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Development and validation of a prediction rule for methicillin-resistant Staphylococcus aureus recurrent infection among a veterans affairs healthcare system population

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DEVELOPMENT AND VALIDATION OF A PREDICTION RULE FOR METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS RECURRENT INFECTION AMONG A VETERANS AFFAIRS HEALTHCARE SYSTEM POPULATION

by

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CERTIFICATE OF APPROVAL

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MASTER'S THESIS

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This is to certify that the Master's thesis of

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To my wife Natalie, thank you for your love, support, and encouragement. I wouldn't be here without you.

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ABSTRACT

Objective: Recurrent methicillin-resistant *Staphylococcus aureus* (MRSA) infections are a significant problem in the healthcare system. Our objective was to create a clinical prediction rule to identify Veterans at high-risk of recurrent MRSA infections.

Methods: A retrospective cohort study of Veterans with MRSA bacteremia was performed using patient data from 2003 to 2011. Recurrent MRSA infection was defined as a positive blood culture between two days and 180 days after discharge from the index hospitalization. Severity of illness was measured at the time of admission using a modified APACHE score. Patients were randomly split into a development or validation cohort. Using the development cohort, variables significant in predicting recurrence on univariate analysis were input into a logistic regression model. The final model, c-statistics, and receiver operating characteristic curves were compared in each cohort.

Results: Of 9,279 patients in the combined cohort, 1,127 (12.1%) had a recurrent MRSA infection within 180 days of the index infection. Using the development cohort, the risk factors identified and included in the logistic regression model were severity of illness, duration of bacteremia, distance to care, lack of MRSA-directed antibiotic therapy, renal failure, coagulopathy, cancer, and cardiac arrhythmia. The model had poor discrimination (c-statistic, 0.657), with 68.9% sensitivity and 54.0% specificity. The validation cohort also had poor discrimination (c-statistic, 0.625), with 66.8% sensitivity and 52.6% specificity.

Conclusions: Our results identify important risk factors for MRSA recurrence and may help to guide clinicians in targeting high-risk patients for treatment and aggressive follow-up.

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INTRODUCTION

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) is associated with significant morbidity and mortality in healthcare settings. It can cause severe infections in the bloodstream, respiratory tract, and skin, and has been associated with higher healthcare costs and longer hospital length of stay than infection with methicillin-susceptible strains (1, 2). The National Healthcare Safety Network estimates that *S. aureus* accounted for 15.6% of healthcare-associated infections (HAI) in the United States in 2009-2010, and over half of these were caused by MRSA (3). The large number of infections caused by this organism is due in part to its ubiquitous nature in the healthcare system. Approximately 2% of the general population carries MRSA in the anterior nares, but this increases to 7-10% in hospital settings (4-6).

As a result of the significant number of infections caused by MRSA each year, rigorous infection control measures have been studied and introduced at healthcare facilities. In 2007, the Veteran Affairs (VA) Healthcare System began a nationwide directive to prevent MRSA infections. The directive included "universal nasal surveillance for MRSA colonization, contact precautions for patients who were carriers of MRSA, hand hygiene, and an institutional culture change whereby infection control became the responsibility of everyone who had contact with patients" (7). The directive appears to have been successful. Jain et al. reported a 62% reduction in the rates of healthcare-associated MRSA infections across 153 hospitals, and other studies have noted a decline since the directive was set in place (7-9).

Following the success of the nationwide VA directive, there is a continuing need to address other areas of importance that arise as a result of MRSA infection in healthcare settings. The directive targeted exogenous infections, or those that arise as a result of infection spreading patient to patient or from the environment. The points of emphasis of the directive are less effective at preventing endogenous infections, or those that are spread from one body site on the patient to another body site. Bacteremia resulting from nasal colonization in a patient would be an example of an endogenous infection. Recurrence of infection is another example of an endogenous complication that can result from infection with *S. aureus* and, unfortunately, little research has been done on the risk factors and effects of recurrence. Even less research has been carried out that narrows the focus of recurrence to MRSA, even though early detection, therapy, and focus identification are extremely important for a positive patient outcome.

Recurrence of bacteremia can cause increased patient morbidity and mortality, lead to higher costs, and may produce a need for additional antibiotic therapy. It could potentially increase the rate of hospital readmissions, which can affect hospital ratings and funding. Recurrence can be defined as the development of *S. aureus* bacteremia after negative blood cultures, and/or clinical recovery after a completed course of antibiotic therapy (10). The estimated proportion of patients who experience recurrence of *S. aureus* bacteremia varies, but is generally thought to be in the vicinity of 5-12% (10-12). However, these estimates are from studies of *S. aureus* (including both MRSA and methicillin-susceptible *S. aureus* [MSSA]), and infection specifically with MRSA may cause an increase in recurrence rates. Patients infected with MRSA may be more likely to have a compromised immune system than those infected with MSSA, and vancomycin,

the antibiotic of choice for MRSA infections, has been shown to be less effective at terminating *S. aureus* bacteremia than other antibiotics normally used to treat MSSA (10, 13). A study of *S. aureus* bacteremia in a veteran population found that 17% of these patients had recurrent *S. aureus* bacteremia, and there was an increased risk associated with MRSA (14).

Recurrence can be divided into two categories: relapse, which is the emergence of the original infecting organism, or reinfection, which is infection with a differing strain (11). The difference between relapse and reinfection is usually deduced using pulsed-field gel electrophoresis (PFGE) patterns or molecular subtyping (10-12). By analyzing PFGE patterns of the bacterial isolates from the original infection and the recurrent infection, the recurrent strain can be identified as a persistent infection or an entirely new infecting strain.

Relapse occurs far more often than reinfection, making up 80 to 90% of recurrence, and usually takes less time to present (10-12). One explanation of the large ratio of relapse to reinfections may be differences in exposure to high-risk therapies. Presence of an indwelling prosthetic device and hemodialysis therapy have been shown to be risk factors for relapse (11). Other possible explanations could include the continued presence of the infection in the patient's body (e.g. endocarditis) or contamination of the patient's contacts or environment. In contrast, patients with reinfections may be exposed to situations where multiple MRSA strains are in circulation. Injection drug use, dermatitis, and presence of multiple surgical wounds have been associated with reinfection (11). Another possible explanation could be discharge to high-risk areas such as nursing homes or homeless shelters. Chang et al.

found that relapse followed *S. aureus* bacteremia after a median of 36 days, and reinfection followed after a median of 99 days (10). This emphasizes the importance of continued surveillance and follow-up.

Several other risk factors are linked to recurrence of *S. aureus* bacteremia. Comorbidities such as HIV, diabetes, and renal failure are associated with recurrence, possibly due to weakening of the immune system (13, 14)). Infection sites deep in the body such as the heart (endocarditis) or bone (osteomyelitis), and the failure to remove foreign devices such as a central venous catheter, may cause a continuing presence of MRSA (10, 11, 13). The type of antibiotic therapy (specifically vancomycin) has been shown to increase recurrence, although this could be due to confounding by MRSA since these studies included all *S. aureus* strains (11, 14-16).

Knowing risk factors is important in clinical care, and identifying factors such as these may make it possible to predict which patients are at high risk for recurrent infection and target them for more aggressive treatment. Nasal decolonization with mupirocin ointment and skin decontamination with chlorhexidine gluconate bathing are two examples of targeting methods that may be effective. Aggressive follow-up, perhaps including visits at 30 day intervals, could be an additional way to prevent recurrence.

Clinical prediction rules have been used with varying success to identify patients at risk of MRSA colonization and infection (5-6, 17). One study was able to predict MRSA colonization at a university research hospital with a sensitivity of 76% using just one variable, which was prior hospital admission within one year (5). When evaluated in a veteran population, the effectiveness of this prediction rule dropped, which may mean that prediction rules for a general hospital are not generalizable to a VA medical center

(6). In contrast to this simple prediction rule, Robicsek et al. derived and validated a comprehensive prediction rule that incorporated 27 separate variables. It was designed to be used "in a setting with very good electronic data availability and strong computational capacity" (17). VA medical centers have excellent electronic data availability and use identical electronic medical record software. Therefore, we could potentially use several variables, and thus the number of variables in our prediction rule was expected to fall in between the two previous examples.

Significance

Recurrent MRSA infections are a significant problem in the healthcare system, and there is a major gap in knowledge about risk factors and techniques to prevent this disease. Clinical prediction rules are an effective way to establish risk factors and enable clinicians to target high-risk patients. Unfortunately, while prediction rules are available for MRSA colonization and infection, none have been extended to recurrence of MRSA infection. Additionally, the VA directive has focused on exogenous infections, but is not likely to greatly reduce endogenous infections like MRSA recurrence, so other means must be used to stop these infections.

To our knowledge, this would be the first prediction rule to target recurrent MRSA infection and, if it proves to be highly sensitive, it could be utilized by the VA system upon diagnosis of initial infection to determine treatment options and aggressiveness of follow-up. A prediction rule for MRSA recurrence implemented in the VA system could be a cost-effective, straightforward way to reduce infection and improve patient outcomes.

Hypothesis

We hypothesize that a clinical prediction rule can be established to predict MRSA recurrence in the VA healthcare population. We expect that MRSA recurrence can be predicted with a sensitivity of 70% and a specificity of 95%.

Objective

The objective of this study is to create a clinical prediction rule to identify Veterans at high-risk of recurrent MRSA infections. Using patient data from the entire VA Healthcare System, we will construct a cohort composed of veterans with MRSA bloodstream infections. The cohort will be split into two halves: one half for development of the prediction rule and one half for validation. We aim to create a model to develop a prediction rule in one half of the veteran population cohort. We will measure the performance of the model and prediction rule in the second half of the cohort with the aim to identify patients with a sensitivity of 70% and a specificity of 95%.

METHODS

Study Design and Patient Population

We conducted a retrospective cohort study that included veterans admitted to approximately 130 acute care VA Medical Centers between the years 2003 and 2011 (18). Each patient in the cohort had MRSA bacteremia during their index hospitalization, defined as a MRSA positive culture collected from the blood. Patients were followed for 180 days with the observation time beginning at discharge from the healthcare facility.

Exclusion criteria included patients who were infected with methicillin-susceptible *Staphylococcus aureus* (MSSA) during the initial infection or the recurrent infection and patients who died during the index hospitalization. Patients who died before the completion of the 180 day follow-up period were excluded in order to give each patient sufficient time to develop a recurrent MRSA infection. Patients who developed a recurrent MRSA infection before death were not excluded.

We examined demographic, clinical, and pharmaceutical variables for associations with recurrent MRSA infections. All variables excluding recurrence were measured at the index hospitalization. Data was accessed through the VA Informatics and Computing Infrastructure (VINCI). This study received approval from the University of Iowa institutional review board and the Iowa City VA Research and Development Committee.

This study exclusively contained veterans. VA medical center populations tend to be overwhelmingly male and have a higher mean age than a general medical center, though both of these trends are gradually changing as veterans from Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (conflicts in Afghanistan

and Iraq) enter the population. According to a prior study, the mean age of patients admitted to VA acute care facilities from 2007 to 2010 was about 62 years, and 95% of the patients were male (7).

Variable Definitions

We defined recurrence as a positive MRSA blood culture between two days and 180 days after index hospitalization discharge. Recurrence was not subdivided into relapse and reinfection because the retrospective data did not provide strain information or genotyping patterns. Positive MRSA blood cultures occurring within two days of discharge were considered to be the original infection and were not counted as a recurrence. Distance to care was defined as the number of miles between the patient's home zip code and the index hospital zip code and was divided into four categories approximately by quartiles. Duration of bacteremia was defined as the number of days between the first positive culture and the final positive culture. Healthcare-acquired infections were defined as an initial positive blood culture occurring greater than 48 hours after admission. Patients were considered to have received a MRSA-active antibiotic if at least one of the following antibiotics was received: vancomycin, daptomycin, linezolid, clindamycin, ceftaroline, tigecycline, dalfopristin with quinupristin, and trimethoprim with sulfamethoxazole.

We used the International Statistical Classification of Disease and Related Health Problems, 9th Revision, Clinical Modification (ICD-9-CM) coding system to assess each of 31 Elixhauser comorbidities and three Charlson comorbidities as presented by Quan et al (19). Cancer was defined by combining the Elixhauser comorbidities lymphoma, metastatic cancer, and solid tumor without metastasis. We used the modified Acute

Physiology and Chronic Health Evaluation (APACHE) III score to evaluate severity of illness at hospital admission (20). The components and point range of the score is described in Table 1. The urine output and Glasgow coma score components of the APACHE score were not present in the VINCI database and thus are not included in the score. Arterial pH levels, partial pressure of oxygen, and the alveolar-arterial gradient were not included in the score due to many missing values, since these components are measured on intensive care unit (ICU) admission and we included non-ICU patients. We used ICD-9-CM codes to identify endocarditis and osteomyelitis.

Statistical Analysis

A split-sample approach was used to create the prediction rule. The sample was randomly split into two cohorts with an equal number of subjects, one of which was used for development of the prediction rule, and the other for validation. Each continuous variable was categorized, and we performed a chi-square test analysis on each variable to assess associations between variables and MRSA recurrence. Odds ratios and p-values were also obtained. Variables with a p-value of less than 0.3 were entered into a logistic regression model and logistic regression analysis was performed using the development cohort. Stepwise selection and backward elimination analysis methods were carried out using 0.05 as the entry and removal requirement. Along with these methods, we ranked variables based on suspected clinical relevance and removed variables by rank using 0.05 as the removal requirement. Analysis using all three methods determined the final model. This model was then applied to the validation cohort.

The c-statistics of each cohort were calculated to assess the fit of the model. The sensitivity and specificity of the model were evaluated using a receiver operating

characteristic (ROC) curve. The c-statistic and ROC curve of the development cohort and the validation cohort were compared. All analyses were performed using SAS Enterprise Guide.

RESULTS

A total of 27,579 patients were contained in the VINCI database. Of these, 12,339 patients were infected with MSSA and were excluded. An additional 5,961 patients were excluded due to death within 180 days of discharge. The remaining 9,279 patients were included in the study. 4,640 patients were randomly placed into the development cohort, and 4,639 were placed into the validation cohort (Figure 1).

The number of patients that had recurrent MRSA bacteremia within 180 days of initial hospitalization was 1,127 (12.1%). Table 2 shows the univariate comparison between patients with a recurrent MRSA infection and patients without a recurrent MRSA infection in the development cohort. Patients with a recurrent MRSA infection were significantly older, lived closer to the VA facility, had a longer duration of bacteremia during the initial infection, and presented with more severe illness at the index hospitalization. Patients with a recurrent MRSA infection were more likely to not have received an antibiotic with MRSA-directed activity during the initial MRSA infection. They were also more likely to have acquired their initial bacteremia during the index hospitalization. Several comorbidities were significantly associated with a higher risk of recurrence. These included congestive heart failure, cardiac arrhythmias, hypertension (complicated), renal failure, cancer, and coagulopathy. Paralysis and osteomyelitis had a protective effect against recurrence.

Using stepwise regression and backward elimination logistic regression analysis, along with clinical relevance, eight variables included in the final prediction model (Table 3). Duration of bacteremia was categorized into four groups with a duration of one day serving as the reference group. Patients with duration of bacteremia for greater

than or equal to seven days had the highest risk of recurrent MRSA infection (OR = 2.08, P< .0001) compared to the reference group. Distance to care was categorized into four groups with a distance of greater than or equal to 61 miles serving as the reference group. Patients living between seven and 20 miles from their VA facility showed the highest risk of recurrent MRSA infection (OR = 1.67, P = 0.0002) compared to the reference group. The modified APACHE III score was categorized into four group, with a score of 0-20 serving as the reference group. Patients with a score of 41 or greater showed the highest risk of recurrent MRSA infection (OR = 1.64, P = 0.0010) compared to the reference group. A lack of MRSA-directed therapy (OR = 2.18, P< .0001), renal failure (OR = 1.71, P< .0001), coagulopathy (OR = 1.54, P = 0.0231), cancer (OR = 1.47, P = 0.0066), and cardiac arrhythmias (OR = 1.40, P = 0.0024) were also included in the final model.

The model was analyzed in the validation cohort and results compared with the development cohort. The model showed poor discrimination in each cohort. The development cohort had a c-statistic of 0.657, 68.9% sensitivity, and 54.0% specificity. The validation cohort had a c-statistic of 0.625, 66.8% sensitivity, and 52.6% specificity. The receiver operating characteristic (ROC) curves for the development and validation cohorts are shown in Figures 2 and 3, respectively. These curves show the tradeoff between sensitivity and specificity and illustrate the discrimination of our model.

Time-to-death statistics were calculated for the 5,961 patients who were excluded due to death. 58% of excluded patients died within 30 days of their index hospitalization, 75% died within 60 days, and 84% died within 90 days. The modified APACHE III score was compared in patients excluded due to death and the development cohort. 21.6% of patients in the development cohort had a modified APACHE III score in the

highest category (≥41). 38.5% of excluded patients were in the highest score category, indicating more severe illness among patients excluded due to death.

DISCUSSION

We used a large database of Veterans with MRSA bacteremia to find risk factors and create a prediction rule for recurrent MRSA infections. Our prediction rule contained eight variables based on a logistic regression model, which were severity of illness, duration of bacteremia, distance to care, lack of MRSA-directed antibiotic therapy, renal failure, coagulopathy, cancer, and cardiac arrhythmia. The sensitivity, specificity, and c-statistic indicated a poor predictive model.

This study was very different from other studies that have been done on *S. aureus* recurrence. Our study contained thousands of patients, while almost all other studies include between 250 and 350 patients (10, 11, 15, 16). Only one study included more patients (10,891), and it focused on all *S. aureus* strains and had a large range of follow-up time (90-5654 days) (13). Our study contained only Veterans, and contained only patients with MRSA bacteremia. As such, it was suspected that our findings may not be consistent with other studies, which proved to be accurate. Our model identified risk factors that were not identified in previous studies, and did not include other risk factors that were thought to have importance.

The retrospective nature of our study prevented us from identifying the source of the initial infection and whether that source was removed, which was identified as a risk factor for recurrence in 3 studies (11, 13, 16). Endocarditis had no association with recurrence and differences in the variable definition may explain these results. One study followed endocarditis patients for three years, and, along with another study, used the Duke criteria for endocarditis diagnosis (10, 15). The direction of association of the distance-to-care variable in our model was unexpected. One explanation for this

association is that patients closer to the VA hospital may be more likely to be readmitted if the infection returns, whereas those that live further away may not seek care or may seek care at another facility closer to their home. The association of coagulopathy and renal failure with recurrence may be explained by the intravenous therapy required to treat these conditions. Renal failure itself has been associated with recurrence (13), and could be a proxy for hemodialysis, which has also been associated with recurrence (11).

This study had several strengths. With over 9,200 patients in the combined cohort over an eight year period, this study includes thousands more patients than most other studies of *S. aureus* recurrence 10-12, 15, 16). The amount of power in this study may have helped us identify risk factors that were not found in previous studies. Hundreds of variables were available to study and were obtained exclusively from the VA system, so the variables were collected consistently through the VA electronic medical records. We had very reliable microbiologic data from VA laboratories, which was advantageous for identifying MRSA infections rather than relying on ICD-9 codes.

This study also had limitations. Due to the retrospective nature of the study, certain variables that may be important risk factors for recurrence were not available. For example, the source of the initial infection (e.g. catheter) and whether that source was removed has been shown to be important in predicting MRSA recurrence (11, 13, 16). Certain variables like immunosuppressant therapy, corticosteroid therapy, and homelessness that could potentially be clinically relevant were not available in our data. The retrospective nature of the study made it necessary to rely on ICD-9 codes to find comorbidities and co-infections. Since this is a study of a Veteran population, consisting

of mostly older males, it may not be generalizable to other medical centers and healthcare systems.

A major limitation to this study is the exclusion of 5,478 patients who died within six months of the initial infection. The six month follow-up time was chosen to give sufficient time for a recurrent infection to develop, but the exclusion of so many patients has the potential to bias the results. Another limitation to our data is that we are not aware of patients that received medical care for a recurrent infection at a hospital outside of the VA system. The results could be biased if these dual-use patients are different than those who receive care exclusively in the VA system. A final limitation is that we did not distinguish between relapse (recurrence with the initial strain) and reinfection (an entirely new infection). Differences in strains would normally be identified using genotyping, something we were not able to do with retrospective data.

Our study may be a step in preventing hospital readmissions, an important hospital quality indicator. The Hospital Readmissions Reduction Program requires the Centers for Medicare and Medicaid Services (CMS) to reduce payments to hospitals with an excess of readmissions (21). A reduction in recurrent MRSA infections may play a part in reducing readmissions, thereby saving hospitals from financial penalties.

To our knowledge, this is the first prediction rule that has been created for MRSA recurrence, and several risk factors were identified in our study that have not previously been seen. It may be beneficial for future research to focus on these risk factors instead of a prediction rule, as the sensitivities and specificities found in this study are likely not at a high enough level for the prediction rule to be implemented in the VA system.

Further research could also explore the reason for admission of the patients in our cohort, and a survival analysis may be a useful tool for studying patients that were excluded.

In conclusion, we created a prediction rule with eight variables, all of which can easily be found in the patient's electronic medical record prior to discharge. This rule had poor sensitivities and specificities for predicting MRSA recurrence. Future studies should be performed to further explore identified risk factors, validate this prediction rule in other populations, and determine whether this rule could assist in clinician decision-making in regards to aggressiveness of follow-up after an initial MRSA bacteremia.

Table 1: Components of the modified Acute Physiology and Chronic Health Evaluation (APACHE) III score

Components of Modified APACHE III	Assigned Points
Age[a]	0-24
Comorbid conditions[b]	
AIDS	23
Hepatic Failure	16
Lymphoma	13
Metastatic cancer	11
Leukemia/multiple myeloma	10
Immunosuppression	10
Cirrhosis	4
Acute physiologic abnormalities[c]	
Pulse rate	0-17
Mean blood pressure	0-23
Temperature	0-28
Respiratory rate	0-18
Partial pressure of oxygen	0-15
Hematocrit	0-3
White blood cell count	0-19
Creatinine	0-7
Blood urea nitrogen	0-12
Sodium	0-4
Albumin	0-11
Bilirubin	0-16
Glucose	0-9

[a] Patients who are $\leq$ 44 years old receive zero points whereas patients who are $\geq$ 85 years receive 24 points.

[b] Patients without the comorbid condition receive zero points whereas patients with the condition receive the points provided in the column.

[c] Patients within the normal range of an acute physiologic test receive zero points whereas patients farthest away from the normal range receive the highest points.

Table 2: Characteristics of 4,640 patients with MRSA bacteremia according to occurrence of recurrent MRSA infection

Characteristic	Recurrence N=557	No Recurrence N=4,083	All Patients N=4,640	P-value	Odds Ratio (95% CI)
Male Gender	546 (98.0)	3971 (97.3)	4517 (97.3)	0.2897	1.40 (0.75, 2.61)
Age (years)					
18-55	107 (19.2)	1029 (25.2)	1136 (24.5)	-	1.00
56-62	137 (24.6)	1083 (26.5)	1220 (26.3)	0.1506	1.22 (0.93, 1.59)
63-73	150 (26.9)	935 (22.9)	1085 (23.4)	0.0013	1.54 (1.19, 2.01)
≥74	163 (29.3)	1036 (25.4)	1199 (25.8)	0.0017	1.51 (1.17, 1.96)
Geographic Region					
Northeast	95 (17.1)	709 (17.4)	804 (17.3)	0.2534	1.12 (0.88, 1.64)
South	267 (47.9)	1857 (45.5)	2124 (45.8)	0.0577	1.29 (0.99, 1.67)
Midwest	112 (20.1)	774 (19.0)	886 (19.1)	0.0923	1.30 (0.96, 1.75)
West	83 (14.9)	743 (18.2)	826 (17.8)	-	1.00
Distance to Care (miles)					
0-7	168 (30.2)	1124 (27.5)	1292 (27.8)	<.0001	1.58 (1.21, 2.05)
7-20	172 (30.9)	989 (24.2)	1161 (25.0)	0.0007	1.83 (1.41, 2.38)
21-60	117 (21.0)	916 (22.4)	1033 (22.3)	0.0382	1.35 (1.02, 1.78)
≥61	100 (18.0)	1054 (25.8)	1154 (24.9)	-	1.00
Duration of Bacteremia (days)					
1	433 (77.8)	3469 (85.0)	3902 (84.1)	-	1.00
2-3	47 (8.4)	245 (6.0)	292 (6.3)	0.0102	1.54 (1.11, 2.13)
4-6	28 (5.0)	163 (4.0)	191 (4.1)	0.1298	1.38 (0.91, 2.08)
≥7	49 (8.8)	206 (5.0)	255 (5.5)	0.0001	1.91 (1.37, 2.64)
Severity of Illness (modified APACHE III score)					
0-20	87 (15.6)	996 (24.4)	1083 (23.3)	-	1.00
21-30	148 (26.6)	1183 (29.0)	1331 (28.7)	0.0113	1.43 (1.09, 1.89)
31-40	166 (29.8)	1058 (25.9)	1224 (26.4)	<.0001	1.80 (1.37, 2.36)
≥41	156 (28.0)	846 (20.7)	1002 (21.6)	<.0001	2.11 (1.60, 2.79)

Table 2 Continued

Admission/Treatment Characteristics					
ICU Admission	106 (19.0)	731 (17.9)	837 (18.0)	0.5164	1.08 (0.86, 1.35)
Healthcare Acquired	320 (57.5)	2145 (52.5)	2465 (53.1)	0.0292	1.22 (1.02, 1.46)
Received Vancomycin Only	334 (60.0)	2435 (59.6)	2769 (59.7)	0.8828	1.01 (0.85, 1.21)
Lack of MRSA-active Therapy	96 (17.2)	391 (9.6)	487 (10.5)	<.0001	1.97 (1.54, 2.51)
Comorbidities					
Congestive Heart Failure	125 (22.4)	644 (15.8)	769 (16.6)	<.0001	1.55 (1.24, 1.92)
Cardiac Arrhythmias	134 (24.1)	701 (17.2)	835 (18.0)	<.0001	1.53 (1.24, 1.89)
Valvular Disease	33 (5.9)	258 (6.3)	291 (6.3)	0.7188	0.93 (0.64, 1.36)
Pulmonary circulation disorders	12 (2.2)	153 (3.7)	165 (3.6)	0.0569	0.56 (0.31, 1.02)
Peripheral vascular disorders	54 (9.7)	384 (9.4)	438 (9.4)	0.8262	1.03 (0.77, 1.40)
Hypertension, uncomplicated	167 (3.0)	1394 (34.1)	1561 (33.6)	0.0513	0.83 (0.68, 1.00)
Hypertension, complicated	153 (2.7)	654 (16.0)	807 (17.4)	<.0001	1.99 (1.62, 2.43)
Paralysis	15 (2.7)	201 (4.9)	216 (4.7)	0.0191	0.53 (0.31, 0.91)
Other neurological disorder	31 (5.6)	298 (7.3)	329 (7.1)	0.135	0.75 (0.51, 1.10)
Chronic pulmonary disease	105 (18.9)	740 (18.1)	845 (18.2)	0.6766	1.05 (0.84, 1.32)
Diabetes, uncomplicated	133 (23.9)	1026 (25.1)	1159 (25.0)	0.5224	0.93 (0.76, 1.15)
Diabetes, complicated	111 (19.9)	677 (16.6)	788 (17.0)	0.0484	1.25 (1.00, 1.57)
Hypothyroidism	23 (4.1)	170 (4.2)	193 (4.2)	0.9696	0.99 (0.64, 1.55)
Renal failure	181 (32.5)	816 (20.0)	997 (21.5)	<.0001	1.93 (1.59, 2.34)
Liver disease	54 (9.7)	346 (8.5)	400 (8.6)	0.3356	1.16 (0.86, 1.57)
Peptic ulcer disease (excluding bleeding)	5 (0.9)	18 (0.4)	23 (0.5)	0.1499	2.05 (0.76, 5.53)
AIDS/HIV	12 (2.2)	97 (2.4)	109 (2.3)	0.7463	0.90 (0.49, 1.66)
Cancer	74 (13.3)	383 (9.4)	457 (9.8)	0.0037	1.48 (1.13, 1.93)
Rheumatoid arthritis/collagen vascular disease	10 (1.8)	87 (2.1)	97 (2.1)	0.6037	0.84 (0.43, 1.63)
Coagulopathy	38 (6.8)	173 (4.2)	211 (4.5)	0.006	1.65 (1.15, 2.38)
Obesity	11 (2.0)	143 (3.5)	154 (3.3)	0.0591	0.56 (0.30, 1.03)
Weight Loss	29 (5.2)	208 (5.1)	237 (5.1)	0.9102	1.02 (0.69, 1.52)
Fluid and electrolyte disorders	109 (19.6)	922 (22.6)	1031 (22.2)	0.1087	0.83 (0.67, 1.04)

Table 2 Continued

Blood loss anemia	8 (1.4)	41 (1.0)	49 (1.1)	0.3493	1.44 (0.67, 3.08)
Deficiency anemia	33 (5.9)	189 (4.6)	222 (4.8)	0.179	1.30 (0.89, 1.90)
Alcohol abuse	45 (8.1)	317 (7.8)	362 (7.8)	0.7948	1.04 (0.75, 1.45)
Drug abuse	25 (4.5)	232 (5.7)	257 (5.5)	0.2479	0.78 (0.51, 1.19)
Psychoses	15 (2.7)	150 (3.7)	165 (3.6)	0.241	0.73 (0.42, 1.24)
Depression	38 (6.8)	367 (9.0)	405 (8.7)	0.0893	0.74 (0.52, 1.05)
Myocardial infarction	30 (5.4)	185 (4.5)	215 (4.6)	0.3679	1.20 (0.81, 1.78)
Cerebrovascular disease	36 (6.5)	268 (6.6)	304 (6.6)	0.9283	0.98 (0.69, 1.41)
Dementia	5 (0.9)	43 (1.1)	48 (1.0)	0.7337	0.85 (0.34, 2.16)
Co-infections					
Endocarditis	17 (3.1)	116 (2.8)	133 (2.9)	0.7795	1.08 (0.64, 1.81)
Osteomyelitis	46 (8.3)	477 (11.7)	523 (11.3)	0.0165	0.68 (0.50, 0.93)

Table 3: Logistic regression analysis for prediction of recurrent MRSA infection in the development cohort

Characteristic	P-value	Odds Ratio (95% CI)
Lack of MRSA-active Therapy	<.0001	2.18 (1.69, 2.80)
Duration of Bacteremia (days)		
1	-	1.00
2-3	0.0107	1.55 (1.11, 2.17)
4-6	0.0634	1.49 (0.98, 2.27)
≥7	<.0001	2.08 (1.48, 2.91)
Renal Failure	<.0001	1.71 (1.40, 2.10)
Distance to Care (miles)		
0-7	0.0063	1.45 (1.11, 1.89)
7-20	0.0002	1.67 (1.28, 2.18)
21-60	0.1596	1.23 (0.92, 1.63)
≥61	-	1.00
Severity of Illness (modified APACHE III score)		
0-20	-	1.00
21-30	0.1046	1.26 (0.95, 1.68)
31-40	0.0087	1.46 (1.10, 1.94)
≥41	0.0010	1.64 (1.22, 2.19)
Coagulopathy	0.0231	1.54 (1.06, 2.24)
Cancer	0.0066	1.47 (1.11, 1.94)
Cardiac Arrhythmias	0.0024	1.40 (1.13, 1.73)

Figure 1: An outline of patients included the study of MRSA recurrent bacteremia

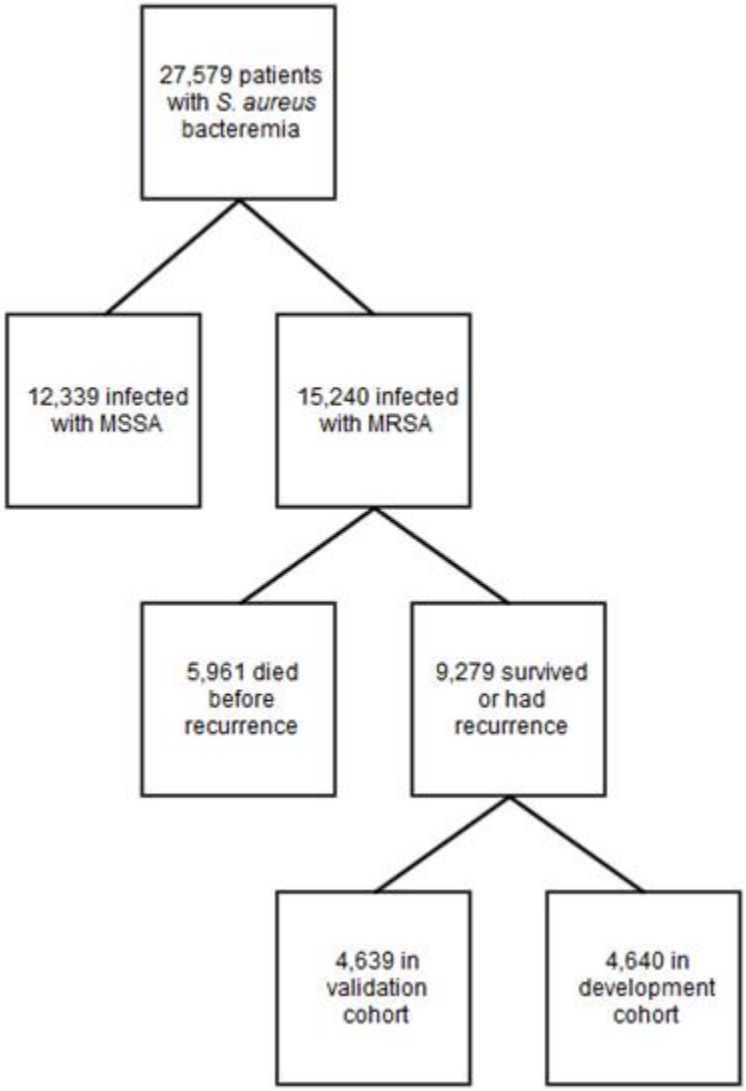


Figure 2: ROC curve for the development cohort. Area under the curve = 0.657

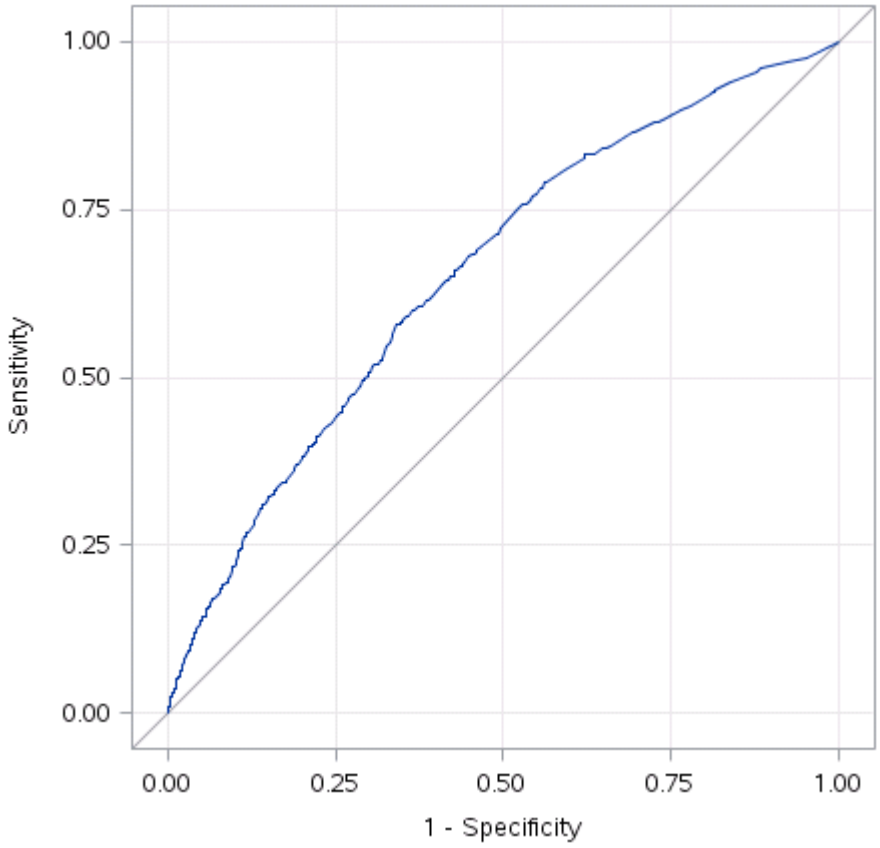
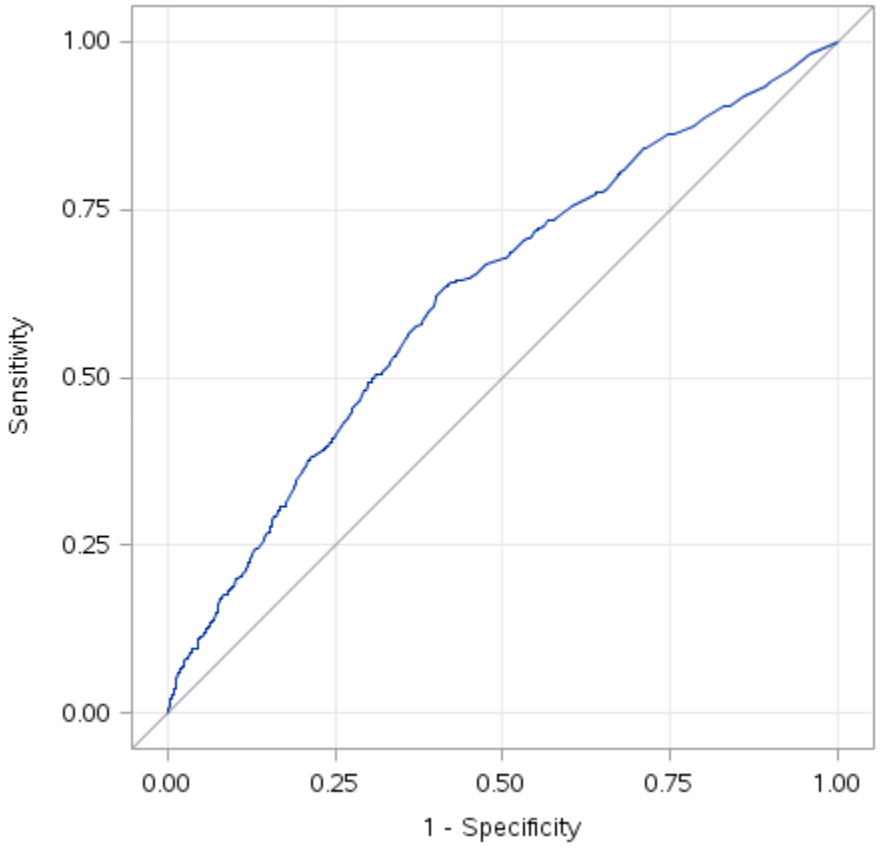


Figure 3: ROC curve for the validation cohort. Area under the curve = 0.625



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