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Mortality associated with in-hospital bacteraemia caused by *Staphylococcus aureus*: a multistate analysis with follow-up beyond hospital discharge

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Objectives: The main objective was to study the impact of in-hospital bacteraemia caused by *Staphylococcus aureus* on mortality within 90 days after admission. We compared methicillin-resistant *S. aureus* (MRSA) with methicillin-susceptible *S. aureus* (MSSA).

Patients and methods: The study population consisted of adult residents of Tayside, Scotland, UK, from 1 January 2005 to 30 September 2006 who had a new admission to Ninewells Hospital between 1 July 2005 and 30 June 2006. All patients ($n=3132$) in the same wards as the patients infected with *S. aureus* were included. We addressed key weaknesses in previous studies by using a cohort design and applying a multistate model, which addressed the temporal dynamics. Critically, the model recognized that death and discharge from the hospital are competing events and that delay in discharge independently increases the risk of death.

Results: The cohort included 3132 patients, of whom 494 died within 90 days after admission, 34 developed MRSA bacteraemia and 26 MSSA bacteraemia in the hospital. In comparison with patients without *S. aureus* bacteraemia, the death hazard was 5.6 times greater with MRSA [95% confidence interval (CI) 3.36–9.41] and 2.7 times greater with MSSA bacteraemia (95% CI 1.33–5.39). After adjustment for co-morbidity, hospitalization, age and sex, the death hazard was 2.9 times greater with MRSA (95% CI 1.70–4.88) and 1.7 times greater with MSSA bacteraemia (95% CI 0.84–3.47).

Conclusions: Time-dependent models such as the proposed multistate model are necessary to address the temporal dynamics of admission, infection, discharge and death. The impact of *S. aureus* bacteraemia on mortality should be considered on two levels: the burden of disease, i.e. nosocomial infection with *S. aureus* bacteraemia, and the burden of resistance to methicillin.

Keywords: statistical modelling, antibiotic resistance, event history analysis, *S. aureus*, hospital epidemiology

Introduction

Antimicrobial resistance has been recognized as a major public health problem for many decades, and methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most virulent micro-organisms causing bacteraemia in hospitalized patients.[1–5] Nonetheless, previous studies have produced conflicting results about the impact of MRSA on mortality.

We designed a cohort study to address five critical weaknesses in the design and analysis of previous studies. Firstly, the comparison within most case–control and cohort studies has been between patients with MRSA and those with methicillin-susceptible *S. aureus* (MSSA) bacteraemia. However, the exposure variable should be *S. aureus* bacteraemia, with a comparison made between cases with either MRSA or MSSA bacteraemia and comparators without *S. aureus* bacteraemia. Secondly, the time-dependency of exposure has often been either neglected or inadequately addressed, which has resulted in time-dependent bias.[6] Thirdly, only a few previous analyses have accounted for the competing risks of death and discharge

from hospital following infection.[7,8] This has previously been shown to be critical in the analysis of infections in the intensive care unit.[9] Fourthly, most previous studies have only measured inpatient mortality,[10–13] but further information about general mortality beyond hospital stay is likely to have substantial added value, especially from the patient's perspective. Finally, most studies have used crude statistical models that do not reflect the time-dependency issue of the data.

This study was carried out as part of the EU project 'Burden of Resistance and Disease in European Nations' (BURDEN) and focused on the impact of *S. aureus* on mortality (burden of disease) and on the comparison between MRSA and MSSA (burden of resistance).[14]

Materials and methods

Study design

The study used the unique capacity for record linkage in epidemiological research in Scotland.[15] The study population consisted of adult residents of Tayside, Scotland, UK, from 1 January 2005 to 30 September 2006 who had a new admission to Ninewells Hospital between 1 July 2005 and 30 June 2006. The cohort enrolled retrospectively the first episode of patients from this population who were admitted to wards with at least one case of *S. aureus* bacteraemia during the study period. *S. aureus* bacteraemia was ascertained by clinical sampling. There was no attempt to influence the clinical decision to take blood cultures. We focused on hospital-acquired (HA) bacteraemia and included only patients who stayed for 2 or more days in the hospital. At the time of the study there was no routine screening for MRSA. Reporting of MRSA bacteraemia has been mandatory in Scottish hospitals since 2003.[16] Mortality up to 30 September 2006 was derived from data in the national registry of deaths. Thus, our outcome, death within 90 days after admission, was obtained for all patients. The following baseline variables were collected as potential confounders: age in years (continuous), sex (male/female) and the Charlson co-morbidity index (continuous score). Hospitalization was defined as the time from admission until discharge and only the first episode within 90 days was considered.

Ethics Committees do not usually need to review studies that use data that do not require contact with individual patients. Since the BURDEN project is a clinical research project, approval from NHS R&D was obtained.

Statistical methods

Multistate model and concept of hazards

A multistate model[17] with seven states was developed (Figure 1). A transition, i.e. a change of state, was displayed as an arrow and represented the hazard of moving between two states. The full statistical model specified the state structure and the form of the hazard function for each possible transition. The concept of hazards can be explained as follows. The smallest time unit in a typical hospital setting is the *day*. The hazard rates between two states (e.g. states 1 and 2) are generally time dependent. For a simplified interpretation, a constant hazard of 5% was presumed for moving from state 1 to state 2 in a given time interval. This meant that the *daily* risk of entering state 2 from state 1 was 5%. Since the risk was calculated *per day*, the cumulative hazard plots were therefore reasonable quantities with a straightforward interpretation.

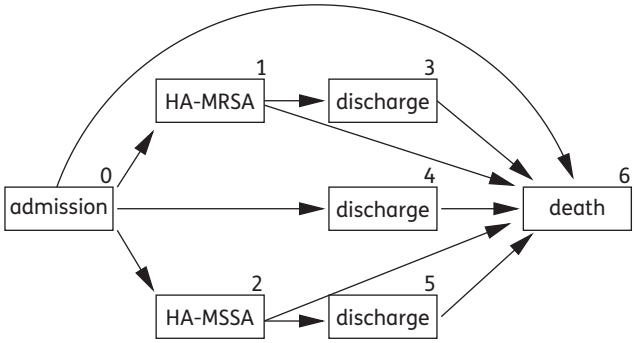

Figure 1. Multistate model with seven states. Each arrow represents a transition hazard of moving from one state to another. Once admitted to hospital, each patient is in one of the following states at each timepoint: 0, admission without HA *S. aureus*; 1, HA-MRSA; 2, HA-MSSA; 3, discharge after HA-MRSA infection; 4, discharge without HA *S. aureus* infection; 5, discharge after HA-MSSA infection; 6, death. A patient can only move between the states that are given in Figure 1 according to the arrows.

Regression modelling on the death hazard rate

To obtain hazard ratios, we studied three Cox regression models with progressively increasing adjustment. The first model had two time-dependent covariates (HA-MRSA and HA-MSSA). Then, we further adjusted for baseline factors such as age, sex and the Charlson co-morbidity index. Finally, we further adjusted for hospitalization (first episode) as a time-dependent covariate. In all models, the time from the day of admission until the day of death was modelled. Patients who survived the 90-day window were artificially censored.

Software

The cumulative hazards for multistate models were calculated using the R-package mvna,[18] which is available at http://cran.r-project.org.[19] The regression calculations were performed with the procedures PROC PHREG from the statistical software SAS system version 9.2. The level of significance was set to $\alpha = 5\%$.

Results

The cohort included 3132 patients, of whom 34 developed MRSA bacteraemia and 26 MSSA bacteraemia in hospital. Detailed characteristics of study participants are given in Table 1. The crude in-hospital mortality was 6.5% whereas the 90 day mortality was 15.8% (Table 2).

The cumulative hazards and the corresponding risk sets are displayed in Figure 2 and Figure 3. Once a patient enters hospital, he or she is confronted with four competing types of hazard: the hazard of being discharged without an HA *S. aureus* infection (the daily risk is about 15% at the beginning of the stay and later decreasing), the hazard of dying in the hospital without an HA *S. aureus* infection (about 0.5%), or the hazard of acquiring an HA-MRSA (about 0.1%) or HA-MSSA (about 0.05%).

Once a patient was discharged without HA *S. aureus*, he or she was subject to the hazard of dying *after being discharged* (about 0.12%). Once a patient acquired an HA-MRSA (HA-MSSA) infection, there were two competing hazards affecting the patient: dying during the first episode (about 2%, for

Table 1. Characteristics of study participants

General		
Number of patients	3132	
Length of hospital stay (of first episode) in days, median (IQR)	7 (4–13)	
Baseline risk factors		
Age, mean (SD)	65.5 (17.3)	
Charlson co-morbidity index, mean (SD)	1.9 (2.3)	
Female, *n* (%)	1450 (46.3)	
Time-dependent risk factors	**Number of events (%)**	**Time in days to *S. aureus* bacteraemia,[a] median (IQR)**
HA-MRSA	34 (1.09)	14.5 (9–34)
HA-MSSA	26 (0.83)	7.5 (5–12)

IQR, interquartile range.
[a]Retrospectively calculated, conditioning on infection status.

Table 2. Crude mortality proportions [number of deaths/total number (%)]

	In hospital[a]	90 days after admission
HA-MRSA	12/34 (35.3%)	15/34 (44.1%)
HA-MSSA	5/26 (19.2%)	8/26 (30.8%)
No HA *S. aureus*	186/3072 (6.1%)	471/3072 (15.3%)
Total	203/3132 (6.5%)	494/3132 (15.8%)

[a]During first episode.

HA-MSSA about 0.5%) or being discharged alive (about 2%, for HA-MSSA about 2%).

Comparisons via hazard ratios

The first model revealed that patients infected with HA-MRSA might have a more than five times greater hazard of dying compared with those who were not infected with HA *S. aureus* (Table 3). Patients with the susceptible type (HA-MSSA) had an almost three times higher hazard of dying. Comparing the resistant (HA-MRSA) with the susceptible (HA-MSSA) type, the hazard ratio was about 2, but was not statistically significant. In order to control for potential confounders, the impact of *S. aureus* bacteraemia was reflected in models 2 and 3 (Table 3). Hospitalization turned out to have the strongest confounding effect and the interpretation is as follows. If (only) this variable is included in the model together with the *S. aureus* variables, one averages two effects: first, one compares hospitalized *S. aureus* patients with patients without *S. aureus* who stay in the hospital; second, one compares discharged *S. aureus* patients with patients without *S. aureus* who were discharged from the hospital.

Discussion

We developed an appropriate multistate model to study the impact of nosocomial infections on mortality. Particular attention was given to the temporal dynamics during and after the first hospital stay to address the (additional) time-dependent hospitalization effect on mortality. This cohort study showed that the length of hospital stay affected the study of bacteraemia caused by *S. aureus* in hospital in two different ways: patients with *S. aureus* bacteraemia had already stayed a couple of days in hospital before the infection occurred and, once they were infected, their hospital stay was furthermore considerably increased. These facts are crucial since hospitalization has a very strong impact on the death hazard or the other way around: once discharged from the hospital, the risk of dying is considerably reduced because discharged patients are usually in a better health condition. Taking this fact into account we demonstrated the risk of death attributable to MRSA bacteraemia. This effect was still present after adjusting for several confounders. HA-MSSA was also associated with an increased mortality, but this effect was not significant after adjusting for hospitalization and other risk factors. We found a small difference between MRSA and MSSA (burden of resistance), which was not statistically significant.

The major strengths of this study are 4-fold. Its first strength is related to the study design: we used a full and complete cohort, and thus no matching was required. This design has known advantages over the case–control design, which has often been used in this epidemiological context.[20] Secondly, since patients' data were linked to the national death registry, survival data were available beyond hospital discharge. Thus, mortality could be studied in the same time window for the entire cohort. Thirdly, most studies only compared MRSA with MSSA patients,[10,11] whereas we were able to offer a comparison of *S. aureus* patients with patients who did not have *S. aureus* bacteraemia. Fourthly, the statistical methods we used took HA *S. aureus* as time-dependent exposures into account. This approach is superior to the crude approach using logistic regression.[9] The special focus on the timing of events (exposure as well as the outcome) is important since the time of *S. aureus* acquisition in hospital is usually quite late. Last, but not least, our findings show that MRSA bacteraemia seems to occur somewhat

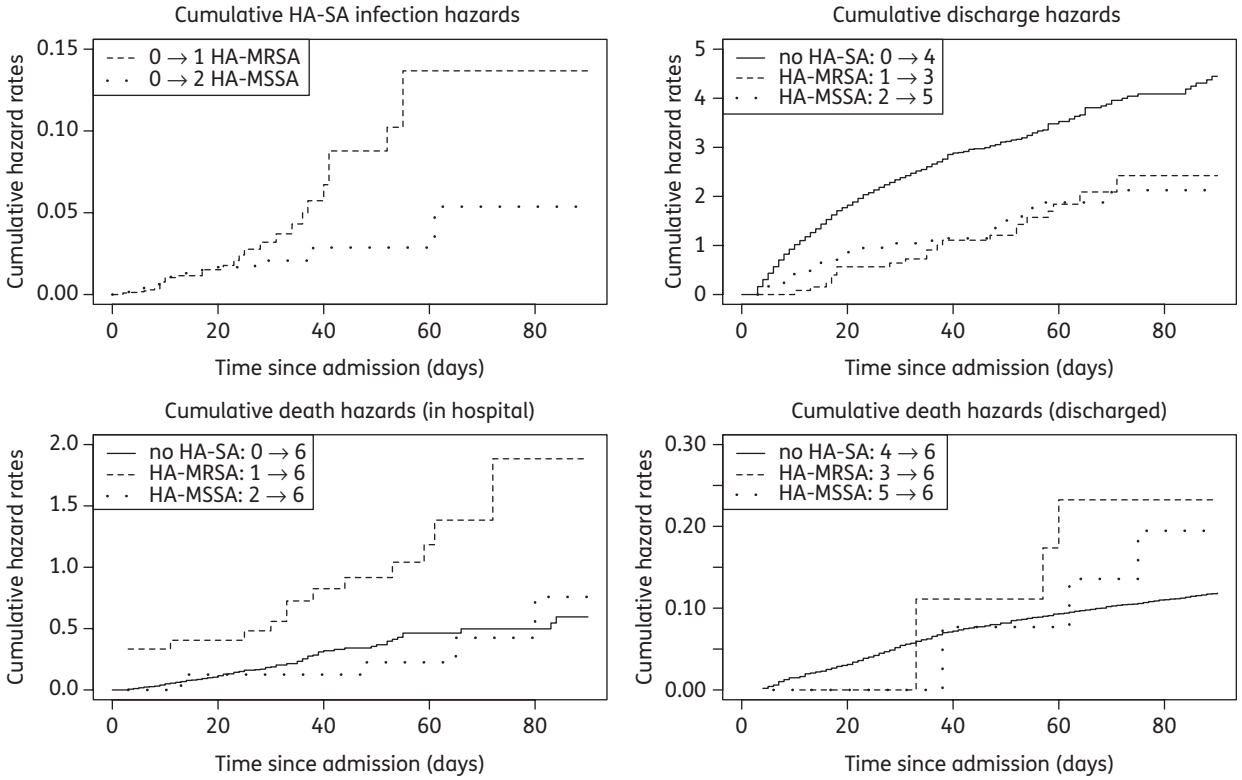

Figure 2. Cumulative transition-specific infection, discharge and death hazard rates estimated by the method of Nelson-Aalen. The slope of the cumulative hazard is the actual hazard, i.e. the daily risk of moving from one state to the other. Note that the scales on the *y*-axes differ.

Table 3. Impact of HA-MRSA and HA-MSSA on mortality: time-averaged hazard ratios (HRs) (estimated by multivariable regression)

	HR (95% CI)		
	model 1[a]	model 2[b]	model 3[c]
HA-MRSA versus no HA *S. aureus*	5.62 (3.36–9.41)	4.68 (2.79–7.84)	2.88 (1.70–4.88)
HA-MSSA versus no HA *S. aureus*	2.68 (1.33–5.39)	2.87 (1.43–5.80)	1.70 (0.84–3.47)
HA-MRSA versus HA-MSSA	2.10 (0.89–4.95)	1.63 (0.69–3.85)	1.69 (0.72–4.00)

[a]HA-MRSA and HA-MSSA as time-dependent covariates.
[b]As model 1 plus adjustment for age (continuous), gender and Charlson co-morbidity index (continuous).
[c]As model 2 plus adjustment for being hospitalized (first admission) as time-dependent covariate.

later after hospital admission than MSSA bacteraemia (Figure 4), a finding that is consistent with previous studies.[12,21,22] Our results also have important implications for future studies that will use inpatient mortality as the primary outcome measure. In our results, the hazard rate with which patients with *S. aureus* bacteraemia were discharged alive from the hospital was greatly reduced compared with the rate for those without bacteraemia (Figure 2, top right). Consequently, *S. aureus* patients might stay much longer in hospital and will therefore have an additional risk of death in hospital for every additional day of hospitalization. This indirect effect on mortality due to extended length of hospital stay is a well-known phenomenon in competing risks analyses.[9,23]

Our study had limitations. It was a cohort study, but data were collected retrospectively. Thus, we could only adjust for confounders that were available and we did not collect any variables that reflect management (e.g. early appropriate antibiotic treatment). However, we believe that the most important confounders were accounted for. Further, the number of *S. aureus* patients was relatively small to run a stable analysis: in particular, survival beyond discharge from hospital could not reliably be analysed since many *S. aureus* patients had already died in hospital.

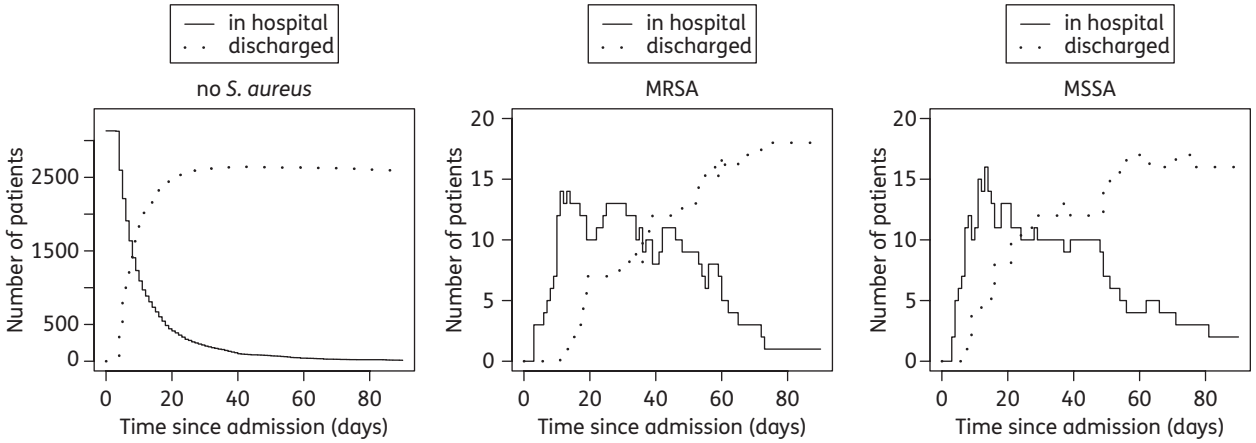

Figure 3. Risk sets (numbers of patients at risk of death) for each state defined in Figure 1. Note that the scales on the *y*-axes differ.

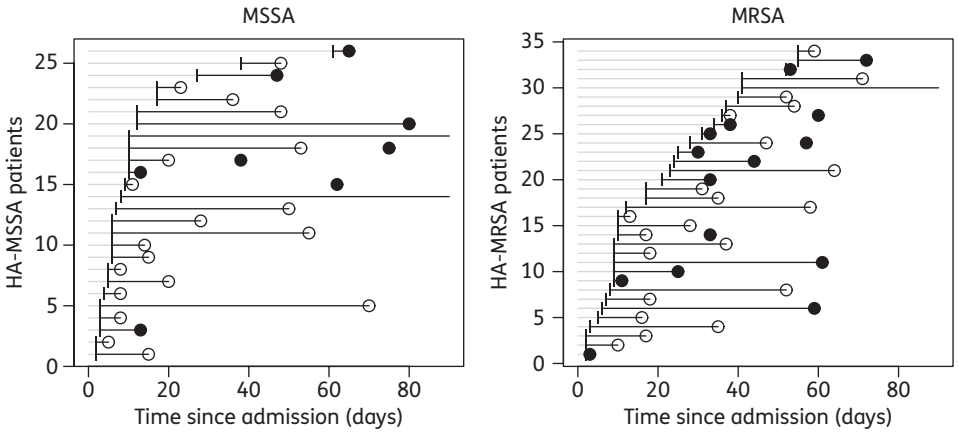

Figure 4. Each line represents a patient (grey, uninfected; black, infected) and the circles represent status at the end of the first episode in hospital (open circles, alive; filled circles, dead). Patients may die after being discharged from hospital (first episode); if this happens this is also displayed as a filled circle. Only *S. aureus* patients are displayed. For example, in the left-hand panel, Patient 17 acquires HA-MSSA at day 10, is discharged (alive) at day 20 and dies 38 days after admission.

To compare our results with those from previous studies, we would like to refer to two meta-analyses that compared in-hospital mortality associated with MRSA and MSSA bacteraemia.[10,11] Using nine studies, Whitby *et al.*[11] calculated a pooled death odds ratio (OR) of 2.03 [95% confidence interval (CI) 1.55–2.65] comparing MRSA with MSSA patients. Cosgrove *et al.*[10] calculated a pooled death OR of 1.93 (95% CI 1.54–2.42) on the basis of 31 studies. To make these measures comparable to our setting, we calculated the OR due to hospital mortality: OR=2.45 (95% CI 0.69–8.70). The major weakness of all the studies in these reviews is that they ignored the timing of events. Hurley pointed out that in most studies the length of stay before onset of bacteraemia was longer for patients with MRSA compared with those with MSSA infection,[24,25] and mortality rate seemed to increase with length of stay.

In conclusion, we demonstrated an increased mortality associated with MRSA bacteraemia in comparison with MSSA bacteraemia that cannot be explained by differences in pre-infection length of stay or in prolongation of hospital stay after the onset of infection. This innovative multistate model can be applied to any other nosocomial infections. The 'hospitalization effect' on mortality should be taken into account in survival studies in hospital epidemiology.

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Transparency declarations

None to declare.

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