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A Sharma, *Atlanta Veterans Affairs Medical Center*
C Rogers, *Atlanta Veterans Affairs Medical Center*
David Rimland, *Emory University*
C Stafford, *Atlanta Veterans Affairs Medical Center*
Sarah Satola, *Emory University*
E Crispell, *Atlanta Veterans Affairs Medical Center*
Robert Gaynes, *Emory University*

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Post-discharge mortality in patients hospitalized with MRSA infection and/or colonization

A. SHARMA[1,2], C. ROGERS[1], D. RIMLAND[1,3], C. STAFFORD[1], S. SATOLA[1,3], E. CRISPELL[1,3] AND R. GAYNES[1,3]*

[1] *Atlanta Veterans Affairs Medical Center, Decatur, GA, USA*
[2] *Department of Epidemiology, Emory University Laney Graduate School, Atlanta, GA, USA*
[3] *Emory University School of Medicine, Atlanta, GA, USA*

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SUMMARY

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is known to increase in-hospital mortality, but little is known about its association with long-term health. Two hundred and thirty-seven deaths occurred among 707 patients with MRSA infection at the time of hospitalization and/or nasal colonization followed for almost 4 years after discharge from the Atlanta Veterans Affairs Medical Center, USA. The crude mortality rate in patients with an infection and colonization (23·57/100 person-years) was significantly higher than the rate in patients with only colonization (15·67/100 person-years, $P=0·037$). MRSA infection, hospitalization within past 6 months, and histories of cancer or haemodialysis were independent risk factors. Adjusted mortality rates in patients with infection were almost twice as high compared to patients who were only colonized: patients infected and colonized [hazard ratio (HR) 1·93, 95% confidence interval (CI) 1·31–2·84]; patients infected but not colonized (HR 1·96, 95% CI 1·22–3·17). Surviving MRSA infection adversely affects long-term mortality, underscoring the importance of infection control in healthcare settings.

Key words: Epidemiology, hygiene and hospital infections, infectious disease control, methicillin-resistant *S. aureus* (MRSA), prevention.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an antimicrobial-resistant human pathogen initially described in 1961 [1] which is associated with severe morbidity and mortality in hospitalized patients [2–6]. Strategies are needed to prevent nosocomial emergence and spread of MRSA because infections with antimicrobial-resistant organisms are associated with higher healthcare costs compared to infections with antimicrobial-susceptible organisms [7, 8]. The Veterans Health Administration (VHA) issued a directive in January 2007 to reduce healthcare-associated MRSA infections in acute-care facilities [9]. The directive focuses on limiting MRSA transmission within the Veterans Affairs (VA) hospitals using active surveillance through nasal screening, implementation of contact isolation precautions for those found to be positive on admission, and hand hygiene measures. It also requires that a MRSA

* Author for correspondence: Dr R. Gaynes, Atlanta Veterans Affairs Medical Center, 1670 Clairmont Road, Decatur, GA 30033, USA.
(Email: robert.gaynes@va.gov)

culture be performed at transfer within or discharge from the facilities to look for possible hospital-acquired MRSA.

Previous studies have shown that MRSA colonization of the nares increases the risk for clinical infection [10–14]. Patients who have persistent rather than intermittent colonization appear to have a higher bacterial burden [2]. However, the duration of colonization with MRSA is not well defined [15–19]. Patients with previous MRSA colonization are often assumed to be colonized on readmission, and are isolated or empirically treated on that assumption. One recent study in the USA suggests that nearly half of all MRSA-colonized patients continue to remain colonized during the first year and ~21% remain colonized at 4 years, although this study did not examine bacterial burden and its role in the duration of colonization [16]. Long-term carriers of MRSA are at high risk for subsequent morbidity thereby increasing the need for preventive interventions in this cohort [20]. If factors associated with prolonged MRSA colonization could be determined, screening could be targeted and made more efficient and less costly.

In an effort to explore this issue, we initiated a study to determine the duration of and factors associated with MRSA colonization in patients from the Atlanta Veterans Affairs Medical Center (VAMC) having a MRSA infection at the time of hospitalization and/or nasal colonization at discharge, the results of which will be detailed elsewhere. During medical record review we observed that the post-discharge mortality in these patients was high; almost one-third of the patients who either had a MRSA infection at the time of hospitalization and/or a positive nasal culture at discharge were deceased. Several studies have found an association between MRSA bloodstream infection and increased in-hospital mortality, after controlling for demographic and other potential confounding factors [3, 4, 6, 21, 22]. However, these studies were not designed to describe long-term mortality in patients with either a MRSA infection or colonization. One study in Germany found significant additional mortality beyond 30 days in patients with *Staphylococcus aureus* bacteraemia (SAB) followed for 1 year after discharge [23]. Another recent study in Iceland evaluating all-cause mortality trends in three time periods in patients with SAB also examined 30-day and 1-year survival [24]. The retrospective study determining the duration of colonization with MRSA mentioned above, had a long follow-up period but no information on patient mortality [16]. In our study we sought to identify some independent risk factors for post-discharge mortality in a group of veterans from the Atlanta VAMC followed for almost 4 years. We also investigated the relationship between initial characterization of MRSA as an infection at the time of hospitalization and/or nasal colonization at discharge and time until death, after adjusting for other comorbidities.

METHODS

The Atlanta VAMC is a 128-bed acute-care facility with about 500 admissions per month located in Georgia, USA. After the VHA directive was instituted at the Atlanta VAMC in September 2007, MRSA infections were identified on a monthly basis by utilizing the microbiology option for specific organisms in the Veterans Health Information Systems and Technology Architecture (VistA). VistA is an electronic medical record system used within VA hospitals which integrates both inpatient and outpatient health records. All clinical MRSA cultures and corresponding clinical data (electronic medical record, anatomical site of culture, radiographic studies, laboratory results, physician notes) were reviewed by the same experienced infectious disease physician on a monthly basis to identify true infections in the blood and other body sites. Infections were classified according to the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) surveillance criteria [25].

Under the VHA directive a nasal swab was obtained on initial arrival or transfer to the ward or intensive-care unit (ICU) for each admission. The swab was then sent to the microbiology laboratory for analysis using the BD GeneOhm MRSA real-time PCR system (BD Diagnostics, USA), demonstrated to have a high sensitivity and specificity in clinical validation studies [26, 27]. If positive, the patient was placed in contact isolation precautions either in a private room or in a room with other MRSA-positive patients. On discharge from the hospital, a nasal swab was obtained and cultured on CHROMagar MRSA agar assay (BD Diagnostics), also known to have high sensitivity and specificity [28, 29]. Colonization with MRSA was classified as a positive microbiological culture from a nasal swab in a patient not meeting the CDC/NHSN criteria for infection.

We conducted a retrospective cohort study using medical record review to examine long-term mortality

in patients discharged from the Atlanta VAMC between 1 October 2007 and 31 July 2009. All patients alive at discharge having a MRSA infection during at least one immediately previous hospitalization, MRSA colonization of their anterior nares documented in at least one discharge record, or both, were included. We considered only the first discharge where a patient had an infection at the time of hospitalization or was nasally colonized at discharge, to ensure that our study population was comprised of unique individuals. Patients discharged from the psychiatry wards at the Atlanta VAMC were excluded. Follow-up began on the day of discharge from the hospital and every patient was followed until death or 31 July 2011, whichever occurred earlier. Therefore, the follow-up time for all patients in this study ranged from a minimum of 2 years up to potentially 3·83 years.

Patient identifiers were collected on a master list maintained on a secure server with restricted access. Before the data collection process began, we assigned each patient a unique study identification number to protect their privacy. Based on patients' MRSA infection and colonization status, we defined three mutually exclusive comparison cohorts:

(1) Patients who had both a MRSA infection at the time of hospitalization and nasal colonization at discharge (cohort A).
(2) Patients who had a MRSA infection at the time of hospitalization but no nasal colonization at discharge (cohort B).
(3) Patients who did not have a MRSA infection at the time of hospitalization but had nasal colonization at discharge (cohort C).

Information including demographic characteristics, underlying conditions, functional status, previous and current infections, and antibiotic use from patients in cohorts A, B, and C was collected on paper data collection forms, and subsequently entered into an electronic database. Demographic information included age at discharge, race/ethnicity, gender, location at admission to the Atlanta VAMC (home, nursing home, or some other hospital), number of previous admissions within the past 8 years, and additional hospitalization within the past 6 months. We recorded information regarding PCR results for MRSA on nasal swabs at admission, presence of any admission wounds, and diagnosis of MRSA bloodstream infection at the time of hospitalization. History of any type of cancer, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), diabetes, human immunodeficiency virus (HIV) infection, haemodialysis, and stroke was obtained through medical record review. We also collected data on the presence of any medical devices at discharge [gastrostomy tube, urinary catheter, peripherally inserted central catheter (PICC) line, intravenous (i.v.) line, or tunnelled catheter], surgical wounds at discharge, and number of antibiotics prescribed at discharge. Information pertaining to the patients' social history included current and past i.v. drug abuse, homelessness within 3 months of study inclusion and incarceration within 3 months of study inclusion.

Statistical analyses were performed using SAS version 9.2 [30]. We obtained crude estimates of post-discharge mortality rates and compared these in cohorts A and B with cohort C (referent). We also compared the crude rate in patients with both a MRSA infection at the time of hospitalization and nasal colonization at discharge with that in patients who were neither infected nor colonized. Systematic sampling was used to estimate the rate for this group wherein every fiftieth patient was selected from an alphabetically ordered list containing last names of all such patients discharged during the same time period. Descriptive frequencies and χ^2 tests were performed after stratification by MRSA infection and colonization status to examine any significant differences between patients in the three cohorts. Variables with small numbers were not considered for stratification in further analyses. First, we used bivariate logistic regression to describe the demographic and clinical characteristics associated with post-discharge mortality. For categorical variables, we calculated crude odds ratios (cORs) and 90% confidence intervals (CIs) *vs.* referent groups. Next, variables found to have at least one significant categorical level ($P<0{\cdot}10$) in the bivariate analysis were included in the initial multivariate logistic regression model. We used a stepwise selection approach ($\alpha=0{\cdot}10$) to identify independent risk factors for post-discharge mortality, and obtained adjusted odds ratios (aORs) and 90% CIs after controlling for potential confounders. We also performed tests to detect any collinearity in the independent variables [31, 32].

Using significant predictors of post-discharge mortality obtained from our multivariate logistic regression, we performed a survival analysis to describe the relationship between the initial characterization of MRSA as an infection and/or colonization and time until death. The proportional hazards assumption

was tested both statistically, by finding the correlation between Schoenfeld residuals for a particular covariate and the ranking of individual failure times, and graphically, by looking for parallelism in the log-log survival curves for each variable [33]. This assumption requires that the hazard ratios (HR) are constant over time. We used Cox proportional hazards regression to obtain HRs and 95% CIs, and generated adjusted survival curves comparing cohorts A and B with cohort C (referent) after controlling for demographic and clinical factors.

RESULTS

Between 1 October 2007 and 31 July 2009, 10436 unique patients were discharged from the Atlanta VAMC. Of these, 10099 (97%) had been screened using PCR for MRSA colonization of their anterior nares on admission, and 9609 (92%) were screened using CHROMagar at discharge. Seven hundred and thirty-eight (7%) patients had either a documented MRSA infection at the time of hospitalization, or nasal colonization at discharge, or both, and were therefore eligible for this study. Because of our focus on post-discharge mortality, 31 patients who died during that hospitalization were excluded (10 from cohort A, three from cohort B, 18 from cohort C). The resulting final analytical sample comprised 707 patients: 89 in cohort A (having infection at the time of hospitalization and nasal colonization at discharge), 93 in cohort B (having only infection at the time of hospitalization), and 525 in cohort C (having only nasal colonization at discharge).

Overall, 237 deaths occurred in patients having a documented MRSA infection at the time of hospitalization and/or nasal colonization at discharge during 1457 person-years (py) of follow-up (16·27 deaths/100 py): 37 in cohort A over 157 py, 27 in cohort B over 196 py and 173 in cohort C over 1104 py. The crude post-discharge mortality rate in cohort A (23·57/100 py) was significantly higher than the rate in cohort C (15·67/100 py) (Fisher's exact test $P=0{\cdot}037$). The rate in cohort B (13·78/100 py) did not significantly differ from that in cohort C (Fisher's exact test, $P=0{\cdot}612$). Fifty-three deaths occurred in our additional sample of 195 patients (after excluding five in-hospital deaths) not having either infection at the time of hospitalization or nasal colonization at discharge over 454 py of follow-up. This crude post-discharge mortality rate (11·67/100 py) was significantly lower than the rate in cohort A (Fisher's exact test, $P=0{\cdot}002$).

Table 1 summarizes the demographic and clinical characteristics of patients, stratified by MRSA infection at the time of hospitalization and nasal colonization at discharge status. Cohort A was the oldest with more than one-third of the patients aged $\geqslant 70$ years at time of discharge. This cohort had the highest proportions of cancer and stroke histories, and more than half the patients had multiple admissions in the past 8 years. Cohort B had the lowest prevalence of nasal MRSA colonization on admission. However, this cohort had the highest proportion of wounds, with almost two-thirds of the patients having admission wounds and more than 50% having surgical wounds at discharge. Cohort C had the lowest percentage of patients with admission wounds, and medical devices or surgical wounds at discharge. Less than 2% of patients in cohorts A, B and C combined were actively using i.v. drugs, $\sim$4% had a history of i.v. drug abuse, less than 2% were homeless and none were incarcerated within 3 months of study inclusion (data not shown in table).

Table 2 shows results from the bivariate and multivariate analyses of factors associated with post-discharge mortality in patients having a MRSA infection at the time of hospitalization and/or nasal colonization at discharge. Factors associated with post-discharge mortality in the crude analyses included multiple admissions in the past 8 years, MRSA bloodstream infection at the time of hospitalization, history of COPD, and transfer to the Atlanta VAMC from a nursing home *vs.* direct admission from home. Variables included in the initial multivariate logistic regression model were age at discharge, race/ethnicity, gender, location at admission to the Atlanta VAMC, number of previous admissions within the past 8 years, additional hospitalization within the past 6 months, PCR results for MRSA on nasal swabs at admission, presence of any admission wounds, diagnosis of MRSA bloodstream infection at the time of hospitalization, history of any type of cancer, history of CAD, history of COPD, history of diabetes, HIV status at study inclusion, history of hemodialysis, history of stroke, presence of any medical devices at discharge, presence of surgical wounds at discharge, and number of antibiotics prescribed at discharge. MRSA infection at the time of hospitalization, older age at time of discharge, additional hospitalization within the past 6 months, nasal MRSA colonization on admission, and histories of cancer or haemodialysis were independent predictors of long-term mortality, after adjusting for other comorbidities.

Table 1. *Demographic and clinical characteristics of patients stratified by MRSA infection at the time of hospitalization and/or nasal colonization at discharge* from the Atlanta VAMC between 1 October 2007 and 31 July 2009 (n = 707)*

Characteristic	Cohort A *n* (%)	Cohort B *n* (%)	Cohort C *n* (%)	*P*†
Age at discharge (years)				0·016
<60	32 (36)	44 (47)	161 (31)	
60–69	25 (28)	32 (34)	198 (38)	
70–79	15 (17)	10 (11)	71 (13)	
⩾80	17 (19)	7 (8)	95 (18)	
Race/ethnicity				0·175
White, non-Hispanic	56 (64)	59 (65)	283 (56)	
Black, non-Hispanic	32 (36)	32 (35)	220 (44)	
Gender				–
Male	88 (99)	89 (96)	510 (97)	
Female	1 (1)	4 (4)	15 (3)	
Location at admission to Atlanta VAMC				–
Home	81 (91)	90 (97)	482 (92)	
Nursing home	7 (8)	3 (3)	17 (3)	
Some other hospital	1 (1)	0 (0)	23 (4)	
Number of previous admissions in the past 8 years				0·018
Three or more	34 (38)	29 (31)	151 (29)	
Two	12 (14)	18 (19)	64 (12)	
One	24 (27)	18 (19)	103 (20)	
None	19 (21)	28 (31)	207 (39)	
Additional hospitalization within past 6 months				0·197
Yes	15 (17)	13 (14)	112 (21)	
No	74 (83)	80 (86)	413 (79)	
PCR results on nasal swab at admission				<0·001
Positive	83 (93)	50 (54)	442 (85)	
Negative	6 (7)	43 (46)	79 (15)	
Wounds on admission				<0·001
Present	45 (51)	59 (63)	39 (7)	
Absent	44 (49)	34 (37)	486 (93)	
MRSA bloodstream infection at the time of hospitalization				–
Present	16 (18)	12 (13)	0 (0)	
Absent	73 (82)	81 (87)	525 (100)	
History of any type of cancer				0·029
Present	27 (30)	13 (14)	115 (22)	
Absent	62 (70)	80 (86)	410 (78)	
History of CAD				0·547
Present	19 (21)	26 (28)	138 (26)	
Absent	70 (79)	67 (72)	387 (74)	
History of COPD				0·150
Present	26 (29)	18 (19)	107 (20)	
Absent	63 (71)	75 (81)	418 (80)	
History of diabetes				0·033
Insulin-dependent	25 (28)	22 (24)	150 (29)	
Non-insulin-dependent	14 (16)	16 (17)	43 (8)	
Absent	50 (56)	55 (59)	331 (63)	
HIV status at study inclusion				–
Infected: CD4 ⩽200	2 (2)	4 (4)	11 (2)	
Infected: CD4 >200	3 (3)	5 (5)	10 (2)	
Not infected	84 (95)	84 (91)	503 (96)	

Table 1 (*cont.*)

Characteristic	Cohort A *n* (%)	Cohort B *n* (%)	Cohort C *n* (%)	*P*†
History of haemodialysis				0·137
Present	5 (6)	9 (10)	66 (13)	
Absent	84 (94)	84 (90)	458 (87)	
History of stroke				<0·001
Present	16 (18)	7 (8)	29 (6)	
Absent	73 (82)	86 (92)	496 (94)	
Medical devices at discharge‡				<0·001
Present	27 (30)	29 (31)	42 (8)	
Absent	62 (70)	64 (69)	483 (92)	
Surgical wounds at discharge				<0·001
Present	30 (34)	50 (54)	73 (14)	
Absent	59 (66)	43 (46)	452 (86)	
Number of antibiotics prescribed at discharge				–
Two or more	8 (9)	15 (16)	10 (2)	
One	44 (49)	54 (58)	78 (15)	
None	37 (42)	24 (26)	437 (83)	

MRSA, Methicillin-resistant *Staphylococcus aureus*; VAMC, Veterans Affairs Medical Center; PCR, polymerase chain reaction; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; PICC, peripherally inserted central catheter; i.v., intravenous.

* Patients who had a MRSA infection at the time of hospitalization and were nasally colonized at discharge (cohort A, $n=89$); patients who had a MRSA infection at the time of hospitalization but were not nasally colonized at discharge (cohort B, $n=93$); patients who did not have a MRSA infection at the time of hospitalization but were nasally colonized at discharge (cohort C, $n=525$). Numbers might not add to total because of missing data.

–, Indicates that the χ^2 test may not be valid due to expected cell counts <5.

† χ^2 test ($\alpha=0{\cdot}05$).

‡ Gastrostomy tube, urinary catheter, PICC line, i.v. line, or tunnelled catheter.

Table 3 presents adjusted HRs obtained from a Cox proportional hazards regression describing the relationship between initial characterization of MRSA as an infection at the time of hospitalization and/or nasal colonization at discharge and time until death. The Schoenfeld residuals for each covariate included in the Cox model and the ranking of individual failure times were not correlated, and the log-log survival curves were parallel, indicating that the proportional hazards assumption was satisfied. The adjusted post-discharge mortality rates in patients in cohorts A and B, who had a MRSA infection at the time of hospitalization, were almost twice as high compared to patients in cohort C, who had only MRSA colonization of their anterior nares at discharge. Additional hospitalization within the past 6 months and histories of cancer or haemodialysis were associated with poorer survival, whereas being non-Hispanic black, having a history of stroke or having surgical wounds at discharge were associated with better survival. Figure 1 shows the adjusted survival curves for each of the three comparison groups. These indicate that patients in cohorts A and B had similar long-term survival which was consistently worse compared to patients in cohort C. Patients in cohort A were followed up to 3·62 years (1320 days), those in cohort B were followed up to 3·72 years (1358 days), and those in cohort C were followed up to 3·74 years (1366 days). The median time to death for patients in cohort A was 152 days, for those in cohort B 185 days, and for those in Cohort C 198 days. The last death in cohort A occurred at 555 days, in cohort B at 830 days, and in cohort C at 1236 days, as is indicated by the endpoints of the three survival curves. MRSA infection at the time of hospitalization, regardless of nasal colonization at discharge, adversely affects mortality particularly in the first 2 years of follow-up (indicated by the steep decline in the adjusted survival curves for cohorts A and B).

DISCUSSION

MRSA infections occur commonly in healthcare settings, and are a serious medical and public health

Table 2. *Risk factors associated with post-discharge mortality in patients with a MRSA infection at the time of hospitalization and/or nasal colonization at discharge from the Atlanta VAMC between 1 October 2007 and 31 July 2009* ($n = 707$)

	Bivariate analysis		Multivariate analysis	
Characteristic	OR	(90% CI)	OR	(90% CI)
Cohort*				
A *vs.* C	1·45	(0·99–2·13)	2·32	(1·43–3·77)
B *vs.* C	0·83	(0·56–1·25)	2·59	(1·51–4·44)
Age at discharge (years)				
60–69 *vs.* <60	1·44	(1·03–2·00)	1·06	(0·73–1·55)
70–79 *vs.* <60	2·61	(1·72–3·97)	1·96	(1·22–3·15)
⩾80 *vs.* <60	2·56	(1·73–3·79)	1·65	(1·03–2·63)
Race/ethnicity				
Black, non-Hispanic *vs.*White, non-Hispanic	0·71	(0·54–0·93)	0·70	(0·51–0·96)
Gender				
Male *vs.* female	2·93	(1·04–8·27)	–	–
Location at admission to Atlanta VAMC				
Nursing home *vs.* home	2·55	(1·33–4·88)	–	–
Some other hospital *vs.* home	0·68	(0·31–1·49)	–	–
Number of previous admissions in the past 8 years				
Three or more *vs.* none	1·88	(1·35–2·60)	–	–
Two *vs.* none	1·98	(1·31–3·00)	–	–
One *vs.* none	1·26	(0·86–1·83)	–	–
Additional hospitalization within past 6 months				
Yes *vs.* no	2·78	(2·02–3·82)	2·83	(1·99–4·02)
PCR results on nasal swab at admission				
Positive *vs.* negative	2·12	(1·44–3·11)	1·93	(1·24–2·99)
Wounds on admission				
Present *vs.* absent	0·56	(0·39–0·79)	0·59	(0·36–0·94)
MRSA bloodstream infection at the time of hospitalization				
Present *vs.* absent	2·05	(1·08–3·86)	–	–
History of any type of cancer				
Present *vs.* absent	2·68	(1·98–3·65)	2·80	(1·98–3·97)
History of CAD				
Present *vs.* absent	0·96	(0·71–1·29)	–	–
History of COPD				
Present *vs.* absent	1·63	(1·20–2·22)	–	–
History of diabetes				
Insulin-dependent *vs.* absent	0·80	(0·59–1·08)	–	–
Non-insulin-dependent *vs.* absent	0·63	(0·39–1·00)	–	–
HIV status at study inclusion				
Infected: CD4 ⩽200 *vs.* not infected	0·60	(0·23–1·55)	–	–
Infected: CD4 >200 *vs.* not infected	0·56	(0·22–1·43)	–	–
History of haemodialysis				
Present *vs.* absent	2·44	(1·65–3·62)	2·16	(1·38–3·39)
History of stroke				
Present *vs.* absent	0·51	(0·29–0·91)	0·45	(0·24–0·84)
Medical devices at discharge†				
Present *vs.* absent	1·18	(0·81–1·71)	–	–
Surgical wounds at discharge				
Present *vs.* absent	0·41	(0·28–0·59)	0·41	(0·26–0·65)

Table 2 (*cont.*)

Characteristic	Bivariate analysis		Multivariate analysis	
	OR	(90% CI)	OR	(90% CI)
Number of antibiotics prescribed at discharge				
Two or more *vs.* None	0·82	(0·43–1·57)	–	–
One *vs.* None	0·86	(0·63–1·17)	–	–

MRSA, Methicillin-resistant *Staphylococcus aureus*; VAMC, Veterans Affairs Medical Center; OR, odds ratio; CI, confidence interval; PCR, polymerase chain reaction; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; PICC, peripherally inserted central catheter; i.v., intravenous.
* Patients who had a MRSA infection at the time of hospitalization and were nasally colonized at discharge (cohort A, $n=89$); patients who had a MRSA infection at the time of hospitalization but were not nasally colonized at discharge (cohort B, $n=93$); patients who did not have a MRSA infection at the time of hospitalization but were nasally colonized at discharge (cohort C, $n=525$).
† Gastrostomy tube, urinary catheter, PICC line, i.v. line, or tunnelled catheter.

Table 3. *Adjusted hazard ratios* for post-discharge mortality in patients with a MRSA infection at the time of hospitalization and/or nasal colonization at discharge from the Atlanta VAMC between 1 October 2007 and 31 July 2009* ($n=707$)

Characteristic	HR	(95% CI)
Cohort†		
A *vs.* C	1·93	(1·31–2·84)
B *vs.* C	1·96	(1·22–3·17)
Age at discharge (years)		
60–69 *vs.* <60	1·00	(0·70–1·42)
70–79 *vs.* <60	1·49	(1·00–2·26)
⩾80 *vs.* <60	1·32	(0·88–1·98)
Race/ethnicity		
Black, non-Hispanic *vs.* White, non-Hispanic	0·72	(0·54–0·95)
Additional hospitalization within past 6 months		
Yes *vs.* no	2·09	(1·57–2·78)
PCR results on nasal swab at admission		
Positive *vs.* negative	1·53	(1·00–2·35)
Wounds on admission		
Present *vs.* absent	0·65	(0·42–1·02)
History of any type of cancer		
Present *vs.* absent	2·21	(1·66–2·95)
History of haemodialysis		
Present *vs.* absent	1·70	(1·19–2·43)
History of stroke		
Present *vs.* absent	0·53	(0·28–0·99)
Surgical wounds at discharge		
Present *vs.* absent	0·46	(0·30–0·70)

MRSA, Methicillin-resistant *Staphylococcus aureus*; VAMC, Veterans Affairs Medical Center; HR, hazard ratio; CI, confidence interval; PCR, polymerase chain reaction.
* Cox proportional hazards model where the dependent variable was survival time (days) after discharge from the Atlanta VAMC. Only demographic and clinical risk factors significant in the multivariate logistic regression ($\alpha=0·10$) were included.
† Patients who had a MRSA infection at the time of hospitalization and were nasally colonized at discharge (cohort A, $n=89$); patients who had a MRSA infection at the time of hospitalization but were not nasally colonized at discharge (cohort B, $n=93$); patients who did not have a MRSA infection at the time of hospitalization but were nasally colonized at discharge (cohort C, $n=525$).

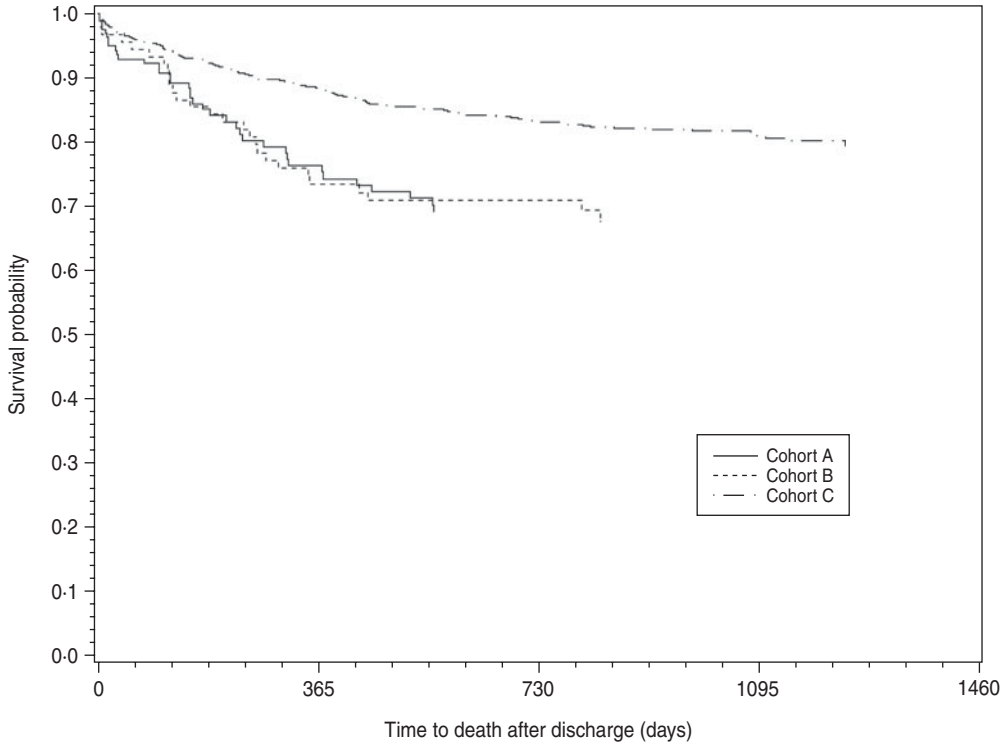

Fig. 1. Adjusted survival curves of time to death (all-cause mortality) for patients discharged from the Atlanta VAMC between 1 October 2007 and 31 July 2009 stratified by MRSA infection at the time of hospitalization and/or nasal colonization at discharge (cohort A *vs.* C: HR 1·93, 95% CI 1·31–2·84; cohort B *vs.* C: HR 1·96, 95% CI 1·22–3·17). VAMC, Veterans Affairs Medical Center; MRSA, methicillin-resistant *Staphylococcus aureus*. Patients who had a MRSA infection at the time of hospitalization and were nasally colonized at discharge (cohort A, $n=89$); patients who had a MRSA infection at the time of hospitalization but were not nasally colonized at discharge (cohort B, $n=93$); patients who did not have a MRSA infection at the time of hospitalization but were nasally colonized at discharge (cohort C, $n=525$). HR, Hazard ratio; CI, confidence interval.

issue [3–5]. Colonization of the anterior nares with MRSA is known to increase the risk for clinical infection [10–13]. Although the association between MRSA bacteraemia and increased in-hospital mortality has been well documented [3, 4, 6, 21, 22], we were unable to find studies examining long-term mortality in patients surviving a MRSA infection at the time of hospitalization and/or having nasal MRSA colonization. Previous studies on post-discharge mortality have studied 1-month and 1-year survival in patients with SAB, but were limited in their ability to collect data on long-term health outcomes by design [23, 24]. In our study, we followed a group of veterans having a documented MRSA infection at the time of hospitalization and/or nasal colonization at discharge from the Atlanta VAMC for almost 4 years. After identifying some independent predictors of post-discharge mortality, we compared adjusted mortality rates and examined the association between initial characterization of MRSA as an infection and/or nasal colonization and death.

The crude post-discharge mortality rate in patients with a MRSA infection at the time of hospitalization and nasal colonization at discharge was 1·50 times the rate in patients with only nasal MRSA colonization at discharge (95% CI 1·04–2·13). After controlling for other comorbidities, this association strengthened even further. The adjusted post-discharge mortality rates in patients with an infection (with or without nasal colonization) were almost twice the rate in patients with only nasal colonization at discharge. The survival probability for patients in cohorts A and B was consistently lower than that for patients in cohort C, with the steep decline in the survival curves indicating poor prognosis during the initial follow-up period. These results suggest that surviving a MRSA infection at the time of hospitalization, regardless of nasal colonization at discharge, may be a marker of long-term poor health and adverse outcomes. Indicators suggestive of morbidity such as additional hospitalization within the past 6 months and histories of cancer or haemodialysis, were expectedly

associated with poorer survival. Interestingly, being discharged with any kind of surgical wounds was protective against mortality in study veterans in the follow-up period. One explanation for patients' improved survival post-discharge could be an improvement in their clinical status over time, after having survived the high-risk period immediately following inpatient surgery. We wish to emphasize that it is not our intention to establish a cause-and-effect relationship between MRSA infection and long-term mortality. However, our findings do suggest that in-hospital MRSA infection is an independent predictor of post-discharge mortality after controlling for other comorbidities, underscoring the importance of infection control in acute healthcare settings.

Consistent electronic documentation of patient medical records ensured that we were able to identify all patients having a MRSA infection during at least one previous hospitalization, MRSA colonization of their nares on at least one discharge, or both. Because the majority of the veterans who have ever used VA healthcare continue to receive most of their care within the VA network [34], we most likely did not lose any patients to follow-up. Patient mortality was ascertained from the Veterans Benefits Administration's (VBA) Beneficiary Identification Records Locator Subsystem (BIRLS) Death File, in conjunction with the Medicare Vital Status File, the Social Security Administration's Death Master File (SSA DMF), and the VHA Medical SAS Inpatient Datasets (MSID). The sensitivity and specificity of classifying veterans as deceased using these sources compared to the gold standard of the National Death Index (NDI) have been established at 98·3% and 99·8%, respectively [35]. Because the outcome measures for our analyses were all-cause mortality and time until death, the potential for misclassification was negligible. Patients in this study had a follow-up period of almost 4 years, allowing us to examine long-term survival after hospital discharge in those with a MRSA infection at the time of hospitalization and/or colonization of their anterior nares.

Our study is not without limitations. First, it was based on a population of veterans who were older and primarily male. They may have had differing underlying factors compared to the general population, thereby attenuating our study's external validity. Next, we relied upon physician diagnoses documented in medical records for clinical information. For example, history of stroke documented in 52 patients was associated with a lower mortality rate after adjusting for other risk factors, a finding that remains unexplained. It is possible that this history may not have been accurately recorded. MRSA colonization was classified as a positive microbiological culture from only the anterior nares, and it is likely that we misclassified some patients colonized in other anatomical sites such as the groin. Moreover, because CHROMagar is less reliable than PCR in patients with a low MRSA nasal burden [36], it is possible that patients classified as having only an infection at the time of hospitalization (cohort B), were also nasally colonized at discharge. We studied post-discharge mortality in patients having only a MRSA infection and/or nasal colonization, and can therefore not comment on whether a similar phenomenon might be observed with methicillin-sensitive *Staphylococcus aureus* (MSSA) infections. Because we did not perform molecular typing of MRSA isolates, we cannot comment on the impact of strains such as USA300 on long-term post-discharge mortality. USA300 bacteraemia has recently been associated with increased in-hospital mortality in one study [37], but lower mortality compared to other genotypes in another [38]. Due to limited resources, we were unable to collect demographic and clinical data on the sample of patients without a MRSA infection or nasal colonization. However, we estimated a crude post-discharge mortality rate using this systematic sample in an effort to provide the reader with some information on baseline mortality. We acknowledge that the availability of detailed information on this group of veterans would have helped us make additional comparisons of adjusted rates.

Despite these limitations, our study exploring post-discharge mortality over a long follow-up period contributes to the current epidemiological literature on MRSA infection and colonization. Surviving MRSA infection, regardless of nasal colonization, adversely affects mortality particularly in the initial years after discharge. Efforts in infection control within hospitals and healthcare settings continue to be essential.

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DECLARATION OF INTEREST

None.

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