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Original research article

Excess mortality due to pandrug-resistant *Acinetobacter baumannii* infections in hospitalized patients

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SUMMARY

Background. Pandrug-resistant *Acinetobacter baumannii* (PDRAB) is increasingly being reported as a nosocomial pathogen worldwide but determining its clinical impact is challenging.

Aim. To assess the spectrum of excess mortality attributable to PDRAB infection in acute care settings.

Methods. This 4-year cohort study was conducted in a tertiary-care referral hospital in Greece to estimate excess in-hospital mortality due to PDRAB infection by comparing patients infected to those colonized with PDRAB by means of competing risks survival analysis.

Findings. The study cohort comprised 91 patients (median age 67 years, 77% men). For most patients, PDRAB was first isolated in the intensive care unit (ICU) (n=51; 57%) or following ICU discharge (n=26; 29%). Overall in-hospital mortality was 68% (95% confidence interval (CI) 57.5%-77.5%). PDRAB-infected patients (n=62; 68%) and PDRAB-colonized patients (n=29; 32%) had similar baseline characteristics, but the absolute excess risk of 30-day mortality in infected patients compared to colonized patients was 34% (95%CI 14%-54%). Multivariable competing risks regression showed that PDRAB infection significantly increased the daily hazard of 30-day in-hospital death (cause-specific hazard ratio (csHR) 3.10; 95%CI 1.33 – 7.21) while simultaneously decreasing the daily rate of discharge (csHR 0.24; 95%CI 0.08 – 0.74), thereby leading to longer hospitalization. Stronger effects were observed for bloodstream infections.

Conclusion. New effective antimicrobials would be expected to prevent mortality in 1 of every 3 patients treated for PDRAB infection and reduce their length of hospitalization. However, available therapeutic options remain extremely limited and emphasis on preventing healthcare-associated transmission of PDRAB is ever more important.

Keywords: Pan-drug resistant bacteria; *Acinetobacter baumannii*; hospital epidemiology; survival; competing risks.

Introduction

Pandrug-resistant (PDR) gram-negative bacteria, including PDR *Acinetobacter baumannii* (PDRAB), are increasingly being reported in several countries worldwide [1]. PDR organisms are typically isolated from patients in intensive care units (ICU) but intra- and inter-hospital dissemination, and even international spread, may be substantial [1]. Few data exist regarding the impact of PDRAB on clinical outcomes, particularly mortality. Pooling data from few case-reports and small case-series, all-cause mortality in patients with lower respiratory tract infection (LRTI) and bloodstream infection (BSI) caused by PDRAB is as high as 50% and 71%, respectively [1]. However, the spectrum of mortality attributable to PDRAB infection remains unclear and has not been investigated in large patient cohorts to date.

Patients affected by PDR infections are characterised by critical illness, multimorbidity, long hospital stay and exposure to multiple invasive procedures [1–3]. Therefore, even an effective antimicrobial treatment would only reduce the overall hospital mortality to the rate of non-infection-related mortality, which is already expected to be high in these patients. To determine the maximal potential impact of therapeutic interventions, it is necessary to estimate the excess mortality attributable to the infection, over and above other contributing factors [4]. One way to achieve this is by comparing all-cause mortality in patients infected with PDRAB to that observed in patients colonized but not infected with the same organism [5]. This is because non-infection-related mortality can be approximated in patients colonized with *A. baumannii*, who similarly to patients infected with *A. baumannii,* are typically severely ill with chronic underlying comorbidities requiring various interventions and intensive care [6,7]. Another important consideration when assessing the survival prospects of hospitalized patients is that in-hospital death and discharge (alive) act as competing events [8,9]. Failing to account for competing risks generally leads to overestimation of the cumulative mortality incidence [8,9].

In this study, we sought to assess the direct clinical impact of PDRAB infection by comparing patients infected with PDRAB to those colonized with PDRAB and by simultaneously examining the risks of in-hospital mortality and discharge (alive) by means of competing risks survival analysis.

Methods

Setting and study design

This cohort study was performed at the University Hospital of Heraklion, a 750-bed tertiary-care centre that serves ca. 70,000 patients per year and is the referral hospital for the island of Crete in Greece. The study cohort comprised all patients who were infected or colonized with PDRAB during their hospital stay, between January 2016 and December 2019. Patients were included in the study only once at the time of first occurrence of infection or colonization.

The hospital's Research Ethics Committee approved the study and waived the requirement for patient informed consent. The study is reported according to the STROBE recommendations [10].

Outcomes

The primary study outcome was time to in-hospital death from any cause within 30 days from PDRAB isolation. Secondary outcomes included in-hospital mortality at 90 days post culture [11] and on hospital discharge. Excess mortality attributable to PDRAB was defined as 30-day all-cause mortality in patients infected with PDRAB after subtracting 30-day all-cause mortality in patients colonized with PDRAB [5].

Study size

The sample size was calculated with the Fleiss method with continuity correction [12]. We assumed a baseline mortality risk of 20% in patients colonized with PDRAB versus 55% in patients infected with PDRAB [1]. To have 80% power to detect a difference of this magnitude with 95% confidence, we calculated that we required 87 patients (22 colonized and 65 infected).

Clinical data

Patient data were collected from electronic records, including: dates of admission and discharge, ward on admission and at time of PDRAB isolation, hospitalization in the previous year and outcome on hospital discharge. Infections were prospectively identified according to the ECDC criteria [13] as part of hospital-wide active surveillance coordinated by the hospital's Infection Control Committee. PDRAB isolation not fulfilling criteria for infection was considered to represent colonization. LRTI in this study includes pneumonia, bronchitis, tracheobronchitis, bronchiolitis, and tracheitis, without bacteraemia [13]. BSI includes primary infections (catheter-related BSI and BSI of unknown origin) and secondary infections [13].

Microbiology

Species identification and susceptibility testing were conducted with VITEK-2 (bioMérieux), based on the contemporary CLSI breakpoints [14]. Susceptibility to tigecycline was based on MIC ≤2mg/ml for *Enterobacteriaceae* [15]. Colistin resistance detected by VITEK-2 was confirmed by disk diffusion (50µg colistin disk, cut-off for susceptibility ≥15mm). *A. baumannii* was defined as PDR when it was non-susceptible to all antibiotics tested, including ampicillin/sulbactam, trimethoprim/sulfamethoxazole, ciprofloxacin, levofloxacin, aztreonam,

imipenem, meropenem, amikacin, gentamicin, tobramycin, tetracycline, minocycline, colistin and tigecycline. Newer antibiotics (cefiderocol, plazomicin or eravacycline) were not available during the study period.

Statistics

In-hospital mortality was described and compared over time between PDRAB colonized and PDRAB infected patients using cumulative incidence function plots [16]. Discharge alive from the hospital was treated as a competing event [8,9,16]. Competing risks regression models were used to adjust for baseline patient characteristics. To estimate the direct impact of PDRAB infection on each competing outcome of interest (i.e. discharge alive and in-hospital death), we used cause-specific hazard ratios (csHR) estimated with the Cox model. In this analysis, a low csHR for discharge alive reflects a low daily rate of discharge resulting in prolonged hospital stay. Additionally, we confirmed the prognostic association of PDRAB infection with the overall cumulative incidence of mortality by estimating subdistribution hazard ratios (sdHR) with the Fine-Gray model [9,16]. In all models, we adjusted for potential prognostic effects by age, sex, history of previous hospitalization, ICU admission, length of stay before PDRAB isolation, polymicrobial culture and infection site. None of the study variables had missing data. Statistical modelling was performed using STATA version 13 (STATA Corp., College station, TX, USA).

Results

Patients

152 PDRAB were isolated from 91 patients over the 4-year study period, for an overall incidence rate of 0.19 (95%CI 0.16 - 2.2) isolations per 1,000 patient-days. Patients were

typically middle-aged or elderly (median age 67 years; range 20 – 88 years), men (n=70; 77%), who were colonized (n=29; 32%) or infected (n=62; 68%) by PDRAB following a lengthy hospital stay (median 23 days; IQR 14-46 days). For most patients, PDRAB was first isolated during ICU stay (n=51; 57%) or following ICU discharge (n=26; 29%). However, 14 patients (15%) had no history of ICU admission.

Dominant infections were LRTI (n=28; 45% of all infections) and primary (n=14; 23%) or secondary (n=14; 23%) BSI. Sources of secondary BSI were LRTI (n=7), central line (n=3), soft tissue infection (n=2), concurrent LRTI and urinary tract infection (n=1), and intra-abdominal infection (n=1). Other cases (n=6; 10%) comprised 3 urinary tract infections, 1 surgical site infection, 1 concurrent urinary tract and surgical site infection and 1 soft tissue infection.

Clinical impact

Table I compares baseline characteristics and outcomes between patients infected and those colonized with PDRAB. The two groups were similar in age, sex, history of previous hospitalization, ward type, length of stay prior to PDRAB isolation and frequency of polymicrobial cultures.

However, in-hospital death rates at 30 days, 90 days and on discharge were significantly higher in patients infected with PDRAB (58%, 74% and 79%, respectively) compared to those colonized with PDRAB (24%, 41% and 45%, respectively). The excess 30-day mortality due to PDRAB infection was 34% (95%CI, 14%-54%). Estimated excess mortality remained unaltered when analysis time was extended to 90 days post culture (33%; 95%CI, 12%-54%) or hospital discharge (34%; 95%CI, 13%-55%). Excess 30-day mortality was substantially higher in BSI (51%; 95%CI 29%-73%) compared to LRTI (22%; 95%CI, -2% to 46%). Cumulative incidence function plots showed that the disparity in the rates of in-hospital death between patients with BSI and

those with LRTI was rapid in the first few days following infection onset and increased with time (**Figure 1)**.

Multivariable competing risks analysis (**Table II**) showed that, on any given day, patients who were currently alive in the hospital had more than a 3-fold increased hazard of dying in the hospital as opposed to patients colonized with PDRAB (csHR = 3.10; 95%CI 1.33 – 7.21). A similarly increased overall incidence of 30-day mortality was detected in the analysis of sub-distribution hazards (sHR = 3.37; 95%CI 1.33 – 8.52). The analysis of cause-specific hazards also quantified a significant decrease in the csHR for being discharged alive (csHR = 0.24; 95%CI 0.08 – 0.74); therefore, the daily rate of discharge (alive) was significantly lower for patients infected with PDRAB, leading to a longer hospitalization after being infected, compared to those who were colonized with PDRAB.

Site-specific analysis confirmed a much stronger prognostic effect for PDRAB BSI (sdHR = 6.17; 2.25 – 16.93) compared to PDRAB LRTI (sdHR = 2.54; 95%CI 0.85 – 7.57). These effects attenuated but remained significantly high when analysis was extended to 90 days after PDRAB isolation (**Table III**). For both infection sites, we found decreased csHR for hospital discharge, that is, increased chances of prolonged hospital stay. Restricting analysis to 30 days following infection onset did not allow us to quantify the effect of BSI on length of stay because no patient with BSI in our cohort was discharged alive prior to day 30. Nevertheless, by extending analysis time to 90 days, the substantial impact that both BSIs (csHR = 0.05; 95%CI 0.01 – 0.42) and LRTIs (csHR = 0.20; 95%CI 0.06 – 0.67) had on lowering the daily rate of discharge became evident. Apart age (sdHR = 1.73; 95%CI 1.33 – 2.26), no other patient-related characteristic had substantial prognostic effect.

Discussion

We assessed the direct clinical impact of PDRAB infection by comparing a cohort of patients infected with PDRAB with a control cohort of patients colonized with PDRAB. Given the severe underlying condition of these patients, the overall in-hospital mortality was high in both cohorts (79% and 45%, respectively). By definition, any treatment given to PDRAB infected patients did not include antimicrobials matching the in vitro susceptibility of the pathogen. The absolute excess 30-day mortality due to PDRAB infection was 34%, suggesting that if new effective antibiotics were available we would expect to prevent hospital mortality in one of every three treated patients.

Using multivariable competing risk models, we confirmed a more than 3-fold increase in the daily hazard of in-hospital death following PDRAB infection as opposed to PDRAB colonization (csHR = 3.10; sHR = 3.37). We also quantified a decrease in the daily rate of discharge (csHR = 0.24) associated with PDRAB infection. This implies that hospitalization is prolonged following PDRAB infection, which increases healthcare costs and may increase the risk of patients acquiring other nosocomial infections and the risk of spreading PDRAB to other vulnerable patients.

The debate about how antimicrobial resistance affects outcomes in the hospital is vivid [17,18]. An early systematic review prior to July 2016 identified only four studies describing 14 human deaths directly due to PDR strains and suggested that mortality attributable to PDR infections might be exceedingly low [19]. By contrast, we recently identified 34 case-reports or series by May 2019, describing 75 deaths (53%) in 142 patients infected with PDR bacteria, but the spectrum of mortality attributable to the infection was again unclear [1]. In those studies, 36 PDRAB infections were identified and crude mortality was 50% in LRTIs and 71% in BSIs [1]. In

line with the latter, we observed high all-cause mortality in our study cohort (58% at 30 days, 79% on discharge).

Crude in-hospital mortality has been the most common measure of mortality in studies of the impact of antimicrobial resistance (or interventions to combat it) likely because it is objective in its assessment [4,11]. However, this definition of mortality does not distinguish patients for whom infection clearly resulted in death as opposed to those for whom infection occurred but was likely unrelated to mortality (e.g. infection occurred long before death). To overcome this problem, we took methodological approaches in this study that deserve attention.

First, we restricted analysis time to 30 days following PDRAB isolation. We assumed we would sufficiently capture early and delayed fatalities influenced by the infection but beyond this time occurrence of mortality would be unrelated to the infection. However, a recent consensus report suggested that 90-day survival should be the primary outcome in clinical trials investigating treatment options for Gram-negative BSI [11]. We found that the absolute excess risk of in-hospital mortality remained unaltered irrespective of the time window of analysis (30 days, 90 days, or discharge). However, the relative daily hazard attenuated over time in terms of in-hospital mortality and was strengthened with time in terms of discharge alive. This illustrates the importance of treating discharge alive and in-hospital death as competing events in time-to-event analysis. The latter is especially useful when endpoints such as length of hospital stay or ICU-free days are of primary interest [20].

Another important methodological approach in this study was the counterfactual impact evaluation of PDRAB infection mimicking as much as possible a randomized controlled trial design. We achieved this by taking patients colonized with PDRAB to form a comparison group that allows us to understand what would have happened to the patients had they not

been infected with PDRAB (the counterfactual case). This approach was suggested recently by Hauck et al to estimate excess mortality due to carbapenem-resistant *Klebsiella pneumoniae* infection [5]. They convincingly demonstrated that colonized patients represented the background population from which cases of infection arose [5]. Similarly, in this study, we found that patients colonized with PDRAB and those infected with PDRAB had similar baseline characteristics, thereby all-cause mortality in colonized patients may be used to approximate non-infection-related mortality.

A different approach to assessing infection-related mortality was recently implemented by Kofteridis et al in a microbiologically diverse cohort of PDR infections [3]. Using clinical judgement they attributed mortality to the infection as either the immediate or underlying cause and found that the attributable mortality was 32% [3]. While this approach may more directly designate mortality from the infection, its criteria remain quite subjective. Of note, studies of other pathogens that used both this approach and crude in-hospital mortality as outcomes found no substantive differences in final study results [21,22]. Our estimate of mortality attributable to PDRAB infection (34%) was also strikingly close to that reported by Kofteridis et al [3].

Finally, a different approach is to compare infections by PDRAB to those caused by extensively drug-resistant *A. baumannii* (XDRAB). This is useful to assess mortality attributed to the resistance phenotype per se within the cohort of infected patients. Three small studies have demonstrated higher mortality in PDRAB compared to XDRAB infections in unadjusted analysis (71% vs 55% [23], 67% vs 57% [24] and 67% vs 30% [25]), but the differences were not statistically significant. The approach used in this study (comparison between PDRAB infected and PDRAB colonized patients) aimed to address a different question, the excess mortality attributable to the PDRAB infection over and above mortality attributable to other factors, such

as underlying diseases. A comparison between patients with XDR infection and those with PDR infection may underestimate excess mortality due to PDR infection mainly because of confounding by antimicrobial treatment.

This study has potential limitations we should acknowledge. The single-center setting might limit the generalizability of our findings to some extent. For example, there were very few urinary tract infections in our cohort and one may expect lower mortality for those infections [5]. Importantly, data on potential confounders directly related to treatment and management of the patients were not available in this study and our list of potential confounders may not be exhaustive. Severe comorbidities and need for invasive procedures are common in both colonized and infected patients by multi-drug-resistant *A. baumannii* [6,7], but these risk factors have been reported to be more frequent in infected than colonized patients [26,27]. In this study, we accounted for several indirect indices (age, prior hospitalizations, length of stay before PDRAB isolation and ICU admission) and found similar baseline characteristics between colonized and infected patients. However, we cannot exclude entirely the possibility that some residual confounding may still be present.

Interpreting the role of PDRAB in polymicrobial infections (pathogen vs bystander) remains challenging, especially considering potential interactions with other pathogens [28]. In agreement with other studies [24,25,29,30], polymicrobial *A. baumannii* cultures were common in our study, especially in LRTIs. However, polymicrobial culture was not significantly associated with in-hospital death or discharge alive in this study. Similar to our finding, mortality did not differ significantly in a study comparing polymicrobial to monomicrobial *A. baumannii* BSI [29]. By contrast, outcomes were worse in patients with monomicrobial compared to polymicrobial *A. baumannii* pneumonia in another study [30], suggesting that other, more susceptible, pathogens may occasionally have a more virulent role [30].

In conclusion, this study estimated that one of every three patients infected by PDRAB die in the hospital because of the infection. For patients still alive in the hospital, PDRAB infection prolongs substantially the length of hospitalization. New effective antimicrobials would thus be expected to considerably reduce hospital mortality and length of stay of patients with PDRAB infection. However, currently available therapeutic options remain extremely limited and emphasis on understanding and preventing healthcare-associated transmission of PDRAB is ever more important.

Transparency declarations

Conflict of interest:

The authors have no conflicts of interest to declare.

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Author contributions:

Conception and study design: SK, EIK, AG, EA; *Data acquisition:* SK, AG, EA. *Data management*: SK; *Statistical modelling*: EIK; *Drafting the article*: SK, EIK; *Critical revisions*: AG, EA; F*inal approval of be submitted version*: SK, AG, EA EIK.

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Table I

Baseline characteristics and outcomes of patients colonized or infected with pandrug-resistant *Acinetobacter baumannii*

	Colonization	**Infection**		**Infection site**			
Variables	**(n=29) #**	**(n=62)**	**P ***	**BSI (n=28)**	**P ***	**LRTI (n=28)**	**P ***
Age (years), median (IQR)	66 (54-78)	68 (53-76)	0.802	68 (56-76)	0.678	67 (49-76)	0.615
Male sex, n (%)	22 (75.9)	48 (77.4)	0.869	23 (82.1)	0.561	21 (75.0)	0.940
Previous hospitalization, n (%)	8 (27.6)	26 (41.9)	0.187	10 (35.7)	0.509	12 (42.9)	0.227
Ward on admission							
Surgical ward, n (%)	8 (27.6)	21 (33.9)	0.755	9 (32.1)	0.770	8 (28.6)	0.987
Medical ward, n (%)	9 (31.0)	20 (32.3)		10 (35.7)		9 (32.1)	
Intensive care unit, n (%)	12 (41.4)	21 (33.9)		9 (32.1)		11 (39.3)	
Ward on isolation							
Surgical ward, n (%)	6 (20.7)	12 (19.4)	0.091	4 (14.3)	0.225	4 (14.3)	0.067
Medical ward, n (%)	12 (41.4)	13 (22.0)		7 (25.0)		5 (17.9)	
Intensive care unit, n (%)	11 (37.9)	37 (59.7)		17 (60.7)		19 (67.9)	
Polymicrobial culture, n (%)	10 (34.5)	17 (27.4)	0.492	4 (14.3)	0.077	9 (32.1)	0.851
Pre-culture LOS, days							
Median (IQR)	23 (14-46)	24 (13-41)	0.966	26 (13-45)	0.943	23 (14-37)	0.962
30-day outcome							

Died in hospital, n (%)	7 (24.1)	36 (58.1)	0.001	21 (75.0)	<0.001	13 (46.4)	0.130
Discharged alive, n (%)	11 (37.9)	6 (9.7)		0 (0.0)		5 (17.9)	
Remain hospitalized, n (%)	11 (37.9)	20 (32.3)		7 (25.0)		10 (35.7)	
90-day outcome							
Died in hospital, n (%)	12 (41.4)	46 (74.2)	<0.001	24 (85.7)	<0.001	18 (64.3)	0.024
Discharged alive, n (%)	15 (51.7)	8 (12.9)		1 (3.6)		5 (17.9)	
Remain hospitalized, n (%)	2 (6.9)	8 (12.9)		24 (85.7)		5 (17.9)	
Overall outcome							
Died in hospital, n (%)	13 (44.8)	49 (79.0)	0.001	26 (92.3)	<0.001	19 (67.8)	0.080
Discharged alive, n (%)	16 (55.2)	13 (21.0)		2 (7.1)		9 (32.1)	
Post-culture LOS, days							
Died in hospital, median (IQR)	17 (6-52)	11 (3-32)	0.452	8 (3-18)	0.179	21 (7-61)	0.848
Discharged alive, median (IQR)	19 (8-33)	80 (9-105)	0.196	93 (80-105)	0.049	15 (9-113)	0.497
All patients, median (IQR)	17 (7-35)	14 (4-57)	0.645	10 (3-29)	0.157	18 (8-75)	0.615

BSI, bloodstream infection; LRTI, lower respiratory tract infection without secondary bacteraemia; IQR, interquartile range; LOS, length of stay.

[#] Sites of colonization: respiratory tract n=15, central line colonization n=5, urinary tract n=5, surgical drain n=2, superficial wound n=2.

* Pearson's Chi-square test or Fisher's exact test was used to test equality of proportions. The Mann–Whitney U test was used to test equality of medians. All two-way comparisons were done with respect to the group of patients colonized with pandrug-resistant *Acinetobacter baumannii*.

Table II

Multivariable competing risk survival analysis for **30-day** in-hospital mortality of patients infected with pandrug-resistant *Acinetobacter baumannii*

	Cause-specific hazards						Sub-distribution hazards		
	In hospital death			Discharge alive			In hospital death		
Risk factor	**csHR**	**95%CI**	**P**	**csHR**	**95%CI**	**P**	**sdHR**	**95%CI**	**P**
Male sex	1.13	0.56 - 2.31	0.729	0.53	0.15 - 1.87	0.324	1.09	0.56 - 2.11	0.804
Age, 10-year increase	1.66	1.26 - 2.17	<0.001	1.01	0.75 – 1.36	0.947	1.73	1.33 – 2.26	<0.001
Previous hospitalization	0.62	0.31 - 1.24	0.176	0.52	0.15 - 1.83	0.305	0.71	0.29 - 1.71	0.440
Admission in the ICU	0.80	0.37 - 1.74	0.574	1.25	0.37 - 4.24	0.717	0.78	0.30 - 2.05	0.614
Pre-culture LOS, 1-day increase	1.00	0.99 - 1.01	0.755	0.96	0.93 - 0.99	0.010	1.01	1.00 - 1.02	0.018
Polymicrobial culture	0.74	0.36 - 1.54	0.429	1.96	0.56 - 6.80	0.290	0.77	0.34 - 1.73	0.522
Infection (versus colonization) *	3.10	1.33 - 7.21	0.009	0.24	0.08 - 0.74	0.013	3.37	1.33 – 8.52	0.010
Site of infection*									
Lower respiratory tract	2.33	0.88 - 6.13	0.088	0.39	0.11 - 1.38	0.145	2.54	0.85 - 7.57	0.093
Bloodstream	5.19	2.07 - 13.01	<0.001	0.00^	na	1.000	6.17	2.25 - 16.93	<0.001
Colonization	1.00	-	-	1.00	-	-	1.00	-	-

csHR, cause-specific hazard ratio; sdHR, sub-distribution hazard ratio; CI: confidence interval; ICU, intensive care unit; LOS, length of stay.

* Two separate models were fitted to contrast colonization with (any) infection and with specific sites of infection.

^ No patient with BSI was discharged alive within 30 days from positive culture.

Table III

Multivariable competing risk survival analysis for **90-day** in-hospital mortality of patients infected with pandrug-resistant *Acinetobacter baumannii*

	Cause-specific hazards						Sub-distribution hazards		
	In hospital death			Discharge alive			In hospital death		
Risk factor	**csHR**	**95%CI**	**P**	**csHR**	**95%CI**	**P**	**sdHR**	**95%CI**	**P**
Male sex	1.33	0.68 - 2.62	0.411	0.54	0.17 - 1.67	0.285	1.63	0.81 - 3.28	0.168
Age, 10-year increase	1.50	1.21 - 1.85	<0.001	0.93	0.72 - 1.21	0.600	1.39	1.15 - 1.69	0.001
Previous hospitalization	0.81	0.43 - 1.52	0.508	0.78	0.24 - 2.48	0.670	0.92	0.47 - 1.83	0.820
Admission in the ICU	0.74	0.37 - 1.48	0.391	0.93	0.33 - 2.61	0.892	0.77	0.36 - 1.64	0.505
Pre-culture LOS, 1-day increase	1.00	0.99 - 1.01	0.962	0.99	0.98 - 1.01	0.394	1.00	0.99 - 1.01	0.725
Polymicrobial culture	0.81	0.44 - 1.49	0.489	1.15	0.39 - 3.35	0.798	0.73	0.39 - 1.38	0.335
Infection (versus colonization) *	2.08	1.05 - 4.11	0.035	0.22	0.09 - 0.58	0.002	2.66	1.32 - 5.38	0.006
Site of infection*									
Lower respiratory tract	1.54	0.70 - 3.39	0.281	0.20	0.06 - 0.67	0.009	1.90	0.83 - 4.35	0.128
Bloodstream	3.35	1.55 - 7.23	0.002	0.05	0.01 - 0.42	0.006	4.68	2.21 - 9.91	<0.001
Colonization	1.00	-	-	1.00	-	-	1.00	-	-

csHR, cause-specific hazard ratio; sdHR, sub-distribution hazard ratio; CI: confidence interval; ICU, intensive care unit; LOS, length of hospital stay.

*Two separate models were fitted to contrast colonization with (any) infection and with specific sites of infection.

Figure 1. Cumulative incidence functions for in-hospital mortality by site of infection caused by pandrug-resistant *Acinetobacter baumannii*.

Note: LTRI, lower respiratory tract infection; BSI, bloodstream infection; PDR, pandrug resistant.