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ORIGINAL ARTICLE

A new simplified predictive model for mortality in methicillin-resistant *Staphylococcus aureus* bacteremia

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Abstract

Adjustment for confounding is important in observational methicillin-resistant *Staphylococcus aureus* bacteremia (MRSAB) studies due to the wide spectrum of disease severity and baseline health status that patients present with. The objectives of this study were to develop a simplified MRSAB-specific scoring model to estimate the risk of 30-day all-cause mortality and to compare its performance to the APACHE II and Pitt Bacteremia scores. Retrospective, singe-center, cohort study in adults with MRSAB 2008 to 2018. Independent predictors of mortality were identified through multivariable logistic regression. A scoring model was derived using a regression coefficient-based scoring method. Discriminatory ability was assessed using the *c* statistic. A total of 455 patients were included. Thirty-day mortality was 16.3%. The MRSAB score consisted of six variables: age, respiratory rate, Glasgow Coma scale, renal failure, hospital-acquired MRSAB, and infective endocarditis or lower respiratory tract infection source. The score demonstrated very good discrimination (*c* statistic 0.8662, 95% CI 0.824–0.909) and was superior to the APACHE II ($P = 0.043$) and the Pitt bacteremia ($P < 0.001$) scores. A weighted combination of six independent variables routinely measured in patients with MRSAB can be used to predict, with high discrimination, 30-day all-cause mortality. External validation is required before widespread use.

Keywords Methicillin-resistant *Staphylococcus aureus* · Bacteremia · Risk stratification · APACHE II · Pitt bacteremia score

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be one of the most important antibiotic-resistant pathogens responsible for bloodstream infections with case fatality rates ranging from 15 to 45% [1–5]. Treatment is challenging due MRSA's remarkable ability to evade immunologic defenses and antimicrobial killing [4, 6]. For many years, vancomycin was the only widely available agent to treat invasive MRSA infections and is still considered the standard of care by many clinicians and experts [1, 4, 7]. However, confidence in its effectiveness has waned in recent years due to increasing reports of clinical and microbiological failure associated with the emergence of strains with reduced vancomycin susceptibility [8, 9]. Additional features that may contribute to suboptimal response include vancomycin's sluggish bactericidal activity, susceptibility to the inoculum effect, and poor penetration into a variety of tissues [8]. Despite calls for a reappraisal of vancomycin's positioning in the treatment of MRSA bacteremia (MRSAB), there has been only one randomized controlled trial (RCT) evaluating an alternative [10]. In circumstances where execution of RCTs is not feasible, observational studies can provide valuable insight into real-world effectiveness of treatment alternatives. However, treatment is not assigned randomly in these studies and confounding by indication is always a potential issue. Appropriate adjustment for confounding is especially important in MRSAB studies due to the wide spectrum of disease severity and baseline health status that patients present with and which clearly impacts morbidity and mortality [2, 4]. Two of the most frequently used severity-of-illness scoring systems that have been applied in risk adjustment for MRSAB observational studies are the

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Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Pitt Bacteremia score [11–14]. The APACHE II score was originally developed in intensive care unit (ICU) patients and is used to evaluate a patient's severity of illness and predict their risk of hospital death based on 12 physiological parameters along with age and four categories of chronic organ system insufficiency or immunodeficiency [11]. However, the majority of patients with MRSAB do not require ICU admission and many of the variables used in this complex scoring system may not be pertinent to MRSAB. The Pitt Bacteremia score is a simple score originally developed in patients with Gram-negative bacteremia but has been widely applied in MRSAB studies to predict short-term mortality based on five physiological parameters which are readily assessable at the initial evaluation [2, 3, 12, 13]. However, clinical variables not included in this score such as age, the presence of comorbidities, and source of infection also have prognostic significance in MRSAB [2, 4].

With the recent expansion of the anti-MRSA antibiotic armamentarium as well as renewed interest in alternative settings of care, treatment durations, and drug administration routes for MRSAB [1, 15], comparative observational research is anticipated to play a key role in informing future treatment paradigms. Adequate risk stratification is critically important to minimize the risk of drawing incorrect conclusions about treatment effects. The objective of the present study was to develop a new simplified MRSAB-specific scoring model with which to estimate the risk of 30-day all-cause mortality and to compare the predictive performance of the MRSAB-specific scoring model to the APACHE II and Pitt Bacteremia scores. Findings of this study will provide valuable data to guide future MRSAB comparative observational research.

Methods

Study design and population

This was a retrospective cohort study conducted at the Detroit Medical Center (DMC), an eight-hospital healthcare system in Southeast Michigan with a combined total of approximately 2000 beds, including 150 ICU beds. Patients admitted to the DMC between January 2010 and December 2017 meeting the following criteria were eligible for inclusion: (1) age ≥ 18 years, (2) at least one positive blood culture for MRSA meeting the Centers for Diseases Control and Prevention (CDC) criteria for bloodstream infection [16], and (3) intravenous (IV) vancomycin initiated within 48 h of blood culture collection. For each patient, only the initial eligible episode of MRSAB during the study period was included. Patients with polymicrobial bacteremia and those who expired within 24 h of blood culture collection were excluded. During the study period, clinical pharmacists were responsible for vancomycin dosing and targeted a trough of 15 to 20 mg/L or an area under the concentration time characteristic (AUC) curve to MIC ratio of at least 400 in patients with invasive MRSA infections. Approval was obtained from the Wayne State University Institutional Review Board and DMC Research Committee with a waiver for informed consent.

Study definitions and data management

The main outcome variable was all-cause 30-day mortality measured from the day of blood culture collection. Relevant patient demographic and clinical and treatment information was extracted from the electronic medical record using a structured data collection form and entered into REDCap (Research Electronic Data Capture, Vanderbilt University), a secure electronic data capture tool hosted at Wayne State University [17]. MRSAB was classified as hospital-acquired if the index blood culture was obtained greater than 48 h after admission or the patient was transferred from an outside hospital; otherwise, it was classified as community-onset. Immunosuppression was defined as previously described [15]. The primary MRSAB source was determined according to CDC criteria [16]. Infective endocarditis was defined according to the modified Duke Criteria [18]. The APACHE II and the Pitt Bacteremia scores were calculated using the most abnormal biochemical and physiological measurements recorded within 24 h of blood culture collection. Serum bicarbonate was used in the APACHE II score calculation when arterial blood gases were not measured [11].

Statistical analysis

Univariate relationships between baseline patient and infection characteristics and 30-day mortality were evaluated by logistic regression analysis and presented as odds ratios (ORs) and 95% confidence intervals (CIs). Candidate predictors of mortality were selected a priori based on previous literature (Appendix 1 in the supplement) [2, 4, 6, 7, 19–22]. Continuous and polychotomous variables were grouped for model entry using classification and regression tree (CART) analysis [23]. Independent predictors of 30-day mortality were identified by stepwise logistic regression; all candidate variables were entered into the initial model and removed sequentially based on the probability of the likelihood-ratio statistic based on the maximum partial likelihood estimates. Variables were maintained in the final model if the adjusted P value was less than 0.05. Multicolinearity was assessed via the variance inflation factor, with values of less than three being considered acceptable and second-order interactions were explored. Model calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test. Independent predictive variables were assigned a standardized weight-proportional integer value using the beta-coefficients to reflect predictive power

[24, 25]. Beta-coefficients were adjusted for overfitting by applying a shrinkage factor as described by van Houwelingen, et al. [26]. For each patient, the MRSAB risk score was calculated as an arithmetic sum of point values assigned to each independent predictor.

The discriminatory capacity of the MRSAB risk score for predicting 30-day mortality was evaluated using the area under to receiver operating characteristic curve (*c* statistic) as a measure of model performance [27]. The *c* statistic reflects the concordance of model predictions with true outcomes in rank order; a value of 1.0 indicates perfect discrimination and a value 0.5 indicates no better than chance [27]. Although there are no universal thresholds, a *c* statistic greater than 0.80 is generally considered to show very good discrimination while *c* statistic greater than 0.90 suggests excellent discrimination [27]. The discriminatory capacity of the MRSAB risk score model was compared to the final multivariable model as well as the APACHE II and Pitt Bacteremia scores by the method of DeLong et al. [28]. Pre-specified subgroup analysis was performed with stratification by age, comorbidity burden, bacteremia source, and ICU residence. Exploratory analyses were conducted to evaluate the discrimination of the MRSAB risk score for 7-, 14-, and 90-day all-cause mortality. CART analysis, modeling the MRSAB risk score as an ordinal variable, was used to derive homogeneous 30-day mortality risk groups. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated using CART-derived score cut-points to dichotomize the population into low- and high-risk groups.

A sample size of 450 patients was targeted to allow for inclusion of up to eight independent predictors in a parsimonious scoring model assuming an all-cause mortality rate of approximately 18%. Analyses were performed using SAS 9.4 Statistical Software (SAS Institute Inc., Cary, NC) and SPSS, version 24 (IBM Corp. Armonk, NY). A two-tailed *P* value less than 0.05 was considered statistically significant.

Results

A total of 455 patients were included. The mean age was 60.3 (16.3) years, 78.5% were African American, the median Charlson Comorbidity Index score was 3 (1, 5), and 16.9% were residents of the ICU at the time of index blood culture collection. The most common MRSAB sources were skin and soft tissue (22.0%), pneumonia (21.8%), IV catheter (20.2%), and infective endocarditis (19.6%). All-cause 30-day mortality was 16.3%. Univariate associations between baseline characteristics and mortality are displayed in Table 1. As shown, non-survivors were older, were more likely to be admitted from a skilled nursing facility, to have congestive heart failure, hospital-acquired MRSAB, a respiratory source, ICU residence, and mechanical ventilation. Skin and soft tissue and osteoarticular sources were protective against mortality. The median APACHE II and Pitt Bacteremia scores were significantly higher in patients who died compared to those who survived [26 (22, 31) vs. 16 (10, 21) and 3 (2, 5) vs. 1 (0. 3), respectively, all $P < 0.001$].

Table 2 displays the final multivariable logistic regression model for 30-day mortality. A total of six independent predictors of 30-day mortality were found: age, abnormal respiratory rate (< 10 or > 24 breath/min), serum creatinine ≥ 3.5 mg/dL (acute or chronic), Glascow Coma scale, hospital-acquired bacteremia, and endovascular or pulmonary source. The final multivariable model and the MRSAB risk score demonstrated very good discrimination (*c* statistic 0.868, 95% CI 0.826–0.911; 0.8662, 95% CI 0.824–0.909, respectively; $P = 0.1374$) and calibration ($P = 0.735$, $P = 0.976$, respectively). The discrimination of the MRSAB risk score was superior to the APACHE II and the Pitt Bacteremia scores (*c* statistic 0.813, 95% CI 0.763–0.864, $P = 0.043$; 0.717, 95% CI 0.6531–0.782, $P < 0.001$, respectively) (Fig. 1). The APACHE II score had better discrimination compared to the Pitt Bacteremia Score ($P = 0.003$). The MRSAB risk score additionally demonstrated very good discrimination for 7-, 14-, and 90-day mortality (*c* statistic 0.876, 95% CI, 0.826, 0.926; 0.884, 95% CI 0.845, 0.924; 0.830, 95% CI 0.781, 0.879).

The sensitivity, specificity, PPV, NPV, and accuracy of the MRSAB risk score as a binary classification test at CART-derived score cut-points are displayed in Table 3. Mortality among patients in the highest score group (≥ 17 points) was 49.5%, representing a greater than 60-fold-graded increase between those with a risk score in the lowest score group (< 5 points) ($P_{(\text{trend})} < 0.001$). Using a threshold score ≥ 17 to indicate high mortality risk provided the best overall accuracy (83.5%) with a NPV of 93.7%. A more conservative approach, using a threshold score ≥ 5, improved sensitivity and NPV to 98.7 and 99.6%, respectively, but at the expense of specificity and PPV. As shown in Table 4, the discriminatory capacity and calibration of the MRSAB scoring model were consistent across a number of pre-specified subgroups stratified age, comorbidity burden, infection source, and ICU residence.

Discussion

We have developed a simple scoring model, based on six variables that are routinely collected in patients with MRSAB. When used in combination with a simple integer-weighting system, these basic risk factors constitute a robust scoring model that can be easily used as a framework for analyses stratified by risk. Although we used 30-day all-cause mortality as our primary outcome variable and demonstrated high discriminatory capacity, we observed that the scoring model had very good

Table 1 Univariate risk for 30-day mortality stratified by presenting characteristics

	Total cohort *N* = 455	Odds ratio (95% CI)	*P* value
Age, (years), mean (SD)	60.34 (16.26)		
Age		1.049 (1.031, 1.068)	< 0.001
Male gender	287 (63.1)	0.729 (0.440, 1.208)	0.218
Race, *n* (%)			
Caucasian	86 (18.9)	Reference	–
African American	357 (78.5)	0.827 (0.460, 1.485)	0.524
Body mass index, (kg/m^2) mean (SD)			
Underweight (BMI < 18.5 kg/m^2)	30 (6.6)	1.463 (0.597, 3.589)	0.406
Normal/overweight	93 (20.4)	Reference	–
Obese (BMI ≥ 30 kg/m^2)	332 (73.0)	0.668 (0.360, 1.238)	0.200
Admission Source, n (%)			
Community	316 (69.5)	Reference	–
Nursing home	112 (24.6)	2.314 (1.367, 3.916)	0.002
Comorbidities, *n* (%)			
Heart failure	104 (22.9)	2.829 (1.667, 4.801)	< 0.001
Diabetes	181 (39.8)	0.907 (0.543, 1.514)	0.709
Chronic hemodialysis	113 (24.8)	0.968 (0.542, 1.728)	0.911
Liver disease	60 (13.2)	1.034 (0.499, 2.146)	0.928
Malignancy	29 (6.4)	1.373 (0.539, 3.499)	0.504
Charlson Comorbidity Score, median (IQR)	3 (1, 5)		
		1.129 (1.021, 1.249)	0.018
IV drug use, *n* (%)	68 (14.9)	0.548 (0.240, 1.251)	0.148
Immunosuppression, *n* (%)	29 (6.4)	1.373 (0.539, 3.499)	0.504
Prior hospitalization,[a] *n* (%)	181 (39.8)	1.186 (0.717, 1963)	0.506
Prior antibiotics,[a] *n* (%)	162 (35.8)	0.719 (0.419, 1.235)	0.231
Hospital-acquired MRSAB	90 (19.8)	2.117 (1.228, 3.649)	0.006
Bacteremia source, *n* (%)			
Infective endocarditis	89 (19.6)	1.535 (0.857, 2.748)	0.147
Pneumonia	99 (21.8)	5.145 (3.026, 8.747)	< 0.001
Osteoarticular	55 (12.1)	0.172 (0.41, 0.772)	0007
Central nervous system	8 (1.8)	0.979 (0.965, 0.994)	0.364
Skin/soft tissue	100 (22.0)	0.269 (0.113, 0.641)	0.002
IV catheter	92 (20.2)	1.217 (0.669, 2.212)	0.519
Unknown	52 (11.4)	0.928 (0.418, 2.062)	0.855
ICU at index culture	77 (16.9)	4.471 (2.563, 7.798)	< 0.001
Mechanical ventilation	78 (17.1)	6.510 (3.738, 11.337)	< 0.001
APACHE II score, median (IQR)	18 (11, 23)		
		1.129 (1.094, 1.164)	< 0.001
Pitt Bacteremia score, median (IQR)	2 (0, 3)		
		1.343 (1.208, 1.492)	< 0.001

APACHE Acute Physiology and Chronic Health Evaluation, BMI body mass index, CI confidence interval, ICU intensive care unit, IQR interquartile range, IV intravenous, MRSAB methicillin-resistant *Staphylococcus aureus* bacteremia, n number, SD standard deviation

[a] Within 90 days

discrimination at both early and later mortality time-points. In addition, the predictive capacity of the risk score was stable across a number of key pre-specified subgroups defined by baseline health status and illness acuity.

The variables considered in our analysis were not novel and those that remained independent predictors of mortality in our final model supported an extensive body of MRSAB outcomes research. Consistent with the findings of the present

Table 2 Independent risk factors for 30-day mortality and point allocation in MRSAB risk score

Variable	Adjusted odds ratio (95% confidence interval)	Beta[a]	Points
Age			
< 70 years	Reference	Reference	0
70–79 years	2.973 (1.387, 6.373)	1.007	5
80–89 years	3.497 (1.471, 8.317)	1.158	6
≥ 90 years	8.413 (2.281, 31.036)	1.970	10
Glascow Coma Scale[b]			
14–15	Reference	Reference	0
10–13	2.891 (1.283, 6.511)	0.981	5
≤ 9	4.285 (2.071, 8.867)	1.346	7
Respiratory rate < 10 or > 24 breaths/min[b]	2.342 (1.221, 4.489)	0.787	4
Serum creatinine ≥ 3.5 mg/dL[b, c]	3.307 (1.684, 6.494)	1.106	6
Hospital-acquired bacteremia	2.092 (1.058, 4.139)	0.683	3
Infective endocarditis or pulmonary bacteremia source	4.101 (2.129, 7.900)	1.305	7

MRSAB methicillin-resistant *Staphylococcus aureus* bacteremia

[a] Following shrinkage by factor = (model X^2 –df)/model X^2 = 0.925

[b] Worst physiological value within 24 h of index blood culture collection

[c] In the setting of acute or chronic kidney impairment

analysis, age has repeatedly been found to be among the strongest independent predictors of mortality in *S. aureus* bacteremia cohort studies [2, 21, 29–31]. This association persists after controlling for problems that come with aging such as the presence of comorbidities, invasive medical devices, and healthcare exposures. The higher morality with increasing age may be partly attributed to differences in investigations and management of MRSAB in the elderly [21, 32]. However, we did not observe differences in rates of infectious diseases specialist consultation or source control across age groups. Furthermore, the proportion of patients with an unknown source of infection was not modified by age suggesting diagnostic efforts to identify a source were not less extensive in the elderly. Thus, it appears that the increased mortality observed in elderly MRSAB patients is a direct consequence of changes that occur within the host as a result of the of the aging process [21], underscoring its importance in risk adjustment.

It is notable that a number of comorbidities (ex. diabetes, heart failure, cancer, liver disease) associated, albeit inconsistently, with increased mortality in previous studies were not independent predictors in this analysis. We surmise that the retention of hospital-acquired bacteremia and renal failure in our model better captures risk in patients with the poorest baseline health status without the diluting effects of well-controlled comorbidities that do not impact on the host's ability to clear infection. Other investigators have observed that comorbidities are more impactful on longer-term outcomes (i.e. ≥ 90 days) [2]. Although our model demonstrated very good discrimination for 90-day mortality, it is possible that alternative models, which include select comorbidities, may demonstrate superior performance for mortality prediction at later time-points.

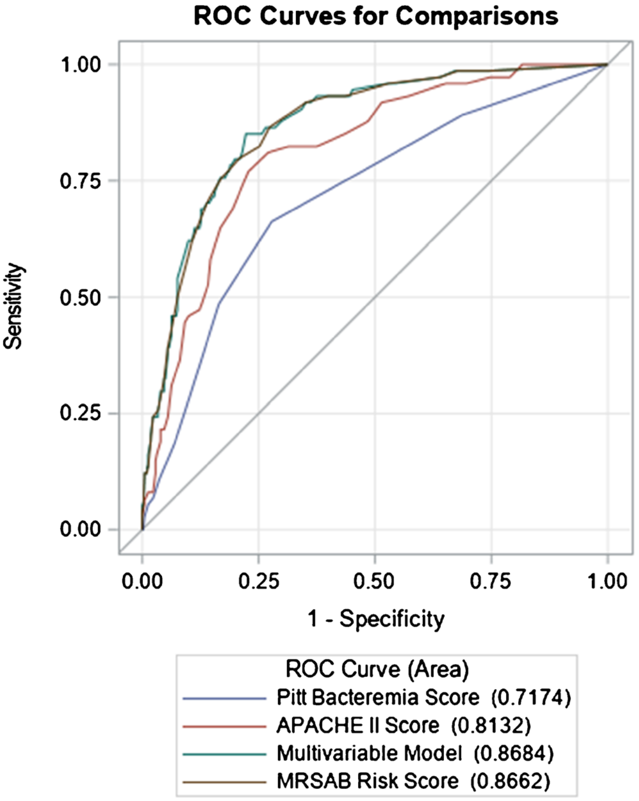

Fig. 1 Receiver operator characteristic (ROC) curves for the prediction of 30-day mortality

Table 3 Scoring system performance with groups dichotomized at CART-derived cut-points

MRSAB risk score (Percent of cohort)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Accuracy (%) (95% CI)
≥ 17	70.27	86.09	49.52	93.71	83.52
(23.08)	(58.52, 80.34)	(82.20, 89.40)	(42.32, 56.74)	(91.29, 95.50)	(79.78, 86.81)
≥ 11	91.89	64.83	33.66	97.63	69.23
(44.40)	(83.18, 96.97)	(59.80, 69.62)	(30.35, 37.14)	(95.01, 98.89)	(64.76, 73.44)
≥ 5	98.65	48.91	22.05	99.60	55.27
(72.75)	(92.70, 99.97)	(44.47, 53.37)	(20.56, 23.63)	(97.24, 99.94)	(51.11, 59.37)

CART classification and regression tree, *CI* confidence interval, *MRSAB* methicillin-resistant *Staphylococcus aureus* bacteremia, *NPV* negative predictive value, *PPV* positive predictive value

Consistent with other studies, both the APACHE II and Pitt Bacteremia scores were significant predictors of mortality; however, both had inferior discrimination compared to the MRSAB risk score. The Pitt Bacteremia score was developed nearly three decades ago in patients with Gram-negative bacteremia which differs in many respects to MRSAB in terms of underlying patient health status, pathogen virulence, the potential for metastatic spread, and treatment approaches [4, 6, 12, 13]. Thus, it is not unexpected that this scoring system demonstrated only moderate discriminatory power in our study. Our finding is in agreement with that of Roth et al., who recently found that the PITT bacteremia score had only moderate predictive value for all-cause 30-day mortality in MSSA bacteremia (*c* statistic 0.71, 95% CI 0.614, 0.807) [33]. The APACHE II score, by contrast, was originally developed and validated in ICU populations with a wide range of diagnoses [11, 34]. It is noteworthy that the majority of patients in the present study were not residents of the ICU at the time of blood culture collection. Both scoring systems lack parameters that are powerful prognostic indicators in MRSAB such as site of infection. Indeed, consistent with previous studies [2, 20, 21, 35], the presence of endocarditis or a pulmonary source of infection conferred an approximately 4-fold increased risk of mortality after controlling for other risk factors.

Some limitations in the present study should be considered. First, the study is subject to inherent bias with its use of retrospective data. In-depth review of the EMRs allowed us to obtain detailed patient-level data that has not been available in many prognostic scoring derivation studies that used existing administrative databases. However, it is possible that certain risk factors were not documented or were under-reported. In particular, a growing body of evidence has demonstrated the prognostic importance of certain biomarkers as surrogates for both the hyper-inflammatory response to infection as well the ensuing state of immunoparalysis [3, 35]. More nuanced approaches to the measurements of response to infection, including novel biomarkers, may yield models with

Table 4 MRSAB scoring model discrimination and calibration in subgroups of interest

Subgroup	Number of patients	C statistic (95% CI)	Hosmer-Lemeshow *P*
Age < 65 years	284	0.877 (0.825, 0.929)	0.764
Age ≥ 65 years	171	0.820 (0.749, 0.892)	0.443
Charlson Comorbidity Score < 4	265	0.885 (0.835, 0.935)	0.275
Charlson Comorbidity Score ≥ 4	190	0.845 (0.775, 0.915)	0.188
IV drug users	68	0.856 (0.738, 0.974)	0.958
Low-risk source[a]	93	0.813 (0.673, 0.954)	0.497
Moderate-risk source[b]	176	0.878 (0.737, 1.00)	0.575
High-risk source[c]	187	0.797 (0.730, 0.864)	0.847
Non-intensive care unit at bacteremia onset	378	0.869 (0.814, 0.925)	0.674
Intensive care unit at bacteremia onset	77	0.719 (0.605, 0.833)	0.180

CI confidence interval, *IV* intravenous

[a] IV catheter, urinary tract, ear-nose-larynx, gynecologic, and manipulation-related [29]

[b] Osteoarticular, skin and soft tissue, and unknown [29]

[c] Endovascular, lower respiratory tract, abdominal, and central nervous system foci [29]

higher discrimination. It must be remembered however that the score is intended to be used for risk adjustment in retrospective observational studies and therefore from a pragmatic perspective, predictors should be limited to those that can be reliably obtained from the EMR. Next, all patients included in this study received early active antibiotic therapy. Delayed initiation of appropriate therapy for MRSAB has been shown to have a profound impact on outcomes [22] and thus, our score would likely underestimate mortality when applied in this setting. The score may however serve as a reference to evaluate the efficacy of novel antibiotics since it would easily allow for the estimation of expected mortality in included patients receiving the current standard of care. Next, our model is based on physiological measurements obtained within 24 h of blood culture collection. This time frame may not have always corresponded to the true MRSAB onset, particularly among patients presenting from the community. This is an inherent problem with any study that includes patients with community-onset infection. MRSA is no longer an exclusively nosocomial pathogen, and broadly restricting analyses to hospital-acquired bacteremia would not be representative of the MRSAB population. Finally, our data were obtained from a single medical center in urban Detroit and may not be generalizable to other institutions in distinct geographic areas or serving a different patient population by age, baseline health status, and other prognostic factors. Our study population was however comprised of a heterogeneous group of patients intended to reflect the real-world setting. Furthermore, our findings agree with previous *S. aureus* bacteremia studies suggesting idiosyncrasies in our dataset did not have a major impact on results. External validation is, of course, necessary before widespread use.

For more than half a century, the standard of care for MRSAB has been prolonged courses of IV vancomycin with little evidence to support alternatives [1, 7]. This lack of data stems from the well-rehearsed financial, ethical, and practical constraints that prevent RCTs from being conducted in complex MRSA BSI patients [1]. Thus, there is great opportunity for observational studies to fill evidence gaps pertaining to novel treatment strategies. However, confounding is a particular threat in observational studies when comparison groups are different due to non-random treatment allocation [36]. Treatment choices are often informed by a patient's clinical and infection characteristics and studies that do not account for this are at risk of obtaining spurious results [36]. Future focus should shift from criticism of observational studies to developing and validating tools, such as the MRSAB risk score, which allow for greater rigor in research so that we optimize our ability to gain insight into important MRSAB management issues.

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Compliance with ethical standards

Conflict of interest MJR has received funding support, consulted or participated in speaking bureaus for Allergan, Achaogen, Bayer, Melinta, Merck, Theravance, The Medicine Company, Sunovian and Zavante, and NIAID (all unrelated to this study). SCJJ, AML, and SB have nothing to declare.

Ethical approval This study was approved by the Wayne State University Institutional Review Board (IRB# 122916MP2E) and the Detroit Medical Center Research Committee (14081) with a waiver for informed consent.

Informed consent Due to the retrospective nature of this study, informed consent was not required.

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