Age-specific Comparative Clinical Outcomes of Chemonucleolysis with Condoliase versus Microendoscopic Discectomy in Patients with Lumbar Disc Herniation

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Abstract:

Introduction: Condoliase-based chemonucleolysis and microendoscopic discectomy (MED) are considered to be minimally invasive treatments for lumbar disc herniation (LDH). The aim of this study was to compare the clinical outcomes of both treatments, specifically focusing on whether the outcomes vary by age group.

Methods: Patients with LDH who received intradiscal condoliase injections (condoliase group) or underwent MED (MED group) with 1-year follow-up were enrolled in this study. A numerical rating scale (NRS) was developed for leg and back pains. Using magnetic resonance imaging, changes in disc height and degeneration were evaluated. The data were assessed at baseline and at 3-month and 1-year follow-ups. The therapy was considered effective in patients whose NRS for leg pain improved by ≥50% at 1 year from baseline and for whom surgery was not required. Comparative analyses were conducted between the condoliase and MED groups and among the <20, 20-39, 40-59, and ≥60 year age groups.

Results: In this study, a total of 345 patients (condoliase group, n=233; MED group, n=112) were enrolled. Subsequent surgery was required in 23 patients (9.9%) in the condoliase group because of the ineffectiveness of the condoliase therapy. Because of herniation recurrence, reoperation was required in five patients (4.5%) in the MED group. The efficacy rates were respectively 74.4% and 74.6% in the condoliase and MED groups, and no intergroup or age-group differences were found. The condoliase group had a significantly higher decrease in disc height when compared with the MED group (9.0% vs. 4.4%, $p<0.05$). Compared with the older age group, the younger age group had a greater decrease in disc height and disc degeneration; however, their recovery was better than that of the older age group. Among the age groups, the herniation reduction rate did not significantly vary.

Conclusions: Condoliase and MED had equivalent 1-year outcomes, with no differences observed in efficacy across age groups. For informed decision-making, the advantages and disadvantages of each treatment must be understood.

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Introduction

Lumbar disc herniation (LDH) is a degenerative spinal condition that commonly presents with symptoms such as leg pain, lower back pain, and numbness. It is a condition in which the nucleus pulposus protrudes through a damaged annulus fibrosus, which compresses the nerve root. This can cause restrictions on daily physical activities, resulting in remarkable social and financial impacts due to decreased productivity[1]. In most cases, sufficient pain relief is achieved through conservative treatment[2,3]. Nonetheless, when serious symptoms persist and affect daily activities after an appropriate period of conservative treatment, surgical intervention must be considered. Surgical outcomes for LDH are generally positive and offer greater and faster pain relief when compared with conservative treatment[2,3].

Recently, through advances in technology, minimally invasive surgery has been introduced, which can attain smaller incisions and earlier return to daily activities and is less invasive and less painful when compared with conventional open surgery. Of the various surgical techniques, the most popular and widely accepted minimally invasive surgery technique for LDH surgery is microendoscopic discectomy (MED), which was proposed by Foley and Smith[4]. A meta-analysis[5] showed that in terms of reoperation rate, recurrence, clinical outcome, complication rate, or length of hospital stay, MED and open discectomy have no significant differences. Nevertheless, MED resulted in less intraoperative blood loss but with a longer operation time.

Chemonucleolysis, which induces chemical dissolution of the nucleus pulposus in the intervertebral disc, is a less invasive procedure and is considered to be an intermediate treatment option between conservative and surgical approaches for LDH[6-8]. Since its approval in Japan in 2018, chemonucleolysis, with the use of condoliase, has been recognized as a standard alternative treatment for LDH[9,10]. This treatment is highly effective for LDH symptoms, accounting for a success rate of 62%-87% with no any serious adverse events[11-20].

Although the safety and efficacy of both treatments for LDH have been established, there is no existing study that directly compared the clinical results of the two treatments. Thus, this study aimed to compare the clinical outcomes of condoliase therapy and MED in patients with LDH, specifically focusing on whether the outcomes vary by age.

Materials and Methods

Patient recruitment

This retrospective multicenter study was carried out based on the Declaration of Helsinki and was approved by the ethical review boards of all participating institutions. Due to the retrospective nature of this study, the requirement for informed consent was waived.

In this study, patients who received intradiscal condoliase injections (condoliase group) or underwent MED (MED group) for LDH between August 2018 and October 2020 in 10 participating institutions and with a minimum follow-up period of 1 year were evaluated. The following conditions were indicated for treatment: unilateral lower extremity pain with or without accompanying back pain; confirmed nerve root compression via a herniated disc through magnetic resonance imaging (MRI); the presence of neurological signs consistent with the affected nerve root distribution; and resistance to conservative treatments, including medication and anesthetic block, for at least 1 month. Contraindications for intradiscal condoliase injections are the presence of cauda equina syndrome, severe and worsening motor deficits, symptoms that indicate nerve root involvement across multiple spinal segments due to multilevel disc herniation, and other preexisting spinal disorders. Patients with protrusion and transligamentous herniation were excluded from the analysis.

Data collection and clinical assessment

Patient data, including age, sex, herniation level, history of discectomy at the same level, duration of symptoms before injection, and adverse events were acquired from medical records. Adverse events for the condoliase group included back pain, leg pain, anaphylactic shock, and skin rash, whereas those for the MED group included surgical complications. To assess pain intensity, a numerical rating scale (NRS) for leg and back pain was employed at baseline and at the 3-month and 1-year follow-ups. Patients whose NRS score for leg pain improved by ≥50% at 1 year from baseline and for whom surgery was not required were defined as receiving effective therapy.

If the pain persists after condoliase therapy, an operation is considered based on a discussion between the patient and the doctor. In general, we do not conduct operations for 3 months after a condoliase injection to evaluate its effect. However, if the pain is extremely severe and intolerable, an operation may be decided upon even within that period.

Table 1. Comparison of Demographic Characteristics between Condoliase and MED.

	Condoliase (n=233)	MED (n=112)	p-value
Age (years)	45.8±17.2	45.1±15.3	0.870
Sex (male/female)	147/86	68/44	0.670
Herniation level			<0.001*
L1/2	4 (1.7%)	0	
L2/3	11 (4.7%)	0	
L3/4	9 (3.9%)	18 (16.1%)	
L4/5	104 (44.6%)	41 (36.6%)	
L5/S	105 (45.1%)	53 (47.3%)	
Symptom duration (months)	9.9±16.4	7.8±12.1	0.287
History of discectomy at the same level	8 (3.4%)	1 (0.9%)	0.166
Pfirrmann classification			0.607
Grade II	7 (3.0%)	3 (2.7%)	
Grade III	121 (51.9%)	65 (58.0%)	
Grade IV	101 (43.3%)	41 (36.6%)	
Grade V	4 (1.7%)	3 (2.7%)	
Disc height (mm)	10.0±2.2	10.5±8.2	0.619
NRS for leg pain	6.5±2.6	7.5±2.5	<0.001*
NRS for back pain	4.8±2.9	4.8±3.1	0.927

Continuous data are presented as mean±standard deviation (range). Categorical data are presented as number (%). Abbreviations: MED, microendoscopic discectomy; NRS, numerical rating scale

*p<0.05.

Radiographic assessment

MRI results were investigated at baseline and at 3 months and 1 year after the injection. Based on the central slice of the sagittal image, the disc height was calculated at the midpoint of the endplate. Using the Pfirrmann classification system, the degree of disc degeneration was assessed[21]. The bulging ratio of herniation (i.e., the proportion of the anteroposterior diameter of herniation to the anteroposterior diameter of the canal space) and the reduction ratio (i.e., the postoperative bulging ratio to the preoperative bulging ratio) were calculated[14]. Three spinal surgeons performed the radiographic assessment, which was decided based on majority consensus. To evaluate the Pfirrmann classification, interobserver and intraobserver agreements were calculated. The mean interobserver agreement was 0.78 (95% confidence interval [CI]: 0.49, 0.99), which indicates substantial agreement. Conversely, the intraobserver agreement was almost perfect, with values of 1.0 (95% CI: 1.0, 1.0), 0.82 (95% CI: 0.50, 1.0), and 0.82 (95% CI: 0.50, 1.0).

Statistical analyses

Between the condoliase and MED groups, demographic data, clinical outcomes, and radiographic parameters were compared. Moreover, the patients were divided into four age groups: <20, 20-39, 40-59, and ≥60 years. Then, among the groups, a comparative analysis was then conducted.

To verify the assumption regarding the normal distribution of the data, the Shapiro-Wilk test was employed. Student's *t*-test and the Mann-Whitney U test were used to evaluate between-group differences for continuous variables, whereas the chi-squared test and Fisher's exact test were employed for categorical data. Using a one-way analysis of variance, which was followed by Tukey's post-hoc test, the statistical significance of the differences between each period was evaluated. All statistical analyses were carried out using SPSS version 23.0 (IBM Corp., Armonk, NY, USA); $p<0.05$ was considered to be statistically significant.

Results

In the study, a total of 345 patients (215 men and 130 women; mean age, 45.5±16.6 years) with LDH were enrolled. Among them, 233 patients were treated with condoliase injection, and 112 patients were treated with MED.

Comparison of the baseline demographic and radiographic data between the condoliase and MED groups revealed no cases of L1/2 of L2/3 herniation in the MED group and four cases of L1/2 herniation and 11 cases of L2/3 herniation in the condoliase group, which indicates a significant difference (Table 1). The mean NRS scores for leg pain were significantly higher in the MED group than in the condoliase group (7.5±2.5 vs. 6.5±2.6, $p<0.05$), whereas no intergroup differences were found in age, sex, symptom duration, history of discectomy at the same level, preoperative Pfirrmann classification, disc height, and NRS of back pain (Table 1).

Adverse events were observed in 15 patients (6.4%) in the condoliase group: rash in six cases, leg pain in seven, and

Table 2. Reoperation Rates in Condoliase and MED.

Age (years)	Condoliase	MED	p-value
<20	2/10 (20.0%)	0/3 (0%)	0.580
20-39	7/82 (8.5%)	1/42 (2.4%)	0.177
40-59	7/84 (8.3%)	2/46 (4.3%)	0.321
60≤	7/57 (12.3%)	1/21 (4.8%)	0.307
Total	23/233 (9.9%)	5/112 (4.5%)	0.085

Abbreviation: MED, microendoscopic discectomy

Table 3. Effective Rates in Condoliase and MED.

Age (years)	Condoliase	MED	p-value
<20	7/10 (70.0%)	1/1 (100%)	0.727
20-39	52/66 (78.8%)	19/23 (82.6%)	0.300
40-59	55/71 (77.5%)	18/25 (72.0%)	0.582
60≤	31/48 (64.6%)	12/18 (66.7%)	0.874
Total	145/195 (74.4%)	50/67 (74.6%)	0.965

Abbreviation: MED, microendoscopic discectomy

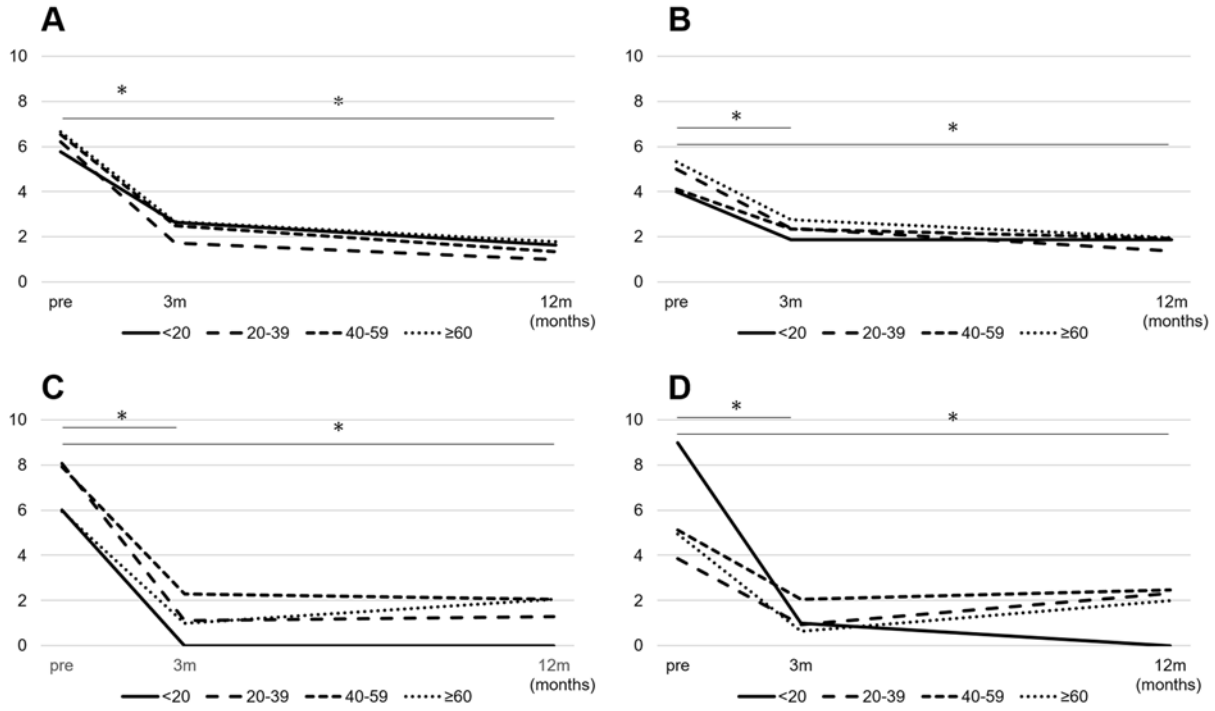

Figure 1. Changes over time in the numerical rating scale (NRS) for leg and back pain by age group in the condoliase and microendoscopic discectomy (MED) treatment groups.
NRS of leg pain (A) and back pain (B) in the condoliase group. NRS of leg pain (C) and back pain (D) in the MED treatment group. *Statistically significant change. NRS, numerical rating scale; MED, microendoscopic discectomy

back pain in seven. None of the patients experienced anaphylactic shock or neurological sequelae after the intradiscal condoliase injection. In the MED group, seven patients (6.3%) experienced surgical complications: incidental durotomy in four cases and hematoma in three cases. Because of the ineffectiveness of the condoliase therapy, subsequent surgery was required in 23 patients (9.9%) in the condoliase group. Meanwhile, reoperation at the same level was required in five cases (4.5%) in the MED group because of herniation recurrence. No intergroup or age-group differences were observed (Table 2). Among the patients who achieved a 1-year NRS score, the effective rates were 74.4% in the condoliase group and 74.6% in the MED group. No intergroup or age-group differences were observed (Table 3).

Fig. 1 shows the time course changes in NRS (leg and back pain) in each age group. Among the patients who did not necessitate surgical treatment after the initial treatment, the mean NRS scores for both leg and back pain in each group significantly improved from 3 months to 1 year after injection when compared with baseline in every age group ($p<0.05$).

In terms of disc degeneration, Pfirrmann grade deterioration at 1 year from the baseline was observed in 64 (38.9%) patients in the condoliase group and in nine (29.0%) patients in the MED group; however, the difference was not significant (Table 4). Despite that the disc heights at baseline and at 1 year were not significantly different, the decrease in disc height was significantly greater in the condoli-

ase group than in the MED group (9.0% vs. 4.4%, p<0.05, Table 4).

Comparison of the MRI findings across different age groups in the condoliase group showed that Pfirrmann grade deterioration at 3 months from baseline tended to be more pronounced in younger patients than in older ones. Noteworthily, the rate of patients with Pfirrmann grade recovery at 1 year was significantly higher in those aged <20 years than in the other age groups (Table 5). There were no significant differences in disc height at any time point, nor in the decrease in disc height (Table 5). Nevertheless, a slight disc height recovery from 3 months to 1 year was observed in the younger age group in comparison with the older age group (Fig. 2). The reduction rate of herniation did not significantly vary among the age groups (Table 5).

Discussion

In clinical practice, chemonucleolysis with condoliase is now widely utilized as a less invasive treatment option for patients with LDH[9,10]. It demonstrates high efficacy in alleviating LDH symptoms, with success rates that range from 62% to 87% without any serious adverse events[11-20]. The advantages of condoliase treatment are its safety, low invasiveness, and cost-effectiveness[22]. Nevertheless, its disadvantages include lower reliability, slower onset of effects, and the potential for disc degeneration[9,11-13,15,18]. By contrast, MED is one of the most widely accepted minimally invasive surgeries for LDH. The advantages of MED include reliable herniation removal, nerve root decompression, and immediate pain relief. Nevertheless, its disadvantages include technical demands, surgical complications, higher costs, and the need for hospitalization. The appropriate treatment for each patient must be selected by considering these characteristics.

To the best of our knowledge, this study is the first to compare clinical outcomes across different age groups between chemonucleolysis with condoliase and MED in patients with LDH. MED is difficult to adapt to the upper lumbar region (Table 1); therefore, for upper lumbar herniation, condoliase is preferred. In the MED group, the mean preoperative NRS score for leg pain was significantly higher than in the condoliase group (Table 1). This indicates that many patients with severe preoperative leg pain may prefer surgery in the hope of immediate pain relief.

Subsequent surgery was mandatory in 23 patients (9.9%) in the condoliase group because of ineffectiveness and in five patients (4.5%) in the MED group because of herniation recurrence (Table 2). The rate tended to be higher in the condoliase group; however, this difference was not statistically significant. Previous reports have shown that the rate of subsequent surgery after condoliase therapy was approximately 10%[9,12-15,18]. By contrast, a systematic review reported a 4% reoperation rate following MED[23]. Our results are consistent with the frequencies reported in previous studies. However, the implications of reoperation after MED and condoliase treatment may vary.

In terms of effectiveness, both treatments were almost equivalent until 1 year after treatment, and no difference

Table 4. Time Course Changes of MRI Findings between Condoliase and MED.

	Condoliase (n=149)	MED (n=31)	p-value
Pfirrmann grade deterioration	58 (38.9%)	9 (29.0%)	0.300
Disc height [pre-op] (mm)	10.1±2.1	9.4±1.6	0.079
Disc height [1 y] (mm)	9.1±2.0	9.0±2.0	0.844
Disc height decrease (%)	9.0±13.5	4.4±14.1	0.006*

Abbreviation: MED, microendoscopic discectomy
*p<0.05.

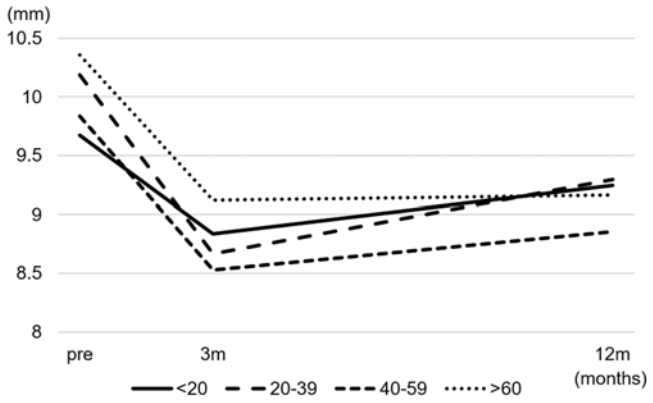

Figure 2. Time course of changes in disc height by age group in the condoliase group.

Table 5. Generation Differences of MRI Findings in the Condoliase Group.

	<20 n=7	20-39 n=51	40-59 n=56	60≤ n=35	p-value
Pfirrmann grade deterioration [3 m]	4 (57.1%)	29 (56.9%)	25 (44.6%)	8 (22.9%)	0.017*
Pfirrmann grade recovery [1 y]	2 (50.0%)	0	5 (20.0%)	0	0.004*
Disc height [pre-op] (mm)	9.7±1.4	10.2±1.7	9.8±2.4	10.4±2.3	0.647
Disc height [3 m] (mm)	8.8±1.9	8.7±1.8	8.5±2.2	9.1±2.0	0.629
Disc height [1 y] (mm)	9.2±1.5	9.3±1.7	8.9±2.2	9.2±2.2	0.715
Disc height decrease (%)	4.2±10.1	9.0±9.5	8.5±17.8	10.7±10.9	0.690
Herniation reduction rate (%)	17.3±27.3	35.6±28.7	28.1±31.2	35.7±19.9	0.218

*p<0.05.

was observed across age groups (Table 3). Oshita et al.[19] showed that the clinical outcomes of condoliase therapy did not vary among age groups and could be effective even for patients older than 70 years or younger than 20 years. Nonetheless, condoliase therapy is recommended for use in patients with LDH aged 20-70 years because individuals within this age range were included in previous clinical trials[9,10]. According to the appropriate use guidelines, condoliase should be administered with caution to patients younger than 20 years because of concerns on the impact of this treatment on growth plates and to patients older than 70 years because of the possible lumbar instability and vertebral degeneration. However, due to its minimally invasive nature, condoliase therapy, under proper informed consent, can be considered as an alternative to surgery in cases that do not adequately respond to conservative treatments.

Surgical treatment outcomes in younger patients with LDH are reportedly more favorable than those in older patients[24-27]. Conversely, older patients have been reported to show worse outcomes[28,29]. Although there was no significant difference due to the small number of cases, a similar trend was observed in this study (Table 3).

By contrast, surgery tended to be conducted following condoliase treatment, particularly in younger patients (Table 2). Because of their high activity levels, they may not be able to continue conservative treatment if it proves ineffective, which leads to a transition to surgery. Although the number of cases was small and numerous uncertainties remain, previous reports have indicated that condoliase therapy may have limited efficacy in patients aged <20 years; therefore, special caution is warranted when considering its use in patients aged <20 years. Both treatments were effective for patients aged ≥60 years, which is similar to other age groups (Table 2, 3). Nonetheless, when considering each treatment, preoperative instability and degenerative changes must be evaluated to achieve sufficient outcomes.

In our study, adverse events including back pain (seven cases, 3.0%), leg pain (seven cases, 3.0%), and skin rash (six cases, 2.6%) following condoliase administration were also observed, which similar to a previous report[9]. In most cases, these symptoms were temporary, and no serious adverse events were reported after condoliase administration. Nonetheless, these adverse events must be thoroughly explained to patients before administration. Meanwhile, postoperative complications were also observed in the MED group, including incidental durotomy (four cases, 3.6%) and hematoma (three cases, 2.7%). In a systematic review, the incidence of durotomy in MED and open discectomy was 4.4% and 6.6%, respectively[23]. Advancements in technology have made less invasive surgery possible; however, postoperative complications remain impossible to completely eliminate. Any surgery inherently carries the risk of complications.

The primary concern following intradiscal condoliase injection is the potential risk of progressive disc degeneration. The dissolution of the nucleus pulposus has been demonstrated to promote disc degeneration after chemonucleolysis. The reported incidence of Pfirrmann grade progression after condoliase injection ranges from 41.3% to 57.1%[9,11-13,15,18]. In the present study, Pfirrmann grade progression tended to occur at a higher rate in the condoliase group than in the MED group, but the difference was not statistically significant. Moreover, we found that the decrease in disc height 1 year after treatment compared with the preoperative measurement was significantly greater in the condoliase group than in the MED group (Table 4). These results suggest clinically important information, and the long-term impact of disc degeneration, which could lead to back pain or lumbar instability, must be evaluated.

Considering the age-group differences in disc degeneration in the condoliase group, younger individuals tended to show more progression of disc degeneration but also showed a greater tendency for recovery (Table 5). This trend was also observed in the time course changes in disc height (Fig. 2). Some authors have reported that disc degeneration induced by chemonucleolysis can recover, particularly in young patients[12,30]. Sugimura et al.[31] carried out a study with monkeys and found that glycosaminoglycan content partially recovered 28 weeks after condoliase injection. They observed temporary effects on the nucleus pulposus, with disc regeneration occurring after the enzyme activity ceased. However, the mechanisms that underly disc regeneration after condoliase therapy and its long-term effects are still unclear.

No studies have compared the herniation reduction rate according to age. In this study, the herniation reduction rate after condoliase therapy did not vary among age groups (Table 5). This result indicates that even in degenerative discs, condoliase enables the reduction of herniation.

This study has some limitations. The number of enrolled patients, especially young patients (aged <20 years), was relatively small, and the follow-up period was short. To confirm the efficacy of both treatments in these patients, further clinical studies that involve larger numbers of patients with longer follow-up periods are warranted. However, this study is the first to compare age-group differences in clinical outcomes between condoliase and MED for patients with LDH. These results can provide valuable information to patients when selecting treatment options.

To conclude, condoliase and MED, which are minimally invasive treatments for LDH, exhibit equivalent 1-year outcomes. Among the different age groups, no differences in treatment efficacy were found. To make an informed treatment decision, the characteristics, including the advantages and disadvantages, of each treatment must be understood.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

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Author Contributions: T.B., T.T., and T.H. designed the

study. T.B. conducted the statistical analysis and wrote the manuscript. T.T. and T.H. conducted data collection and data entry. The final manuscript was approved by all authors.

Ethical Approval: The Ethics Committee of the Japanese Society for Spine Surgery and Related Research approved the study design (IRB number: #16)

Informed Consent: Given the retrospective nature of the research, patient informed consent was waived.

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