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Risk Factors for Pseudarthrosis After Surgical Site Infection of the Spine

DOUGLAS A. HOLLERN, MD,^{1,2,3} BARRETT I. WOODS, MD,^{1,2} NEIL V. SHAH, MD, MS,³ GREGORY D. SCHROEDER, MD,^{1,2} CHRISTOPHER K. KEPLER, MD, MBA,^{1,2} MARK F. KURD, MD,^{1,2} I. DAVID KAYE, MD,^{1,2} PAUL W. MILLHOUSE, MD, MBA,³ BASSEL G. DIEBO, MD,³ CARL B. PAULINO, MD,³ ALAN S. HILIBRAND, MD,^{1,2} ALEXANDER R. VACCARO, MD, PHD, MBA,^{1,2} KRIS E. RADCLIFF, MD^{1,2}

¹Rothman Institute, Philadelphia, Pennsylvania, ²Department of Orthopaedic Surgery, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania, ³Department of Orthopaedic Surgery and Rehabilitation Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York

ABSTRACT

Background: Pseudarthrosis following spinal fusion is a complication that frequently requires revision surgery. Reported rates of pseudarthrosis after surgical site infection (SSI) range from 30% to 85%, but few studies have identified infection as an independent risk factor for its development. The purpose of this study was to determine the incidence of clinically symptomatic pseudarthrosis in patient who developed SSI following lumbar fusion and to identify factors associated with its development.

Methods: This was a retrospective review of a prospectively collected database. Patients who underwent spinal surgery and developed SSI between January 2005 and March 2015 with a minimum 2-year follow-up were included. Patient-specific and procedural characteristics were recorded. Presence of pseudarthrosis was determined clinically by the treating surgeon and was confirmed radiographically. All those in the Pseudarthrosis group required a revision procedure after the eradication of infection. Univariate and multivariate analyses were conducted as appropriate.

Results: A total of 416 patients were included. Of these, 21 (5.0%) developed symptomatic pseudarthrosis following SSI. In this cohort, multivariate regression showed that age, Charlson Comorbidity Index, male sex, and surgical approach were not significant predictors of pseudarthrosis formation. However, number of levels fused was found to be the leading predictor for pseudarthrosis development (odds ratio [OR], 1.356/level, $P < .001$), followed by body mass index (OR, 1.083/point, $P < .009$) in this cohort. The number of levels fused was found to be a significant predictor of hardware removal (OR, 1.190/level, $P < .001$). Of the 21 pseudarthrosis cases, 85.7% found staphylococcal species, of which 27.8% exhibited methicillin-resistant *Staphylococcus aureus*.

Conclusions: The number of spinal levels fused and body mass index are independent predictors of pseudarthrosis in patients who develop SSI after spinal fusion.

Level of Evidence: Level 4

Clinical Relevance: This is the first known study to specifically identify risk factors for the development of symptomatic pseudarthrosis.

Complications

Keywords: symptomatic pseudarthrosis, risk factors, spinal fusion

INTRODUCTION

Spinal surgery is associated with many serious complications, including pseudarthrosis, neurological injury, paralysis, sepsis, and even death. One of the major problems after spinal surgery is development of surgical site infection (SSI). The literature reports^{1–7} the incidence of infection following spinal surgery to be between 0.5% and 7%. Significant scientific effort has been exerted to identify risk factors that may predispose patients to infection. Several patient-specific factors such as age, body mass index (BMI), subcutaneous fat thickness, and

nutritional status have been implicated, in addition to extrinsic factors such as volume of allogenic transfusion and length of surgery.^{8–10} Interventions such as the intraoperative application of vancomycin powder to the surgical site and use of negative-pressure dressings have improved infection rates following spinal surgery.^{11–13} Despite these advancements, infections following spinal procedures continue to present a significant challenge to surgeons and serve as a cause of significant morbidity for patients. In addition to the morbidity,

the financial implications of infection and revision surgery cannot be overstated.

The ultimate goal in management of postoperative spinal infections is to eradicate the pathogen without compromising patient function. Aggressive irrigation and debridement of the wound bed with supplemental antibiotic treatment is the standard of care for all deep and most superficial infections. In each case, the surgeon must decide whether to remove existing spinal instrumentation. Hardware retention is typically achievable in cases where the infection is identified early, appropriate antibiotics are started, and the wound is aggressively debrided. However, certain organisms, such as *Staphylococcus aureus*, coagulase-negative staphylococci, and *Pseudomonas aeruginosa*, possess the ability to create adherent biofilms on implanted instrumentation, typically necessitating hardware removal for successful treatment. Early hardware removal, aggressive debridement of bone graft, and the physiological implications of infection can all contribute to the development of pseudoarthrosis.¹⁴

Reported rates of pseudarthrosis after deep spinal wound infections range from 30% to 85% in the literature, but few studies have identified independent risk factors for the development of pseudarthrosis following infection.¹⁵ The purpose of this study was to determine the incidence of symptomatic pseudarthrosis in a cohort of patients who developed SSI after spinal fusion and to identify specific factors that may increase the risk of this complication. In addition, we evaluated whether removal of hardware in the setting of infection resulted in higher rates of pseudarthrosis. To our knowledge, this is the single largest study to date of pseudarthrosis in the setting of infection.

MATERIAL AND METHODS

Study Population

A prospectively collected database at a single institution was retrospectively reviewed to identify all patients who underwent spinal surgery and developed a SSI, as defined by National Healthcare Safety Network criteria, between January 2005 and March 2015.¹⁶ Patients who underwent spinal procedures (instrumented decompression and fusion) for trauma, degenerative pathologies, and deformity were included.

Patient Demographics

Clinical data regarding each patient were collected using operative records, billing code queries, patient charts, and clinic notes. Patient characteristics recorded included age, sex, BMI, tobacco use, and Charlson Comorbidity Index (CCI) score.

Surgical Data

Surgical data collected included number of levels fused, duration of surgery, approach, time until development of infection, number of irrigation and debridement procedures, organisms identified in intraoperative specimens, removal of hardware, presence or absence of radiographic and/or clinical/symptomatic pseudarthrosis, and use of vacuum-assisted closure. Pseudarthrosis was determined clinically by the treating surgeon and confirmed radiographically.

All patients included in the Pseudarthrosis group required an instrumented revision procedure following eradication of infection. All patients received prophylactic antibiotic treatment per the standard of care. Microbiologic cultures were collected from all patients who developed deep SSI.

Statistical Methods

Univariate analysis was conducted to compare patients who developed pseudarthrosis after infection with those who did not. Variables included in the analysis were type of surgery, number of spinal levels fused, number of washouts needed for infection control, whether removal of hardware was required, timing of hardware removal (if applicable), whether vacuum-assisted closing devices were used, and pathogens identified in culture.

Multivariate analysis was performed on R version 3.2.2 (Lucent Technologies, Murray Hill, New Jersey) using a Random Forest technique, including a χ^2 test, to account for the large number of patient-related factors included in the data analysis and identify potential risk factors for pseudarthrosis. Multiple logistic regression analysis was also performed to determine risk factors for the development of pseudarthrosis, with pseudarthrosis as the categorical dependent variable and the following outcomes/factors as independent variables: age, BMI, sex, CCI number of spinal levels fused, removal of hardware, and surgical approach.

Data management and statistical analysis were performed using Excel 2010 and SPSS version 20

Table 1. Univariate analysis comparison of demographic information between patients who developed pseudarthrosis and those who did not.

	Pseudarthrosis (n = 21)	No Pseudarthrosis (n = 395)	P Value*
Sex: n (%)			
Male	7 (33.3)	231 (58.5)	.353
Female	14 (66.7)	164 (41.5)	.353
Age, y, mean (range)	56.52 (28–83)	57.57 (17–87)	.943
BMI, mean (range)	31.50 (21.3–51.5)	30.50 (14.8–63)	.017
CCI, mean (range)	1.07 (0–4)	1.16 (0–13)	.648

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index.

* Bold indicates significance ($P < .05$).

(IBM Corp, Armonk, New York). Results were considered statistically significant when $P \leq .05$.

RESULTS

Demographics and Clinical Data

A total of 416 patients were included, consisting of 238 men (57.2%) and 178 women (42.9%) who developed surgical site infection following spinal fusion. Mean age of included patients was 57.1 years (range, 17–87 years). Of 416 patients, 21 (5.0%) developed a clinically apparent pseudarthrosis (Pseudarthrosis group). More detailed information about patient-specific and procedural characteristics can be found in Table 1 and Table 2, respectively. Of the individuals with available BMI values, 112 (30%) patients were overweight, 82 (22%) were obese, and 98 (26.3%) were morbidly obese. There were 81 (21.7%) individuals with a BMI < 25 , of whom only 5 (1.3%) were underweight.

The average CCI did not vary significantly between groups: For patients with pseudarthrosis after infection, mean CCI was 3.57 (range, 0–11), compared with 3.30 for patients without pseudarthrosis (Nonpseudarthrosis group; range, 0–17; $P = .648$). Among Pseudarthrosis patients, 15 cultures were monomicrobial, whereas 6 patients had

polymicrobial culture results. More detailed characteristics of the patients who developed pseudarthrosis can be found in Table 3.

Aside from spinal fusions involving the lumbar segment (256 patients, 61.5%), all remaining curves were equally affected (cervical: 140 patients, 33.7%; thoracic: 146 patients, 35.1%; and sacral: 113 patients, 27.2%). Surgeries on multiple segments were slightly more frequent than unisegmental fusions (221 patients, 53.1% versus 195 patients, 46.1%, respectively). Almost half of the fusions involved 2 segments only (cervicothoracic: 66 patients, 15.9%; thoracolumbar: 40 patients, 9.6%; and lumbosacral: 98 patients, 23.6%; total = 204 individuals, 49%), whereas surgeries of ≥ 3 spinal curves were rare (17 patients in total, 4%; of whom only one individual underwent an entire cervicothoraco-lumbo-sacral fusion).

Multivariate regression identified the number of spinal levels fused (odds ratio [OR], 1.356/level, 95% CI, 1.15–1.54, $P < .001$) as the most significant predictor for the development of pseudarthrosis, followed by BMI (OR, 1.083/point, 95% CI, 1.02–1.15, $P = .008$; Figures 1 and 2). Age, CCI, sex, and surgical approach were not found to be significant predictors ($P > .05$). Timing of hardware removal was not significantly associated

Table 2. Univariate analysis of procedural parameters comparing those who developed pseudarthrosis with those who did not.

	Pseudarthrosis (n = 21)	No Pseudarthrosis (n = 395)	χ^2	P Value*
Number of I&D procedures, mean (range)	1.48 (1 – 3)	1.29 (1 – 4)129
Removal of hardware, n (%)	7 (33.3)	42 (10.6)	3.95	.049
Type of procedure, n (%)			...	
Fusion	19 (90.4)	318 (80.5)		.249
Re-fusion	1 (4.8)	35 (8.9)		.517
Laminectomy	1 (4.8)	43 (10.9)		.376
Fused levels, n (%)	6.24 (95% CI, 4.28–8.20)	3.36 (95% CI, 3.09–3.63)	12.6	.001
0	0 (0)	39 (9.4)		
1–2	6 (1.4)	150 (36.1)		
3–4	2 (0.5)	96 (23.1)		
≥ 5	13 (3.1)	110 (26.4)		

Abbreviation: I&D, incision and drainage.

* Bold indicates significance ($P < .05$).

Table 3. Patients with pseudarthrosis.

Patient	Sex	Age, y	Fusion	No. of Levels Fused	Approach	No. of I&D Procedures	Removal of Hardware	Mono- vs Polymicrobial	Pathogens
1	F	55	Thoracic	9	Posterior	3	No	Monomicrobial	MSSA
2	F	60	Cervical	1	Posterior	1	Yes	Monomicrobial	<i>Pseudomonas aeruginosa</i>
3	M	49	Cervical, thoracic	6	Combined	1	Yes	Monomicrobial	MSSA
4	F	70	Cervical, thoracic	14	Combined	1	No	Polymicrobial	<i>Enterococcus faecalis</i> Group D <i>Bacteroides fragilis</i> CoNS
5	F	40	Cervical, thoracic	5	Posterior	1	No	Polymicrobial	MSSA CoNS
6	F	66	Cervical, thoracic	1	Anterior	1	No	Monomicrobial	MSSA
7	M	41	Cervical, thoracic	8	Combined	2	No	Monomicrobial	MRSA
8	M	50	Lumbar, sacral	8	Combined	1	Yes	Monomicrobial	MSSA
9	F	65	Cervical	10	Combined	1	No	Monomicrobial	<i>Hafnia alvei</i>
10	F	59	Lumbar	10	Posterior	1	Yes	Monomicrobial	MRSA
11	M	61	Lumbar	6	Posterior	1	Yes	Monomicrobial	MRSA
12	M	28	Lumbar, sacral	6	Posterior	1	Yes	Monomicrobial	MRSA
13	M	55	Lumbar	2	Combined	3	No	Polymicrobial	<i>Citrobacter koseri</i> <i>B. fragilis</i> <i>Eggerthella lentum</i> <i>Corynebacterium</i> spp.
14	F	64	Cervical, thoracic	3	Posterior	2	No	Polymicrobial	<i>Corynebacterium</i> spp. <i>Proteus mirabilis</i> CoNS
15	F	57	Lumbar	11	Combined	1	No	Monomicrobial	MSSA
16	M	55	Cervical, thoracic	2	Combined	3	No	Polymicrobial	<i>C. koseri</i> <i>B. fragilis</i> <i>E. lentum</i> <i>Corynebacterium</i> spp.
17	F	73	Thoracic	3	Posterior	2	Yes	Monomicrobial	MRSA
18	F	64	Lumbar, sacral	1	Posterior	1	No	Monomicrobial	MSSA
19	F	83	Cervical	2	Posterior	2	No	Monomicrobial	MSSA
20	F	40	Thoracic, lumbar	5	Posterior	1	No	Polymicrobial	MSSA CoNS
21	F	46	Lumbar, sacral	16	Combined	1	No	Monomicrobial	MSSA

Abbreviations: CoNS, coagulase-negative staphylococci; I&D, incision and drainage; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*.

with development of pseudarthrosis ($P = .967$). The number of levels fused was found to be a statistically significant predictor of hardware removal (OR, 1.19/level, 95% CI, 1.08–1.30, $P < .001$; Figure 3).

Pathogen Culture

Among all 416 patients who developed SSI, cultures showed that 24 pathogens, including 23 bacterial pathogens and 1 fungus, were isolated. Eighteen patients (4.6%) either had no cultures taken or showed no growth once cultures resulted.

The prevalence of gram-positive rods in culture did not vary significantly between groups (80.9% Pseudarthrosis versus 86.3% Nonpseudarthrosis, $P = .959$); this was also the case for gram-positive cocci (14.3% among Pseudarthrosis versus 9.9% without, $P = .435$). Rate of identification in culture of gram-negative rods also did not differ significantly between the 2 groups (28.6% in those with pseudarthrosis versus 44.3% in those without,

$P = .324$). Anaerobes were identified significantly more frequently in patients who developed pseudarthrosis than in those who did not (14.3% versus 6.3%, $P = .01$).

Among the 21 pseudarthrosis cases, staphylococcal species were the most common etiologic agents of infection among all gram-positive cocci (18/21 isolates; 85.7%), with 27.8% of these exhibiting methicillin resistance (5/18). Of the 395 isolates from patients without pseudarthrosis, staphylococcal species were also the most common isolate among gram-positive cocci and were present in 86.1% (324/395) of positive cultures (including 1 case with polymicrobial culture results). Of these isolates, 26.2% (85/324) were further demonstrated to be methicillin-resistant *Staphylococcus aureus*; the culture rates were comparable between patients with and without pseudarthrosis ($P > .05$). Overall, methicillin-sensitive *S. aureus* culture rates did not vary significantly between groups (42.9% among Pseudarthrosis versus 30.6% without, $P > .05$). Coagulase-negative staphylococci were the next

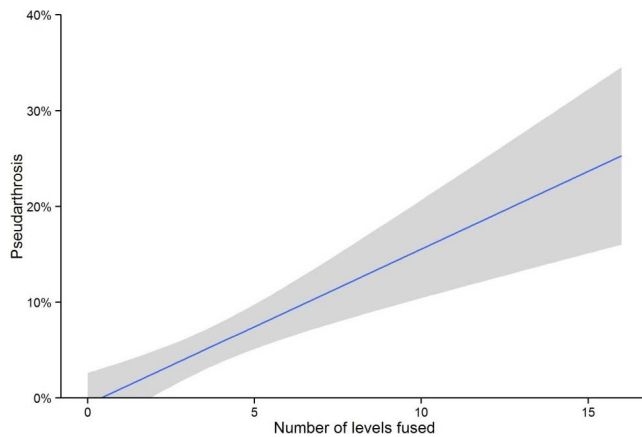


Figure 1. Variable importance plot of the number of levels fused, showing a statistically significant association with the development of pseudarthrosis. The grey shadow spans the 95% confidence interval region.

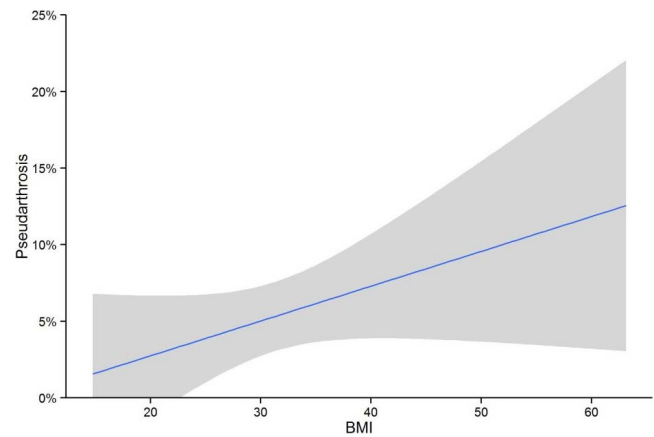


Figure 2. Variable importance plot of body mass index (BMI), showing a statistically significant association with the development of pseudarthrosis. The grey shadow spans the 95% confidence interval region.

most common agent identified in patients without pseudarthrosis, occurring in 30.6% of nonpseudarthrosis cultures (118/395). More detailed culture results can be found in Table 4.

DISCUSSION

Despite the use of modern antibiotics, SSI remains a relatively common postoperative complication. Infections associated with spinal surgery have a large impact on a patient's postoperative course, often requiring additional open procedures; infection may also increase the risk of other complications, such as pseudarthrosis. As previously mentioned, the postoperative infection rate for spinal procedures has been reported in recent literature^{1–6} to range from 0.7% to 15.0%.

The present study sought to examine the rate of development of pseudarthrosis in patients with postoperative infection after spinal fusion surgery and to identify patient-specific and procedural characteristics that predicted pseudarthrosis development. To our knowledge, this study examined the largest such infection cohort. Comparison of our results with those of previous studies was difficult, given the dearth of literature describing spinal pseudarthrosis in the context of infection. Nonetheless, several illuminating contrasts were highlighted. In 1997, Weiss et al¹⁵ reported on the relationship between SSI and the development of pseudarthrosis in a relatively large series. Of 900 patients who underwent a posterolateral lumbar fusion, 29 (3.2%) developed SSI. Of these, 11 (38%) were subsequently diagnosed with pseudarthrosis. This was a far higher rate than observed in the present study, which may partly be explained by improve-

ments in surgical techniques and implant technology with a resultant increase in successful fusions over the past 20 years.^{17–19} The fact that the pseudarthrosis patients in the present study were selected specifically because they were diagnosed first clinically and then confirmed radiographically may also have contributed to this discrepancy, because nearly 30% of pseudarthroses have been suggested to be asymptomatic.²⁰ In addition, in the Weiss et al¹⁵ study model, female sex, fusion involving the sacrum, and the use of allografts were significant predictors of pseudarthrosis development. Whereas the present study did not identify female sex as a risk factor for development of pseudarthrosis, the percentage of men in the Nonpseudarthrosis group was nearly twice that of the Pseudarthrosis group. The potential for an association between female sex and pseudarthrosis development merits further study.

The results of the present study also contradicted those of Mok et al,²¹ who performed a small case-control study to determine the impact of SSI on clinical outcomes of posterior spinal fusion as measured by patients' Short Form-36 questionnaire scores. Of 16 patients with postoperative infections, 3 underwent reoperation for pseudarthrosis (19%). The rate of development of pseudarthrosis in the noninfected group did not differ significantly from that of the control group. In addition, none of the variables evaluated—including number of levels fused—were associated with a significant difference in outcomes between the infection group and the control group. However, the number of patients included in the study was very small. Thus, it was possible that associations were missed, which may

Table 4. Results of microbial cultures taken from all patients included in this study.

Category	Pseudarthrosis (n = 21), no. (%)	No Pseudarthrosis (n = 395), no. (%)	P Value*
Gram-positive cocci	18 (85.7)	341 (86.3)	.959
<i>Staphylococcus aureus</i>	18 (85.7)	324 (86.1)	
MRSA	5 (23.8)	85 (21.5)	>.050
MSSA	9 (42.9)	121 (30.6)	>.050
Other	4 (19.0)	118 (29.9)	
<i>Streptococcus</i> spp.	0 (0)	17 (4.3)	
Gram-positive rods	3 (14.3)	36 (9.9)	.435
<i>Corynebacterium</i> spp.	3 (14.3)	25 (6.3)	
<i>Lactobacillus</i> spp.	0 (0)	2 (0.5)	
<i>Propionibacterium</i> spp.	0 (0)	9 (2.3)	
Gram-negative rods	6 (28.6)	175 (44.3)	.324
<i>Enterococcus</i> spp.	1 (4.8)	34 (8.6)	
<i>Klebsiella</i> spp.	0 (0)	1 (0.3)	
<i>Pseudomonas</i> spp.	1 (4.8)	0 (0)	
<i>Escherichia coli</i>	0 (0)	32 (8.4)	
<i>Citrobacter</i> spp.	0 (0)	39 (9.9)	
<i>Enterobacter</i> spp.	2 (4.5)	5 (1.3)	
<i>Acinetobacter</i> spp.	1 (4.8)	0 (0)	
<i>Delftia acidovorans</i> (<i>Comamonas</i>)	0 (0)	24 (6.1)	
<i>Fusobacterium varium</i>	0 (0)	2 (0.5)	
<i>Hafnia alvei</i>	1 (4.8)	19 (4.8)	
<i>Haemophilus</i> spp.	0 (0)	2 (0.5)	
<i>Prevotella</i> spp.	0 (0)	13 (3.3)	
<i>Serratia marcescens</i>	0 (0)	4 (1.0)	
Anaerobes	3 (14.3)	25 (6.3)	.010
<i>Bacteroides</i> spp.	0 (0)	13 (3.3)	
Anaerobic gram positive cocci	3 (14.3)	8 (2.0)	
<i>Clostridium</i> spp.	0 (0)	4 (1.0)	
Fungi	0 (0)	3 (0.76)	.646
<i>Candida</i> spp.	0 (0)	3 (0.76)	

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*; spp, species.

* Bold indicates significance ($P < .05$).

have helped to explain the contradiction with the results of the present study, which identified BMI and number of spinal levels fused as possible predictors of pseudarthrosis development. Chen et al²² conducted a larger cohort study examining long-term treatment outcomes after postoperative wound infection in patients with posterior spinal instrumentation. They found that 10 of 51 patients required implant removal (19.6%), with an overall pseudarthrosis rate of 31.4%. The overall hardware

removal rate was comparable with that of the present study (49/416, or 11.8%), but the pseudarthrosis rate was again much higher in the smaller cohort. This was likely attributed to similar factors described above in contrast with the Weiss et al¹⁵ cohort.

Etiologic agents of infection were, overall, comparable between patients with and without pseudarthrosis in this study; we identified staphylococcal species to be the most common infectious agents found in pseudarthroses, a finding consistent with multiple other studies.^{1,6,8,10} We were surprised that removal of hardware was not a significant predictor in the multivariate regression model despite showing significance in the univariate analysis. This was likely due to bicornelation; removal of hardware showed a significant association with the number of levels fused (OR, 1.19/level). Thus, each additional level included in the fusion operation may increase the risk of complications, such as subsequent requirement of removal of hardware.

Limitations of the present study included inclusion all of surgical approaches in a single group, without the ability to separately analyze the impact

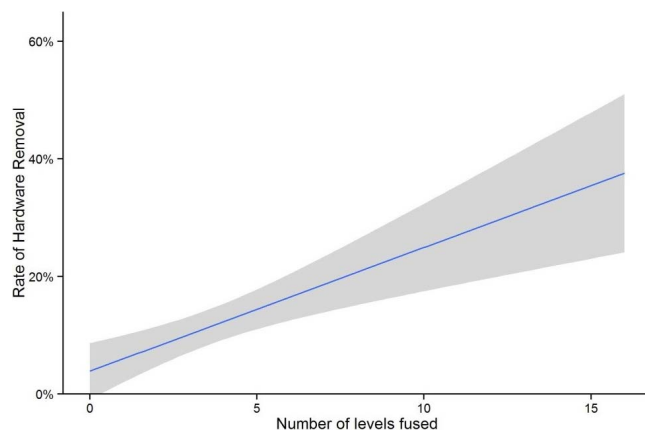


Figure 3. Number of levels fused associated with removal of hardware. The gray shadow spans the 95% confidence interval region.

of approach. Posterior approach has a reported association with lower rates of pseudarthrosis development, and an ideal regression model may have better accounted for this covariate.²⁰ In addition, though the sample size was much larger than those of many previous studies, this study identified no impact of sex on pseudarthrosis development, though such an effect has been suggested before.¹⁵ Comparison of asymptomatic pseudarthrosis patients with both symptomatic pseudarthroses and patients without pseudarthrosis may prove useful in future studies for further evaluation of the effects of female sex. Future studies with additional radiographic analysis would also aid in examining the effects of spinal alignment on patient-reported outcome measures following revision for pseudarthrosis. Finally, none of the aforementioned studies evaluated risk factors for pseudarthrosis following infection in the specific regional context of the lumbar spine. In this study, 2 factors that were most highly associated with the development of pseudarthrosis following infection were the number of levels fused and BMI. The impact of BMI is well documented in the literature, with obesity established as a risk factor for pseudarthrosis.^{20,23,24} However, the interplay between patient-specific factors such as BMI, procedural characteristics such as number of levels fused or approach, and the presence of postoperative infection may vary by involved spinal region.²⁵ The present study examined this interplay in the lumbar spine, and future region-specific research should be conducted to examine the specific risks at each level.

CONCLUSION

In a cohort of unprecedented power with specific focus on patients with clinically apparent pseudarthrosis, multivariate logistic regression analysis identified number of spinal levels fused in the index procedure and BMI as significant predictors of pseudarthrosis development following spinal surgical site infections. Further research is recommended to explore the impact of surgical site infection and inflammation on the subsequent development of pseudarthrosis as well as regional specificity of risk factors.

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Corresponding Author: Douglas A. Hollern, MD, Department of Orthopaedic Surgery and Rehabilitation Medicine, SUNY Downstate Medical Center, 450 Clarkson Ave, MSC 30, Brooklyn, NY 11203. Phone: (718) 221-5270; Email: doughollern@gmail.com.

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