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SHORT REPORT
Impact of *vanB* vancomycin-resistant enterococcal bacteraemia analysed as a time-varying covariate on length of hospital stay

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SUMMARY

The impact of *vanB* vancomycin-resistant enterococci (VRE) bacteraemia on length of stay (LOS) in hospital, after adjusting for the time-varying nature of enterococcal bacteraemia (variable onset of bacteraemia post-admission), is unknown. Survival analyses (time-varying Cox and competing risks regression) were performed on *vanB* VRE bacteraemia patients, matched 1:1 with vancomycin-susceptible enterococci bacteraemia patients to determine the factors associated with LOS in these patients. In Cox regression analysis, *vanB* VRE bacteraemia, intensive-care-unit admission, Charlson co-morbidity index score $\geqslant 4$, and an increase in the time to receive appropriate antibiotics were associated with prolonged LOS. Competing risks regression which accounts for the influence of in-patient mortality on the ability to observe the event discharge alive from hospital suggests that, *vanB* VRE bacteraemia was not significantly associated with prolonged LOS. For the first time, the rate of discharge from hospital in patients with *vanB* VRE bacteraemia has been quantified.

Key words: Antibiotic resistance, bacterial infections, *Enterococcus*, epidemiology.

Vancomycin-resistant enterococcal bacteraemia is a healthcare-associated infection that has been linked to prolonged length of stay (LOS), and higher costs of hospitalization [1, 2]. Previous studies have analysed the effect of bacteraemia caused by *vanA* and *vanB* vancomycin-resistant enterococci (VRE) on LOS using multivariable linear or quantile regression methods [1, 2]. These methods do not account for the time-varying nature of healthcare-associated infections [3]; that is, during their hospital stay, a patient could acquire VRE or vancomycin-susceptible enterococci (VSE), the latter used as a comparator [1, 2]. As such, results of these studies are subject to time-dependent bias (bias resulting from assuming that variable onset of infection after hospital admission was known at the start of observation) [4], and may lead to overestimation of the impact of VRE bacteraemia on LOS [5]. In Australia, the predominant VRE genotype is *vanB* [6], and the impact of *vanB* VRE bacteraemia on LOS in hospital, after accounting for the time-varying nature of enterococcal bacteraemia, is unknown.

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LOS is the time from initial admission to discharge from hospital and is therefore amenable to time-to-event (i.e. survival) analysis [3]. To overcome the time-dependent bias associated with linear and quantile regression analyses in earlier studies [1, 2], we utilized survival analysis with a time-dependent variable to determine factors associated with LOS in patients with enterococcal bacteraemia. In general terms, such an analysis is applicable when the presence or absence of a condition at baseline is not known and the onset of the condition is time-dependent [5]. It allows exploration of the association between a studied variable that may change over time (e.g. onset of enterococcal bacteraemia) and an outcome (e.g. LOS). To the best of our knowledge, this type of analysis has not been used to investigate the factors impacting LOS in patients with enterococcal (VRE and VSE) bacteraemia.

We performed survival analyses (Cox proportional hazards and competing risks regression) on patients admitted between January 2002 and March 2010 (inclusive) to two tertiary teaching hospitals in Melbourne, Australia. Patients with LOS >2 days and at least one positive *vanB* VRE or VSE blood culture detected ⩾48 h after hospital admission were included. Those aged <18 years or who were pregnant were excluded. Patients from the same institutions who had *vanB* VRE isolated from blood were matched 1:1 with VSE patients according to date of admission (within 2 years), and where possible, unit of admission. Where more than one VSE patient was eligible for matching, the VSE patient was randomly chosen (without prior knowledge of patient outcome) from the list of eligible patients. Severity of illness on the day of positive blood culture was measured as the presence or absence of sepsis [7]. Patient co-morbidities were determined using the Charlson co-morbidity index (CCI) [8]. Additional details on methods and definitions have been presented in an earlier analysis which used quantile regression to determine the factors associated with LOS in patients with enterococcal bacteraemia [2]. For this study, we utilized the same group of patients with enterococcal bacteraemia, excluding those with LOS <48 h.

Survival analysis with adjustment for patient matching (cluster option in Stata) was utilized to assess the impact of *vanB* VRE bacteraemia, relative to VSE bacteraemia, on the rate of discharge from hospital. We explored all possible interactions between variables in the final models. Hazard proportionality was assessed through analysis of scaled Schoenfeld residuals. All P values were two-tailed and $P<0{\cdot}05$ was considered significant. Analyses were performed with Stata v. 12.0 (StataCorp, USA).

The main outcome of interest was LOS after hospital admission, analysed as the event discharge from hospital. In the Cox regression analysis, patients were censored when they experienced in-hospital mortality and censoring was originally assumed to be non-informative; in line with previous studies [3, 9]. The analysis was adjusted for variables associated with risk of in-hospital mortality, i.e. days to appropriate antibiotics, patient co-morbidities and admission to the intensive care unit (ICU) [2], to minimize bias due to the assumption that censoring was non-informative. To assess the validity of this censoring assumption, we ran competing risks regression (an extension of Cox proportional hazards regression) where in-patient death was the competing risk. This permitted assessment of whether in-patient mortality was likely to interfere with the study's ability to observe the outcome of interest (non-death discharge).

A total of 152 bacteraemia patients (76 *vanB* VRE matched with 76 VSE patients) were included in the study. In-hospital all-cause mortality was observed in 59 (39%) patients and 93 (61%) patients were discharged alive from hospital. The median total LOS was 35 [interquartile range (IQR) 23·5–50·5] and 29·5 (IQR 18–45·5) days in VRE and VSE bacteraemia patients, respectively. The corresponding LOS prior to bacteraemia was 18·5 (IQR 10·5–26) and 12 (IQR 6–27) days, respectively. The median time from positive blood culture to discharge alive from hospital for patients with *vanB* VRE and VSE bacteraemia was 21 (IQR 12–34) and 16 (IQR 11–24) days, respectively. Table 1 shows the results of univariable and multivariable Cox and competing risks regression analyses on factors associated with being discharged from hospital. There were no significant interactions for variables in the final multivariable model. Hazard ratios (HRs) represent the rate of discharge in one group compared to another group, with HR <1·00 indicating a reduction in rate of discharge (i.e. increased LOS).

Cox regression analysis of patients with enterococcal bacteraemia identified four factors associated with decreased rate of discharge from hospital (Table 1). *VanB* VRE bacteraemia was associated with a 41% decrease in the rate of being discharged from hospital [adjusted hazard ratio (aHR) 0·586, 95% confidence interval (CI) 0·392–0·877]. The

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Table 1. *Factors associated with the event, discharge from hospital, in patients with enterococcal bacteraemia*

	Time-varying Cox regression analysis				Time varying competing risks regression analysis			
	Univariable		Multivariable		Univariable		Multivariable	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (10-year units)	1·188 (1·025–1·378)	0·022	1·130 (0·981–1·303)	0·090	1·017 (0·884–1·171)	0·812	0·889 (0·769–1·029)	0·114
Female	1·061 (0·690–1·631)	0·788			1·131 (0·753–1·697)	0·553		
ICU admission	0·340 (0·222–0·521)	<0·001	0·343 (0·222–0·531)	<0·001	0·288 (0·181–0·460)	<0·001	0·283 (0·167–0·479)	<0·001
Charlson co-morbidity index score ⩾4	0·915 (0·615–1·363)	0·663	0·659 (0·453–0·960)	0·030	0·741 (0·502–1·092)	0·129	0·578 (0·380–0·880)	0·011
Any infection (other than enterococcal bacteraemia)	0·450 (0·282–0·718)	0·001	0·796 (0·510–1·243)	0·316	0·610 (0·387–0·961)	0·033	0·966 (0·536–1·742)	0·910
Enterococcus species								
E. faecalis	Reference				Reference			
E. faecium	0·481 (0·303–0·764)	0·002			0·473 (0·320–0·700)	<0·001		
E. casseliflavus, E. galinarum or *E. durans*	0·457 (0·029–7·187)	0·578			0·596 (0·039–9·012)	0·709		
E. faecalis and *E. faecium*	—	—			—	—		
VanB VRE bacteraemia	0·633 (0·437–0·917)	0·016	0·586 (0·392–0·877)	0·010	0·730 (0·469–1·136)	0·163	0·770 (0·490–1·208)	0·255
Sets of positive cultures ⩾2	0·638 (0·410–0·992)	0·046			0·640 (0·416–0·984)	0·042		
Sepsis	0·601 (0·375–0·963)	0·034	0·899 (0·595–1·356)	0·611	0·432 (0·273–0·682)	<0·001	0·616 (0·368–1·031)	0·065
Days to appropriate antibiotic therapy	0·972 (0·830–1·139)	0·729	0·987 (0·978–0·996)	0·004	0·982 (0·913–1·056)	0·625	0·987 (0·975–0·998)	0·021

HR Hazard ratio; CI, confidence interval; ICU, intensive-care unit; VRE, vancomycin-resistant enterococci.

remaining three factors were ICU admission (aHR 0·343, 95% CI 0·222–0·531), a higher burden of patient co-morbidities as quantified by CCI (aHR 0·659, 95% CI 0·453–0·960), and an increase in the time to appropriate antibiotic therapy (aHR 0·987, 95% CI 0·978–0·996).

In the competing risks regression analysis, *vanB* VRE bacteraemia was not significantly associated with rate of discharge (aHR 0·770, 95% CI 0·490–1·208). Compared to VSE patients, VRE bacteraemia patients were not more likely to die as an in-patient; 33 (43%) and 26 (34%) of VRE and VSE bacteraemia patients died in hospital, respectively. The large in-patient death rate of 39% and results of the competing risks model suggest that in-patient mortality may affect the power of the Cox regression model to identify the true size of the association between *vanB* VRE bacteraemia and the rate of discharge from hospital. Similar to the Cox regression analysis, ICU admission (aHR 0·283, 95% CI 0·167–0·479), a higher burden of patient co-morbidities as quantified by the CCI (aHR 0·578, 95% CI 0·380–0·880) and an increase in the time to appropriate antibiotic therapy (aHR 0·987, 95% CI 0·975–0·998) were associated with reduced discharge rate in the competing risks analysis. For VRE bacteraemia, monotherapy (linezolid, teicoplanin) or combination therapies with these and other antibiotics were administered and for VSE bacteraemia, monotherapy (vancomycin, penicillins) or combination therapies with these and other antibiotics were used [2]. Adjustment for the competing risk of in-patient mortality influenced the association between sepsis and rate of discharge (although the association was not statistically significant). Patients with sepsis are more severely ill and likely to die in hospital.

It is important to compare and contrast findings from quantile, Cox, and competing risks regression analyses. Quantile regression provides an easily interpretable quantification of factors associated with a continuous outcome for a skewed dataset [10]. Using this method, we have previously reported that *vanB* VRE bacteraemia is associated with increased LOS [2]. When quantile regression was performed on the patient population described here, *vanB* VRE bacteraemia was also associated with increased LOS (data not shown). However, quantile regression was unable to generate an estimate of the rate of discharge from hospital in patients with *vanB* VRE compared to VSE bacteraemia. A significant advantage of the survival analysis method in the present study is that it generated an estimate of the rate of discharge that may be converted to a probability value, and employed in economic evaluations of treatment options for *vanB* VRE bacteraemia. As competing risks regression controls for the effect of in-patient mortality on the rate of discharge from hospital, it is probably a more accurate estimate of the impact of VRE bacteraemia on LOS, compared to Cox regression analysis. In contrast to quantile regression that adjusted for in-patient mortality [2], competing risks regression accounted for the time-varying nature of enterococcal bacteraemia.

Furthermore, in contrast to the present survival analysis, a previous study using quantile regression analysis [2] did not identify ICU admission, patient co-morbidities and time to appropriate antibiotic therapy as factors associated with LOS. When quantile regression was performed on the same patient population used in this study, the aforementioned factors were not identified to have significantly influenced LOS (data not shown), highlighting the need to select the optimal analytical technique when assessing factors associated with LOS for healthcare-associated infections.

In summary, competing risks regression analysis revealed that *vanB* VRE bacteraemia was not significantly linked to prolonged LOS. Moreover, our findings highlight the importance of timely initiation of appropriate therapy for enterococcal bacteraemia. Future studies on factors associated with LOS (time-to-event data) for other healthcare-associated infections should consider survival analysis as it accounts for time-dependent bias.

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DECLARATION OF INTEREST

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