Association of Methicillin-Resistant Coagulase-Negative Staphylococci on Preoperative Skin and Surgical Site Infection in Patients Undergoing Spinal Surgery: A Retrospective Cohort Study

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Abstract:

Introduction: The aim of this study was to investigate the association of methicillin-resistant coagulase-negative staphylococci (MRCNS) on preoperative skin and surgical site infections (SSIs) in patients undergoing spinal surgery.

Methods: A total of 507 cases (239 males and 268 females; mean age: 56.1 years) were included in this retrospective study, using prospectively collected data. All patients underwent skin culturing of the surgical site preoperatively. To identify independent risk factors for SSIs as the dependent variable, sequential multivariate logistic regression analyses were conducted. Age, sex, body mass index, presence of rheumatoid arthritis (RA), steroid uses, the American Society of Anesthesiologists Physical Status (ASA-PS) ≥3, MRCNS-positivity on skin bacterial culture, instrumentation, and Japanese Orthopedic Association (JOA) score were used as independent variables.

Results: Preoperatively, MRCNS was detected from skin culture in 50 (9.9%) cases. The frequency of RA, steroid uses, and ASA-PS ≥3 was significantly higher in MRCNS-positive cases than in MRCNS-negative cases. There were 21 (4.1%) post-spinal surgery SSI cases. Multivariate logistic regression analyses revealed that JOA scores (odds ratio (OR), 0.864; 95% confidence interval (CI), 0.764-0.977) and MRCNS-positivity (OR, 5.060; 95% CI, 1.787-14.323) were significantly associated with SSIs.

Conclusions: Preoperatively, the incidence of MRCNS was 9.9%; it was the most common cause of postoperative SSIs. MRCNS-positivity was the most associated factor for SSIs.

Keywords:

Surgical site infection, Spine surgery, Skin culture, Methicillin-resistant coagulase-negative staphylococci

Introduction

Surgical site infections (SSIs) lead to increased other complications, reoperation, readmission, poor outcomes, and costs. The National Healthcare Safety Network (NHSN) reported that the incidence of SSIs after spinal surgeries was a 0.72% incidence for laminectomy, compared to an 8.7% incidence for spinal refusion in patients[1]. Postoperative SSIs are often the multifactorial etiology such as a combination of pre-, intra-, and postoperative factors. One factor that causes SSIs is contamination from the patient's skin flora. Coagulase-negative *Staphylococcus* (CNS) species, such as *S. epidermidis*, *S. hominis*, *S. capitis*, and *S. lugdunensis*, are the most common skin bacterial colonizers[2]. On the other hand, the most common pathogens that cause SSIs after spinal surgeries are *Staphylococcus aureus*[3] and CNS[4]. Methicillin-resistant (MR) strains that are relatively common include MR *S. aureus* (MRSA) or MR *S. epidermis* (MRSE). MRSE causes a type of MRCNS infection that frequently occurs in revision[4] or instrumentation surgery[2]. The new CDC Guidelines for the Prevention of Surgical Site Infection recommends administration of prophylactic antibiotics via intravenous drip infusion during the perioperative period[3]; the selected antibiotics should work against the most common surgical site pathogens. Therefore, cephazolin, which has activity for *Staphylococcus* and is safe, is recom-
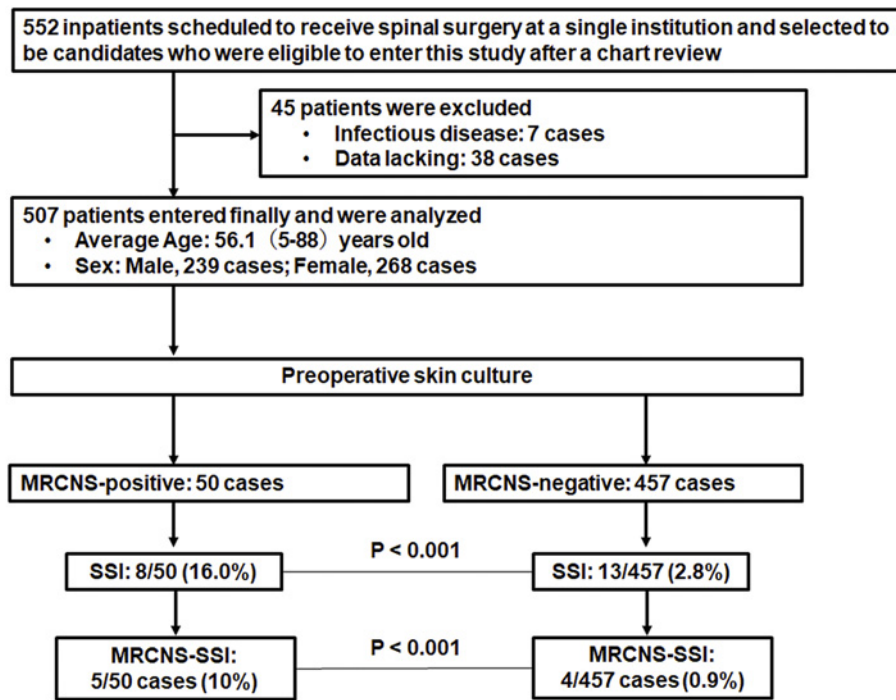
Figure 1. Flow diagram in this study.

The subjects included 507 patients who underwent posterior spine surgery at our department. The frequency of SSIs and MRCNS-SSI was significantly higher in patients who were MRCNS-positive (8/50 and 5/50 cases) than in those who were negative (13/457 and 4/457 cases).

Table 1. Preoperative Diagnosis.

Diagnosis	Cases	Received instrumentation, N (%)
Trauma		
Cervical	6	6 (100)
Thoracic, lumbar	12	11 (91.7)
Degenerative disease		
Cervical	154	50 (32.5)
Thoracic, lumbar	163	60 (36.8)
Spinal cord tumor	56	5 (8.9)
Spinal deformity	88	81 (92.0)
RA	5	5 (100)
DSA	6	3 (50)
Others	16	5 (31.3)
Total	507	229 (45.2)

RA, rheumatoid arthritis; DSA, destructive spondyloarthropathy

mended as the first choice in spinal surgery. However, the administration of cephazolin is crucial for patients with MR bacteria preoperatively. Moreover, the association between the prevalence of MRSA or MRCNS in the patient's skin at the surgical site before surgery and SSIs remains unclear.

The purpose of this study was to clarify the characteristics of the patients with MR strains in their skin flora and to examine whether preoperative skin bacteria of the surgical site are associated with the pathogenesis of SSIs after spinal surgery.

Materials and Methods

Subjects

This was a retrospective cohort study for consecutive patients undergoing spinal surgery at a single institution between March 2015 and February 2021. Patients with preoperative infectious disease, infectious wound conditions, and lacking data were excluded from this study. A total of 507 cases (239 males and 268 females) were included in the study (Fig. 1). We prospectively collected demographic, clinical, and microbiological data for all patients. The average age of the patients was 56.1 (range: 5-88) years. The percentage of posterior surgery was 98.4% (499/507). The distribution of prior diagnoses and the incidence of required instrumentation surgery are shown in Table 1. The percentage of patients requiring instrumentation surgery was 45.2%. All of the patients gave written informed consent and explicitly provided permission for this study before the assessments. This research has been approved by the IRB of the authors' affiliated institution (approval number: 2019-1038).

Preoperative protocol to prevent for SSIs

We performed perioperative management for this study as previously described[4]. Patients who smoke were instructed to cease smoking at least 4 weeks prior to surgery. Patients who were diagnosed with diabetes and hemoglobin A1C values >7 underwent glycemic control prior to surgery. Pa-

tients over the age of 60 controlled their blood glucose levels using a sliding scale for 1-2 weeks post-surgery until their blood glucose levels were normal.

We administered prophylactic antibiotics via intravenous drip infusion only in the pre- and intraoperative periods of all consecutive spinal surgeries. An additional dose of antibiotics was given every 4 h intraoperatively. Cephazolin was administered (based on weight) as the first choice, unless the patient had a history of significant allergy, such as anaphylactic shock, systemic skin eruption, or toxic kidney or liver dysfunction. Vancomycin was administered based on weight 3 h preoperatively in 7 of 16 patients (43.8%) with MR strains detected preoperatively between May 2019 and February 2021. We removed hair in the cervical surgical area using clippers in the operating room before surgery when necessary. We washed the surface of the surgical site using chlorhexidine and then immediately coated with an iodine drape. During surgery, the surgical site was irrigated using a saline solution every 30 min before closure of the surgical site. The continuous negative pressure suction drainage was removed 48 h after surgery.

SSI definitions and treatments

We defined postoperative SSIs according to the CDC/ NHSN definition and identification of SSIs and confirmed by a positive culture of wound site specimens after the index procedure[5]. Superficial SSIs were defined only as the skin or subcutaneous tissue of the incisions. Deep SSIs were defined as the fascia and muscle layers of the incision. We administrated cephazolin immediately as the first choice when the patient had evidence of an SSI. If the patient had presented with MR bacteria preoperatively, we administered sensitive antibiotics. All subjects were assessed for the development of additional SSIs within 1 year.

Culture analysis

All patients underwent a skin culture examination of the surgical site in the outpatient room 7 days preceding surgery. All culture specimens were obtained with sterile rayon-tipped swabs. The swab was immediately brought to the microbiology laboratory at our institution. All cultures were monitored for 7 days. If bacteria were detected, their sensitivity to various antibiotics was tested.

Evaluation of clinical outcomes and ASA-PS ≥3

To assess the severity of clinical symptoms, all patients were evaluated by the Japanese Orthopedic Association (JOA) score to assess cervical myelopathy prior to surgery. The American Society of Anesthesiologists Physical Status (ASA-PS) Classification System has been in use for over 60 years. The purpose of the system is to assess and communicate a patient's pre-anesthesia medical comorbidities. After modifications in 1962 and recent years, the ASA established a system of six classes. Class I indicates "a normal, healthy patient," class II "a patient with mild systemic disease," class III "a patient with severe systemic disease," class IV "a

patient with severe systemic disease that is a consistent threat to life," class V "a moribund patient who is not expected to survive without the operation," and class VI "a declared brain-dead patient whose organs are being removed for donor purposes." The classification system alone does not predict the perioperative risks, but when used with other factors (e.g., type of surgery, frailty, level of deconditioning), it can be helpful in predicting perioperative risks.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) ver.24.0J was used for statistical calculations. We compared the patients who were MRCNS-positive or negative using a Mann-Whitney U test and a chi-square test to analyze quantitative and qualitative data, respectively. The threshold of statistical significance was set at $p<0.05$. Sequential univariate and multivariate logistic regression analyses were performed to identify the independent risk factors for SSI. The independent variables of multivariate analysis included factor with $p<0.05$ after univariate analysis. Age, sex, body mass index (BMI), ASA-PS ≥3 (a patient with severe systemic disease), JOA score, and MRCNS-positivity on skin bacterial culture were used as the independent variables, which had p-values of <0.05 from the univariate analysis. We employed the receiver operating characteristic (ROC) curve to evaluate the association between the JOA score and SSI. Values are presented as median and interquartile range.

Results

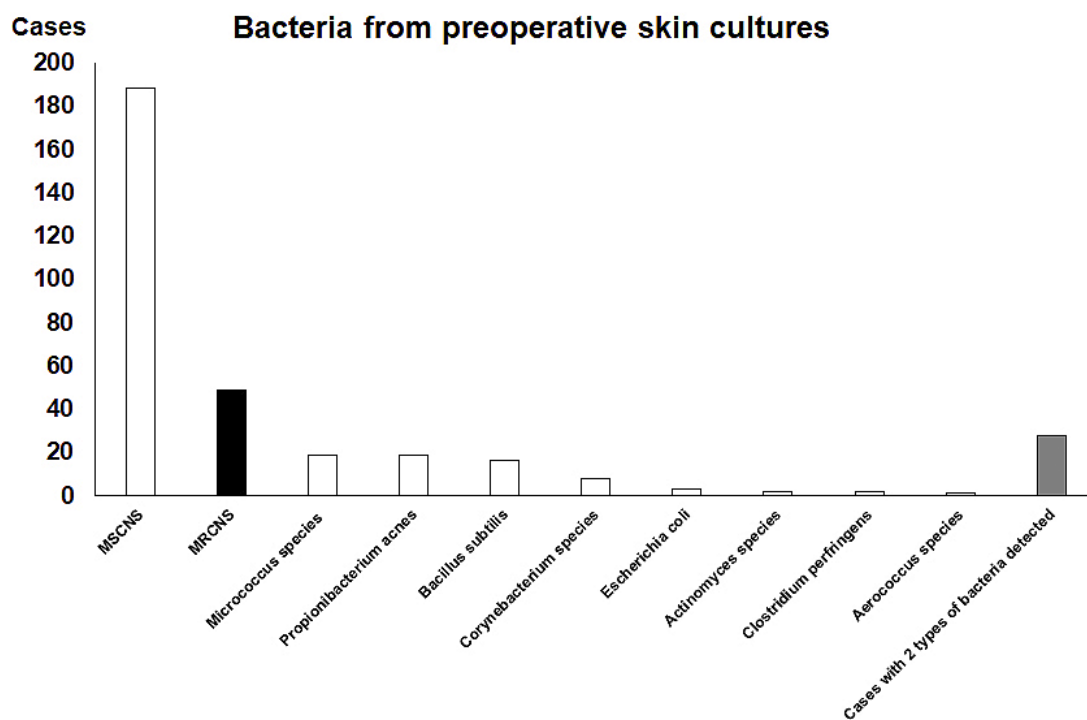### Preoperative skin bacterial culture

Preoperatively, 188 (37.1%) patients had methicillin-sensitive coagulase-negative staphylococci (MSCNS), whereas 50 (9.9%) had MRCNS (Fig. 2). A total of 28 patients tested positive for the two types of bacteria. There were no cases in which MRSA was detected.

Characterization of patients with MRCNS-positive

To characterize MRCNS-positive patients, we compared them with those who were negative on preoperative skin culture (Table 2). The frequency of rheumatoid arthritis (RA), steroid use, and ASA-PS ≥3 was significantly higher (p=0.004, 0.05, and 0.033) in patients who were MRCNS-positive than in those who were negative (Table 2).

Incidence of SSIs and associated factors

In the present study, 21 (4.1%) patients had SSIs after spinal surgery; these patients were classified as the SSI group. There were 10 superficial and 11 deep SSIs. Moreover, 18 of the 21 patients (85.7%) had comorbidities, whereas 17 (81.0%) had undergone spinal instrumentation surgery. Cases of SSIs are shown in Table 3. Causative bacteria of SSIs were MRCNS in 8 (38.1%) patients, MSCNS in 2, *Bacillus subtilis* in 2, *Enterobacter cloacae* in 2, *Propi-*

Table 3. Cases of SSI.

Age, gender	Diagnosis	Medical history	Bacteria of skin culture	Inst.	Type of SSI (SSI lesion)	Bacteria of SSI	Additional surgery
56, male	CSM	Athetoid cerebral palsy	MSCNS	Yes	Superficial (cervical)	MRCNS	Yes
66, female	Trauma	Collagen disease (steroid)	MRCNS	Yes	Superficial (thoracic)	MSCNS MSSA	No
80, male	LSS	Post-operation of cancer	*Bacillus subtilis*	Yes	Superficial (lumbar)	N.D.	No
69, female	LSS	Chronic renal failure	MRCNS	Yes	Superficial (lumbar)	MRCNS	No
84, female	LDH	None	N.D.	Yes	Superficial (lumbar)	N.D.	No
88, female	Trauma	Hypertension	MSCNS	Yes	Superficial (thoracic)	N.D.	No
13, male	Scoliosis	Mental retardation	MSCNS	Yes	Superficial (thoracic)	N.D.	No
62, male	Cervical OPLL	Cirrhosis	N.D.	No	Superficial (cervical)	*Propionibacterium acnes*	No
52, female	LSS	Asthma, diabetes, obesity	MRCNS	Yes	Superficial (lumbar)	MRCNS	No
64, male	Tethered syndrome	Hypertension	*Escherichia coli, Bacillus subtilis*	No	Superficial (lumbar)	*Corynebacterium striatum*	No
14, female	Scoliosis	Rett syndrome	N.D.	Yes	Deep (lumbar)	*Escherichia coli*	Yes
51, male	Cervical OPLL	Scabies (steroid)	MSCNS	No	Deep (cervical)	*Enterobacter cloacae*	Yes
72, female	CSM	RA (steroid)	N.D.	Yes	Deep (cervical)	MRCNS	Yes
48, female	CSM	Athetoid cerebral palsy	MRCNS	Yes	Deep (cervical)	MRCNS	Yes
65, male	LSS	Diabetes	MRCNS	Yes	Deep (lumbar)	MRCNS	Yes
66, male	Trauma	None	MRCNS	Yes	Deep (thoracic)	MRCNS	Yes
75, female	CSM	Post-operation of cancer	N.D.	Yes	Deep (cervical)	MRCNS	Yes
43, female	Cervical and thoracic OPLL	Obesity	MSCNS	Yes	Deep (cervical)	MSCNS	Yes
40, male	Spinal tumor	None	N.D.	Yes	Deep (thoracic)	*Propionibacterium acnes*	Yes
76, male	LSS	Hypertension, malignant lymphoma	MSCNS	No	Deep (lumbar)	*Enterococcus faecalis*	Yes
75, female	Atlantoaxial subluxation	RA, infection of THA	MSCNS	Yes	Deep (cervical)	MRSA	Yes

SSI, surgical site infection; Inst., instrumentation surgery; LSS, lumbar spinal stenosis; LDH, lumbar disc herniation; CSM, cervical spondylotic myelopathy; OPLL, ossification of the posterior longitudinal ligament; RA, rheumatoid arthritis; THA, total hip arthroplasty; MSCNS, methicillin-sensitive coagulase-negative staphylococci; MRCNS, methicillin-resistant coagulase-negative staphylococci; MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; N.D., not detected

results for MRCNS was significantly higher in patients with SSI than in those without SSI (Table 4). A Mann-Whitney *U* test showed that the JOA score was significantly higher in patients with SSI than in those without SSI (Table 4). Univariate logistic regression analyses revealed a significant association between the prevalence of SSI and the ASA-PS ≥3 (odds ratio (OR), 2.953; 95% confidence interval (CI), 1.064-8.195), JOA scores (OR, 0.828; 95% CI, 0.730-0.941), and positive results for MRCNS (OR, 3.667; 95% CI, 1.185-11.352) (Table 4). Multivariate logistic regression analyses revealed that the JOA scores (OR, 0.864; 95% CI, 0.764-0.977) and positive results for MRCNS (OR, 5.060; 95% CI, 1.787-14.323) were significantly associated with postoperative SSIs (Table 4). We employed the ROC curve to determine the cutoff value of the JOA score, which correlated with postoperative SSI. The optimal cutoff point of the JOA score was measured at 11.25 with 50.0% and 74.2%

sensitivity and specificity, respectively, with an area under the curve (AUC) of 0.302 (95% CI, 0.174-0.429, p=0.003, Fig. 3).

Discussion

To the best of our knowledge, this is the first study that elucidates the association between MR strains from preoperative skin culture and SSIs after spinal surgery. MRCNS was the most common cause of postoperative SSIs, and being MRCNS-positive by skin bacterial culture and neurological status were risk factors for SSIs.

CNS is the most common skin flora bacteria[6]. In our study, 37.1% of the detected bacteria were MSCNS, similar to previous reports. Further examination showed that MRCNS was detected at 9.9%. Regarding MRSA colonialization, patients with ≥7 days preoperative hospitalization,

Table 4. Univariate and Multivariate Predictors of SSI in Patients after Spinal Surgeries.

Variables	Patients with SSI (n=21)	Patients without SSI (n=486)	p-Value[b]	Univariate analysis			Multivariate analysis		
				OR	95% CI	p-Value	OR	95% CI	p-Value
Age[a], years	65.50 (51.25–75.00)	54.44 (47.00–73.00)	0.832	1.044	0.985–1.044	0.338	0.998	0.971–1.025	0.874
Female sex	11	257	1.000	0.978	0.361–2.654	0.965	1.596	0.607–4.195	0.343
BMI[a], kg/m^2	24.42 (20.40–28.56)	23.90 (20.65–27.03)	0.649	1.014	0.871–1.180	0.857	1.018	0.927–1.118	0.709
Obesity, n (%)	10	201	0.653	1.750	0.372–8.240	0.479	–	–	–
Hypertension, n (%)	6	172	0.643	0.757	0.226–2.530	0.651	–	–	–
Diabetes, n (%)	2	99	0.277	0.278	0.056–1.372	0.116	–	–	–
Hyperlipidemia, n (%)	1	29	1.000	1.020	0.113–9.237	0.986	–	–	–
Chronic renal failure, n (%)	1	25	1.000	0.434	0.030–6.168	0.537	–	–	–
Cancer, n (%)	3	35	0.203	1.303	0.267–6.350	0.744	–	–	–
RA, n (%)	2	6	0.039[#]	1.966	0.169–22.913	0.589	–	–	–
Steroid use, n (%)	4	14	0.005[#]	3.398	0.688–16.792	0.133	–	–	–
Immunosuppressive drugs use, n (%)	1	11	0.402	0.903	0.044–18.411	0.947	–	–	–
Smoking, n (%)	0	28	0.621	0.000	0	0.998	–	–	–
ASA-PS ≥3, n (%)	12	143	0.013[#]	2.953	1.064–8.195	0.038	2.566	0.961–6.854	0.060
JOA score[a]	10.70 (7.00–13.50)	13.20 (11.00–16.00)	0.042*	0.828	0.730–0.941	0.004	0.864	0.764–0.977	0.020
MRCNS-positive preoperatively, n (%)	7	42	0.002[#]	3.667	1.185–11.352	0.024	5.060	1.787–14.323	0.002
Primary surgical lesion—cervical spine, n (%)	9	178	0.645	0.026	−0.025–0.047	0.563	–	–	–
Instrumentation, n (%)	15	214	0.023[#]	2.422	0.687–8.541	0.169	–	–	–
No. of surgical levels[a], n (%)	4.50 (2.00–5.00)	4.00 (2.00–5.00)	0.189	1.164	0.959–1.412	0.124	–	–	–
Duration of surgery[a], min	276.00 (183.25–371.75)	217.00 (154.25–321.00)	0.167	0.998	0.993–1.003	0.404	–	–	–
Blood loss[a], ml	355.00 (112.50–737.50)	150.00 (50.00–400.00)	0.178	1.000	1.000–1.001	0.297	–	–	–

SSI, surgical site infection; OR, odds ratio; CI, confidence interval; BMI, body mass index; RA, rheumatoid arthritis; ASA-PS, American Society of Anesthesiologists Physical Status; JOA, Japanese Orthopaedic Association
[a]Values are presented as median and interquartile range. [b]Significant differences (p<0.05) between values for patients with and without SSI were calculated using the *Mann–Whitney U test. [#]Chi-square test

MRSA carriers, those with a history of MRSA infection, liver cirrhosis, and chronic skin disease, or those with prior nursing home admission had a high MRSA colonization risk[7]. In our study, although there were no cases in which MRSA was detected from the skin of the surgical site, we found that those who became MRCNS-positive were immunosuppressed and had severe systemic diseases. Therefore, we recommend preoperative skin culture screening for this category of patients since performing this procedure for all patients is a problem in medical insurance.

Contamination from the patient's skin flora is the common source of SSIs. Cronquist et al. investigated the density of bacterial counts on the skin of neurosurgical patients and examined the association between total colony-forming unit counts of the skin flora at the operative site and SSIs. They found no association between preoperative bacterial skin counts and SSIs[8]. However, Whyte et al. showed that the patient's skin has been demonstrated to be a very significant source of contamination in general surgery[9]. Although the concordance rate between bacteria of the preoperative skin culture and bacteria of SSI was not high in our study (28.6%), detecting five MRCNS cases in the postoperative skin culture indicated that contamination from the skin flora might be a risk factor for SSIs.

S. aureus is the most frequent pathogen that causes SSIs[10], accounting for approximately 50% of all SSIs[11]. *S. epidermidis* is a common pathogen in immunosuppressed hosts or patients with indwelling intravascular catheters or cardiac prostheses[12]. *S. epidermidis* is also a common organism often associated with spinal instrumentation surgeries and accounts for up to 31.4% of SSIs[13]. *P. acnes* is also part of the normal skin flora. Recently, it has been identified as a common cause of delayed SSIs and is also associated with spinal instrumentation surgeries[14]. Antimicrobial-resistant pathogens, such as MRSA and vancomycin-resistant enterococci that cause SSIs are increasing in recent years[15] and account for up to 35% of *S. aureus* infections in primary cases and up to 48% in revision surgeries[13]. MRSE, a type of
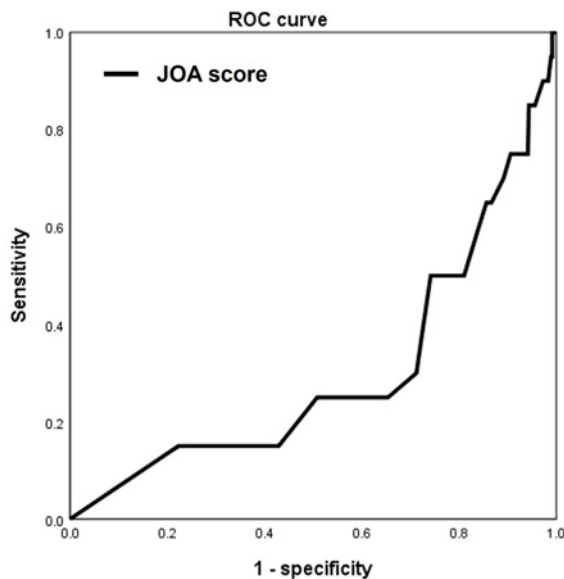
Figure 3. The ROC curve to determine the cutoff value of the JOA score, which was correlated with postoperative SSI.

MRCNS, first emerged in the 1960's[16] and is an increasing cause of infection in patients with granulocytopenia[17]. In our study, the most common source of SSI was MRCNS (38.1%). The pathogenesis of MRCNS included a wide distribution of the *mecA* gene, which has been previously reported to be associated with methicillin resistance[18]. Multivariate logistic analyses showed that MRCNS was the most significant risk factor after spinal surgery. In addition, all eight cases in which the cause of SSIs was MRCNS required instrumentation surgery, which has been reported to be significantly associated factor in spinal surgery[2]. Additionally, a previous report suggested that individualized prophylaxis reduces SSIs by gram-negative bacteria based on urine cultures from patients who met one of the following risk criteria for urinary tract colonization: hospitalization duration longer than 7 days, indwelling catheter, neurogenic bladder, history of urinary incontinence, or a history of recurrent urinary tract infections[19]. The association between MR bacteria detected preoperatively at the surgical site and SSI remains unclear. Low administration rate of vancomycin prophylaxis during the preoperative period might be a possible cause (14%, 7/50 patients who had MRCNS preoperatively detected). Therefore, we recommend individual administration of sensitive antibiotics in cases of an MRCNS-positive preoperative skin culture.

A meta-analysis revealed 13 risk factors that included ASA-PS ≥3, diabetes, obesity, BMI, revision surgery, smoking, urinary tract infection, hypertension, cerebrospinal fluid (CSF) leak, and dural tears in spinal surgery[20]. Although another study showed that diabetes was a risk factor for postoperative SSIs after spinal surgery[21], only two patients with SSIs had diabetes, and diabetes was not associated with SSIs in our study. These results suggest that tighter glycemic control mitigates the risk of postoperative SSIs. Our study suggested that the severity of neurological findings according to the JOA score was associated with SSIs. Therefore, we must be attentive in preventing SSIs in patients with neurological deficit such as severe cervical spondylotic myelopathy and spinal cord injuries.

The current study had several limitations. First, we used qualitative cultures rather than quantitative culture data. Therefore, an increase in the risk of infection is unclear. Moreover, it is difficult to prove that the pathogenesis of SSI was preoperative skin bacteria. Second, we evaluated clinical outcome using the JOA score to assess cervical myelopathy for all included patients diagnosed with trauma or spinal deformity. Third, we did not distinguish between patients who received instrumentation and those who did not. Lastly, in our protocol, cephazolin or vancomycin was administered to patients who had MRCNS preoperatively. Therefore, we should prospectively evaluate an SSI prevention protocol for high-risk patients with a medical record of MR strains[7]. Yamada et al. administered selected high-risk patients with vancomycin (VCM) prophylaxis immediately after initial routine antibiotic prophylaxis to maximize MRSA protection[7]. Our results also recommend routine antibiotic and VCM prophylaxis to patients who had MRCNS after the preoperative screening.

Conclusions

The incidence of MRCNS was the most common cause of postoperative SSI after spinal surgery. The preoperative presence of bacteria on the skin of the surgical site may predict SSIs in patients especially in those who are immunosuppressed or have severe systemic diseases.

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