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Clinical Study

Outcomes of additional instrumentation in elderly patients with pyogenic vertebral osteomyelitis and previous spinal instrumentation

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Abstract

BACKGROUND CONTEXT: In patients with pyogenic vertebral osteomyelitis (PVO) and previous instrumentation requiring surgical treatment, a decision must be made between a less-invasive noninstrumented surgery, including retaining the previous instrumentation, or a more invasive additional instrumented surgery involving the complete removal of the infected tissue and firm restabilization.

PURPOSE: To evaluate the clinical outcomes of using additional instrumentation in patients with PVO and previous instrumentation and determine the significant risk factors related to recurrent infection.

STUDY DESIGN/SETTING: Retrospective cohort study (case control study).

PATIENT SAMPLE: PVO patients with previous instrumentation.

OUTCOME MEASURES: Recurrence of PVO and mortality.

METHODS: Patients were divided into two groups (instrumented or noninstrumented) according to the presence or absence of additional instrumentation. The baseline characteristics, infection profile, and treatment outcomes were compared between the two groups, and a multivariate logistic regression analysis was performed to identify the risk factors for infection recurrence.

RESULTS: A total of 187 postoperative patients with PVO and previous spinal instrumentation were included. There were no significant differences in the baseline characteristics except the presence of a titanium cage. Surgery for additional instrumentation in patients with PVO and previous instrumentation showed similar rates of infection recurrence and mortality compared with noninstrumented surgery despite a larger number of involved vertebral levels and greater incidence of epidural abscesses. However, instrumented patients with PVO and previous instrumentation who experienced infection recurrence had worse clinical outcomes than those of the noninstrumented patients with PVO. Severe medical comorbidities, the presence of a psoas abscess, and methicillin-resistant *Staphylococcus aureus* infection were associated with a higher risk of infection recurrence.

CONCLUSIONS: Surgery for additional instrumentation in patients with PVO and previous instrumentation showed similar rates of infection recurrence and mortality to those who underwent

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noninstrumented surgery despite a larger number of involved vertebral levels and an increased frequency of epidural abscesses.

Keywords: Instrumentation; Postoperative infection; Psoas abscess; Previous instrumentation; Pyogenic vertebral osteomyelitis; Recurrence

Introduction

Pyogenic vertebral osteomyelitis (PVO) is a bacterial infection of the vertebral body and surrounding tissues. Vertebral osteomyelitis is more common in older patients [1] with medical comorbidities [2], and the incidence of this infection has been increasing due to the aging population, the increased availability of magnetic resonance imaging (MRI), and increased spinal interventions or surgeries [3]. The economic burden of this disease is rapidly increasing [4,5], and recently published articles reported a mortality rate of 4% to 29% [6].

Despite new antibiotics and advances in surgical techniques, the treatment of PVO remains challenging. Intravenous antibiotic administration over a 6-week period is strictly required [7], and patients are immobilized using a rigid brace for 3 to 4 months [8,9]. Under such strict conservative treatment, a significant number of patients with PVO exhibit neurologic deficits, symptoms of spinal cord compression, and progressive infection during treatment [10]. Accordingly, approximately 40% of patients with PVO require surgical intervention [11], a rate that is steadily increasing [12–14].

Significant bone loss during PVO treatment, caused directly by the causative organisms and indirectly by immobilization and limited sunlight exposure [8,9,15], complicates surgical treatment for PVO. Permanent and extensive stabilization using spinal instrumentation is often required to counteract the aggressive bone loss, but the applied instrumentation paradoxically disturbs infection control by encouraging biofilm formation [16]. Fortunately, the outcomes of spinal instrumentation in native or primary spine infection are encouraging [17–20], and researchers consistently recommend that spinal instrumentation be performed in native infections when it is indicated. However, no comparative studies support the use of spinal instrumentation in patients with PVO and previous instrumentation.

To evaluate aspects beyond the successful outcomes of spinal instrumentation in native PVO [21], we focused on the clinical outcomes of spinal instrumentation in patients with PVO and previous instrumentation. A retrospective cohort study evaluated the clinical outcomes of using additional instrumentation in patients with PVO and previous instrumentation, and determined the significant risk factors related to infection recurrence.

Materials and methods

Study design and ethical considerations

This retrospective cohort study included patients with PVO and previous spinal instrumentation who visited our institution from January 2000 to March 2017. This study was designed and conducted according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines [22]. The study protocol was approved by our facility's institutional review board of our institution.

Study patients

Our university medical center is one of the largest in our nation and consists of six general hospitals. This study was performed in the main institute of our medical center, which serves as a tertiary referral center from the other five general hospitals and numerous local hospitals.

Elderly patients aged ≥60 years who underwent surgery for postoperative PVO at the site of their previous spinal instrumentation were initially included (Fig. 1). The patients who underwent only implant removal without additional instrumentation during PVO treatment were excluded. Patients who underwent previous spine surgery without instrumentation and those who underwent previous spine surgery caused by an infection or malignancy were excluded. In addition, patients with an inadequate follow-up period (<6 months) were excluded. Other reasons for exclusion were incomplete medical records or imaging data.

Postoperative PVO was defined using the following criteria: (1) suggestive clinical symptoms including fever, axial and radicular pain, and/or neurologic deficit; (2) accompanying typical radiological features on MRI; and (3) microbiological identification [23]. Typical MRI findings included were as follows [24–26]: (1) alteration of the normal marrow signal intensity with ill-defined margins including a decrease on T1-weighted sequences and an increase on fat-suppressed T2-weighted sequences; (2) involvement of the disc space and two adjacent vertebral bodies; (3) periosteal reaction and adjacent soft-tissue edema; and (4) soft-tissue abscess, especially in the epidural space from gadolinium contrast imaging. Microbiological confirmation was based upon isolation from blood culture, computed tomography-guided needle biopsy, or surgical biopsy.

Data collection

The patients' medical records were retrospectively reviewed for baseline characteristics, infection profiles, and treatment outcomes for PVO. The baseline characteristics included demographic information, underlying illness, smoking status, information about previous surgery, bone mineral density, and initial laboratory data. The Charlson Comorbidity Index (CCI), a validated instrument used to

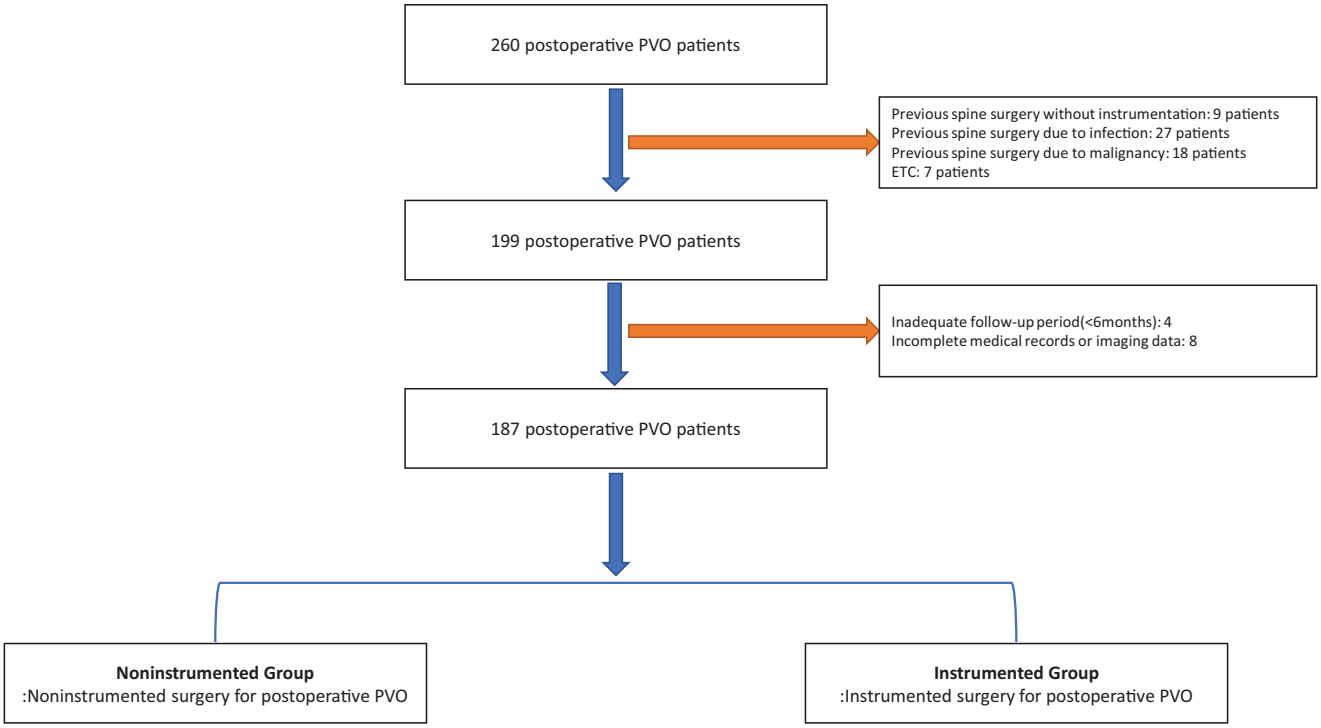

Fig. 1. Flowchart of patients included in the study. PVO, pyogenic vertebral osteomyelitis.

predict morbidity caused by comorbid conditions, was derived from the medical records [27]. The infection profiles included the interval between the previous surgery and the PVO surgery, presumed source of infection, neurologic deficit by American Spinal Injury Association grade, anatomical involvement of the infection, isolated microorganisms, and laboratory data (white blood cell count, C-reactive protein level, and erythrocyte sedimentation rate). From the initial spine MRI at the time of PVO diagnosis, the number of involved vertebral levels (counted as the number of involved vertebral bodies) was identified. The infection severity in patients with PVO was evaluated by the validated classification of Pola et al. [28], which divided pyogenic spondylodiscitis into three types: (1) type A, cases without biomechanical instability, neither acute neurologic impairment, or epidural abscesses; (2) type B, cases with radiological evidence of significant bone destruction or biomechanical instability without acute neurologic impairment or epidural abscesses; and (3) type C, cases with epidural abscesses or acute neurologic impairment. The treatment outcomes included information about the PVO surgery, surgical and medical complications, use of antibiotics including combination therapy with rifampin [29,30], hospital stay, infection recurrence, and mortality.

Grouping

Instrumentation was defined as a surgical treatment that used external devices including titanium cages, plates, screws, rods, and hooks [21]. Postoperative patients with PVO and previous instrumentation were divided into two groups based upon the placement of additional of additional instrumentation (instrumented and noninstrumented groups).

Definitions

Infection recurrence was defined as recurrent symptoms and signs after the completion of antibiotic treatment requiring a second course of parenteral antibiotics [31]. Infection recurrence was divided into two categories: microbiologically confirmed recurrence and clinical recurrence [31]. Microbiologically confirmed recurrence was further divided into two categories depending on whether cultures revealed the same organism of the initial infection or a new organism. Clinical recurrence was diagnosed when cultures did not reveal any causative organism but both clinical and laboratory improvements were evident after parenteral antibiotic therapy [31].

Statistical methods

Data are presented as mean±standard deviation. Comparisons of the patients' baseline characteristics, infection profiles, and treatment outcomes between the two groups were analyzed using the independent t test or Mann-Whitney U test for continuous variables and the Pearson chi-square test, Fisher exact test, or linear-by-linear association for categorical variables. The Kaplan-Meier survival curve was used to display the cumulative probability of survival. The log-rank test was used to compare the survival curves

between the two groups. Logistic regression analysis was performed to identify the risk factors for recurrence, and all significant variables in the univariate analysis ($p<.05$) were included in a multivariate logistic regression analysis. The p values $\leq.05$ were considered statistically significant. All analyses were performed using SPSS 24 (IBM Corp, Armonk, NY, USA).

Results

Enrollment and grouping

A total of 187 postoperative patients with PVO and previous spinal instrumentation were identified who did not meet the exclusion criteria (Fig. 1). Among them, 86 (46.0%) underwent noninstrumented surgery and 101 (54.0%) underwent instrumented surgery. The mean patient age was 69.3 years. A total of 86 patients (46.0%) were male, whereas the other 101 (54.0%) were female.

Intergroup comparison of baseline patient characteristics

The patients who underwent noninstrumented surgery for PVO were older than those who underwent instrumented surgery (70.0±4.9 years vs. 68.6±9.9 years, respectively), although the difference was not statistically significant (p=.066; Table 1). The most common reason for previous spine surgery was degenerative disease (Table 1). The most common region for previous spine surgery was the lumbar spine, and most patients underwent a one- or two-level spinal instrumentation with pedicle screws (Table 1). There were no differences in the patients' baseline characteristics except for the presence of a titanium cage (Table 1). A titanium cage was more frequently used

Table 1
Intergroup comparison of baseline patient characteristics

Baseline characteristics		Noninstrumented group	Instrumented group	p value
Number of patients		86	101	
Age		70.0±4.9	68.6±9.9	0.062
Gender ratio (F:M)		43: 43	43: 58	0.310
BMI (kg/m^2)		25.1±3.9	25.1±4.0	0.645
	<20	8 (9.3)	8 (7.9)	0.979
	20 to <25	37 (43.0)	46 (45.5)	
	25 to <30	29 (33.7)	30 (29.7)	
	≥30	12 (14.0)	17 (16.8)	
Charlson Comorbidity Index score		1.6±1.1	1.5±1.1	0.513
Medical history	Coronary artery disease	13 (15.1)	17 (16.8)	
	End-stage renal disease	5 (5.8)	3 (3.0)	
	Liver cirrhosis	4 (4.7)	5 (5.0)	
	Diabetes mellitus	31 (36.0)	35 (34.7)	
Smoking	Nonsmoker	62 (72.1)	71 (70.3)	0.815
	Exit smoker	7 (8.1)	11 (10.9)	
	Current smoker	17 (19.8)	19 (18.8)	
Etiology of previous surgery	Degenerative disease	61 (70.9)	79 (78.2)	0.404
	Trauma	17 (19.8)	17 (16.8)	
	ETC	8 (9.3)	5 (5.0)	
Previous surgical method	Instrumentation with decompressive surgery	62 (72.1)	78 (77.2)	0.420
	Instrumentation with bone graft	80 (93.0)	94 (93.1)	0.990
Previously instrumented region	Cervical	10 (11.6)	8 (7.9)	0.226
	Thoracic	25 (29.1)	21 (20.8)	
	Lumbar	51 (59.3)	72 (71.3)	
Number of previously instrumented level	1 or 2 level	61 (70.9)	69 (68.3)	0.699
	Over 2 level	25 (29.1)	32 (31.7)	
Previous type of instrumentation	Pedicle screw	78 (90.7)	96 (95.0)	0.244
	Titanium cage	21 (24.4)	39 (38.6)	0.038
	Polyetheretherketone (PEEK) cage	24 (27.9)	22 (21.8)	0.332
	Hook	3 (3.5)	0	
Previous wound problem	5 (5.8)	8 (7.9)	0.572	
Serum creatinine (mg/dL)		1.1±1.1	1.2±1.3	0.270
Serum calcium (mg/dL)		8.8±0.5	8.9±0.5	0.239
Serum phosphate (mg/dL)		3.4±0.7	3.4±0.7	0.579
Serum nonspecific alkaline phosphatase (U/L)		92.9±31.6	101.0±32.4	0.116
Baseline BMD (g/cm^2)	Spine (L1–L4)	0.991±0.206	0.982±0.213	0.584
	Femur neck	0.717±0.161	0.735±0.173	0.555
	Trochanter	0.632±0.167	0.648±0.172	0.605
	Total femur	0.772±0.169	0.788±0.178	0.642

Data were presented by number (%) of patients or mean±standard deviation.

in the previous surgery in the instrumented group (59.3%) than in the noninstrumented group (71.3%).

Intergroup comparison of infection profiles

Most patients underwent surgery for PVO within 12 months after their previous surgery (93.0% in the instrumented group vs. 92.1% in the noninstrumented group; Table 1). The source of infection was identified in the majority of the patients (87.2% in the instrumented group vs. 82.2% in the noninstrumented group). The most common causative organism was *Staphylococcus aureus* (50.0% in the instrumented group vs. 57.4% in the noninstrumented group), which was methicillin resistant in 32.5% (14 of 43) of patients in the noninstrumented group and 36.2% (21 of 58) of patients in the instrumented group (Table 2). According to the classification by Pola et al., type C infection was the most common in our PVO cohort (70.9% in the instrumented group vs. 73.3% in the noninstrumented group).

In the instrumented group, PVO involved more vertebral levels (p=.041) and more frequently involved epidural abscesses (p=.047) compared with the noninstrumented group (67.4% vs. 80.2%, respectively; Table 2). No statistically significant differences were observed in the interval between previous surgery and surgery for PVO (p=.633), presumed source of infection (p=.340), neurologic deficit by American Spinal Injury Association grade (p=.244), presence of a paravertebral (p=.538) or psoas abscess (p=.757), causative organism (p=.552), laboratory results, and severity of infection by Pola et al. (p=.932; Table 2).

Intergroup comparison of treatment methods and outcomes

The most common surgical approach was a posterior-only approach (90.7% in the instrumented group vs. 78.2% in the noninstrumented group), and pedicle screw instrumentation was used in 98% (99 of 101) of patients in the instrumented group (Table 3). Additional instrumentation was predominantly performed at the upper adjacent vertebrae (49.5%; 50 of 101 patients; Table 3). Recently, combination therapy with rifampin is proposed for the treatment of staphylococcal biofilm infections [29,30]. However, rifampin was used in only one patient (1.2%) in the noninstrumented group and in three patients (3.0%) in the instrumented group, making it impossible to evaluate the additive effect of rifampin. Nonsurgical drainage of abscesses was more frequently used in

Table 2
Intergroup comparison of infection profiles

Infection profiles		Noninstrumented group	Instrumented group	p value
Number of patients		86	101	
Interval between previous surgery and surgery for PVO	Mean interval (d)	264±304	247±176	0.369
	Within 6 mo	41 (47.7)	38 (37.6)	0.381
	Between 6 and 12 mo	39 (45.3)	55 (54.5)	
	Over 12 mo	6 (7.0)	8 (7.9)	
Presumed source of PVO	Skin and subcutaneous infection	3 (3.5)	6 (5.9)	0.340
	Urinary tract infection	7 (8.1)	10 (9.9)	
	Endocarditis	1 (1.2)	2 (2.0)	
	Unknown	75 (87.2)	83 (82.2)	
Neurologic deficit by ASIA grade	A	0	0	0.244
	B	0	0	
	C	4 (4.7)	9 (8.9)	
	D	19 (22.1)	29 (28.7)	
	E	63 (73.3)	63 (62.4)	
Number of infected levels	1 or 2 level	70 (81.4)	69 (68.3)	0.041
	Over 2 level	16 (18.6)	32 (31.7)	
Anatomical involvement	Epidural abscess	58 (67.4)	81 (80.2)	0.047
	Paravertebral abscess	49 (57.0)	53 (52.5)	0.538
	Psoas abscess	33 (38.4)	41 (40.6)	0.757
Causative organism of PVO	*Staphylococcus aureus*	43 (50.0)	58 (57.4)	0.552
	Methicillin resistant	14 (16.3)	21 (20.8)	
	Methicillin sensitive	29 (20.8)	37 (36.6)	
	Other gram-positive bacteria	26 (30.2)	22 (21.8)	
	Gram-negative bacteria	11 (12.8)	10 (9.9)	
	Others	6 (7.0)	11 (10.9)	
White blood cell ($\times 10^9$/L)		12107±3759	12461±4202	0.638
C-reactive protein (CRP, mg/L)		102±21	105±25	0.737
Erythrocyte sedimentation rate (ESR, mm/h)		66±26	65±27	0.709
Severity of infection by Pola et al.	Type A	5 (5.8)	7 (6.9)	0.932
	Type B	20 (23.3)	20 (19.8)	
	Type C	61 (70.9)	74 (73.3)	

ASIA, American Spinal Injury Association.
Data were presented by number (%) of patients or mean±standard deviation.

Table 3
Intergroup comparison of treatment methods and outcomes

Treatment methods and outcomes		Noninstrumented group	Instrumented group	p value
Number of patients		86	101	
Follow-up period (mo)		49±42	51±44	0.636
Combination with rifampin		1 (1.2)	3 (3.0)	0.373
Additional nonsurgical drainage of abscess		12 (14.0)	2 (2.0)	0.002
Surgical approach	Anterior only	8 (9.3)	1 (1.0)	
	Posterior only	78 (90.7)	79 (78.2)	
	Combined	0	21 (20.8)	
Type of instrumentation for PVO	Pedicle screw	–	99 (98.0)	
	Titanium cage	–	13 (12.9)	
	Hook	–	2 (2.0)	
Method of instrumentation for PVO	Additional instrumentation without extension	–	5 (5.0)	
	Extension at upper adjacent vertebrae	–	50 (49.5)	
	Extension at lower adjacent vertebrae	–	34 (33.7)	
	Extension at both upper and lower adjacent vertebrae	–	12 (11.9)	
Surgery-related complication	Reoperation	7 (8.1)	11 (10.9)	0.525
	Wound problem	3 (3.5)	7 (6.9)	0.297
Other postoperative complication	At least one following complication	7 (8.1)	9 (8.9)	0.851
	Cardiac event	2 (2.3)	3 (3.0)	
	Respiratory complication	5 (5.8)	6 (5.9)	
	Cerebrovascular complication	2 (2.3)	3 (3.0)	
	Pulmonary embolism	1 (1.2)	0	
Duration of antibiotics (d)		61±17	63±20	0.662
Hospital stay (d)		67±17	69±20	0.621
Change of antibiotic regimen	Overall rate	30 (34.9)	25 (24.8)	0.088
	Additional culture identified resistance to initial antibiotics	3 (10.0)	4 (16.0)	
	Newly identified organism in blood culture	3 (10.0)	2 (8.0)	
	Pseudomembranous colitis	5 (16.7)	6 (24.0)	
	Unidentified cause (without definite evidence of culture study)	19 (63.3)	13 (52.0)	
Recurrence	Overall recurrence	13 (15.1)	18 (17.8)	0.620
	Bacterial type			0.020
	Same organism	9 (69.2)	4 (22.2)	
	New organism	3 (23.1)	10 (55.6)	
	Clinical recurrence	1 (7.7)	4 (22.2)	
	Methicillin-resistant *Staphylococcus aureus*	3 (23.1)	11 (61.1)	0.040
Mortality	In-hospital mortality	5 (5.8)	6 (5.9)	0.971
	1-y mortality	9 (10.5)	15 (14.9)	0.371

Data were presented by number (%) of patients or mean±standard deviation.

the noninstrumented group (12 of 86 patients vs. 2 of 101 patients in the instrumented group; Table 3). Although the surgery-related complication rate, other postoperative complication rate, antibiotic use duration, and hospital stay were higher or longer in the instrumented group, the differences were not statistically significant (Table 3).

Infection recurrence occurred in 15.1% (13 of 86) of patients in the noninstrumented group and 17.8% (18 of 101) of patients in the instrumented group. No intergroup differences were observed in the infection recurrence or mortality rates, including in-hospital mortality and 1-year mortality (Table 3). Although changes in the antibiotic regimen occurred more frequently in the noninstrumented group, the differences were not statistically significant (p=.088; Table 3). The log-rank test analysis showed no statistically significant intergroup differences in the survival curves of infection recurrence (p=.691; Fig. 2) and mortality (p=.215; Fig. 3). Although the infection recurrence rate or recurrence-free survival rates did not differ significantly between the two groups, the bacterial type involved in the recurrence was significantly different (p=.020; Table 3). In the majority of cases, the causative organism of infection recurrence was the same organism responsible for the initial PVO in the noninstrumented group (69.2%, 9 of 13 patients), but the causative organism was a new organism in the instrumented group (55.6%, 10 of 18 patients). Clinical recurrence (with no identified organism) occurred more frequently in the instrumented group than in the noninstrumented group (Table 3). Methicillin-resistant *S. aureus* was also more frequently identified as the causative organism of recurrence in the

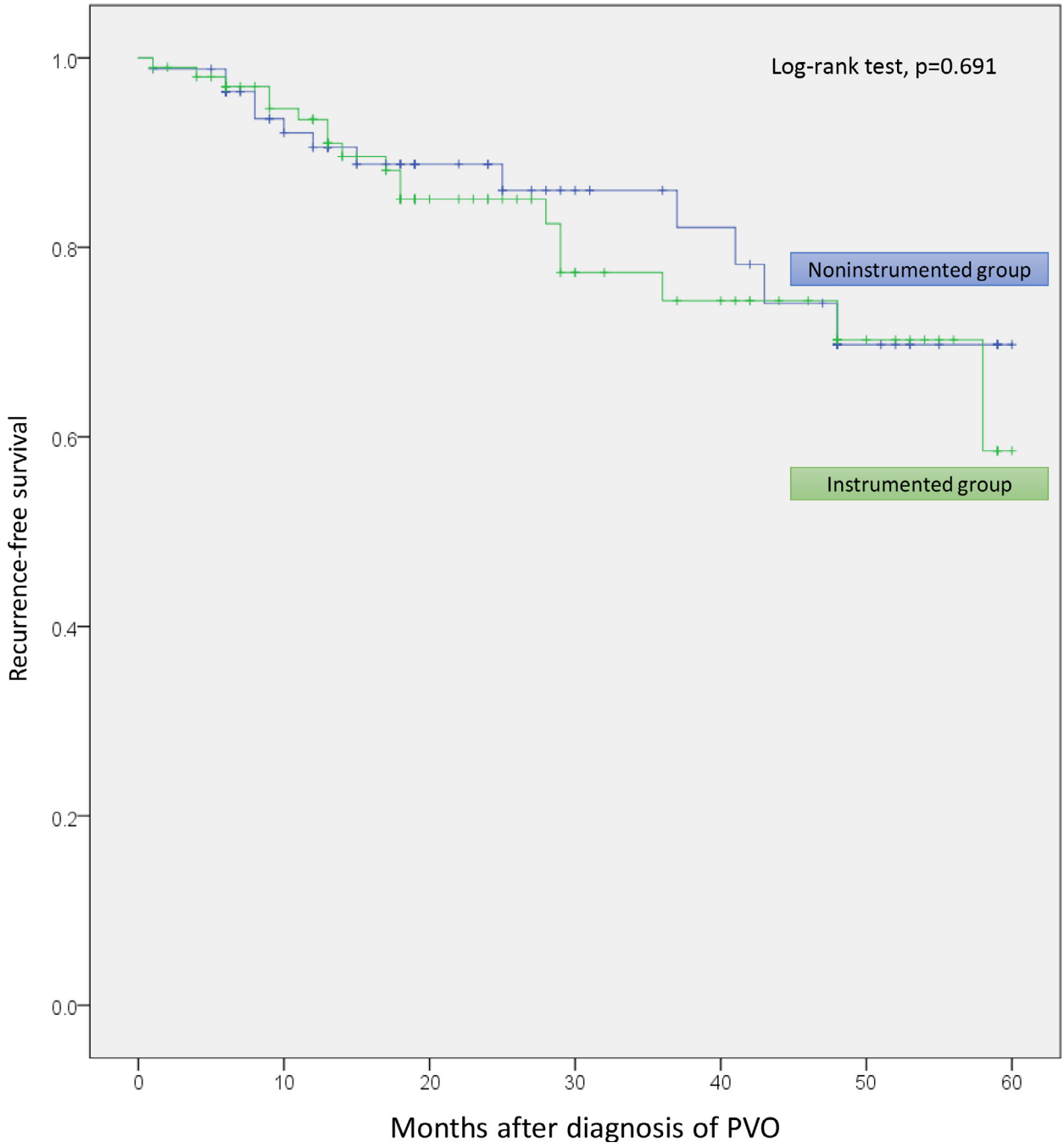

Fig. 2. Cumulative probability of recurrence-free survival by group.

instrumented group than in the noninstrumented group (p=.040; Table 3).

Comparison of treatment methods and outcomes for patients with recurrent pyogenic vertebral osteomyelitis and previous instrumentation

Although there were no statistically significant intergroup differences in mortality rate (Table 4), the patients with recurrent PVO in the instrumented group had significantly worse outcomes in terms of subsequent surgery rate (p=.033), duration of antibiotics (p=.031), and hospital stay (p=.018) than those in the noninstrumented group (Table 4). Furthermore, patients with recurrent PVO in the instrumented group underwent multiple subsequent surgeries (mean 1.9±1.5; Table 5).

Logistic regression analysis of the risk of infection recurrence

Advanced age, higher CCI score, the presence of a psoas abscess, and methicillin-resistant *S. aureus* infection were

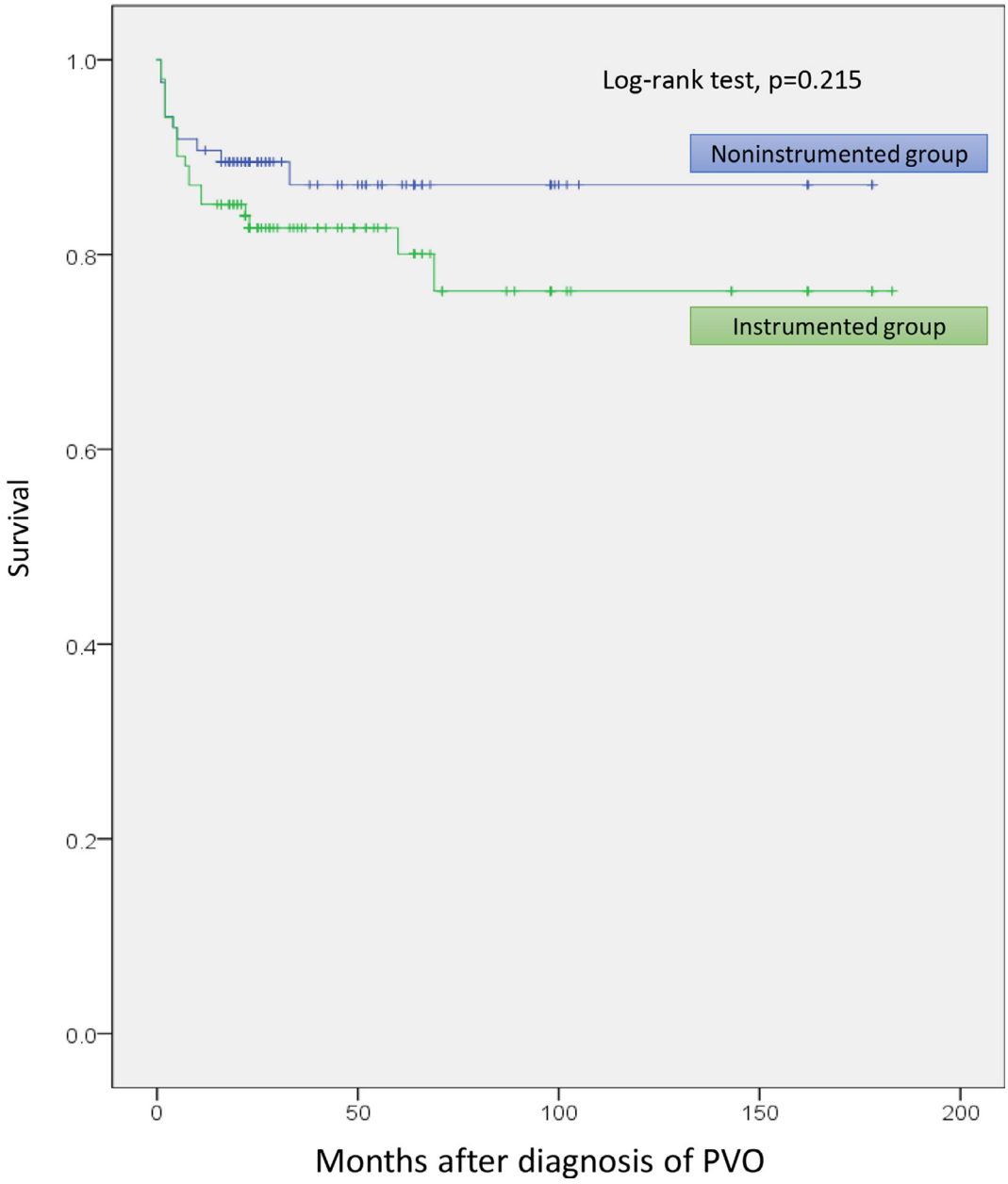

Fig. 3. Cumulative probability of survival by group.

associated with an increased risk of infection recurrence on univariate logistic regression analysis (Table 5). Even on multivariate analysis, a higher CCI score (odds ratio=1.547; p=.030), presence of psoas abscess (odds ratio=2.323; p=.048), and methicillin-resistant *S. aureus* infection (odds ratio=2.672; p=.012) showed statistically significant associations with infection recurrence (Table 6).

Discussion

Over the past few decades, the number of surgical treatments for spinal degenerative disease has been rapidly increasing [32,33], especially in complex fusion procedures that use a variety of spinal instrumentation [33,34]. These complex fusion procedures are associated with an increased risk of major complications [34]. Among the major complications of spine surgery, postoperative infection accounts for nearly half of the readmissions after spinal surgery [35] that range from 1% to 25% depending on the procedure and patient populations [36].

Early-onset postoperative wound infections can be successfully treated by debridement and the use of proper antibiotics with the retention of spinal instrumentation [37]. On the other hand, three surgical treatment options

Table 4
Comparison of treatment methods and outcomes for recurrent PVO patients with previous instrumentation

Independent variable		Recurrent cases in noninstrumented group	Recurrent cases in instrumented group	p value
Number of patients		13	18	
Subsequent treatment	Conservative treatment	9 (69.2)	5 (27.8)	
	Subsequent surgery	4 (30.8)	13 (72.2)	
	Number of subsequent surgeries	0.4±0.7	1.9±1.5	0.033
Duration of antibiotics (d)		79.8±11.9	95.9±22.2	0.031
Hospital stay (d)		82.3±12.0	98.9±22.3	0.018
Mortality	In-hospital mortality	0	1 (5.6)	0.610
(From the day of recurrence)	1-y mortality	2 (15.4)	4 (22.2)	0.501

Data were presented by number (%) of patients or mean±standard deviation.

are initially available for deep postoperative infection: (1) removal of previous instrumentation; (2) noninstrumented surgery including the retaining of previous instrumentation; and (3) instrumented surgery for the complete removal of the infected tissue and firm restabilization. Research and clinical guidelines have consistently recommended that spinal instrumentation be removed in instances of deep postoperative infection including PVO [38]. Unfortunately, despite the definite theoretical advantage of instrument removal for infection control, it is generally not available in patients with PVO and previous instrumentation in clinical practice due to nonunion, extreme structural instability, and resultant long-term bed rest. Of our cohort, 93.6% (175 of 187 patients) had initial neurologic or structural instability requiring instrumentation (type B or C by Pola et al.; Table 2), and removal of previous instrumentation without the placement of additional instrumentation was not attempted as an initial surgical option. Therefore, a decision usually has to be made between a less-invasive noninstrumented surgery, including retaining the previous instrumentation, or a more invasive additional instrumented surgery for the complete removal of the infected tissue and firm restabilization.

The results of our study demonstrate that additional instrumentation in patients with PVO and previous instrumentation showed comparable clinical outcomes in terms of infection recurrence or mortality. No significant intergroup difference was observed in the rate of infection recurrence or mortality (Table 3) despite the larger number of involved vertebral levels and the increased rate of epidural abscesses in the instrumented group (Table 2). We also identified that an increased number of medical comorbidities represented by the CCI score, presence of psoas abscess, and methicillin-resistant *S. aureus* infection was associated with a higher risk of infection recurrence in patients with PVO and previous instrumentation (Table 6). Medical comorbidities are considered a major determinant of treatment outcomes in postoperative infection after spinal instrumentation [37], and the results of such reports correspond with our results (Table 2). According to the guidelines of the Infectious Diseases Society of America, methicillin-resistant *S. aureus* infection is reportedly associated with worse clinical outcomes, although the removal of spinal instrumentation was recommended, especially in cases of later-onset infection [39]. The results of our study may corroborate such guidelines.

We paid special attention to the association between the presence of psoas abscess and worse clinical outcomes in our PVO cohort. In our PVO cohort with previous instrumentation, most surgical treatments were performed using a posterior-only approach (90.7% for the noninstrumented group vs. 78.2% for the instrumented group). Anatomical involvement in our PVO cohort mainly included the posterior elements including the epidural and paravertebral spaces (Table 2). However, psoas abscess, which can only be removed using an anterior approach, was also present in a significant number of patients (38.4% of the noninstrumented group vs. 40.6% of the instrumented group). Additional nonsurgical drainage of the abscess was performed in only a small number of patients (12 of 86 in the noninstrumented group vs. 2 of 101 in the instrumented group; Table 3); thus, the psoas abscess was not completely removed in our PVO cohorts. Spine surgeons are generally very cautious about spinal epidural abscesses, which are directly associated with paralysis and mortality [40]. In contrast, a psoas abscess, which requires an additional anterior approach, is sometimes ignored and remains after the operation. Unfortunately, an undrained psoas abscess was associated with infection recurrence [12], and it was also strongly associated with infection recurrence in our PVO cohort with previous instrumentation (Figs. 4 and 5). Therefore, we conclude that spine surgeons should be cautious about the presence of a psoas abscess during surgery and that an infectious disease specialist should choose whether to perform nonsurgical drainage for patients with PVO and previous instrumentation in whom anterior surgery may not be easily performed.

Although inferring the cause of the similar infection recurrence rate between the instrumented and noninstrumented groups is beyond the scope of this study, such similar recurrence may be accounted for by the bacterial type (Table 3). In the noninstrumented group, the causative

Table 5
Univariate logistic regression analysis for the risk of infection recurrence

Independent variable		Recurrence	No recurrence	Odd ratios	95% confidence interval	p value
Number of patients		31	156			
Group						0.620
	Noninstrumented surgery	13 (41.9)	73 (46.8)	−	−	
	Instrumented surgery	18 (58.1)	83 (53.2)	1.218	(0.558, 2.656)	
Age		71.0±6.8	68.9±4.6	1.084	(1.007, 1.167)	0.033
Gender ratio (F:M)		17:14	69:87	1.531	(0.706, 3.322)	0.281
BMI (kg/m^2)		24.7±3.3	25.4±4.2	0.961	(0.870, 1.061)	0.433
	<20	2 (6.5)	14 (9.0)	−	−	0.374
	20 to <25	18 (58.1)	65 (41.7)	2.178	(0.440, 10.769)	
	25 to <30	8 (25.8)	51 (32.7)	1.085	(0.216, 5.436)	
	≥30	3 (9.7)	26 (16.7)	1.077	(0.175, 6.630)	
Charlson Comorbidity Index score		2.0±1.3	1.4±1.0	1.659	(1.151, 2.391)	0.007
Etiology of previous surgery	Degenerative disease	24 (77.4)	116 (74.4)	−	−	0.895
	Trauma	7 (22.6)	27 (17.3)	1.253	(0.489, 3.209)	
	ETC	0	13 (8.3)	−	−	
Previous surgical method	Instrumentation with decompressive surgery	26 (83.9)	114 (73.1)	1.916	(0.691, 5.315)	0.212
	Instrumentation with bone graft	27 (87.1)	147 (94.2)	0.413	(0.119, 1.438)	0.165
Previously instrumented region	Cervical	2 (6.5)	16 (10.3)	−	−	0.743
	Thoracic	7 (22.6)	39 (25.0)	1.436	(0.269, 7.672)	
	Lumbar	22 (71.0)	101 (64.7)	1.743	(0.373, 8.133)	
Number of previously instrumented level	1 or 2 level	18 (58.1)	112 (71.8)	−	−	0.133
	Over 2 level	13 (41.9)	44 (28.2)	1.838	(0.831, 4.067)	
Previous wound problem	3 (9.7)	13 (8.3)	2.115	(0.695, 6.437)	0.187	
Interval between previous surgery and surgery for infection	Mean interval	232±212	260±249	0.999	(0.997, 1.001)	0.469
	Within 6 mo	14 (45.2)	65 (41.7)	−	−	0.633
	Between 6 and 12 mo	16 (51.6)	78 (50.0)	0.904	(0.433, 2.097)	
	Over 12 mo	1 (3.2)	13 (8.3)	0.340	(0.043, 2.959)	
Presumed source of infection	Skin and subcutaneous infection	2 (6.5)	7 (4.5)	−	−	0.369
	Urinary tract infection	5 (16.1)	12 (7.7)	1.458	(0.221, 9.617)	
	Endocarditis	1 (3.2)	2 (1.3)	1.750	(0.099, 30.837)	
	Unknown	23 (74.2)	135 (86.5)	0.596	(0.117, 3.051)	
Neurologic deficit by ASIA grade	A, B, or C	4 (12.9)	9 (5.8)	3.056	(0.842, 11.092)	0.107
	D	11 (35.5)	37 (23.7)	2.044	(0.871, 4.798)	
	E	16 (51.6)	110 (70.5)	−	−	
Number of infected levels	1 or 2 level	20 (64.5)	119 (76.3)	−	−	0.174
	Over 2 level	11 (35.5)	37 (23.7)	1.769	(0.777, 4.029)	
Anatomical involvement	Epidural abscess	26 (83.9)	113 (72.4)	1.979	(0.714, 5.485)	0.190
	Paravertebral abscess	19 (61.3)	83 (53.2)	1.393	(0.633, 3.063)	0.410
	Psoas abscess	18 (58.1)	56 (35.9)	2.473	(1.128, 5.420)	0.024
Causative organism of initial infection (1)						0.044
	Staphylococcus aureus	24 (77.4)	77 (49.4)			
	methicillin resistant	11 (35.5)	24 (15.4)	2.750	(0.668, 11.324)	
	methicillin sensitive	13 (41.9)	53 (34.0)	1.472	(0.376, 5.760)	
	Other gram-positive bacteria	3 (9.7)	45 (28.8)	−	−	
	Gram-negative bacteria	3 (9.7)	18 (11.5)	0.400	(0.074, 2.170)	
	Others	1 (3.2)	16 (10.3)	0.375	(0.035, 3.977)	
Causative organism of initial infection (2)	Methicillin-resistant *Staphylococcus aureus*	11 (35.5)	24 (15.4)	3.025	(1.287, 7.111)	0.011
	The other organisms	20 (64.5)	132 (84.6)	−	−	
White blood cell ($\times 10^9$/L)		12886±3663	12181±4062	1.000	(1.000, 1.000)	0.370
C-reactive protein (CRP, mg/L)		106±30	103±22	1.006	(0.990, 1.023)	0.453
Erythrocyte sedimentation rate (ESR, mm/h)		66±30	65±26	1.001	(0.987, 1.016)	0.876
Severity of infection by Pola et al.	Type A	0	12 (7.7)			0.621
	Type B	5 (16.1)	35 (22.4)			
	Type C	26 (83.9)	109 (69.9)			

Table 5 (***Continued***)

Independent variable		Recurrence	No recurrence	Odd ratios	95% confidence interval	p value
Surgical approach for infection	Anterior only	1 (3.2)	8 (5.1)	–	–	0.868
	Posterior only	26 (83.9)	131 (84.0)	1.588	(0.190, 13.242)	
	Combined	4 (12.9)	17 (10.9)	1.882	(0.180, 19.677)	
Duration of antibiotics (d)		69±22	63±17	1.018	(0.995, 1.042)	0.132
Hospital stay (d)		62±21	57±17	1.020	(0.997, 1.043)	0.086

ASIA, American Spinal Injury Association.
Data were presented by number (%) of patients or mean±standard deviation.

organisms of infection recurrence were primarily the same organisms responsible for the initial PVO (69.2%; 9 of 13 cases; Table 3). In contrast, the majority of the causative organisms of infection recurrence in the noninstrumented group were new bacteria (55.6%; 10 of 18 cases) or unidentified (22.2%; 4 of 18 cases; Table 3). During instrumented surgery, a more aggressive removal of infected tissues, including abscesses within the intraosseous and intradiscal space, is possible because of the much wider surgical approach. Such aggressive abscess removal during instrumented surgery markedly reduces the infection burden from the original causative organisms and may also prevent infection recurrence by the same bacteria. Although infection recurrence occurred in the instrumented group, it is difficult to determine the original causative organism caused by a greatly reduced infection burden, which may lead to an increased rate of clinical recurrence. However, wider surgical dissection and further instrumentation during instrumented surgery markedly increased the secondary infection rate by another organism during the perioperative period (a possibly increased rate of recurrence by new bacteria); this organism was identified as methicillin-resistant *S. aureus* in 61.1% of patients with infection recurrence (11 of 18 cases; Table 3).

The similar infection recurrence rates noted between the instrumented and noninstrumented group is noteworthy. However, if instrumented patients with PVO experience infection recurrence, their clinical outcomes could be much worse than those of the noninstrumented patients with PVO, including (1) an increased incidence of methicillin-resistant *S. aureus* infection (Table 3); (2) an increased rate of subsequent surgery (or multiple surgeries; Table 5); and (3) an increased duration of both antibiotic use and hospital stay (Table 5). Severe medical comorbidities, the presence of psoas abscess, and methicillin-resistant *S. aureus* infection were associated with a high risk of infection recurrence. Therefore, additional instrumentation for patients with PVO and previous spinal instrumentation should be carefully considered in patients at such a high risk of infection recurrence. In addition, the 1-year mortality of the instrumented group (14.9%) was higher than that of the noninstrumented group (10.5%), even if statistically insignificant (Table 3). A large-scale multicenter study is required to confirm the effect of additional instrumentation on the survival of PVO patients with previous instrumentation.

The main limitation of our study is its retrospective design. The instrumented group may represent healthier patients with less medical comorbidities or less-severe infection than those in the noninstrumented group. Actually, the noninstrumented group was older than the instrumented group, even if statistically insignificant (p=.062; Table 1). We paid great attention to such selection bias and thoroughly retrieved data on various covariates that could influence the results as confounders, including factors from the demographic data, a detailed history of medical comorbidities, including the CCI score, and detailed infection profiles, including the laboratory and radiographic data of infection (Tables 1 and 2). Fortunately, there were no differences in the various covariates. Next, over the 17-year data collection period, there was considerable variation in the following treatment methods of PVO: (1) indications for additional instrumentation; (2) consensus or relative protocol for medical treatment of postoperative PVO; and (3) surgical technique. Therefore, our study results should be carefully

Table 6
Multivariate logistic regression analysis for the risk of infection recurrence

Independent variable	Odd ratios	95% confidence interval	p value
Age	1.039	(0.958, 1.126)	0.356
Charlson Comorbidity Index score	1.547	(1.043, 2.292)	0.030
Psoas abscess	2.323	(1.009, 5.347)	0.048
Methicillin-resistant *Staphylococcus aureus*	2.672	(1.071, 6.667)	0.012

Data were presented by number (%) of patients or mean±standard deviation.

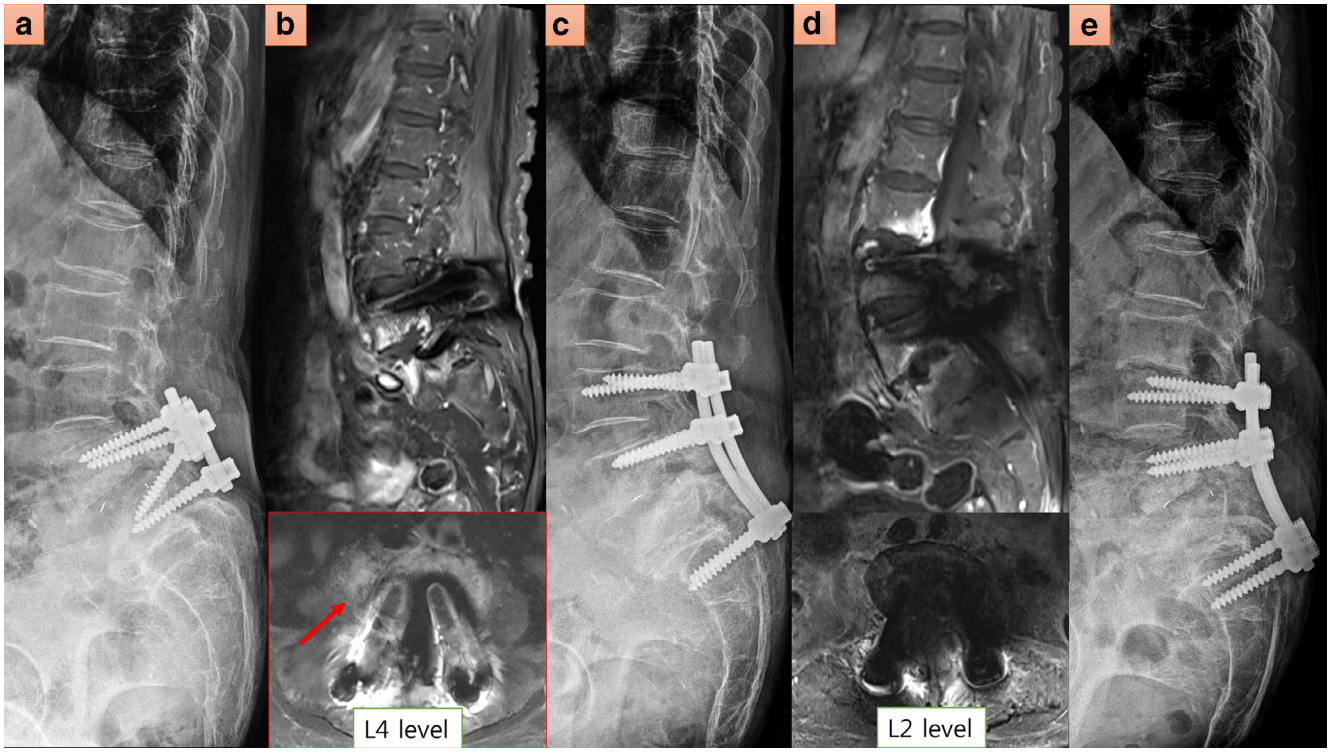

Fig. 4. Recurrent postoperative pyogenic vertebral osteomyelitis (PVO) case with undrained psoas abscess (1). (a) An 83-year-old woman had postoperative PVO 10 months after posterior interbody fusion at the L4–L5 level. (b) Postoperative PVO occurred at the L4–L5 level with a right-side dominant psoas abscess (red arrow). (c) Additional instrumentation and posterolateral fusion were provided (L3–S1) without drainage of the psoas abscess. (d) Five months after the additional instrumentation was placed, PVO recurred at the L2–L3 level with an epidural abscess. (e) Six months after conservative treatment.

interpreted. However, we believe that firm stabilization of neurologically and mechanically unstable spinal structures has a great theoretical advantage for the treatment of PVO. In this respect, we aimed to gather evidence that additional instrumentation can be applied in PVO patients with previous instrumentation without a greatly increased risk of infection recurrence and mortality. Further large-scale prospective randomized studies are required to validate our findings.

In conclusion, surgery for additional instrumentation in patients with PVO and previous instrumentation showed similar infection recurrence and mortality rates to those of

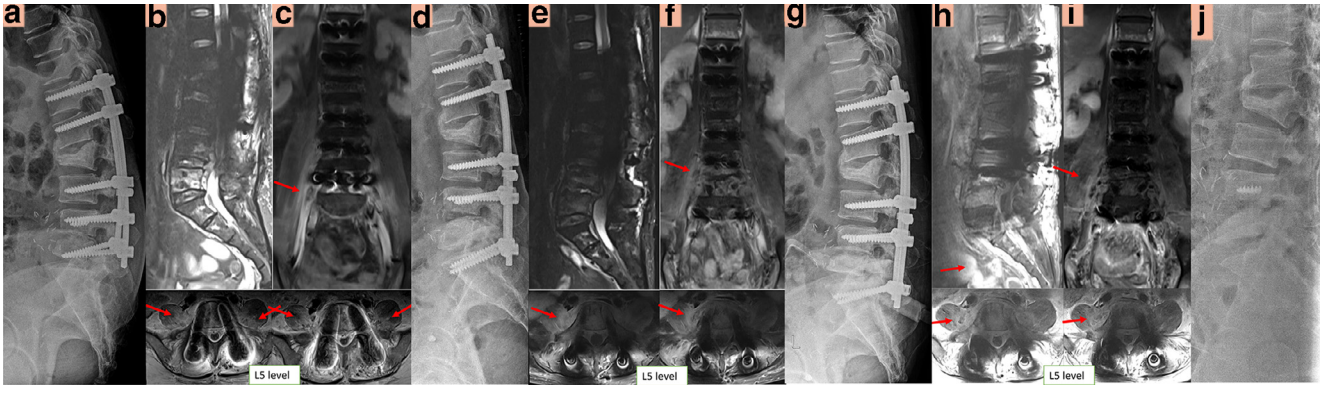

Fig. 5. Recurrent postoperative pyogenic vertebral osteomyelitis (PVO) case with an undrained psoas abscess (2). Anterior surgical approach or nonsurgical drainage of the psoas abscess was not attempted due to her history of multiple abdominal surgeries. (a) A 56-year-old woman had postoperative PVO at the L4–L5 level 8 months after posterolateral fusion at the T12–L5 level. (b, c) Postoperative PVO occurred at the L4–L5 level with an epidural abscess and bilateral psoas abscess (red arrows). (d) Additional instrumentation with posterolateral fusion was done at T12–S1 level. (e, f) After 8-week course of antibiotics, epidural abscess disappeared, but psoas abscess still remained. (g) Narrowing of L4–L5 space and loosening of S1 pedicle screw. (h, i) One month later, epidural abscess reappeared and psoas abscess became more prominent. (j) Caused by uncontrolled infection, removal of the instrument was done.

noninstrumented surgery despite the larger number of involved vertebral levels and increased frequency of epidural abscesses. However, the 1-year mortality rate of the instrumented group was higher than that of the noninstrumented group, although the difference was statistically insignificant. Therefore, our study results should be interpreted with great caution.

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References

[1] Grammatico L, Baron S, Rusch E, Lepage B, Surer N, Desenclos JC, et al. Epidemiology of vertebral osteomyelitis (VO) in France: analysis of hospital-discharge data 2002-2003. Epidemiol Infect 2008;136:653–60.
[2] Nickerson EK, Sinha R. Vertebral osteomyelitis in adults: an update. Br Med Bull 2016;117:121–38.
[3] Kehrer M, Pedersen C, Jensen TG, Lassen AT. Increasing incidence of pyogenic spondylodiscitis: a 14-year population-based study. J Infect 2014;68:313–20.
[4] Akiyama T, Chikuda H, Yasunaga H, Horiguchi H, Fushimi K, Saita K. Incidence and risk factors for mortality of vertebral osteomyelitis: a retrospective analysis using the Japanese diagnosis procedure combination database. BMJ Open 2013;3:e002412.
[5] Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty 2012;27:61–5. e1.
[6] Nickerson EK, Sinha R. Vertebral osteomyelitis in adults: an update. Br Med Bull 2016;117:121–38.
[7] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.
[8] Nasto LA, Colangelo D, Mazzotta V, Di Meco E, Neri V, Nasto RA, et al. Is posterior percutaneous screw-rod instrumentation a safe and effective alternative approach to TLSO rigid bracing for single-level pyogenic spondylodiscitis? Results of a retrospective cohort analysis. Spine J 2014;14:1139–46.
[9] Wood KB, Li W, Lebl DR, Ploumis A. Management of thoracolumbar spine fractures. Spine J 2014;14:145–64.
[10] McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. Clin Infect Dis 2002;34:1342–50.
[11] Pola E, Logroscino CA, Gentiempo M, Colangelo D, Mazzotta V, Di Meco E, et al. Medical and surgical treatment of pyogenic spondylodiscitis. Eur Rev Med Pharmacol Sci 2012;16(Suppl 2):35–49.
[12] Roblot F, Besnier JM, Juhel L, Vidal C, Ragot S, Bastides F, et al. Optimal duration of antibiotic therapy in vertebral osteomyelitis. Semin Arthritis Rheum 2007;36:269–77.
[13] de Graeff JJ, Paulino Pereira NR, van Wulfften Palthe OD, Nelson SB, Schwab JH. Prognostic factors for failure of antibiotic treatment in patients with osteomyelitis of the spine. Spine 2017;42:1339–46.
[14] Tschugg A, Lener S, Hartmann S, Rietzler A, Neururer S, Thome C. Primary acquired spondylodiscitis shows a more severe course than spondylodiscitis following spine surgery: a single-center retrospective study of 159 cases. Neurosurg Rev 2018;41:141–7.
[15] McHenry MC, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. Clin Infect Dis 2002;34:1342–50.
[16] Hoiby N, Bjarnsholt T, Givskov M, Molin S, Ciofu O. Antibiotic resistance of bacterial biofilms. Int J Antimicrob Agents 2010;35:322–32.
[17] Bydon M, De la Garza-Ramos R, Macki M, Naumann M, Sciubba DM, Wolinsky JP, et al. Spinal instrumentation in patients with primary spinal infections does not lead to greater recurrent infection rates: an analysis of 118 cases. World Neurosurg 2014;82:e807–14.
[18] Noh SH, Zhang HY, Lim HS, Song HJ, Yang KH. Decompression alone versus fusion for pyogenic spondylodiscitis. Spine J 2017;17:1120–6.
[19] Than KD, Mummaneni PV. Spinal instrumentation in the setting of primary infection. World Neurosurg 2014;82:e713–4.
[20] Talia AJ, Wong ML, Lau HC, Kaye AH. Safety of instrumentation and fusion at the time of surgical debridement for spinal infection. J Clin Neurosci 2015;22:1111–6.
[21] Park KH, Cho OH, Lee YM, Moon C, Park SY, Moon SM, et al. Therapeutic outcomes of hematogenous vertebral osteomyelitis with instrumented surgery. Clin Infect Dis 2015;60:1330–8.
[22] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.
[23] Jean M, Irisson JO, Gras G, Bouchand F, Simo D, Duran C, et al. Diagnostic delay of pyogenic vertebral osteomyelitis and its associated factors. Scand J Rheumatol 2017;46:64–8.
[24] Zimmerli W. Clinical practice. Vertebral osteomyelitis. N Engl J Med 2010;362:1022–9.
[25] Palestro CJ, Love C, Miller TT. Infection and musculoskeletal conditions: imaging of musculoskeletal infections. Best Pract Res Clin Rheumatol 2006;20:1197–218.
[26] Carragee EJ. The clinical use of magnetic resonance imaging in pyogenic vertebral osteomyelitis. Spine 1997;22:780–5.
[27] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[28] Pola E, Autore G, Formica VM, Pambianco V, Colangelo D, Cauda R, et al. New classification for the treatment of pyogenic spondylodiscitis: validation study on a population of 250 patients with a follow-up of 2 years. Eur Spine J 2017;26:479–88.
[29] Zimmerli W, Sendi P. Role of rifampin against staphylococcal biofilm infections in vitro, in animal models, and in orthopedic-device-related infections. Antimicrob Agents Chemother 2019;63:e01746–18.
[30] Cho OH, Bae IG, Moon SM, Park SY, Kwak YG, Kim BN, et al. Therapeutic outcome of spinal implant infections caused by Staphylococcus aureus: a retrospective observational study. Medicine (Baltimore) 2018;97:e12629.
[31] Park KH, Cho OH, Lee JH, Park JS, Ryu KN, Park SY, et al. Optimal duration of antibiotic therapy in patients with hematogenous vertebral osteomyelitis at low risk and high risk of recurrence. Clin Infect Dis 2016;62:1262–9.
[32] Weinstein JN, Lurie JD, Olson P, Bronner KK, Fisher ES, Morgan TS. United States trends and regional variations in lumbar spine surgery: 1992–2003. Spine 2006;31:2707–14.
[33] Yoshihara H, Yoneoka D. National trends in the surgical treatment for lumbar degenerative disc disease: United States, 2000 to 2009. Spine J 2015;15:265–71.
[34] Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. JAMA 2010;303:1259–65.
[35] Schairer WW, Carrer A, Deviren V, Hu SS, Takemoto S, Mummaneni P, et al. Hospital readmission after spine fusion for adult spinal deformity. Spine 2013;38:1681–9.
[36] Brown EM, Pople IK, de Louvois J, Hedges A, Bayston R, Eisenstein SM, et al. Spine update: prevention of postoperative infection in patients undergoing spinal surgery. Spine 2004;29:938–45.

[37] Chen SH, Lee CH, Huang KC, Hsieh PH, Tsai SY. Postoperative wound infection after posterior spinal instrumentation: analysis of long-term treatment outcomes. Eur Spine J 2015;24:561–70.

[38] Kanayama M, Hashimoto T, Shigenobu K, Oha F, Iwata A, Tanaka M. MRI-based Decision Making of Implant Removal in Deep Wound Infection After Instrumented Lumbar Fusion. Clin Spine Surg 2017; 30:e99–e103.

[39] Liu C, Bayer A, Cosgrove SE, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus aureus Infections in Adults and Children. Clinical Infectious Diseases 2011;52:e18–55.

[40] Shah AA, Ogink PT, Harris MB, Schwab JH. Development of Predictive Algorithms for Pre-Treatment Motor Deficit and 90-Day Mortality in Spinal Epidural Abscess. J Bone Joint Surg Am 2018;100:1030–8.