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MAJOR ARTICLE

The STAPH Score: A Predictor of *Staphylococcus aureus* as the Causative Microorganism of Native Vertebral Osteomyelitis

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Background. *Staphylococcus aureus* (SA) is the most common causative microorganism in native vertebral osteomyelitis (NVO). Few studies have compared the clinical features of NVO due to SA (SA-NVO) and NVO due to other organisms (NSA-NVO). This study was conducted to validate a predictive score for SA-NVO to facilitate NVO treatment without broad-spectrum antimicrobial agents.

Methods. This retrospective study compared the clinical features of patients with SA-NVO and NSA-NVO who were diagnosed from 2004 to 2019. Univariate associations were assessed using χ^2, Fisher's exact, or Mann-Whitney *U* test. Multivariable analysis was conducted using logistic regression. The optimal age cutoff point was determined by classification and regression tree analysis.

Results. Among 155 NVO patients, 98 (63.2%) had a microbiologically confirmed diagnosis: 40 (25.8%) with SA-NVO and 58 (37.4%) with NSA-NVO. Six predictors, either independently associated with SA-NVO or clinically relevant, were used to develop the STAPH prediction score: atopic dermatitis (Skin) (3 points); recent Trauma (2 points); Age < 67 years (1 point); Abscess (1 point); central venous Port catheter (2 points); and History of puncture (2 points). In a receiver operating characteristic analysis, the area under the curve was 0.84 (95% confidence interval, 0.76–0.91). The best cutoff point was 3. A score ≥3 had a sensitivity, specificity, positive predictive value, and negative predictive value of 58%, 84%, 84%, and 73%, respectively.

Conclusions. The STAPH score has relatively high specificity for use by clinicians to predict SA as the causative microorganism in patients with NVO until results of a confirmatory culture are available.

Keywords. clinical prediction rule; native vertebral osteomyelitis; *Staphylococcus aureus*.

Native vertebral osteomyelitis (NVO) is the main manifestation of hematogenous osteomyelitis in adults [1] and represents 3%–5% of all cases of osteomyelitis [2]. The incidence of NVO has been increasing as a result of improved diagnostic techniques, an aging and more immunocompromised population, spinal instrumentation and surgery, and intravenous drug abuse [3, 4].

Staphylococcus aureus (SA) is the leading cause of NVO [5–7] and is the most commonly isolated NVO organism, accounting for 32%–67% of isolates [5]. Native vertebral osteomyelitis caused by *S aureus* (SA-NVO) is associated with a higher infection-related mortality rate and a higher incidence of neurologic complications, such as paraplegia, tetraplegia, and meningitis, associated with paravertebral abscess, especially epidural abscess, than an NVO caused by other microorganisms (NSA-NVO) [8–10]. To our knowledge, there are no scoring systems available to facilitate the prediction, by clinicians, of SA as the causative pathogen of NVO. Therefore, we aimed to identify the risk factors for SA-NVO and to generate a predictive score that will help to treat NVO without broad-spectrum antimicrobial agents, even when the causative organism is unknown.

METHODS

Study Design and Setting

We conducted a single-center retrospective cross-sectional study at St. Luke's International Hospital, a 520-bed teaching hospital in Tokyo, from April 2004 to March 2019.

Inclusion and Exclusion Criteria

Hospitalized adult patients (age ≥18 years) who presented with vertebral osteomyelitis were included. First, we searched the electronic hospital database for discharge diagnoses of vertebral osteomyelitis. Then, vertebral osteomyelitis was defined through the chart review based on the following: (1) clinical symptoms such as fever, chills, spinal

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pain, or localized tenderness; and (2) evidence of spinal bone involvement on magnetic resonance imaging (MRI), including decreased signal intensity in the vertebral body and disk and loss of endplate definition on T1-weighted images and increased signal intensity of the disk and vertebral body on T2-weighted images. Only the first episode of NVO in a given patient was included.

Patients with vertebral osteomyelitis who had undergone prior spinal surgery, with or without spinal instrumentation or decubitus ulcers, were excluded from this study. The presence of Stage 1 decubitus ulcers alone was not an exclusion criterion. Patients with NVO due to unknown microorganisms were also excluded.

Data Collection

Patient data were extracted from inpatient electronic medical records. The study variables included patient demographics, chief complaints, duration of symptoms, recent history of trauma or puncture procedure, comorbidities, vital signs, physical examinations findings, results of laboratory tests conducted within 24 hours after admission, microbiology results, and complications including infective endocarditis, septic arthritis, and abscess (such as paravertebral, epidural, or psoas muscle) formation confirmed by computed tomography or MRI, neurological sequelae, and mortality.

Variable Definitions

We used the following definitions: "neurological symptoms" included muscle weakness, numbness, and/or tingling sensations; "recent history of puncture" was defined as any needle-using procedure including arthrocentesis, intraarticular injection, injection drug use, or acupuncture; "recent history of trauma" was defined as any injury that had disrupted the skin barrier, including abrasions, stabbing, and penetrating trauma within the previous month; "malignancy" was defined as having received chemotherapy, surgery, or irradiation to treat either a solid tumor or a hematological malignancy within the previous 6 months; and "abscess" was defined as a paraspinal, epidural, or psoas abscess identified on MRI. For coagulase-negative staphylococci or other possible skin commensals to be considered as a true pathogen, they had to be isolated from at least 2 blood cultures drawn on separate occasions and/or from a bone biopsy obtained under sterile conditions. Immunosuppressants included systemic corticosteroids, calcineurin inhibitors, antiproliferative drugs such as mycophenolate, mTOR inhibitors, interleukin-2 receptor antibodies, interleukin-6 receptor antibodies, and monoclonal antibodies. Central venous catheters (CVCs) included central venous port catheters (CV ports) and peripherally inserted central catheters (PICCs). Patients with healthcare-associated infections included patients in long-term care facilities, on hemodialysis, and on chemotherapy or total parental nutrition using either CV ports or PICCs.

Statistical Analyses

Bivariate associations were assessed using Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. The association between individual predictors and the risk of SA-NVO was assessed using a binary multivariable logistic regression model. In general, univariate analysis is performed by the evaluation based strictly on 0.05 significance level, but it seems that multiple variables may have a significant effect on the target outcome by interaction in multivariate analysis. Therefore, as in many previous studies [11, 12], we performed a multivariate logistic regression analysis based on the variables with statistical significance of $P < .1$ in this study. The age variable is a continuous value, but in this study, the age variable was binarized by the univariate logistic regression analysis of age and SA, its receiver operating characteristic (ROC) analysis and obtaining a specific cutoff point for age, and a multivariate logistic regression analysis was performed. Linear regression analysis was also performed to assess whether each item was collinear. In addition, the logistic regression model was calibrated by plotting the predicted versus the observed probabilities. To evaluate the performance of the proposed model, we estimated the value of the area under the curve (AUC) and its 95% confidence interval (CI) on the ROC plot. A conservative cutoff for the predictive score was based on the maximization of specificity, as recommended for disease diagnosis. All analyses were performed using SPSS 19.0J statistical software (IBM Japan, Tokyo, Japan).

Patient Consent Statement

This study was approved by the Institutional Review Board of St. Luke's International Hospital in Tokyo, Japan (Number 19-J025). The requirement for patient consent was waived because the study was based on a retrospective analysis of routinely collected data.

RESULTS

Study Participants

A total of 156 patients older than 18 years with NVO were hospitalized at St. Luke's International Hospital from 2004 to 2019. Fifty-eight patients were excluded because no causative microorganism was identified, and 98 patients who met the study criteria were included in this study. Forty patients (41%) had SA-NVO (32 patients with methicillin-susceptible *S aureus* [MSSA] and8 patients with methicillin-resistant *S aureus* [MRSA]) and 58 patients (59%) had NSA-NVO. Patient characteristics according to the causative pathogen and details of pathogens that were identified are shown in Tables 1 and 2, respectively.

Spinal canal stenosis (30.6%), compression fracture (24.5%), and diabetes mellitus (28.6%) were the most common comorbidities at diagnosis of NVO among the study participants. Univariate analysis revealed a significantly higher

Table 1. Patient Characteristics According to the Type of Native Vertebral Osteomyelitis

Characteristics	SA-NVO (n = 40)	NSA-NVO (n = 58)	*P* Value
Sex (male), n (%)	22 (55)	35 (60.3)	.374
Age, median (IQR)	**59 (49.8–74)**	**73 (58.5–79.5)**	**.006**
Vertebral knock pain, n (%)	38 (95)	51 (87.9)	.200
Neurological deficit, n (%)	15 (37.5)	14 (24.1)	.116
Duration of symptoms (days), median (IQR)	5 (2.0–12.5)	6.5 (2–18.5)	.194
Atopic dermatitis, n (%)	**10 (25)**	**1 (1.7)**	**.001**
Recent history of trauma, n (%)	**6 (15)**	**2 (3.4)**	**.048**
Recent history of puncture, n (%)	**11 (27.5)**	**3 (5.2)**	**.002**
Diabetes, n (%)	12 (30)	16 (27.6)	.173
Malignancy, n (%)	3 (7.5)	9 (15.5)	.192
Compression fracture, n (%)	10 (25)	14 (24.1)	.329
Spinal stenosis, n (%)	13 (32.5)	17 (29.3)	.450
Hemodialysis, n (%)	2 (5.0)	4 (6.9)	.527
Immunosuppressant, n (%)	6 (15.0)	8 (13.8)	.545
Chemotherapy, n (%)	0 (0)	2 (3.4)	.348
CV port, n (%)	7 (17.5)	3 (5.2)	.051
Healthcare-associated, n (%)	10 (25)	14 (24.1)	>.99
Temperature (°C), median (IQR)	37.5 (4.8–15)	37.4 (4.9–16)	.761
Systolic blood pressure (mmHg), median (IQR)	122 (100–148)	128 (110–142)	.567
Pulse rate (/minute), median (IQR)	86 (62–112)	80 (58–110)	.622
Respiratory rate (/minute), median (IQR)	22 (15–26)	21 (14–28)	.819
SpO_2 (%), median (IQR)	96 (92–99)	96 (91–99)	>.99
Blood urine nitrogen (mg/dL), median (IQR)	18 (12–25)	16 (12–26)	>.99
Creatinine (mg/dL), median (IQR)	0.68 (0.41–1.1)	0.76 (0.4–1.5)	.472
White blood cell count (/µL), median (IQR)	12.6 (4.9–16)	12.4 (5.1–15.4)	.791
CRP (mg/dL), median (IQR)	13.2 (4.22–25.7)	9.7 (4.4–17.6)	.188
ESR (mm/hour), median (IQR)	70 (43–100)	61.5 (44.2–89.8)	.409
HbA1c (%), median (IQR)	5.8 (5.5–6.3)	5 (2–12.5)	.752
Site of infection			.523
Cervical, n (%)	6 (15.0)	10 (17.2)	
Thoracic, n (%)	7 (17.5)	8 (13.8)	
Lumbar, n (%)	19 (47.5)	24 (41.4)	
Sacral, n (%)	2 (5.0)	0 (0)	
Cervicothoracic, n (%)	2 (5.0)	7 (12.1)	
Thoracolumbar, n (%)	4 (10.0)	7 (12.1)	
Lumbosacral, n (%)	0 (0)	1 (1.7)	
Thoracolumbosacral, n (%)	0 (0)	1 (1.7)	
Bone biopsy or pus drainage	10 (20.8)	17 (29.3)	.236
Bone or pus culture positive, n (%)	6 (15.0)	15 (25.9)	.222
Blood culture positive, n (%)	38 (95.0)	48 (82.8)	.115
Abscess (paravertebral, epidural, or psoas muscle), n (%)	36 (90)	40 (69.0)	.012
Infective endocarditis, n (%)	7 (17.5)	8 (13.8)	.410
Septic arthritis, n (%)	4 (10.0)	6 (10.3)	.617
Length of treatment IV, median (IQR)	42 (72)	43 (137)	.424
Length of treatment PO, median (IQR)	59 (249)	59 (510)	.385
30-day mortality, n (%)	0	0	NA
90-day mortality, n (%)	2 (5.0)	1 (2.5)	.742
Neurological sequelae	6 (15.0)	4 (6.9)	.313
1-year recurrence, n (%)	1 (2.5)	2 (5.0)	.492

Abbreviations: CRP, C-reactive protein; CV port, central venous port catheter; ESR, erythrocyte sedimentation rate; HbA1c, glycated hemoglobin; IQR, interquartile range; IV, intravenous; NA, not applicable; NSA-NVO, NVO due to other organisms; NVO, native vertebral osteomyelitis; PO, per os; SA-NVO, NVO due to SA; SA, *Staphylococcus aureus*; SpO_2, oxygen saturation measured by pulse oximeter.

proportion of atopic dermatitis, recent trauma, puncture, and abscess among patients with SA-NVO than those with NSA-NVO. Patients with SA-NVO were more likely to have a CV port than those with NSA-NVO (there were no patients with other central devices such as CVCs or PICCs). The reasons for the use of CV ports were total parenteral nutrition (n = 7)

Table 2. Details of Pathogens Identified (n = 98)

Pathogen	Number
Gram-positive	86
Staphylococcus aureus	
Methicillin-sensitive	32
Methicillin-resistant	8
Coagulase-negative *Staphylococcus*	9
Staphylococcus pneumoniae	1
Viridans group streptococci	10
Beta-hemolytic streptococci	
Streptococcus pyogenes	3
Streptococcus agalactiae	12
Streptococcus dysgalactiae	3
Enterococcus spp	2
Parvimonas micra	1
Cutibacterium acnes	4
Gram-negative	13
Escherichia coli	4
Klebsiella spp	3
Nontyphoidal *Salmonella* spp	3
Serratia spp	1
Bacteroides fragilis	2

and chemotherapy (n = 3). There were no significant differences in clinical signs (including vertebral tenderness, neurological deficits), duration of symptoms, other comorbidities, and laboratory findings, or complications such as neurological sequelae, infective endocarditis, and septic arthritis between the 2 groups.

Multivariate analyses revealed that atopic dermatitis, recent history of puncture, and age less than 67 years were independent risk factors for SA-NVO. Recent trauma, abscess, and CV port were associated with SA-NVO, although this association was not statistically significant. Linear regression analysis revealed no collinearity among these parameters. The odds ratios of these models were used to obtain representative weights by rounding to develop a score calculated by beta-coefficient on a scale of 0 to 11 for the risk of SA-NVO. We developed a score, which we named the STAPH score, using the variables selected in the multivariate model. These were atopic dermatitis (Skin) (3 points), recent Trauma (2 points), Age < 67 years (1 point), Abscess (1 point), CV Port (2 points), and a History of recent puncture (2 points). The results of the multivariate model that was used to determine the score are shown in Table 3.

Figure 1 shows a ROC curve of the STAPH score for the patients with SA-NVO and NSA-NVO. The AUC was 0.84 (95% CI, 0.76–0.91). A score ≥3 had the best value for distinguishing between SA-NVO and NSA-NVO (sensitivity, 58%; specificity, 84%; positive predictive value, 84%; and negative predictive value, 73%).

DISCUSSION

To our knowledge, this is the first study to develop a scoring system to predict the presence of SA in patients with NVO. In this study, we determined that atopic dermatitis, age < 67 years, and history of puncture were independent predisposing factors for SA-NVO. Furthermore, adding 3 other clinically important variables, namely, recent trauma, presence of an abscess, and presence of a CV port, to the model enabled us to develop the STAPH score to predict SA-NVO with a high degree of specificity. Among the above-mentioned factors, age, atopic dermatitis, CV port, and SA infection were consistently matched with the results of previous studies, whereas a history of trauma, or puncture, and presence of abscesses were new factors.

The prevalence of SA colonization among patients with atopic dermatitis vary widely, and a recent meta-analysis reported a prevalence of 70% for skin with lesions [13]. Thus, SA could contribute to a skin barrier defect and inflammation in atopic dermatitis by different mechanisms, such as the stimulation of mast-cell degranulation by staphylococcal delta toxin, the induction of keratinocyte apoptosis by alpha toxin, and the modulation of inflammation by the staphylococcal surface proteins—protein A and lipoteichoic acid [14–16]. Atopic dermatitis has also been previously reported to be a risk factor for (1) *S aureus* bacteremia or (2) infective endocarditis [17–20]. Moreover, CVCs, including CV ports and PICCs, have been reported to be risk factors for SA infection [21, 22] and vertebral osteomyelitis [5], consistent with the results of this study.

Few studies have described that a recent history of trauma or puncture could be a risk factor for SA-NVO, although trauma

Table 3. Results of the Multivariate Logistic Regression Analysis Used to Determine the STAPH Score for Predicting a Staphylococcal Vertebral Infection[a]

Variable	Adjusted OR	Beta Coefficient	95% CI	*P* Value	Points
Skin: atopic dermatitis	15.7	2.8	1.7–145	**.015**	3
Trauma	4.9	1.6	0.75–31.8	.096	2
Age < 67 years	3.1	1.1	1.1–8.6	**.031**	1
Abscess	3.0	1.1	0.78–11.2	.111	1
CV Port	5.1	1.6	0.98–26.7	.053	2
History of puncture	7.0	1.9	1.44–29.1	**.019**	2

Those with a *P* value <.05 are shown in bold text.

Abbreviations: CI, confidence interval; CV Port, central venous port catheter; OR, odds ratio.

[a]The STAPH score is based on the 6 items shown in the left column. One to 3 points are assigned to each item (shown in the right column), based on rounding of the beta-coefficient value, for a maximum possible score of 11.

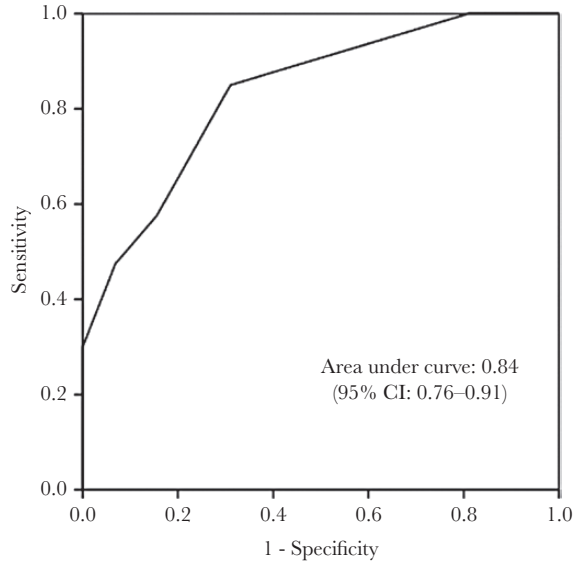

Figure 1. The receiver operating characteristic curve of the STAPH score. CI, confidence interval.

and puncture can cause disruption of the skin barrier and may thus increase the risk of SA-NVO by the same mechanism as in atopic dermatitis or CVCs. It is notable that only 2.0% of the participants were injection drug users, which is lower than most studies conducted in Western countries. In contrast, acupuncture, which is an alternative medicine and a frequent practice in Asia, was the most common type of puncture in patients with SA-NVO. Case reports have shown that acupuncture-transmitted infections include vertebral osteomyelitis and subcutaneous abscess [23, 24], and, therefore, it is essential for clinicians to consider recent acupuncture to be one of the risk factors for SA-NVO as well as other puncture procedures.

With regard to age, our finding that SA-NVO patients were significantly younger than NSA-NVO patients is also consistent with the findings of some previous studies [25], although some previous studies have not found a significant difference in age between patients with NVO caused by Gram-positive cocci and Gram-negative bacilli [9, 26]. Older patients with NVO may be more likely to have secondary vertebral osteomyelitis after urinary tract infection [5, 27], diverticulitis [28], or malignancies [26]. However, younger, previously healthy patients with NVO may be more likely to have exogenously acquired infections due to trauma or a puncture procedure than endogenous primary infections.

More importantly, our analysis newly revealed that patients with SA-NVO had a higher prevalence of abscess, including paravertebral, epidural, and psoas muscle abscess, than those with NSA-NVO. This result might be because polymorphonuclear leukocytes are responsible for the primary cellular host defense reaction against SA infections and are a major component of abscesses caused by SA [29, 30].

Some clinicians may not change their prescription of the initial antimicrobial regimen in patients with NVO, even if they have a high index of suspicion that the patient has SA-NVO. However, if the STAPH score is relatively high, it may prompt these clinicians to search for a metastatic lesion, including infective endocarditis or an abscess [21], while awaiting the culture results. Early initiation of SA-focused treatments, for example, cefazolin and cloxacillin, may also have an earlier bactericidal effect. This is likely to have a positive impact on the outcome, because treatment failure has previously been reported to be associated with delayed diagnosis and treatment [31].

The choice of an empirical antimicrobial therapy is often a challenging issue for clinicians because many different pathogens can cause NVO. The Infectious Diseases Society of America 2015 guidelines of NVO recommend an initial regimen that includes vancomycin in combination with ciprofloxacin, cefepime, or carbapenem for the coverage against staphylococci, including oxacillin-resistant strains, streptococci, and Gram-negative bacilli [3]. Clinicians often have trouble with deciding whether to include empirical treatment for Gram-negative bacilli, which account for approximately 20% of NVO [32]. From an antimicrobial stewardship perspective, broad-spectrum antimicrobials may induce the creation of multidrug-resistant organisms [33, 34] or *Clostridioides difficile* infection [35–37]. Despite the guideline recommendations for a bone biopsy to determine the causative microorganism [3], a bone biopsy may not be feasible because of patient intolerance or in poorly equipped facilities. Thus, some patients complete a course of broad-spectrum antimicrobial therapy without the confirmation of the causative microorganism. Obviously, empirical antimicrobial treatment decisions should be based on patient characteristics, clinical circumstances, and epidemiological risk assessment, but it is also important for clinicians to use narrow-spectrum antimicrobial therapy that poses a lower risk of promoting the development of antimicrobial resistance.

This study has several limitations. First, this study was a relatively small single-center observational study conducted. External validation for implementation of the STAPH score by comparison with patients with NVO at other hospitals and prospective validation of the results of this study are warranted. Second, this STAPH score did not assess whether MSSA and MRSA could be the causative pathogens of NVO. As in previous studies [10, 38, 39], most SA isolates from patients in this study were MSSA, and only 20% of SA strains were methicillin resistant. The STAPH score might be useful to alert clinicians that SA could be the causative organism, to engender further discussion about whether the initial treatment should cover MRSA in addition to MSSA, depending on its regional prevalence and risk factors such as recent MRSA infections, prior antibiotic use [40, 41], or injectable drug use [42]. Further studies

in the regions where the prevalence of MRSA is higher than in Japan are warranted. Third, a relatively large number of patients were excluded in this study because of NVO caused by unknown pathogens. This could be explained by the lower proportion of biopsy. A potential sampling bias could exist. Finally, assessment and recording of neurological symptoms, recent puncture history, and recent trauma are likely to vary among clinicians, and it is possible that some of the clinical variables were underreported in the medical records and the subsequent analysis. Although the limited data from a single center does not allow for generalization, the estimation of SA by this score may demonstrate the usefulness of the STAPH score, because the causative organism is often unknown because a bone biopsy for pathogen identification is not always possible.

CONCLUSIONS

We developed a simple STAPH score to help predict whether cases of NVO are caused by SA. The STAPH score may help clinicians to predict that SA is the causative microorganism in patients with NVO before the confirmatory culture results become available and in cases in which the causative organism cannot be identified.

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