EM, et al. The influence of thoracic inlet alignment on the craniocervical sagittal balance in asymptomatic adults. J Spinal Disord Tech 2012;25:E41-7.
18. Divi SN, Bronson WH, Canseco JA, et al. How do C2 tilt and C2 slope correlate with patient reported outcomes in patients after anterior cervical discectomy and fusion? Spine J 2021;21:578-85.
19. Protopsaltis TS, Ramchandran S, Tishelman JC, et al. The importance of C2 slope, a singular marker of cervical deformity, correlates with patient-reported outcomes. Spine (Phi-

la Pa 1976) 2020;45:184-92.
20. Iyer S, Nemani VM, Nguyen J, et al. Impact of cervical sagittal alignment parameters on neck disability. Spine (Phila Pa 1976) 2016;41:371-7.
21. Hyun SJ, Han S, Kim KJ, et al. Assessment of T1 slope minus cervical lordosis and C2-7 sagittal vertical axis criteria of a cervical spine deformity classification system using long-term follow-up data after multilevel posterior cervical fusion surgery. Oper Neurosurg (Hagerstown) 2019;16:20-6.
22. Massaad E, Hadzipasic M, Kiapour A, et al. Association of spinal alignment correction with patient-reported outcomes in adult cervical deformity: review of the literature. Neurospine 2021;18:533-42.
23. Lee SH, Son ES, Seo EM, et al. Factors determining cervical spine sagittal balance in asymptomatic adults: correlation with spinopelvic balance and thoracic inlet alignment. Spine J 2015;15:705-12.
24. Scheer JK, Tang JA, Smith JS, et al. Cervical spine alignment, sagittal deformity, and clinical implications: a review. J Neurosurg Spine 2013;19:141-59.
25. Sivaganesan A, Smith JS, Kim HJ. Cervical deformity: evaluation, classification, and surgical planning. Neurospine 2020;17:833-42.
26. Staub BN, Lafage R, Kim HJ, et al. Cervical mismatch: the normative value of T1 slope minus cervical lordosis and its ability to predict ideal cervical lordosis. J Neurosurg Spine 2018;30:31-7.
27. International Spine Study G, Klineberg EO, Carlson BB, et al. Can measurements on cervical radiographs predict concurrent thoracolumbar deformity and provide a threshold for acquiring full-length spine radiographs? The Spine Journal 2015;15:S146.
28. Kim CW, Hyun SJ, Kim KJ. Surgical impact on global sagittal alignment and health-related quality of life following cervical kyphosis correction surgery: systematic review. Neurospine 2020;17:497-504.
29. Protopsaltis T, Terran J, Soroceanu A, et al. T1 slope minus cervical lordosis (TS-CL), the cervical answer to PI-LL, defines cervical sagittal deformity in patients undergoing thoracolumbar osteotomy. Int J Spine Surg 2018;12:362-70.
30. Ames CP, Smith JS, Eastlack R, et al. Reliability assessment of a novel cervical spine deformity classification system. J Neurosurg Spine 2015;23:673-83.
31. Pierce KE, Passias PG, Brown AE, et al. Prioritization of realignment associated with superior clinical outcomes for cervical deformity patients. Neurospine 2021;18:506-14.
32. Lee SH, Raad M, Neuman BJ, et al. Friday, September 28, 2018 4:05 PM–5:05 PM abstracts: cervical myelopathy and deformity: 258. The C5-T3 angle: a novel parameter of the cervicothoracic junction. Spine J 2018;18(8 Suppl):S127-8.
33. Makhni MC, Shillingford JN, Laratta JL, et al. Restoration of sagittal balance in spinal deformity surgery. J Korean Neurosurg Soc 2018;61:167-79.
34. Legaye J, Duval-Beaupere G, Hecquet J, et al. Pelvic incidence: a fundamental pelvic parameter for three-dimensional regulation of spinal sagittal curves. Eur Spine J 1998;7:99-103.
35. Park JH, Cho CB, Song JH, et al. T1 slope and cervical sagittal alignment on cervical CT radiographs of asymptomatic persons. J Korean Neurosurg Soc 2013;53:356-9.

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Case Report

Original Surgical Treatment and Long-term Follow-up for Chronic Inflammatory Demyelinating Polyradiculoneuropathy Causing a Compressive Cervical Myelopathy: Review of the Literature

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic relapsing disease of unknown aetiology. The diagnosis of this disease is still very complicated. The treatment is medical but, in some cases, a surgical decompression might be required. In rare cases it develops a radicular hypertrophy that can cause a cervical myelopathy; this pathology should be put in differential diagnosis with neurofibromatosis 1 and Charcot-Marie-Tooth (CMT) syndromes. The cases of CIDP cervical myelopathy reported in the literature are rare and even more rarely a surgical decompression was described. Here we report a first and unique case of CIDP cervical myelopathy treated with an open-door laminoplasty technique with 10-year postoperative follow-up (FU). The surgical decompression revealed to be effective in stopping the progression of myelopathy without destabilizing the spine. The patient that before surgery presented a severe tetraparesis could return to walk and gain back his self-care autonomy. At 10-year FU he did not complain of neck pain and did not develop a cervical kyphosis. In case of cervical myelopathy caused by radicular hypertrophy, CIDP should be kept in mind in the differential diagnosis and an open-door laminoplasty is indicated to stop myelopathy progression.

Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy, Cervical myelopathy, Laminoplasty, Open-door, Cervical decompression, Postoperative kyphosis

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic relapsing disease that chiefly affects the limbs. It is characterised by symmetric sensorimotor impairment with the most common clinical signs being muscular weakness of the limbs, distal sensory impairment, and decreased tendon reflexes. Slowing or blocking in nerve conduction velocities can be seen on electrophysiological examinations.[1]

Although the causes of this disease are unknown, a predominant role is ascribed to immune-mediated inflammation with local cytokine production. Repeated demyelination-regeneration results in onion-bulb formation, leading to high-intensity signal in short tau inversion recovery sequences and thickening of the roots on magnetic resonance imaging (MRI).[2-4] Some authors have advocated a correlation of CIDP with diabetes.[5,6]

CIDP is one of the chief causes of hypertrophic neuropathy and should be put in differential diagnosis with neurofibromatosis 1 (NF-1) and Charcot-Marie-Tooth (CMT) diseases.[3,7] It affects the peripheral nerves, and in rare cases, radicular hyper-

trophy leads to medullary compression.[3] The main treatment consists of immune-modulating agents but in rare cases of severe spinal roots enlargements with medullary compression, a surgical decompression might be needed.[8]

CASE REPORT

Herein we report the case of a 58-year-old male presenting CIDP complicated by cervicomedullary compression resulting from radicular hypertrophy; the patient was followed-up for 10 years with periodical MRI evaluations. The patient was first diagnosed with CIDP in 1987 and the initial clinical signs consisted of paraesthesia and weakness of the hands and feet. Clinical examination during the early phase revealed tendon hyporeflexia and superficial hypersensitivity of the lower limbs. The patient exhibited normal muscle tone, coordination, and cranial nerve status. Electromyography performed at that point showed an increase in distal motor latency, increased latency of sensory response, conduction block in the median and ulnar nerves, and increased F-wave latency. The analysis of cerebrospinal fluid (CSF) revealed albumin-cytological dissociation. No familiar history was reported. The patient was successfully treated with plasmapheresis and corticosteroids, and clinical remission was achieved in 1990. In 1991, he experienced major worsening consisting of cervical myelopathy signs such as muscular hypertonia and ataxic gait, which led to a change of the treatment to Tegeline (Human Immunoglobulins, Vidal, Paris, France) and Cellcept (Mycophenolate Mofetil, Roche, Boulogne-Billancourt, France). These 2 drugs were discontinued in 2008 following further worsening of the disease. Between November 2008 and April 2009, treatment consisting of 5 courses of cyclophosphamide proved ineffective. In May 2009, the patient presented with a tetraparesis, which continued to advance and rendered him virtually bedridden, with triple reflex response in the lower limbs and hypoesthesia extending to T10. Urinary retention of central origin resulting from spasticity of the bladder neck and the striated urinary sphincter was demonstrated. Plasmapheresis was started again as well as bolus corticosteroids, resulting in partial but transient (2 weeks) improvement. An initial stay at a physiotherapy center resulted in improved walking, autonomy in self-care, as well as improved prehension. Because of a following worsening of central nervous system signs (spinal myoclonus, spasticity of the lower limb, acute urinary retention), a cervical MRI was performed in August 2010 and revealed major hypertrophy of the nerve roots after gadolinium injection. T2 medullary hypersignal was also noted at C5-C6-C7 in the cervical spinal canal (Fig. 1). A CSF sample performed at this moment exhibited albumin-cytological dissociation with massive impairment of the blood-brain barrier. Surgical decompression was indicated in view of the mechanical medullary compression resulting from hypertrophy of nerve tissue, and the patient underwent surgery the 31st of August 2010.

The surgical procedure consisted of open-door laminoplasty with insertion of a Centerpiece Plate Fixation System (Medtronic, Memphis, TN, USA) to achieve widening of the canal. The patient was placed in ventral decubitus position and a Mayfield pin head-holder was used to allow moderate neck flexion. The incision extended from C3 to T1 with posterior stripping to the facets. Following splitting of the spinous processes, laminoplasty was carried out with thinning of the left side of the lamina at the lamina-facet junction and an opening was made on the

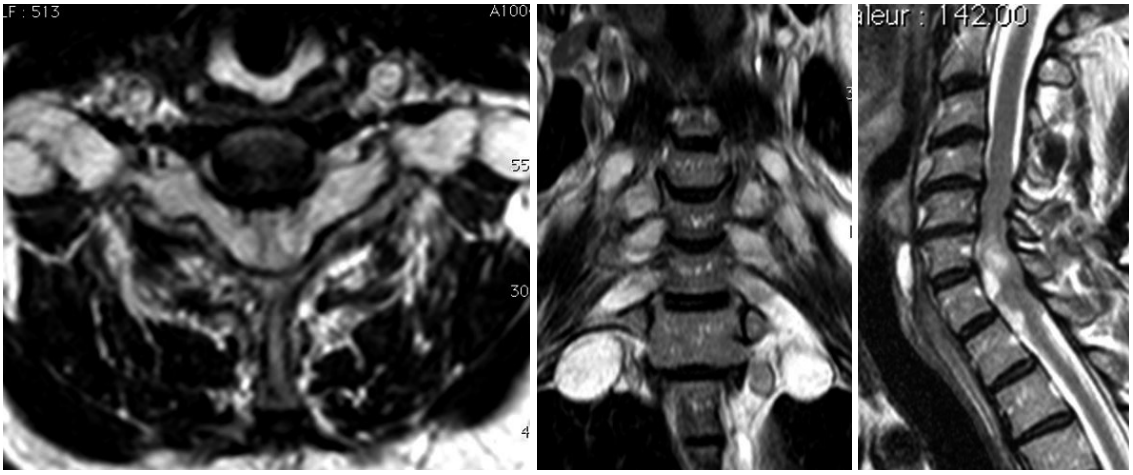

Fig. 1. Preoperative magnetic resonance imaging: multiple level radicular hypertrophy with C5–7 myelopathy signs.

right side of the lamina. The spinal cord was exposed via an open-door technique (Fig. 2). The dura mater was opened, and a major compression of the spinal cord could be appreciated; at this point, a biopsy of the anterior and posterior roots was obtained at level C5 under microscopy. Analysis was performed on the fresh biopsy sample after inclusion. The dura mater was then closed after a duroplasty and the laminoplasty stabilised by osteosynthesis using a plate at each decompressed level. An autologous posterolateral graft was placed in the contralateral side[9] (Fig. 3).

The postsurgical period was uncomplicated, with moderate analgesic intake and on postoperative day 15, the patient was transferred to a physiotherapy center. The biopsy was performed on an accessory radicular nerve to avoid major iatrogenic lesions and the result showed oedematous changes and inflammation in the perineural tissue with limited deposit of amorphous substance which has been described as a characteristic of the CIDP[3] (Fig. 4). The first postoperative clinical and radiological controls performed at 3 and 6 months after the surgery showed a progressive neurological improvement with primary recovery of the upper limbs functions followed by a progressive recuperation of the lower limbs. After 6 months, the patient was able to get out of his seat unassisted and walk a few paces using either a stick or a walking frame. The patient continued to improve and recovered autonomy with a walking frame; he was able to walk a few paces without technical assistance and was practically autonomous in self-care in a specially adapted environment (fine prehension remained deficient with distal sensory deficit).

During the last 10 years, the patients underwent periodical hospitalizations in a recovery center due to relapsing phases of neurological impairment. A therapy with Tegeline (Human Immunoglobulin, Vidal) was carried on with iv perfusions every 6 to 8 weeks. Unfortunately, the patients had a coronavirus disease 2019 infection in November 2020 that strongly affected his general performance status. During his last period at the recov-

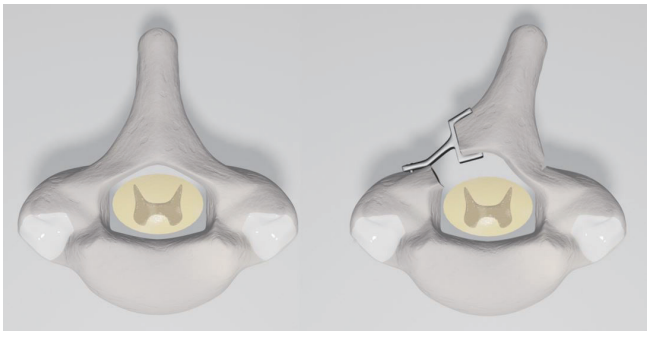

Fig. 2. Open-door laminoplasty technique scheme.

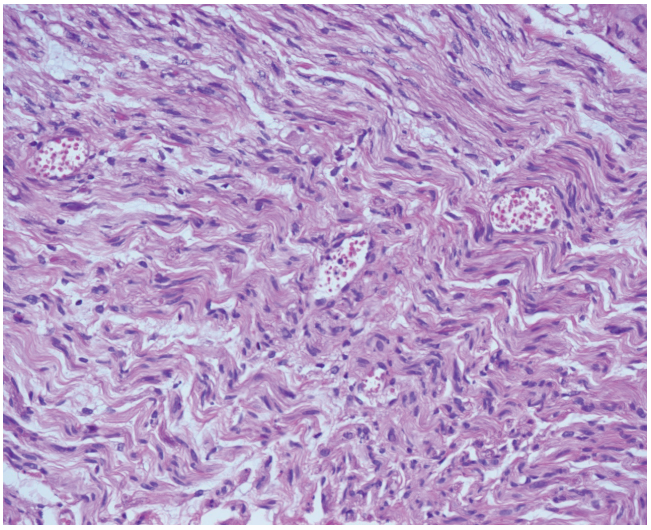

Fig. 4. Pathology picture of the nerve biopsy: HES (haematoxylin, eosin and saffron staining method) coloration showing oedematous and inflammatory tissue with limited amorphous substance.

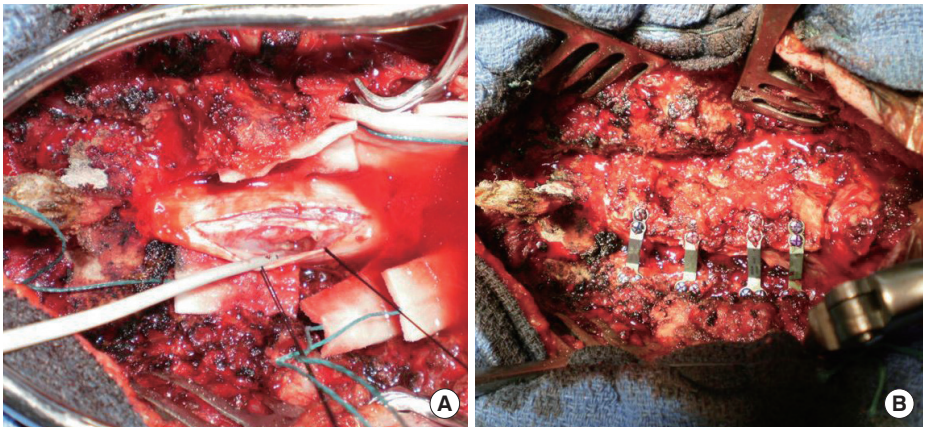

Fig. 3. Intraoperative image: (A) Duroplasty and hypertrophic nerve roots. (B) C4–7 laminoplasty.

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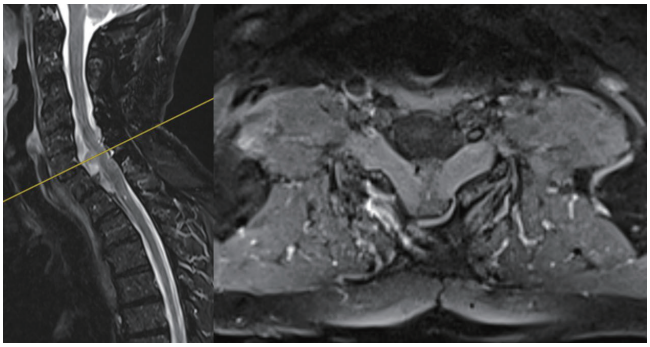

Fig. 5. Postoperative magnetic resonance imaging: persistent radicular hypertrophy without myelopathy signs.

ery center in September 2021, he presented severe amyotrophy of his 4 limbs without signs of cervical myelopathy and was still able to walk and be autonomous in self-care daily activities. A last MRI performed at the end of 2020 showed a stability of the radicular thickening without radiological signs of cervical myelopathy (Fig. 5).

DISCUSSION

Although polyradiculoneuropathy has been described as a progressive chronic disease presenting as bilateral distal motor deficit, loss of sensitivity and hyporeflexia, the absence of clear consensual criteria for diagnosis of CIDP rendered the patient treatment more complex.[10-12] Today the diagnosis of CIDP is based on several points and a good correlation between clinical, laboratory, and radiological findings is essential.[13] The diagnosis should relay on the following elements: (1) complete blood count, electrolyte analysis, screening for underlying diseases such as human immunodeficiency virus, protein electrophoresis (to rule out other coexisting pathologies); (2) electromyogram with conduction blocks, increased motor and sensory latency, absence of F waves; (3) analysis of CSF with screening for albumin-cytological dissociation and monoclonal peak; (4) imaging is also necessary, particularly if there is central nervous system involvement: MRI remains the examination of choice[7,10,13]; (5) nerve or roots biopsy to differentiate CIDP from NF-1 (presence of peripheral nerve sheet tumour) and CMT (both pathologies have the "onion bulb" formation but only CIDP have inflammatory changes such as oedematous stroma with endoneural T-lymphocytes and macrophages).[3]

Radicular hypertrophy in CIDP is rare and was noted in 11% of patients in certain series,[4,7,9,14-19] and mostly responsible for lumbar compressions.[11,14-24] The cervical localisation remains exceptional.[8]

Even though various studies have reported favourable response of such hypertrophy to corticosteroids,[7,17,22] our patient remained refractory to such treatment for several years. Although the cause of this hypertrophy is uncertain, the numerous inflammatory episodes appear to result in demyelination, leading to cell deposition because of regeneration, which then creates an onion-shaped mass.[19,25] Some authors have suggested a relation of CIDP with diabetes, but in our case, we cannot confirm this hypothesis since our patient isn't diabetic.[5,6]

Neural biopsies may be of diagnostic assistance[26] if they reveal deposits of amorphous and inflammatory substances. However, there is some discussion in the current literature concerning the utility of biopsy.[19,25]

The currently recommended treatment for CIDP is medical,[27,28] with first-line therapy consisting of immunoglobulins and intravenous corticosteroids.[27,29-31] Good results have also been achieved with plasmapheresis.[27,31-33] While monoclonal antibodies have also been beneficial to some degree, they have not been given as first-line therapy. Other forms of treatment are used more reluctantly because of the occasionally major associated adverse effects.

The patient described herein presented a very rare complication of CIDP, namely medullary compression due to radicular cervical hypertrophy. This type of compression is described in the literature, but usually not associated to CIDP cases.[34-36] To our knowledge this is the first report in the literature of open-door technique laminoplasty used to treat radicular hypertrophy with spinal canal compression. Our long follow-up shows the good outcome of this conservative technique which didn't destabilizes the spine.[37] Following surgery our patient could gain back his autonomy, returning to his daily activities. Because of the relapsing nature of this pathology, he necessitated of continuous medical intravenous treatment and periods of rehabilitation in a dedicated center. Nevertheless, at 10 years of FU, he keeps his autonomy and did not represent signs of cervical myelopathy which testifies the efficacy of the cervical decompression procedure.[3]

CONCLUSION

The present case illustrates the value of an open-door laminoplasty in the event of medullary compression due to CIDP; the clinical outcome was satisfactory with major recovery of autonomy that was kept at 10-year follow-up without radiological signs of new cervical spine compression. The main treat-

ment of CIDP is medical but in some rare cases a surgical treatment of neural structures compression might be necessary, and this pathology should be kept in mind in the differential diagnosis of spinal roots hypertrophy.

NOTES

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REFERENCES

1. Sander HW, Latov N. Research criteria for defining patients with CIDP. Neurology 2003;60(8 Suppl 3):S8-15.
2. Tanaka K, Mori N, Yokota Y, et al. MRI of the cervical nerve roots in the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy: a single-institution, retrospective case-control study. BMJ Open 2013;3:e003443.
3. Hasan MT, Patil S, Chauhan V, et al. Spinal cord compression from hypertrophic nerve roots in chronic inflammatory demyelinating polyradiculoneuropathy-a case report. Surg Neurol Int 2021;12:114.
4. Tazawa K, Matsuda M, Yoshida T, et al. Spinal nerve root hypertrophy on MRI: clinical significance in the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy. Intern Med 2008;47:2019-24.
5. Bril V, Blanchette CM, Noone JM, et al. The dilemma of diabetes in chronic inflammatory demyelinating polyneuropathy. J Diabetes Complications 2016;30:1401-7.
6. Rajabally YA, Stettner M, Kieseier BC, et al. CIDP and other inflammatory neuropathies in diabetes-diagnosis and management. Nat Rev Neurol 2017;13:599-611.
7. Schady W, Goulding PJ, Lecky BR, et al. Massive nerve root enlargement in chronic inflammatory demyelinating polyneuropathy. J Neurol Neurosurg Psychiatry 1996;61:636-40.
8. Freitas MR, Nascimento OJ, Soares CN, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: two cases with cervical spinal cord compression. Arq Neuropsiquiatr 2005;63:666-9.
9. Duggins AJ, McLeod JG, Pollard JD, et al. Spinal root and plexus hypertrophy in chronic inflammatory demyelinating polyneuropathy. Brain 1999;122:1383-90.
10. Koski CL, Baumgarten M, Magder LS, et al. Derivation and validation of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy. J Neurol Sci 2009;277:1-8.
11. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. Neurology 1991;41:617-8.
12. Barohn RJ, Kissel JT, Warmolts JR, et al. Chronic inflammatory demyelinating polyradiculoneuropathy. Clinical characteristics, course, and recommendations for diagnostic criteria. Arch Neurol 1989;46:878-84.
13. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. J Peripher Nerv Syst 2010;15:295-301.
14. Pytel P, Rezania K, Soliven B, et al. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with hypertrophic spinal radiculopathy mimicking neurofibromatosis. Acta Neuropathol 2003;105:185-8.
15. Staff NP, Figueroa JJ, Parisi JE, et al. Hypertrophic nerves producing myelopathy in fulminant CIDP. Neurology 2010;75:750.
16. Aïdi S, El Alaoui Faris M, Amarti A, et al. Chronic inflammatory demyelinating polyradiculoneuropathy with hypertrophy of spinal roots, brachial plexus and cranial nerves. Rev Neurol (Paris) 2002;158:819-23.
17. Mizuno K, Nagamatsu M, Hattori N, et al. Chronic inflammatory demyelinating polyradiculoneuropathy with diffuse and massive peripheral nerve hypertrophy: distinctive clinical and magnetic resonance imaging features. Muscle Nerve 1998;21:805-8.
18. Midroni G, Dyck PJ. Chronic inflammatory demyelinating

 https://doi.org/10.14245/ns.2143232.616

polyradiculoneuropathy: unusual clinical features and therapeutic responses. Neurology 1996;46:1206-12.
19. Matsuda M, Ikeda S, Sakurai S, et al. Hypertrophic neuritis due to chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): a postmortem pathological study. Muscle Nerve 1996;19:163-9.
20. Kretzer RM, Burger PC, Tamargo RJ. Hypertrophic neuropathy of the cauda equina: case report. Neurosurgery 2004;54:515-8; discussion 518-9.
21. Symonds CP, Blackwood W. Spinal cord compression in hypertrophic neuritis. Brain 1962;85:251-9.
22. Fukae J, Okuma Y, Noda K, et al. A quadriplegic patient with chronic inflammatory demyelinating polyneuropathy (CIDP) who responded well to corticosteroids and intravenous immunoglobulin therapy. No To Shinkei 2001;53:1115-8.
23. Goldstein JM, Parks BJ, Mayer PL, et al. Nerve root hypertrophy as the cause of lumbar stenosis in chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 1996;19:892-6.
24. Ginsberg L, Platts AD, Thomas PK. Chronic inflammatory demyelinating polyneuropathy mimicking a lumbar spinal stenosis syndrome. J Neurol Neurosurg Psychiatry 1995;59:189-91.
25. Dyck PJ, Lais AC, Ohta M, et al. Chronic inflammatory polyradiculoneuropathy. Mayo Clin Proc 1975;50:621-37.
26. Vallat JM, Tabaraud F, Magy L, et al. Importance of the nerve biopsy for the diagnosis of atypical forms of chronic inflammatory demyelinating polyradiculoneuritis: 8 cases. Bull Acad Natl Med 2003;187:387-99; discussion 399-403.
27. Tracy JA, Dyck PJ. Investigations and treatment of chronic inflammatory demyelinating polyradiculoneuropathy and other inflammatory demyelinating polyneuropathies. Curr Opin Neurol 2010;23:242-8.
28. Villa AM, Garcea O, Di Egidio M, et al. Interferon beta-1a in chronic inflammatory demyelinating polyneuropathy: case report. Arq Neuropsiquiatr 2004;62:892-4.
29. Dyck PJ, O'Brien PC, Oviatt KF, et al. Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. Ann Neurol 1982;11:136-41.
30. Van Schaik IN, Winer JB, De Haan R, et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2002;(2):CD001797.
31. Mehndiratta MM, Hughes RA. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2001;(3):CD002062.
32. Dyck PJ, Daube J, O'Brien P, et al. Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. N Engl J Med 1986;314:461-5.
33. Dyck PJ, Pineda A, Swanson C, et al. The Mayo Clinic experience with plasma exchange in chronic inflammatory-demyelinating polyneuropathy (CIDP). Prog Clin Biol Res 1982;106:197-204.
34. Wehling P, Cleveland S, Reinecke J, et al. Magnetic stimulation as a diagnostic tool in cervical nerve root compression and compression-induced neuropathy. J Spinal Disord 1995;8:304-7.
35. Murata K, Morishita S, Nakamuro T, et al. A case report of the compression syndrome due to hypertrophic neuropathy. Rinsho Shinkeigaku 1991;31:213-5.
36. Rosen SA, Wang H, Cornblath DR, et al. Compression syndromes due to hypertrophic nerve roots in hereditary motor sensory neuropathy type I. Neurology 1989;39:1173-7.
37. Ryken TC, Heary RF, Matz PG, et al. Cervical laminectomy for the treatment of cervical degenerative myelopathy. J Neurosurg Spine 2009;11:142-9.

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ing author at the bottom of the page, as well as information on the previous presentation of the manuscript in conferences and funding resources, if necessary.

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• Journal article

1. Sakai K, Okawa A, Takahashi M, et al. Five-year follow-up evaluation of surgical treatment for cervical myelopathy caused by ossification of the posterior longitudinal ligament. Spine (Phila Pa 1976) 2012;37:367-76.

• Book chapter

2. Sweitzer S, Arruda J, DeLeo J. The cytokine challenge: Methods for the detection of central cytokines in rodent models of persistent pain. In: Kruger L, editor. Methods in pain research. Boca Raton, FL: CRC Press; 2001:109-32.

• Entire book

3. Atlas SW. Magnetic resonance imaging of the brain and spine. Philadelphia: Lippincott Williams & Wilkins; 2001.

• Software

4. Epi Info [computer program]. Version 6. Atlanta: Centers for Disease Control and Prevention; 1994.

• Online journals

5. Friedman SA. Preeclampsia: A review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22-37. Available at: BRS Information Technologies; McLean, VA. Accessed December 15, 1990.

• Database

6. CANCERNET-PDQ [database online]. Bethesda (MD): National Cancer Institute; 1996. Updated March 29, 1996.

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7. Gostin LO. Drug use and HIV/AIDS [Internet]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

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7. Process for Identification of and Dealing With Allegations of Research Misconduct

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board will discuss the suspected cases and reach a decision. We will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

Neurospine adheres to the research and publication ethics policies outlined in International Standards for Editors and Authors (http://publicationethics.org) and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://icmje.org). Any studies involving human subject must comply with the principles of the World Medical Association Declaration of Helsinki. Clinical research should be approved by the Institutional Review Board, as well through patient consent. A patient's personal information cannot be published in any form. However, if it is absolutely necessary to use a patient's personal information, the consent of the patient or his/her guardian will be needed before publishing. Animal studies should be performed in compliance with all relevant guidelines, observing the standards described in the NIH Guide for the Care and Use of Laboratory Animals.

Cases that require editorial expressions of concern or retraction shall follow the COPE flowcharts available from: http://publicationethics.org/resources/flowcharts. If correction is needed, it will follow the ICMJE Recommendation for Corrections, Retractions, Republications and Version Control available from: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/corrections-and-version-control.html as follows:

Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Minimum standards are as follows: First, it shall publish a correction notice as soon as possible, detailing changes from and citing the original publication on both an electronic and numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing; Second, it shall post a new article version with details of the changes from the original version and the date(s) on which the changes were made through CrossMark; Third, it shall archive all prior versions of the article. This archive can be either directly accessible to readers; and Fourth, previous electronic versions shall prominently note that there are more recent versions of the article via CrossMark.

8. Handling Complaints and Appeals

The policy of the journal is primarily aimed at protecting the authors, reviewers, editors, and the publisher of the journal. If not described below, the process of handling complaints and appeals follows the guidelines of the Committee of Publication Ethics available from:

https://publicationethics.org/appeals

Who complains or makes an appeal?

Submitters, authors, reviewers, and readers may register complaints and appeals in a variety of cases as follows: falsification, fabrication, plagiarism, duplicate publication, authorship dispute, conflict of interest, ethical treatment of animals, informed consent, bias or unfair/inappropriate competitive acts, copyright, stolen data, defamation, and legal problem. If any individuals or institutions want to inform the cases, they can send a letter to editor through https://www.e-neurospine.org/about/contact.php. For the complaints or appeals, concrete data with answers to all factual questions (who, when, where, what, how, why) should be provided.

Who is responsible to resolve and handle complaints and appeals?

The Editor, Editorial Board, or Editorial Office is responsible for them.

What may be the consequence of remedy?

It depends on the type or degree of misconduct. The consequence of resolution will follow the guidelines of the Committee of Publication Ethics (COPE).

9. Postpublication Discussions and Corrections

The postpublication discussion is available through letter to the editor. If any readers have a concern on any articles published, they can submit letter to the editor on the articles. If there founds any errors or mistakes in the article, it can be corrected through errata, corrigenda, or retraction.

10. Policies on data sharing and reproducibility

Until 2020, authors will be encouraged to share their data openly, but starting in 2021, they will be mandated to do so. The related regulation follows the open data sharing policy outlined below.

1) Open data sharing policy

For clarification on result accuracy and reproducibility of the results, raw data or analysis data will be deposited to a public repository, for example, Harvard Dataverse (https://dataverse.harvard.edu/) after acceptance of the manuscript. Therefore, submission of the raw data or analysis data is mandatory. If the data is already a public one, its URL site or sources should be disclosed. If data cannot be publicized, it can be negotiated with the editor. If there are any inquiries on depositing data, authors should contact the editorial office.

2) Clinical data sharing policy

This journal follows the data sharing policy described in "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors" (https://doi.org/10.3346/jkms.2017.32.7.1051). As of July 1, 2018 manuscripts submitted to ICMJE journals that report the results of interventional clinical trials must contain a data sharing state-

Table. **Examples of Data Sharing Statements That Fulfill These ICMJE Requirements***

	Example 1	Example 2	Example 3	Example 4
Will individual participant data be available (including data dictionaries)?	Yes	Yes	Yes	No
What data in particular will be shared?	All of the individual participant data collected during the trial, after deidentification.	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Not available
What other documents will be available?	Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report, Analytic Code	Study Protocol, Statistical Analysis Plan, Analytic Code	Study Protocol	Not available
When will data be available (start and end dates)?	Immediately following publication. No end date.	Beginning 3 months and ending 5 years following article publication.	Beginning 9 months and ending 36 months following article publication.	Not applicable
With whom?	Anyone who wishes to access the data.	Researchers who provide a methodologically sound proposal.	Investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose.	Not applicable
For what types of analyses?	Any purpose.	To achieve aims in the approved proposal.	For individual participant data meta-analysis.	Not applicable
By what mechanism will data be made available?	Data are available indefinitely at (*Link to be included)*.	Proposals should be directed to xxx@yyy. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at a third party website (*Link to be included)*.	Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University's data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposals and accessing data may be found at (*Link to be provided*).	Not applicable

* These examples are meant to illustrate a range of, but not all, data sharing options.

ment as described below. Clinical trials that begin enrolling participants on or after January 1, 2019 must include a data sharing plan in the trial's registration. The ICMJE's policy regarding trial registration is explained at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record. All of the authors of research articles that deal with interventional clinical trials must submit data sharing plan of example 1 to 4 in Table 1. Based on the degree of sharing plan, authors should deposit their data after deidentification and report the DOI of the data and the registered site.

For the policies on the research and publication ethics not stated in this instructions, International standards for editors and authors (https://publicationethics.org/resources/resources-and-further-reading/international-standards-editors-and-authors) can be applied.

All correspondences, business communications and manuscripts should be mailed to:

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In case of experimenting on human, the author(s) have certified that the process of the research is in accordance with ethical standards of Helsinki declaration, domestic and foreign committees that preside over hum an experiment.

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The author(s) of the journal have clarified everything that interest may arise such as research expenses, consultant expenses, stock, particularly concerned person of the judges on the document of disclosure of conflict of interest.

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1) Formats and contents of the manuscripts are checked by corresponding author. ☐ Yes / ☐ No
2) All manuscripts should be written in English. Manuscripts may be no longer than 5,000 English words for original articles except for references, tables, and figures. ☐ Yes / ☐ No
3) Manuscripts should be prepared in the following orders. ☐ Yes / ☐ No
Original article: external title page, internal title page, abstract, key words, introduction, materials, and methods, results, discussion, conclusion, references, table, and figure legends.
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Only the English title of the manuscript is listed. Any information on the names and affiliations of the authors is not shown on the internal title page. ☐ Yes / ☐ No

4. Abstract

1) Abstract should have no longer than 250 words for original articles and review articles. ☐ Yes / ☐ No
2) Abstract includes Objective, Methods, Results, and Conclusion in clinical or laboratory research. ☐ Yes / ☐ No
3) The selection of Key Words is based on medical subject headings (MeSH) terms. ☐ Yes / ☐ No

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1) Text is written in 11-point fonts with double line spacing. ☐ Yes / ☐ No
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6. References

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3) When more than 2 references are cited at a given place in the manuscript, use hyphens to join the first and last numbers of a closed series; use commas without space to separate other parts of a multiple citation (e.g., As reported previously,[1,3-8,19]...The derived data were as follows[3,4,12]:) ☐ Yes / ☐ No
4) If there are more than 3 authors in end-reference list, name only the first 3 authors and then use et al. ☐ Yes / ☐ No
5) Use superscript numerals outside periods and commas, inside colons and semicolons. ☐ Yes / ☐ No

7. Tables, Figures and Illustrations

1) Tables and figures are prepared in separate files. ☐ Yes / ☐ No
2) Figures are submitted individually not incorporated into one file. ☐ Yes / ☐ No
3) Figures and illustrations are saved in JPG or TIF file format and have a resolution of 300 DPI or more. (Line art should have resolution of 1,200 dpi or more) ☐ Yes / ☐ No

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9. Ethical approval of studies and informed consent

For all manuscripts reporting data from studies involving human participants or animals, formal review and approval, or formal review and waiver, by an appropriate institutional review board or ethics committee is required and should be described in the Materials and Methods section. ☐ Yes / ☐ No