Clinical characteristics of bloodstream infections associated with endemic Methicillin-resistant *Staphylococcus aureus* clones

Amy C. Dupper, MPH, MA[1], Mitchell J. Sullivan, PhD[2], Kieran I. Chacko, BA, BS[2], Aaron Mishkin, MD[1], Brianne Ciferri, MPH[2], Irina Oussenko, PhD[2], Ajay Kumaresh, PhD[2], Colleen Beckford, MS[2], Nathalie E. Zeitouni, PhD[2], Robert Sebra, PhD[2], Camille Hamula, PhD[3], Melissa Smith, PhD[2], Andrew Kasarskis, PhD[2], Gopi Patel, MD, MS[1], Russell B. McBride, PhD, MPH[3,4], Harm van Bakel, PhD[2], and Deena R. Altman, MD, MS[1,2]

[1]Department of Medicine, Division of Infectious Diseases; [2]Department of Genetics and Genomic Sciences; [3]Department of Pathology, Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York City, USA

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Abstract

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) causes life-threatening infections in both community and hospital settings and is a leading cause of healthcare-associated infections (HAIs). We sought to describe the molecular epidemiological landscape of patients with MRSA bloodstream infections (BSIs) at an urban medical center by evaluating the clinical characteristics associated with infection with the major endemic clones.

Methods: Extensive clinical data extraction from the electronic health records of 225 patients (August 2014 to April 2017) with MRSA bacteremia was collected. The descriptive epidemiology and mortality associated with the two dominant clonal complexes (CCs) was compared by univariate and multivariate analyses of clinical features as well as stratified analysis by HAI definitions.

Results: Analysis of first positive, single-patient MRSA isolates revealed that 91% of the MRSA BSIs were one of two genotypes, CC5 (N=116) or CC8 (N=109). The MRSA BSIs were associated with high all-cause in-hospital (23%) and overall (39%) mortality. Aside from the association between age and CC5, few of the other 45 variables reached statistical significance. One notable exception was peripheral intravenous catheters as infection source, which was associated with the CC8 clone (OR=6.27 95% CI [1.72-22.90]).

Conclusions: The descriptive epidemiology of MRSA BSIs in a quaternary urban facility revealed few clinical features distinguish BSIs with the major MRSA clones. The CC8 was associated with infection with peripheral intravenous catheters, suggesting skin colonization from the community presenting as a hospital-onset infection. Ongoing

monitoring and analysis of the dynamic epidemiology of this endemic pathogen is crucial to inform management and forestall disease.

Introduction

Healthcare-associated infections (HAIs) pose a ubiquitous and potentially fatal threat to humans worldwide [1] and *Staphylococcus aureus* is one of the most common causes of HAIs in the United States [2, 3]. Methicillin-resistant *S. aureus* (MRSA) bloodstream infections (BSIs) carry a 20%-30% mortality risk and are associated with long hospital stays and increased healthcare costs [4-6]. MRSA infections have long been present in healthcare settings but are now well established in the community [3, 7]. The two dominant MRSA clones found in the United States are the clonal complex (CC) 5 and CC8 [3, 8, 9]. Prior reports of infection with the CC5 suggest they are more likely to occur in older individuals in contact with hospitals or long-term care facilities, and more likely to involve the respiratory tract, urinary tract, or bloodstream [7, 10, 11]. In contrast, the CC8 clone, predominantly the USA-300 pulsotype, was first reported in the United States in healthy children in Minnesota and North Dakota in the late 1990s and raised concern for its capacity to cause severe disease in otherwise healthy individuals [4, 12-14]. Over the following two decades, the CC8 clone would become established as the predominant community-associated clone, commonly presenting as skin and soft tissue infections (SSTIs) in the homeless, men who have sex with men, athletes, and children in day-care centers. Other significant risk factors include injection drug use and co-infection with human immunodeficiency virus (HIV) [15-20]. Between 2004 and 2008, the reported prevalence of the CC8 clone doubled in healthcare settings and was

associated with as many inpatient infections as the CC5 clone [21].

We sought to update and expand on the descriptive epidemiology and risk factors associated with the MRSA BSIs in a major quaternary academic medical center in New York City. We examined the differences between the clonal complexes and their associated clinical and epidemiological features presenting as MRSA BSIs, and in the context of traditional epidemiological definitions. In this connection, we defined hospital-onset MRSA (HO-MRSA) as occurring >3 days after hospital admission, and community-onset MRSA (CO-MRSA) infections presenting within the 72 hour hospital admission interval [22]. Relative pathogenicity of each clone was estimated by calculating mortality rates adjusted for potentially confounding clinical variables. Enhanced understanding of both the patients and clones causing their invasive disease identifies potential high risk syndromes or populations and may inform or enhance prevention measures. Additionally these detailed clinical correlates should be integrated with other multiscale analyses aimed at understanding *S. aureus* virulence and predictors of outcomes such as mortality [23].

Methods

Patient Selection

The Mount Sinai Hospital (MSH) is a 1,144-bed tertiary- and quaternary-care facility. Study data were captured on a total of 247 patients diagnosed with MRSA BSI through the Mount Sinai Clinical Microbiology Laboratory as part of standard clinical care between August 2014 and April 2017. For each patient, only the first episode of the MRSA BSI was included in the analysis. From a larger whole genome sequencing program for hospital surveillance, we obtained the CC/Multilocus sequence typing

(MLST) using the RESTful interface to the *S. aureus* PubMLST [24, 25] database and spa types using custom scripts and the Ridom SpaServer database [26]. We excluded patients younger than 18 and all non- CC5 or CC8 clones, resulting in a total of 225 patients (Supplementary Table 1) for analysis.

Demographic and clinical data were abstracted from the electronic medical records system including geographic admission data and infection sources (Supplementary Table 2). All abstracted study data were recorded in REDCap, a secure, online database [27]. Additional factors collected were the Charlson Comorbidity Index (CCI) variables and zip codes, which were used to create a map to determine geographical clustering of clones using GIS software [28].

Statistical Analysis

We carefully selected well-established clinical correlates related to molecular epidemiological studies, including demographics, baseline comorbidities, admission sources, and infection sources. We also evaluated in-hospital outcomes, specifically those attributable to the MRSA infection, and death. We collapsed variables to make the final set of covariates as informative and reflective of current published literature. Analyses were performed in SAS (ver.9.4) and R (ver3.4.2) [29, 30]. Differences in categorical variables were tested using chi-square analysis or Fisher's Exact Test for small sample sizes. All non-normally distributed continuous variables were categorized into discrete categorical groups. All variables with $p \leq 0.2$ in univariate analysis were placed into a multivariate logistic regression. The final model was determined through stepwise elimination of covariates with values $p > 0.10$. All variables with $p < 0.05$ were considered statistically significant in the multivariate regression model. Effect

modification was assessed by running the logistic regression model with an interaction term added and examining the *p* value of the interaction term in the model. Confounding was assessed by comparing the crude and adjusted estimates to see if they differed by ≥ 10%.

Results

Baseline Clinical Characteristics

Among the 225 patients included in our analyses 67% were male and the median age at MRSA BSI diagnosis was 64 years (Supplementary Table 2). The racial and ethnic composition included non-Hispanic Whites (N=98; 44%), non-Hispanic Blacks (N=61; 27%), Hispanic/Latinos (N=46; 20%), Asians (N=8; 4%), and not reported (N=12; 5%). The MRSA BSIs were linked to a range of infection sources, with vascular access (N=80; 36%), pneumonia (N=25; 11%), and SSTIs (N=20; 9%) representing the most common. Injection drug use was reported by 10% (N=23) of our population. All-cause in-hospital and overall mortality rates in our population were 23% (N=52) and 39% (N=87), respectively. Recurrent episodes of MRSA BSI were reported in 14% (N=32) of our population, and 41% (N=92) had a prior history of MRSA colonization.

The institution receives a high frequency of intra-facility transfers for receipt of specialized medical care. In this context, we performed a comprehensive analysis of admission sources and found that roughly half of our patients were admitted from home with the remaining patients having been transferred in from nursing homes/rehabilitation/long-term care facilities (N=59; 26%), outside hospitals (N=35; 16%), or homeless shelters (N=4; 2%). Of the 58% of subjects residing at home or group home settings, 32% (N=56) had frequent contact with healthcare centers either

via outpatient dialysis (N=22; 13%) or infusion centers (N=34; 19%). The most common comorbid medical conditions in our dataset were congestive heart failure (N=54; 24%), renal disease (N=55; 24%), and diabetes with end organ damage (N=51; 23%). Ten percent (N=22) of patients with MRSA BSI were co-infected with HIV/AIDS. Additionally, 32 (14%) were organ transplant recipients. The mean CCI of subjects was 5.6 while previous studies cite CCI averages in the 1.5-2 range [31-33] with few quoting a CCI score as high [34]. In all, these data suggest that the MRSA BSIs are occurring in a highly medically complex patient population that is engaged in an advanced medical care network.

Molecular composition of clones causing MRSA BSI

Molecular analysis of single-patient, first episode MRSA BSI revealed the majority of the MRSA BSIs were caused by two major clones. There were 109 patients with BSI from the CC8 (44%) and 116 from the CC5 (47%) out of the total 247 isolates sequenced, representing 91% of the entire population. There were 22 (9%) not designated in the CC5/CC8, and were excluded from the analyses. Within the CC5, the majority were ST5 (N=48; 40%) or ST105 (N=61; 51%), with 8% (N=10) belonging to other STs within the CC5. The majority of clones within the CC8 were ST8 (N=107; 98%) with only 2 (2%) belonging to non-ST8 clones. *Spa* analysis revealed that the majority (N=62; 57%) of ST8 were *spa* type t008, which are predicted to be the USA-300 pulsotype, while 24 (22%) were *spa* type t064, predicted to be of the USA-500 lineage. Although our main analyses centered on the CC level, we further examined the clinical variations apparent within the CC groups.

Dominance and geographic distribution of major MRSA clones at an urban medical center

Two dominant clones were responsible for the majority of the BSIs. As such, we anchored our analyses on comparing the CC5 and CC8. The majority of variables examined were not significantly associated with one clone over the other, with a few notable exceptions. Race was found to confound the effects of HIV/AIDS and injection drug use, so HIV/AIDS and injection drug use were retained in the final model. Univariate and multivariate analyses (Table 1) revealed that the CC8 clone was associated with non-Hispanic Black race (OR=3.14 95% CI [1.39-7.12]), Hispanic/Latino race (OR=2.70 95% CI [1.16-6.24]), and MRSA BSI ≤3 days after hospital admission (OR=2.45 95% CI [1.26-4.75]). Patients ≥ 70 years of age were less likely to have BSI from the CC8 (OR=0.32 95% CI [0.15-0.72]) compared to younger patients. Interestingly, patients with peripheral intravenous catheters (PIV) as the presumed source of the MRSA BSI were significantly more likely to have the CC8 (OR=6.27 95% CI [1.72-22.90]). In addition, there was no clonal predominance found in patients admitted from nursing homes, long term care and rehabilitation facilities (22% vs 30%, p=0.89), suggesting these clones are now equally distributed in these types of institutions [35]. Similarly, on multivariate analysis, there were equal proportions of the CC8 vs CC5 across patient admission sources or physical location. We mapped the clones according to patient zip code, and found no significant clustering aside from the area surrounding the hospital (Figure 1). In summary, few distinguishing features exist that differentiate these two endemic clones.

Subanalysis of clinical characteristics amongst clones

Although we performed our top level analyses at the CC level, we additionally wanted to evaluate for potential clinical relationships within the CC clones. Of note, there were 27 CC8/*spa* type 064, of the USA-500 clone, considered a healthcare-associated MRSA despite being part of the CC8 [4]. We thus compared USA-300 and USA-500 as well as performed the CC8 analysis with and without the USA-500. Interestingly, *spa* type 064 was significantly associated with HIV/AIDS (OR=9.51 95% CI [1.69-53.51]) compared to *spa* type 008. Exclusion of the 27 USA-500 cases did not impact the results of our top level CC8 vs. CC5 analyses, thus these cases were retained in subsequent analyses. All subanalyses can be found in Supplementary Tables 3, 4, 5, and 6.

Addressing epidemiologic definitions in endemic settings

We also sought to examine clinical and demographic differences in relation to the National Healthcare Safety Network (NHSN) definitions of community-onset CO-MRSA vs hospital-onset HO-MRSA BSI [36]. Consistent with previous reports, the majority of infections were classified as CO-MRSA (N=132; 59) vs. HO-MRSA (N=93; 41%) [31, 37, 38]. Univariate and multivariate analyses (Table 2) revealed that patients characterized as CO-MRSA were associated with the CC8 (OR=2.50 95% CI [1.11-5.65]). CO-MRSA was negatively associated with prior invasive procedures (OR=0.16 95% CI [0.07-0.36]), intensive care unit (ICU) admission prior to BSI (OR=0.11 95% CI [0.03-0.35]), as well as vascular access (OR=0.17 95% CI [0.07-0.43]) and peripheral IVs (OR=0.09 95% CI [0.02-0.33]) as presumed sources of BSI. Nevertheless, we found only 27 (12%) patients admitted for MRSA BSI that fit into a true CO definition and the majority of these patients would be better classified as community-onset,

healthcare-associated (CO-HCA) infections [38, 39]. This provides further evidence that surveillance definitions may not accurately depict community-onset infections [4].

Although the CC8 has historically been associated with CO-MRSA infections, it was responsible for 38% of HO-MRSA infections in our study. Among patients grouped into the HO-MRSA stratum (Table 3), those whose MRSA BSI resulted from a peripheral IV (OR=5.49 95% CI [1.10-27.52]) were more likely to be CC8. A diagnosis of lymphoma or multiple myeloma had a non-significant increase in infection with CC8 (OR=3.24 95% CI [0.89-11.80]) in the HO-MRSA stratum. Non-Hispanic Black race (OR=8.48 95% CI [2.18-33.01]) and Hispanic/Latino race (OR=13.03 95% CI [2.67-63.67]) were also positively associated with the CC8 in the HO-MRSA stratum. Among the CO-MRSA stratum (Table 4), non-Hispanic Black race (OR=3.35 95% CI [1.18-9.52]) was associated with the CC8. Those over the age of 70 (OR=0.17 95% CI [0.06-0.52]), prior hospital admission in the past 90 days (OR=0.32 95% CI [0.12-0.83]), and peripheral vascular disease (OR=0.35 95% CI [0.12-0.99]) were negatively associated with the CC8 in the CO-MRSA stratum. Ultimately, after stratifying by NHSN definitions, the CC8 was associated with younger age and non-Hispanic Black race, and the CC5 was associated with prior healthcare interaction [40]. Although stratification by definition assisted in placement of these clones into associated epidemiological definitions, this provides additional evidence that distinguishing differences continue to fade.

Differences in clone-related outcomes and mortality

S. aureus BSI is associated with in-hospital morbidity [2]. Excluding mortality, 80 (36%) individuals suffered a complication related to their infection (Table 5). Few clone-associated differences in morbidity were detected aside from the CC8 clone

approaching significance among ICU admission due to the MRSA BSI (OR=2.29 95% CI [0.98-5.39]) (Table 5A). Interestingly, strictly CO-MRSA was associated with overall worse hospital outcomes, attributing to more ICU admissions (OR=12.00 95% CI [4.36-33.06]) and need for mechanical ventilation (OR=3.45 95% CI [1.30-9.15]) (Table 5B). This is likely linked to the overall medical complexity of those presenting with infection from the community, as well as consistent with prior studies which associate community-onset infections with complicated bacteremia [41].

With regard to mortality, overall all-cause mortality was 39% in our dataset, yet the only difference was decreased mortality among the CC8 infected individuals in the CO-MRSA stratum (OR=0.40 95% CI [0.19-0.83]). Taken together with the increased morbidity in the CO-MRSA group, we postulate that the CC5 classified as CO-MRSA were advanced in their disease course, through either delay of presentation to the hospital or through transfers from other facilities for advanced care (as noted that 50 (39%) of admissions in the CO-MRSA group were admitted from other facilities). While patients grouped into the CO-MRSA stratum appeared to have higher overall mortality, this trend was driven by the CC5 clone.

As a correlate for virulence, we examined all-cause in-hospital and overall mortality. Effect modification was present between clone and the following variables: presence of an invasive device and admission to the ICU prior to the MRSA BSI for all-cause in-hospital mortality, therefore, these variables were stratified (Figure 2A-D). Among all-cause overall mortality, effect modification was present between clone and patients with an invasive device present and age (Figure 2E-I). The CC8 clone had a significantly lower mortality rate among those without an invasive device (HR=0.17 95%

CI [0.03-0.85]) and among those not admitted to the ICU prior to BSI (HR=0.47 95% CI [0.24-0.92]). Alternately, those who were admitted to the ICU prior to the BSI had higher mortality rate among the CC8 clone (HR=2.98 95% CI [1.01-9.10]). The CC8 clone also had a lower all-cause overall mortality rate when an invasive device was not present (HR=0.22 95% CI [0.07-0.69]) and among those aged 55-69 years (HR=0.40 95% CI [0.17-0.95]). Both Cox regression analyses for all-cause in-hospital and overall mortality illustrate that one clone did not contribute to increased mortality over the other in all but very few cases, somewhat contrary the understanding that the CC8 is a hypervirulent clone [38].

To understand specific clinical factors attributing to mortality in those who develop MRSA BSI, a univariate and multivariate Cox regression analysis was performed for both all-cause in-hospital and overall mortality. All-cause in-hospital mortality was associated with presence of lymphoma or multiple myeloma (HR=2.40 95% CI [1.16-4.97]) and history of a transplant (HR=2.61 95% CI [1.27-5.38]) (Table 6). Variables found to be significantly associated with all-cause overall mortality were presence of lymphoma or multiple myeloma (HR=2.19 95% CI [1.22-3.91]), ICU admission prior to the MRSA BSI (HR=1.81 95% CI [1.06-3.08]), and pneumonia as a presumed source of the BSI (HR=2.00 95% CI [1.11-3.63]) (Table 7). Although these underlying conditions are independently associated with increased risk for death, these data suggest that these populations have worse outcomes in the setting of the MRSA BSI, potentially informing clinical management strategies aimed at these at-risk populations.

Discussion

As clones causing invasive MRSA infections are tied to specific populations, syndromes and settings, and are thought to behave differently, we sought to unravel how these associations manifest in bloodstream infections in a high level care institution in an endemic [42] region. This study represents a large cohort of patients who were selected based strictly on presence of invasive disease (bacteremia), and demonstrate highly complex cases linked with significant morbidity and mortality. Out of the total 45 variables tested, the CC8 was only consistently associated with younger age [40] and ethnic minorities, and the CC5 was associated with the presence of an invasive device [3, 43] and invasive procedures. We also found that amongst the USA-300 and USA-500 clones, HIV/AIDS was associated with the USA-500 group [43]. Our analyses demonstrate that the CC8 is now as common as the CC5 in inpatient settings. Additionally, we demonstrate the continued convergence of the associated clinical features, which classically have distinguished these clones [7, 31].

We also describe the association between the CC8 and peripheral intravenous catheter (PIV) infections. The CC8 was also associated with PIV infection when stratified by the HO-MRSA definition. As PIVs are inserted into the skin, are not a sterile procedure, and receive less maintenance as other types of invasive venous access, these data suggest the potential for skin translocation to the bloodstream. As invasive infections are derived from colonizing flora [44], and the CC8 is associated with skin colonization, a possible explanation for this finding is that patients are colonized with the CC8 and then become infected with their colonizing isolate once in the hospital. Although few studies have explored the risks associated with the MRSA BSI from PIV infections, they were associated with longer duration of bacteremia [34]. We specifically

re-reviewed cases and separated PIVs with associated thrombophlebitis from other types of SSTIs not associated with PIVs, and SSTI was not significant in the multivariate analysis. A meta-analysis found that approximately 330 million PIVs are used each year in the United States, with a 0.18% incidence of PIV-related BSIs [45]. Even though the incidence of BSI resulting from PIV is small, the large number of PIVs used annually culminates in a significant portion of PIVs resulting in BSI [45]. A larger sample size and access to colonizing isolates in future work would assist in expansion of this concept and urge aggressive measures to reduce these types of infections and result in efforts to reduce the incidence of PIV related MRSA infections.

This study also examined the challenges of utilizing current definitions for HO-MRSA and CO-MRSA. While CO-MRSA was associated with the CC8 [8, 38, 39, 46-48], the CO-MRSA/CC8 infections approached significance among patients with moderate or severe renal disease. These findings support the growing evidence that classically community associated genotypes involves individuals with frequent healthcare interactions [31, 49]. Similarly, our study revealed very few patients may be defined as pure “community” (n=27) suggesting that the CO definition alone may be misleading. An alternative definition of community-onset healthcare-associated (CO-HCA) includes infections that present within three days of hospital admission, but in patients with frequent healthcare exposure (as evidenced by the presence of an invasive device, prior hospital admission within 90 days, admitted from a nursing home, etc.) [4, 38, 50]. It appears that future descriptions of these classifications should include the changing epidemiology of the patients and their complex medical experiences.

The CC8/USA-300 had been labeled as the “hypervirulent” clone due to severe disease in younger, healthier individuals [31, 38, 51, 52]. The enhanced pathogenicity is thought to be a result of a combination of acquisition of novel genetic components, altered gene regulation, and sequence polymorphisms (Reviewed in [51]). Much of virulence work is derived from animal models and may not actually redemonstrate in complex human infections [53, 54]. This study did not find significant differences in mortality and other outcomes based on MRSA clone. Cox regression did reveal several factors related to increased mortality among patients infected with MRSA, namely presence of lymphoma or multiple myeloma, history of a transplant, and pneumonia as presumed source of the BSI.

This study has several limitations. This was a cohort study, which is subject to errors in chart abstraction and data entry. As it is standard practice to have an Infectious Disease (ID) consultation on all cases of *S. aureus* BSI due to the association with improved outcomes, these specific disease-focused consultation notes were reviewed in all of the cases, in order to minimize chart abstraction errors [52]. Additionally, we describe infections occurring at a single institution. With high mortality rates and CCIs, findings from the medically complex population studied here may not be generalizable to small, low-throughput, community hospitals. Death was likely also underreported since death occurring outside of the hospital may not have been accurately reflected in medical records. While effect modification and confounding were tested and adjusted for in our final model, it is still possible that we could not fully capture and account for all residual confounding.

In a highly complex patient population in an endemic region, there remain few distinct differences in the characteristics between the CC5 and the CC8 clones, historically hospital and community MRSA clones, respectively. However, the CC8 clone has become even more endemic in the hospital setting, and when acquired in the hospital, it behaves similar to CC5 by infecting infirm individuals. Our study highlights certain risk populations, with several well-documented associations between younger age and the CC8, but other findings suggests avenues for immediate investigation such as the role of PIVs and potential preventative avenues by which we may be able to forestall this fatal disease process.

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Table 1. Demographics and Clinical Characteristics of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections in Patients Stratified by Clonal Complex with the Odds of being CC8

Factor	CC8 N = 109 (%)	CC5 N = 116 (%)	Univariate Analysis OR (95% CI)	p value	Multivariate Analysis OR (95% CI)	p value
Male	73 (67)	77 (66)				
*Race/Ethnicity						
Non-Hispanic White	31 (28)	67 (58)	Reference		Reference	
Non-Hispanic Black	40 (37)	21 (18)	4.12 (2.09-8.11)	0.07	**3.14 (1.39-7.12)**	**0.006**
Hispanic/Latino	27 (25)	19 (16)	3.07 (1.49-6.34)	0.44	**2.70 (1.16-6.24)**	**0.02**
Asian	4 (4)	4 (3)	2.16 (0.51-9.21)	0.85	2.26 (0.45-11.23)	0.32
Unknown	7 (6)	5 (4)	3.03 (0.89-10.29)	0.65	2.45 (0.60-9.98)	0.21
Age						
18-54 Years	44 (40)	23 (20)	Reference		Reference	
55-69 Years	38 (35)	31 (27)	0.64 (0.32-1.28)	0.21	0.80 (0.35-1.81)	0.59
≥ 70 Years	**27 (25)**	**62 (53)**	**0.23 (0.12-0.45)**	**<0.001**	**0.32 (0.15-0.72)**	**0.006**
History of Injection Drug Use	**16 (15)**	**7 (6)**	**0.37 (0.15-0.95)**	**0.04**	1.32 (0.44-3.99)	0.62
Body Mass Index (BMI)						
<18.5	17 (16)	11 (9)				
18.5-24.9	39 (36)	45 (39)				
25.0-29.9	21 (19)	29 (25)				
≥30.0	31 (28)	31 (27)				
Admission Source						
Home	77 (71)	54 (47)	Reference		Reference	
NH/Rehab/LTACH	23 (21)	36 (31)	0.45 (0.24-0.84)	0.78	0.55 (0.26-1.15)	0.11
Other Hospital	**9 (8)**	**26 (22)**	**0.24 (0.11-0.56)**	**0.02**	**0.32 (0.13-0.83)**	**0.02**
Prior Hospital Admission (90 Days)	**70 (64)**	**91 (78)**	**2.03 (1.12-3.66)**	**0.02**		
Length of Hospital Stay Prior to BSI						
≤3 Days	**74 (68)**	**58 (50)**	**2.11 (1.23-3.64)**	**0.007**	**2.45 (1.26-4.75)**	**0.008**
>3 Days	35 (32)	58 (50)	Reference		Reference	
Frequent Healthcare Interaction						
Hemodialysis	22 (20)	18 (16)				
Infusion Center	18 (17)	16 (14)				
None	69 (63)	82 (71)				
[a] Presence of Invasive Device	**76 (70)**	**102 (88)**	**0.32 (0.16-0.63)**	**0.001**		
[b] Invasive Procedures	**43 (39)**	**65 (56)**	**1.96 (1.15-3.33)**	**0.01**		
Wound Present	46 (42)	48 (41)				
Comorbidities						
Myocardial Infarction	9 (8)	14 (12)				
Congestive Heart Failure	21 (19)	33 (28)	0.60 (0.32-1.121)	0.11		
Peripheral Vascular Disease	**12 (11)**	**24 (21)**	**0.47 (0.22-1.00)**	**0.05**	0.43 (0.17-1.06)	0.07
*Cerebrovascular Disease	**5 (5)**	**14 (12)**	**0.35 (0.12-1.01)**	**0.05**		
Dementia	**9 (8)**	**20 (17)**	**0.43 (0.19-0.99)**	**0.05**		
Chronic Pulmonary Disease	11 (10)	19 (16)	0.57 (0.26-1.27)	0.17		
*Connective Tissue Disease	2 (2)	3 (3)				
*Peptic Ulcer Disease	2 (2)	6 (5)				
Mild Liver Disease	0 (0)	2 (2)				
Diabetes (no complications)	17 (16)	20 (17)				
Diabetes with Organ Damage	23 (21)	28 (24)				
Para or Hemiplegia	7 (6)	10 (9)				
Moderate/Severe Renal Disease	27 (25)	28 (24)				
Solid Tumor	**8 (7)**	**15 (13)**	0.53 (0.22-1.31)	0.17		
*Leukemia	6 (6)	7 (6)				
Lymphoma/Multiple Myeloma	13 (12)	13 (11)				
*Moderate/Severe Liver Disease	11 (10)	6 (5)				
*Metastatic Solid Tumor	5 (5)	9 (8)				
*HIV/AIDS	**18 (17)**	**4 (3)**	**5.54 (1.81-16.94)**	**0.003**	3.38 (0.94-12.16)	0.06
Charlson Comorbidity Index (CCI)						
0-3	36 (33)	28 (24)				
4-5	20 (18)	26 (22)				
6-8	34 (31)	33 (28)				
>8	19 (17)	29 (25)				
History of Transplant	14 (13)	18 (16)				
History of MRSA Colonization	46 (42)	46 (40)				
Presumed Source of MRSA BSI						
*Peripheral IV	11 (10)	5 (4)	2.49 (0.84-7.42)	0.10	**6.27 (1.72-22.90)**	**0.006**
*Skin & Soft Tissue Infection	**15 (14)**	**5 (4)**	**3.54 (1.24-10.11)**	**0.02**		
Pneumonia	14 (13)	11 (9)				
*Endocarditis	4 (4)	7 (6)				
Diabetic Foot Infection	7 (6)	7 (6)				
Vascular Access	36 (33)	44 (38)				
*Septic Arthritis	1 (1)	2 (2)				
*Urinary Source	1 (1)	4 (3)				
*Sacral Wound	6 (6)	5 (4)				
*Other/Unknown	6 (6)	7 (6)				
ICU Admission Prior to BSI	16 (15)	26 (22)	0.60 (0.30-1.18)	0.14		

Bold = significant at ≤ 0.05

*Analyzed using Fisher's Exact Test

Abbreviations: NH, nursing home; rehab, rehabilitation facility; LTACH, long-term acute care hospital; BSI, bloodstream infection; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ICU, intensive care unit.

[a] Includes devices such as pacemaker, any vascular access, orthopedic hardware, foley catheter, arteriovenous graft placement, percutaneous endoscopic gastronomy (PEG), ostomy, or any type of urinary collection at the time of first positive bloodstream infection.

[b] Includes invasive procedures or surgery within the month prior to first positive bloodstream infection, excluding electroencephalogram (EEG), electrocardiogram (EKG), or transthoracic echocardiogram (TTE).

Table 2. Demographics and Clinical Characteristics of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections in Patients Stratified by Centers for Disease Control and Prevention Definition with the Odds of being CO-MRSA

Factor	CO-MRSA N = 132 (%)	HO-MRSA N = 93 (%)	Univariate Analysis OR (95% CI)	p value	Multivariate Analysis OR (95% CI)	p value
CC8	**74 (56)**	**35 (38)**	**2.11 (1.23-3.64)**	**0.007**	**2.50 (1.11-5.65)**	**0.03**
Male	90 (68)	60 (65)				
*Race/Ethnicity						
Non-Hispanic White	50 (38)	48 (52)	Reference		Reference	
Non-Hispanic Black	40 (30)	21 (23)	1.83 (0.95-3.54)	0.07	1.60 (0.57-4.53)	0.37
Hispanic/Latino	30 (23)	16 (17)	1.80 (0.87-3.72)	0.11	0.88 (0.29-2.67)	0.82
Asian	6 (5)	2 (2)	2.88 (0.55-14.98)	0.21	2.23 (0.32-15.61)	0.42
Unknown	6 (5)	6 (6)	0.96 (0.29-3.18)	0.95	1.31 (0.25-6.77)	0.75
Age						
18-54 Years	40 (30)	27 (29)				
55-69 Years	41 (31)	28 (30)				
≥ 70 Years	51 (39)	38 (41)				
*History of Injection Drug Use	**18 (14)**	**5 (5)**	**2.78 (1.00-7.78)**	**0.05**	0.94 (0.20-4.43)	0.93
Body Mass Index (BMI)						
<18.5	**9 (7)**	**19 (20)**	**0.34 (0.14-0.84)**	**0.02**		
18.5-24.9	49 (37)	35 (38)	Reference			
25.0-29.9	37 (28)	13 (14)	2.03 (0.95-4.38)	0.07		
≥30.0	36 (27)	26 (28)	0.99 (0.51-1.92)	0.97		
Admission Source						
Home	80 (61)	51 (55)	Reference			
NH/Rehab/LTACH	39 (30)	20 (22)	1.24 (0.65-2.37)	0.51		
Other Hospital	**13 (10)**	**22 (24)**	**0.38 (0.17-0.81)**	**0.01**		
Prior Hospital Admission (90 Days)	91 (69)	70 (75)				
*Frequent Healthcare Interaction						
Hemodialysis	**34 (26)**	**6 (6)**	**4.17 (1.65-10.52)**	**0.003**		
Infusion Center	**11 (8)**	**23 (25)**	**0.35 (0.16-0.77)**	**0.009**		
None	87 (66)	64 (69)	Reference			
[a] Presence of Invasive Device	**95 (72)**	**83 (89)**	**0.31 (0.15-0.66)**	**0.002**		
[b] Invasive Procedures	**37 (28)**	**71 (76)**	**0.12 (0.07-0.22)**	**<0.001**	**0.16 (0.07-0.36)**	**<0.001**
Wound Present	59 (45)	35 (38)				
Comorbidities						
Myocardial Infarction	**9 (7)**	**14 (15)**	**0.41 (0.17-1.00)**	**0.05**	0.29 (0.07-1.16)	0.08
Congestive Heart Failure	34 (26)	20 (22)				
Peripheral Vascular Disease	**29 (22)**	**7 (8)**	**3.46 (1.44-8.29)**	**0.005**	3.09 (0.95-10.03)	0.06
Cerebrovascular Disease	10 (8)	9 (10)				
Dementia	20 (15)	9 (10)				
Chronic Pulmonary Disease	16 (12)	14 (15)				
*Connective Tissue Disease	4 (3)	1 (1)				
*Peptic Ulcer Disease	6 (5)	2 (2)				
*Mild Liver Disease	1 (1)	1 (1)				
Diabetes (no complications)	19 (14)	18 (19)				
Diabetes with Organ Damage	**40 (30)**	**11 (12)**	**3.24 (1.56-6.73)**	**0.002**		
*Para or Hemiplegia	11 (8)	6 (6)				
Moderate/Severe Renal Disease	**43 (33)**	**12 (13)**	**3.26 (1.61-6.61)**	**0.001**	**8.35 (2.64-26.37)**	**<0.001**
Solid Tumor	10 (8)	13 (14)	0.50 (0.21-1.21)	0.12		
*Leukemia	**4 (3)**	**9 (10)**	**0.29 (0.09-0.98)**	**0.05**		
Lymphoma/Multiple Myeloma	**7 (5)**	**19 (20)**	**0.22 (0.09-0.54)**	**0.001**		
Moderate/Severe Liver Disease	11 (8)	6 (6)				
*Metastatic Solid Tumor	9 (7)	5 (5)				
*HIV/AIDS	13 (10)	9 (10)	1.02 (0.42-2.49)	0.97	0.45 (0.11-1.82)	0.26
Charlson Comorbidity Index (CCI)						
0-3	36 (27)	28 (30)	Reference			
4-5	21 (16)	25 (27)	0.65 (0.31-1.40)	0.27		
6-8	43 (33)	24 (26)	1.39 (0.69-2.81)	0.35		
>8	32 (24)	16 (17)	1.56 (0.72-3.38)	0.27		
History of Transplant	**13 (10)**	**19 (20)**	**0.43 (0.20-0.91)**	**0.03**		
History of MRSA Colonization	58 (44)	34 (37)				
Presumed Source of MRSA Infection						
*Peripheral IV	**6 (5)**	**10 (11)**	0.40 (0.14-1.13)	0.08	**0.09 (0.02-0.33)**	**<0.001**
Skin & Soft Tissue Infection	13 (10)	7 (8)				
Pneumonia	15 (11)	10 (11)				
*Endocarditis	9 (7)	2 (2)	3.33 (0.70-15.78)	0.13		
Diabetic Foot Infection	14 (11)	0 (0)				
Vascular Access	**37 (28)**	**43 (46)**	**0.45 (0.26-0.79)**	**0.005**	**0.17 (0.07-0.43)**	**<0.001**
*Septic Arthritis	1 (1)	2 (2)				
*Urinary Source	4 (3)	1 (1)				
*Sacral Wound	9 (7)	2 (2)	3.33 (0.70-15.78)	0.13		
*Other/Unknown	6 (6)	7 (6)				
*ICU Admission Prior to BSI	**5 (4)**	**37 (40)**	**0.06 (0.02-0.16)**	**<0.001**	**0.11 (0.03-0.35)**	**<0.001**

Bold = significant at ≤ 0.05

*Analyzed using Fisher's Exact Test

Abbreviations: NH, nursing home; rehab, rehabilitation facility; LTACH, long-term acute care hospital; BSI, bloodstream infection; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ICU, intensive care unit.

[a] Includes devices such as pacemaker, any vascular access, orthopedic hardware, foley catheter, arteriovenous graft placement, percutaneous endoscopic gastronomy (PEG), ostomy, or any type of urinary collection at the time of first positive bloodstream infection.

[b] Includes invasive procedures or surgery within the month prior to first positive bloodstream infection, excluding electroencephalogram (EEG), electrocardiogram (EKG), or transthoracic echocardiogram (TTE).

Table 3. Demographics and clinical characteristics of MRSA BSI in patients > 3 days after admission with the odds of being CC8

Factor	CC8 N = 35 (%)	CC5 N = 58 (%)	Univariate Analysis OR (95% CI)	p value	Multivariate Analysis OR (95% CI)	p value
Male	23 (68)	37 (64)				
*Race/Ethnicity						
Non-Hispanic White	10 (29)	38 (66)	Reference		Reference	
Non-Hispanic Black	**12 (34)**	**9 (16)**	**5.07 (1.67-15.38)**	**0.004**	**8.48 (2.18-33.01)**	**0.002**
Hispanic/Latino	**9 (26)**	**7 (12)**	**4.89 (1.46-16.36)**	**0.01**	**13.03 (2.67-63.67)**	**0.002**
Asian	2 (6)	0 (0)	>999.999 (<0.001->999.999)	0.98	>999.999 (<0.001->999.999)	0.98
Unknown	2 (6)	4 (7)	1.90 (0.30-11.90)	0.49	2.83 (0.40-20.13)	0.30
Age						
18-54 Years	12 (34)	15 (26)				
55-69 Years	11 (31)	17 (29)				
≥ 70 Years	12 (34)	26 (45)				
*History of Injection Drug Use	3 (9)	2 (3)	2.62 (0.42-16.54)	0.30	0.70 (0.08-5.79)	0.74
*Body Mass Index (BMI)						
<18.5	**12 (34)**	**7 (12)**	**5.79 (1.71-19.62)**	**0.005**		
18.5-24.9	8 (23)	27 (47)	Reference			
25.0-29.9	3 (9)	10 (17)	1.01 (0.22-4.59)	0.99		
≥30.0	12 (34)	14 (24)	2.89 (0.96-8.72)	0.06		
*Admission Source						
Home	23 (66)	28 (48)	Reference			
NH/Rehab/LTACH	8 (23)	12 (21)	0.81 (0.28-2.32)	0.70		
Other Hospital	**4 (11)**	**18 (31)**	**0.27 (0.08-0.91)**	**0.04**		
Prior Hospital Admission (90 Days)	26 (74)	44 (76)				
*Frequent Healthcare Interaction						
Hemodialysis	3 (9)	3 (5)	2.20 (0.41-11.87)	0.36		
Infusion Center	12 (34)	11 (19)	2.40 (0.91-6.36)	0.08		
None	20 (57)	44 (76)	Reference			
[a] *Presence of Invasive Device	30 (86)	53 (91)				
[b] Invasive Procedures	27 (77)	44 (76)				
Wound Present	10 (29)	25 (43)	0.53 (0.22-1.30)	0.16		
Comorbidities						
*Myocardial Infarction	6 (17)	8 (14)				
*Congestive Heart Failure	5 (14)	15 (26)	0.48 (0.16-1.46)	0.19		
*Peripheral Vascular Disease	2 (6)	5 (9)				
*Cerebrovascular Disease	2 (6)	7 (12)				
*Dementia	1 (3)	8 (14)	0.18 (0.02-1.54)	0.12	0.08 (0.01-1.12)	0.06
*Chronic Pulmonary Disease	5 (14)	9 (16)				
*Connective Tissue Disease	0 (0)	1 (2)				
Peptic Ulcer Disease	0 (0)	2 (3)				
Mild Liver Disease	0 (0)	1 (2)				
*Diabetes (no complications)	5 (14)	13 (22)				
*Diabetes with Organ Damage	5 (14)	6 (10)				
*Para or Hemiplegia	1 (3)	5 (9)				
*Moderate/Severe Renal Disease	5 (14)	7 (12)				
*Solid Tumor	6 (17)	7 (12)				
*Leukemia	3 (9)	6 (10)				
Lymphoma/Multiple Myeloma	**11 (31)**	**8 (14)**	**2.86 (1.02-8.04)**	**0.05**	3.24 (0.89-11.82)	0.07
*Moderate/Severe Liver Disease	4 (11)	2 (3)	3.61 (0.63-20.85)	0.15		
*Metastatic Solid Tumor	1 (3)	4 (7)				
*HIV/AIDS	5 (14)	4 (7)	2.25 (0.56-9.02)	0.25	1.00 (0.20-4.92)	1.00
*Charlson Comorbidity Index (CCI)						
0-3	10 (29)	18 (31)				
4-5	10 (29)	15 (26)				
6-8	10 (29)	14 (24)				
>8	5 (14)	11 (19)				
History of Transplant	7 (20)	12 (21)				
History of MRSA Colonization	13 (37)	21 (36)				
Presumed Source of MRSA Infection						
*Peripheral IV	**6 (17)**	**4 (7)**	2.79 (0.73-10.70)	0.13	**5.49 (1.10-27.52)**	**0.04**
*Skin & Soft Tissue Infection	4 (11)	3 (5)				
*Pneumonia	4 (11)	6 (10)				
Endocarditis	0 (0)	2 (3)				
Diabetic Foot Infection	0 (0)	0 (0)				
Vascular Access	19 (54)	24 (41)				
Septic Arthritis	0 (0)	2 (3)				
Urinary Source	0 (0)	1 (2)				
Sacral Wound	0 (0)	2 (3)				
*Other/Unknown	1 (3)	4 (7)				
ICU Admission Prior to BSI	12 (34)	25 (43)				

Bold = significant at ≤ 0.05

*Analyzed using Fisher's Exact Test

Abbreviations: NH, nursing home; rehab, rehabilitation facility; LTACH, long-term acute care hospital; BSI, bloodstream infection; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ICU, intensive care unit.

[a] Includes devices such as pacemaker, any vascular access, orthopedic hardware, foley catheter, arteriovenous graft placement, percutaneous endoscopic gastronomy (PEG), ostomy, or any type of urinary collection at the time of first positive bloodstream infection.

[b] Includes invasive procedures or surgery within the month prior to first positive bloodstream infection, excluding electroencephalogram (EEG), electrocardiogram (EKG), or transthoracic echocardiogram (TTE).

Table 4. Demographics and Clinical Characteristics of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections in Patients ≤ 3 days after admission with the Odds of being CC8

Factor	CC8 N = 74 (%)	CC5 N = 58 (%)	Univariate Analysis OR (95% CI)	p value	Multivariate Analysis OR (95% CI)	p value
Male	50 (68)	40 (69)				
*Race/Ethnicity						
Non-Hispanic White	21 (28)	29 (50)	Reference		Reference	
Non-Hispanic Black	**28 (38)**	**12 (21)**	**3.22 (1.34-7.76)**	**0.009**	**3.35 (1.18-9.52)**	**0.02**
Hispanic/Latino	18 (24)	12 (21)	2.07 (0.82-5.21)	0.12	2.27 (0.75-6.88)	0.15
Asian	2 (3)	4 (7)	0.69 (0.12-4.13)	0.68	0.52 (0.06-4.30)	0.54
Unknown	5 (7)	1 (2)	6.90 (0.75-63.51)	0.09	4.23 (0.39-46.27)	0.24
Age						
18-54 Years	32 (43)	8 (14)	Reference		Reference	
55-69 Years	27 (36)	14 (24)	0.48 (0.18-1.32)	0.16	0.47 (0.15-1.45)	0.19
≥ 70 Years	**15 (20)**	**36 (62)**	**0.10 (0.04-0.28)**	**<0.001**	**0.17 (0.06-0.52)**	**0.002**
*History of Injection Drug Use	13 (18)	5 (9)	2.26 (0.76-6.75)	0.14	1.59 (0.43-5.88)	0.49
*Body Mass Index (BMI)						
<18.5	5 (7)	4 (7)				
18.5-24.9	31 (42)	18 (31)				
25.0-29.9	18 (25)	19 (33)				
≥30.0	19 (26)	17 (29)				
*Admission Source						
Home	54 (73)	26 (45)	Reference			
NH/Rehab/LTACH	**15 (20)**	**24 (41)**	**0.30 (0.14-0.67)**	**0.003**		
Other Hospital	**5 (7)**	**8 (14)**	**0.30 (0.09-1.01)**	**0.05**		
Prior Hospital Admission (90 Days)	**44 (59)**	**47 (81)**	**0.34 (0.15-0.77)**	**0.009**	**0.32 (0.12-0.83)**	**0.02**
*Frequent Healthcare Interaction						
Hemodialysis	19 (26)	15 (26)				
Infusion Center	6 (8)	5 (9)				
None	49 (66)	38 (66)				
[a] Presence of Invasive Device	**46 (62)**	**49 (84)**	**0.30 (0.13-0.71)**	**0.006**		
[b] Invasive Procedures	16 (22)	21 (36)	0.49 (0.23-1.05)	0.07		
Wound Present	36 (49)	23 (40)				
Comorbidities						
*Myocardial Infarction	3 (4)	6 (10)	0.37 (0.09-1.53)	0.17		
Congestive Heart Failure	16 (22)	18 (31)				
Peripheral Vascular Disease	**10 (14)**	**19 (33)**	**0.32 (0.14-0.76)**	**0.01**	**0.35 (0.12-0.99)**	**0.05**
*Cerebrovascular Disease	3 (4)	7 (12)	0.31 (0.08-1.25)	0.10		
Dementia	8 (11)	12 (21)	0.47 (0.18-1.23)	0.12		
*Chronic Pulmonary Disease	6 (8)	10 (17)	0.42 (0.14-1.24)	0.12		
*Connective Tissue Disease	2 (3)	2 (3)				
*Peptic Ulcer Disease	2 (3)	4 (7)				
Mild Liver Disease	0 (0)	1 (2)				
*Diabetes (no complications)	12 (16)	7 (12)				
Diabetes with Organ Damage	18 (24)	22 (38)	0.53 (0.25-1.11)	0.09		
*Para or Hemiplegia	6 (8)	5 (9)				
Moderate/Severe Renal Disease	22 (30)	21 (36)				
*Solid Tumor	**2 (3)**	**8 (14)**	**0.17 (0.04-0.85)**	**0.03**		
*Leukemia	3 (4)	1 (2)				
*Lymphoma/Multiple Myeloma	2 (3)	5 (9)				
*Moderate/Severe Liver Disease	7 (9)	4 (7)				
*Metastatic Solid Tumor	4 (5)	5 (9)				
HIV/AIDS	13 (18)	0 (0)				
Charlson Comorbidity Index (CCI)						
0-3	26 (35)	10 (17)	Reference			
4-5	10 (14)	11 (19)	0.35 (0.11-1.08)	0.40		
6-8	24 (32)	19 (33)	0.49 (0.19-1.25)	0.94		
>8	14 (19)	18 (31)	0.30 (0.11-0.82)	0.14		
*History of Transplant	7 (9)	6 (10)				
History of MRSA Colonization	33 (45)	25 (43)				
Presumed Source of MRSA Infection						
*Peripheral IV	5 (7)	1 (2)				
*Skin & Soft Tissue Infection	**11 (15)**	**2 (3)**	**4.89 (1.04-23.00)**	**0.04**		
*Pneumonia	10 (14)	5 (9)				
*Endocarditis	4 (5)	5 (9)				
Diabetic Foot Infection	7 (9)	7 (12)				
Vascular Access	17 (23)	20 (34)	0.57 (0.26-1.22)	0.15		
Septic Arthritis	1 (1)	0 (0)				
*Urinary Source	1 (1)	3 (5)				
*Sacral Wound	6 (8)	3 (5)				
*Other/Unknown	5 (7)	3 (5)				
*ICU Admission Prior to BSI	4 (5)	1 (2)				

Bold = significant at ≤ 0.05

*Analyzed using Fisher's Exact Test

Abbreviations: NH, nursing home; rehab, rehabilitation facility; LTACH, long-term acute care hospital; BSI, bloodstream infection; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ICU, intensive care unit.

[a] Includes devices such as pacemaker, any vascular access, orthopedic hardware, foley catheter, arteriovenous graft placement, percutaneous endoscopic gastronomy (PEG), ostomy, or any type of urinary collection at the time of first positive bloodstream infection.

[b] Includes invasive procedures or surgery within the month prior to first positive bloodstream infection, excluding electroencephalogram (EEG), electrocardiogram (EKG), or transthoracic echocardiogram (TTE).

Table 5. Univariate analysis of outcomes

(A)

Outcome	CC8 N = 109 (%)	CC5 N = 116 (%)	Univariate Analysis OR (95% CI)	p value
Overall Death	36 (33)	51 (44)	0.63 (0.37-1.08)	0.09
Death Attributed to MRSA (Missing=139)	19 (56)	21 (40)	1.87 (0.78-4.48)	0.16
Duration of Bacteremia				
0-1.4 Days	26 (24)	35 (30)	Reference	
1.5-2.9 Days	32 (29)	32 (28)	1.35 (0.67-2.73)	0.41
3.0-6.9 Days	32 (29)	22 (19)	1.96 (0.93-4.12)	0.08
7.0+ Days	19 (17)	27 (23)	0.95 (0.44-2.06)	0.89
Time from Positive Culture to Discharge				
0-7 Days	22 (20)	20 (17)	Reference	
8-14 Days	27 (25)	35 (30)	0.70 (0.32-1.54)	0.38
15-30 Days	32 (29)	34 (30)	0.86 (0.39-1.86)	0.69
>30 Days	28 (26)	26 (23)	0.98 (0.44-2.20)	0.96
ICU Admission Attributed to MRSA (Missing=137)	27 (60)	17 (40)	2.29 (0.98-5.39)	0.06
Mechanical Ventilation Attributed to MRSA (Missing=152)	23 (66)	17 (45)	2.37 (0.92-6.10)	0.07
Metastatic Infection (Missing=2)	24 (22)	22 (19)	1.21 (0.63-2.31)	0.57

(B)

Outcome	CO-MRSA N = 132 (%)	HO-MRSA N = 93 (%)	Univariate Analysis OR (95% CI)	p value
Overall Death	46 (35)	41 (44)	1.47 (0.86-2.54)	0.16
Death Attributed to MRSA (Missing=139)	24 (55)	16 (38)	1.95 (0.83-4.61)	0.13
Duration of Bacteremia				
0-1.4 Days	31 (23)	30 (32)	Reference	
1.5-2.9 Days	37 (28)	27 (29)	1.33 (0.66-2.69)	0.43
3.0-6.9 Days	34 (26)	20 (22)	1.65 (0.78-3.47)	0.19
7.0+ Days	30 (23)	16 (17)	1.81 (0.83-3.99)	0.14
Time from Positive Culture to Discharge				
0-7 Days	27 (20)	15 (16)	Reference	
8-14 Days	41 (31)	21 (23)	1.09 (0.48-2.47)	0.85
15-30 Days	34 (26)	32 (35)	0.59 (0.27-1.31)	0.19
>30 Days	30 (23)	24 (26)	0.69 (0.30-1.59)	0.39
ICU Admission Attributed to MRSA (Missing=137)	**32 (80)**	**12 (25)**	**12.00 (4.36-33.06)**	**<0.001**
Mechanical Ventilation Attributed to MRSA (Missing=152)	**24 (71)**	**16 (41)**	**3.45 (1.30-9.15)**	**0.01**
Metastatic Infection (Missing=2)	32 (24)	14 (15)	1.80 (0.90-3.61)	0.10

(C)

Outcome	CC8 N = 35 (%)	CC5 N = 58 (%)	Univariate Analysis OR (95% CI)	p value
Overall Death	17 (49)	24 (41)	1.34 (0.58-3.11)	0.50
Death Attributed to MRSA (Missing=51)	8 (47)	8 (32)	1.89 (0.53-6.73)	0.33
*Duration of Bacteremia				
0-1.4 Days	11 (31)	19 (33)	Reference	
1.5-2.9 Days	10 (29)	17 (29)	1.02 (0.35-2.99)	0.98
3.0-6.9 Days	10 (29)	10 (17)	1.73 (0.55-5.45)	0.35
7.0+ Days	4 (11)	12 (21)	0.58 (0.15-2.23)	0.42
Time from Positive Culture to Discharge (Missing=1)				
0-7 Days	7 (20)	8 (14)	Reference	
8-14 Days	6 (17)	15 (26)	0.46 (0.11-1.83)	0.27
15-30 Days	13 (37)	19 (33)	0.78 (0.23-2.69)	0.70
>30 Days	9 (26)	15 (26)	0.69 (0.19-2.54)	0.57
*ICU Admission Attributed to MRSA (Missing=45)	3 (18)	9 (29)	0.52 (0.12-2.28)	0.39
*Mechanical Ventilation Attributed to MRSA (Missing=54)	6 (46)	10 (38)	1.37 (0.36-5.27)	0.65
*Metastatic Infection	5 (14)	9 (16)	0.91 (0.28-2.97)	0.87

(D)

Outcome	CC8 N = 74 (%)	CC5 N = 58 (%)	Univariate Analysis OR (95% CI)	p value
Overall Death	**19 (26)**	**27 (47)**	**0.40 (0.19-0.83)**	**0.01**
*Death Attributed to MRSA (Missing=88)	11 (65)	13 (48)	1.97 (0.67-6.88)	0.29
Duration of Bacteremia				
0-1.4 Days	15 (20)	16 (28)	Reference	
1.5-2.9 Days	22 (30)	15 (26)	1.56 (0.60-4.10)	0.36
3.0-6.9 Days	22 (30)	12 (21)	1.96 (0.72-5.29)	0.19
7.0+ Days	15 (20)	15 (26)	1.07 (0.39-2.91)	0.90
Time from Positive Culture to Discharge				
0-7 Days	15 (20)	12 (21)	Reference	
8-14 Days	21 (28)	20 (34)	0.84 (0.32-2.23)	0.73
15-30 Days	19 (26)	15 (26)	1.01 (0.37-2.80)	0.98
>30 Days	19 (26)	11 (19)	1.38 (0.48-4.00)	0.55
*ICU Admission Attributed to MRSA (Missing=92)	24 (86)	8 (67)	3.00 (0.61-14.86)	0.18
*Mechanical Ventilation Attributed to MRSA (Missing=98)	17 (77)	7 (58)	2.43 (0.53-11.11)	0.25
Metastatic Infection	19 (26)	13 (22)	1.22 (0.54-2.74)	0.63

*Results analyzed using Fisher's Exact Test

(A) CC8 vs CC5
(B) CO-MRSA vs HO-MRSA
(C) CC8 vs CC5 among the HO-MRSA stratum
(D) CC8 vs CC5 among the CO-MRSA stratum

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit.

Table 6. Cox Proportional Hazards Model on All-Cause In-Hospital Mortality Adjusted by Other Characteristics

	Univariate Analysis		Multivariate Analysis	
Factor	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
CC8	0.69 (0.40-1.22)	0.20		
Male	1.02 (0.57-1.82)	0.96		
Race/Ethnicity				
Non-Hispanic White	Reference		Reference	
Non-Hispanic Black	0.54 (0.27-1.09)	0.09	0.57 (0.26-1.28)	0.17
Hispanic/Latino	0.47 (0.20-1.07)	0.20	0.57 (0.23-1.45)	0.24
Asian	0.68 (0.20-2.33)	0.54	0.62 (0.16-2.45)	0.49
Unknown	1.52 (0.45-5.08)	0.50	2.49 (0.68-9.12)	0.17
Age				
18-54 Years	Reference			
55-69 Years	0.88 (0.38-2.04)	0.77		
≥70 Years	1.88 (0.94-3.77)	0.07		
History of Injection Drug Use	0.43 (0.13-1.37)	0.15	0.54 (0.15-2.02)	0.36
Body Mass Index (BMI)				
<18.5	**2.23 (1.06-4.68)**	**0.03**	**2.97 (1.24-7.11)**	**0.01**
18.5-24.9	Reference		Reference	
25.0-29.9	1.19 (0.58-2.45)	0.64	1.12 (0.50-2.50)	0.78
≥30.0	**0.45 (0.20-0.99)**	**0.05**	0.46 (0.20-1.05)	0.07
Admission Source				
Home	Reference			
NH/Rehab/LTACH	1.45 (0.79-2.66)	0.23		
Other Hospital	0.69 (0.30-1.59)	0.39		
Prior Hospital Admission (90 Days)	1.74 (0.82-3.71)	0.15		
Length of Hospital Stay Prior to BSI				
≤3 Days	0.69 (0.40-1.19)	0.18		
>3 Days	Reference			
Frequent Healthcare Interaction				
Hemodialysis	0.55 (0.23-1.34)	0.19		
Infusion Center	**1.93 (1.00-3.75)**	**0.05**		
None	**Reference**			
[a] Presence of Invasive Device	1.46 (0.68-3.10)	0.33		
[b] Invasive Procedures	1.06 (0.61-1.83)	0.83		
Wound Present	1.33 (0.77-2.29)	0.31		
Comorbidities				
Myocardial Infarction	0.97 (0.41-2.29)	0.95		
Congestive Heart Failure	1.05 (0.57-1.92)	0.88		
Peripheral Vascular Disease	0.75 (0.35-1.62)	0.46		
Cerebrovascular Disease	0.75 (0.27-2.08)	0.58		
Dementia	0.68 (0.27-1.72)	0.42		
Chronic Pulmonary Disease	1.16 (0.56-2.41)	0.68		
Connective Tissue Disease	1.87 (0.45-7.72)	0.39		
Peptic Ulcer Disease	0.80 (0.19-3.30)	0.75		
Mild Liver Disease	0.82 (0.11-6.06)	0.85		
Diabetes (no complications)	1.06 (0.50-2.25)	0.89		
Diabetes with Organ Damage	0.84 (0.44-1.61)	0.60		
Para or Hemiplegia	0.69 (0.17-2.85)	0.61		
Moderate/Severe Renal Disease	0.79 (0.42-1.49)	0.46		
Solid Tumor	1.23 (0.49-3.11)	0.66		
Leukemia	1.40 (0.55-3.53)	0.48		
Lymphoma/Multiple Myeloma	**2.47 (1.26-4.83)**	**0.008**	**2.40 (1.16-4.97)**	**0.02**
Moderate/Severe Liver Disease	0.91 (0.33-2.53)	0.85		
Metastatic Solid Tumor	2.21 (0.87-5.60)	0.10		
HIV/AIDS	0.85 (0.30-2.36)	0.75	0.39 (0.11-1.41)	0.15
Charlson Comorbidity Index (CCI)				
0-3	Reference		Reference	
4-5	1.66 (0.64-4.32)	0.30	1.25 (0.45-3.45)	0.67
6-8	**3.08 (1.36-6.97)**	**0.007**	**3.54 (1.47-8.57)**	**0.005**
>8	2.30 (0.95-5.53)	0.06	**4.36 (1.62-11.71)**	**0.004**
History of Transplant	**2.20 (1.19-4.09)**	**0.01**	**2.61 (1.27-5.38)**	**0.009**
History of MRSA Colonization	1.04 (0.59-1.84)	0.88		
Presumed Source of MRSA BSI				
Peripheral IV	0.86 (0.27-2.77)	0.80		
Skin & Soft Tissue Infection	**--**	**--**		
Pneumonia	**2.29 (1.17-4.47)**	**0.02**	**2.00 (1.11-3.63)**	**0.02**
Endocarditis	0.83 (0.20-3.42)	0.79		
Diabetic Foot Infection	1.11 (0.40-3.11)	0.84		
Vascular Access	1.02 (0.58-1.78)	0.96		
Septic Arthritis	3.67 (0.88-15.39)	0.08	4.22 (0.91-19.69)	0.07
Urinary Source	2.26 (0.31-16.65)	0.42		
Sacral Wound	--	--		
Other/Unknown	1.39 (0.55-3.50)	0.49		
ICU Admission Prior to BSI	1.43 (0.77-2.64)	0.26		

Bold = significant at ≤ 0.05

*Analyzed using Fisher's Exact Test

Abbreviations: NH, nursing home; rehab, rehabilitation facility; LTACH, long-term acute care hospital; BSI, bloodstream infection; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ICU, intensive care unit.

[a] Includes devices such as pacemaker, any vascular access, orthopedic hardware, foley catheter, arteriovenous graft placement, percutaneous endoscopic gastronomy (PEG), ostomy, or any type of urinary collection at the time of first positive bloodstream infection.

[b] Includes invasive procedures or surgery within the month prior to first positive bloodstream infection, excluding electroencephalogram (EEG), electrocardiogram (EKG), or transthoracic echocardiogram (TTE).

Table 7. Cox Proportional Hazards Model on All-Cause Overall Mortality Adjusted by Other Characteristics

	Univariate Analysis		Multivariate Analysis	
Factor	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
CC8	0.68 (0.45-1.04)	0.08		
Male	1.11 (0.70-1.74)	0.66		
Race/Ethnicity				
Non-Hispanic White	Reference		Reference	
Non-Hispanic Black	**0.58 (0.33-1.01)**	**0.05**	0.57 (0.32-1.03)	0.06
Hispanic/Latino	0.93 (0.55-1.59)	0.80	0.92 (0.53-1.59)	0.09
Asian	1.06 (0.38-2.95)	0.91	1.47 (0.51-4.20)	0.48
Unknown	0.80 (0.29-2.24)	0.67	1.18 (0.41-3.38)	0.76
Age				
18-54 Years	Reference			
55-69 Years	1.36 (0.71-2.58)	0.35		
≥ 70 Years	**2.90 (1.64-5.10)**	**<0.001**		
History of Injection Drug Use	0.78 (0.38-1.61)	0.50		
Body Mass Index (BMI)				
<18.5	1.25 (0.68-2.30)	0.48		
18.5-24.9	Reference			
25.0-29.9	0.68 (0.38-1.22)	0.19		
>30.0	**0.57 (0.32-0.99)**	**0.05**		
Admission Source				
Home	Reference			
NH/Rehab/LTACH	1.33 (0.82-2.14)	0.25		
Other Hospital	1.10 (0.61-2.00)	0.76		
Prior Hospital Admission (90 Days)	**1.87 (1.10-3.18)**	**0.02**		
Length of Hospital Stay After BSI				
≤3 Days	0.74 (0.49-1.14)	0.17		
>3 Days	Reference			
Frequent Healthcare Interaction				
Hemodialysis	1.04 (0.60-1.82)	0.89		
Infusion Center	1.41 (0.80-2.47)	0.23		
None	Reference			
[a] Presence of Invasive Device	1.82 (0.99-3.35)	0.06		
[b] Invasive Procedures	0.98 (0.64-1.50)	0.93		
Wound Present	0.98 (0.64-1.50)	0.91		
Comorbidities				
Myocardial Infarction	**1.88 (1.06-3.34)**	**0.03**		
Congestive Heart Failure	1.51 (0.96-2.40)	0.08		
Peripheral Vascular Disease	1.15 (0.67-1.99)	0.61		
Cerebrovascular Disease	1.19 (0.58-2.46)	0.64		
Dementia	1.37 (0.78-2.44)	0.28		
Chronic Pulmonary Disease	1.13 (0.61-2.08)	0.70		
Connective Tissue Disease	1.11 (0.27-4.53)	0.88		
Peptic Ulcer Disease	1.09 (0.35-3.45)	0.88		
Mild Liver Disease	2.96 (0.73-12.06)	0.13		
Diabetes (no complications)	1.09 (0.63-1.91)	0.75		
Diabetes with Organ Damage	1.35 (0.84-2.17)	0.21		
Para or Hemiplegia	0.77 (0.33-1.78)	0.54		
Moderate/Severe Renal Disease	1.17 (0.73-1.87)	0.52		
Solid Tumor	1.08 (0.54-2.16)	0.82		
Leukemia	1.96 (0.95-4.07)	0.07		
Lymphoma/Multiple Myeloma	**1.89 (1.07-3.31)**	**0.03**	**2.19 (1.22-3.91)**	**0.009**
Moderate/Severe Liver Disease	1.25 (0.60-2.59)	0.55		
Metastatic Solid Tumor	**2.39 (1.20-4.78)**	**0.01**		
HIV/AIDS	0.74 (0.34-1.60)	0.44	0.49 (0.21-1.13)	0.09
Charlson Comorbidity Index (CCI)				
0-3	Reference		Reference	
4-5	1.91 (0.92-3.96)	0.08	1.74 (0.83-3.64)	0.14
6-8	**2.89 (1.51-5.53)**	**0.001**	**3.24 (1.68-6.23)**	**<0.001**
>8	**3.48 (1.79-6.75)**	**<0.001**	**5.13 (2.56-10.30)**	**<0.001**
History of Transplant	1.47 (0.85-2.53)	0.17		
History of MRSA Colonization	0.83 (0.55-1.27)	0.40		
Presumed Source of MRSA BSI				
Peripheral IV	0.76 (0.31-1.87)	0.55		
Skin & Soft Tissue Infection	**0.27 (0.09-0.87)**	**0.03**		
Pneumonia	**2.05 (1.16-3.64)**	**0.01**	**2.00 (1.11-3.63)**	**0.02**
Endocarditis	1.62 (0.71-3.72)	0.25		
Diabetic Foot Infection	1.14 (0.50-2.61)	0.76		
Vascular Access	1.13 (0.73-1.74)	0.59		
Septic Arthritis	2.76 (0.68-11.25)	0.16		
Urinary Source	1.17 (0.29-4.77)	0.82		
Sacral Wound	--	--		
Other/Unknown	1.29 (0.56-2.96)	0.55		
ICU Admission Prior to BSI	1.50 (0.91-2.47)	0.11	**1.81 (1.06-3.08)**	**0.03**

Bold = significant at ≤ 0.05

*Analyzed using Fisher's Exact Test

Abbreviations: NH, nursing home; rehab, rehabilitation facility; LTACH, long-term acute care hospital; BSI, bloodstream infection; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; ICU, intensive care unit.

[a] Includes devices such as pacemaker, any vascular access, orthopedic hardware, foley catheter, arteriovenous graft placement, percutaneous endoscopic gastronomy (PEG), ostomy, or any type of urinary collection at the time of first positive bloodstream infection.

[b] Includes invasive procedures or surgery within the month prior to first positive bloodstream infection, excluding electroencephalogram (EEG), electrocardiogram (EKG), or transthoracic echocardiogram (TTE).

Figure 1

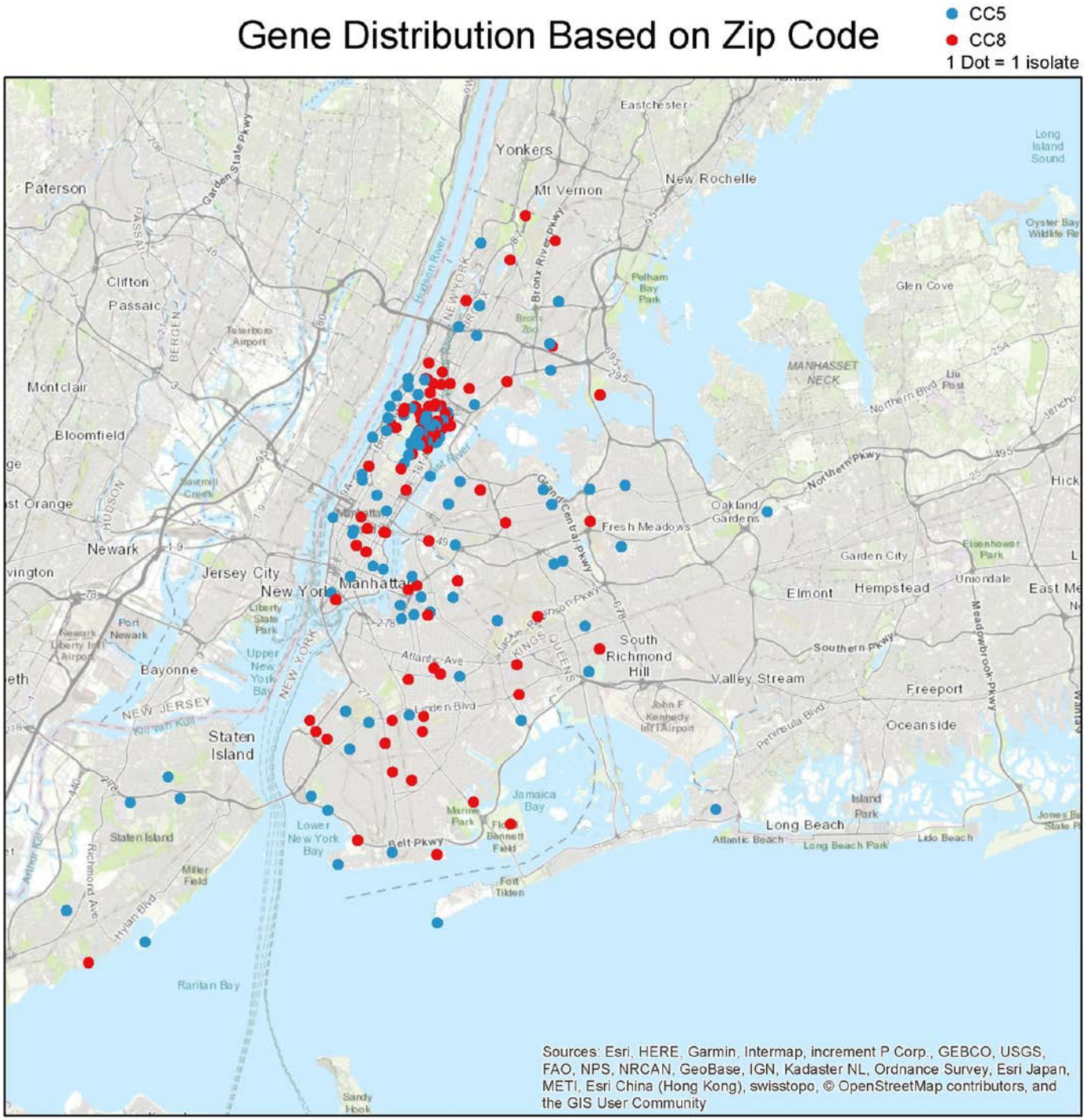
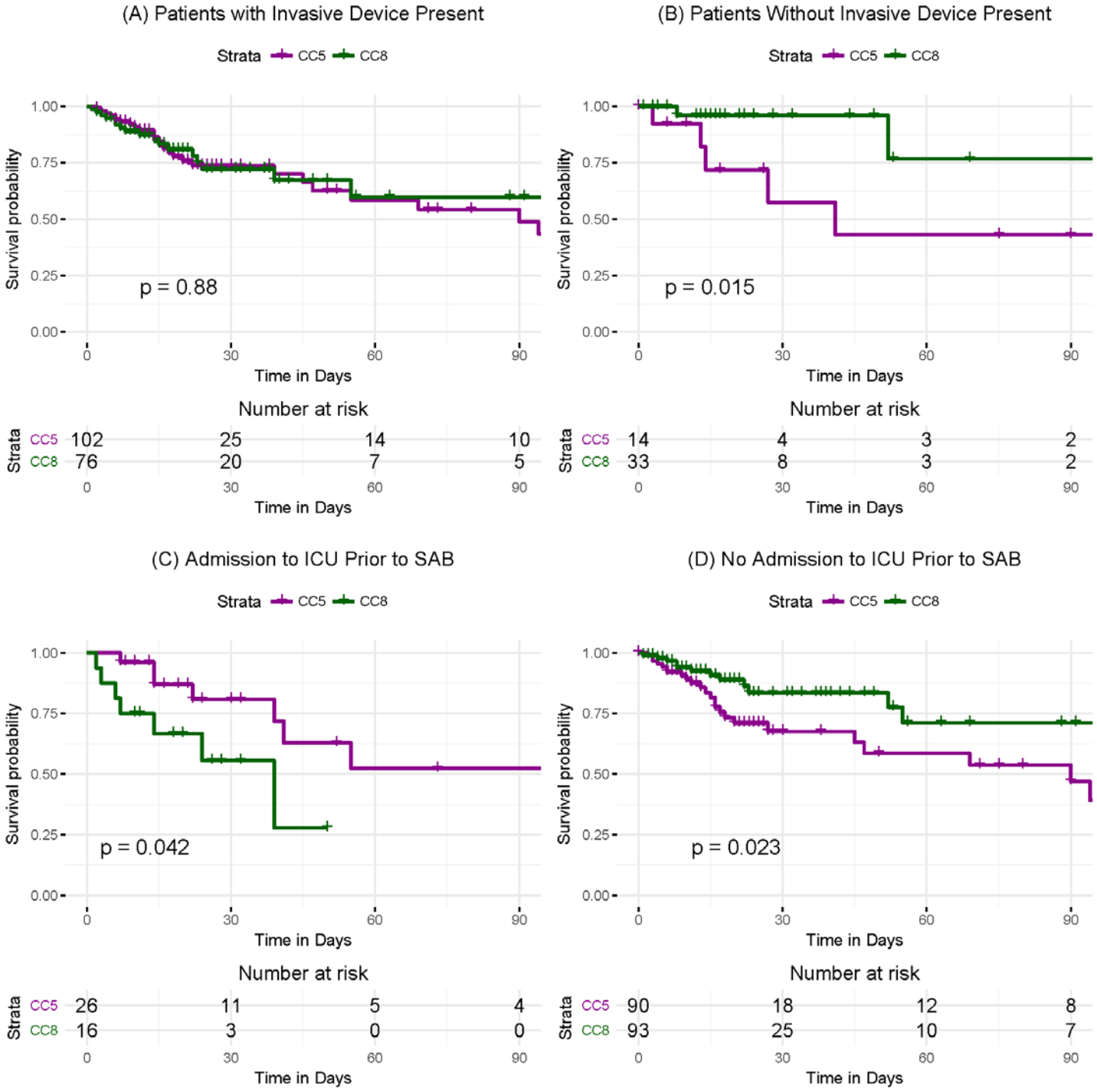


Figure 1 Legend

- CC5
- CC8

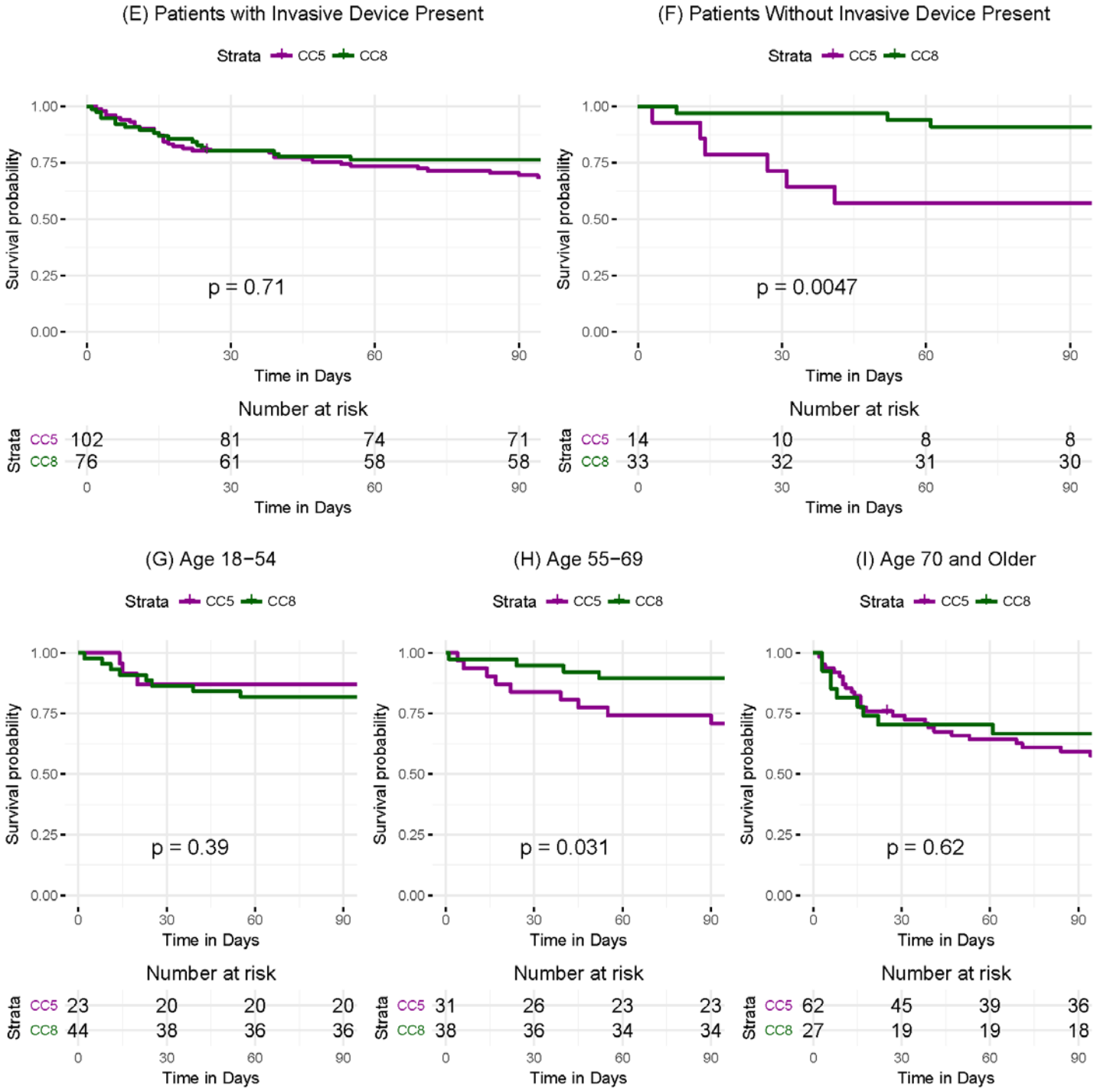
1 Dot = 1 Isolate

Figure 2. In-Hospital Mortality Stratified by Clone



*Figures reflect the variables that were found to have effect modification.

Figure 3. All-Cause Overall Mortality Stratified by Clone



*Figures reflect the variables that were found to have effect modification.