Received Date : 20-Feb-2013
Revised Date : 15-Apr-2013
Accepted Date : 20-Apr-2013
Article type : Original Article

Impact of Carbapenem Resistance on Clinical and Economic Outcomes among Patients with *Acinetobacter baumannii* Infection in Colombia

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1469-0691.12251
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Running title: *Acinetobacter baumannii* resistance in Colombia (40 characters, including spaces)

Keywords: Acinetobacter, Mortality, LOS, Cost, Resistance

ABSTRACT

Background: *Acinetobacter baumannii* is a major cause of healthcare-associated infection, often affecting critically ill patients.

Objective: The purpose of the study was to examine the associations of carbapenem resistance with mortality, length of hospital stay, and hospital costs among patients infected with *A. baumannii* in intensive care units (ICUs) in Colombia.

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Methods: A prospective, multicenter cohort study was conducted among 165 patients with *A. baumannii* infection admitted to ICUs between April 2006 and April 2010.

Results: Patients with carbapenem-resistant *A. baumannii* (CRAB) had higher risk of 30-day mortality than patients with carbapenem-susceptible *A. baumannii* (CSAB) in the univariate analysis (unadjusted HR = 2.12; 95% CI = 1.14, 3.95; p = 0.018). However, carbapenem resistance was not significantly associated with risk of mortality (adjusted HR = 1.45; 95% CI = 0.74, 2.87; p = 0.28) after adjusting for APACHE II score and other confounding factors. We did not find a significant difference in length of stay in ICU after the onset of infection between the two groups in the multivariate analysis (adjusted mean = 13.1 days vs. 10.5 days; p = 0.14). The average total cost of hospitalization among patients with CRAB was significantly higher than that among patients with CSAB in the multivariate analysis (adjusted cost; US$11,359 vs. US$7,049; p <0.001).

Conclusion: Carbapenem resistance was not significantly associated with mortality, though we are unable to rule out an increased risk due to the limited sample size. Carbapenem resistance was associated with an additional cost of hospitalization.

INTRODUCTION

Healthcare-associated infections are associated with an increase in morbidity, mortality, and healthcare costs. *Acinetobacter baumannii* is a major cause of healthcare-associated infection, often affecting critically ill patients [1-3]. This pathogen has become one of the most difficult pathogens to control and treat because of its prolonged survival and possibly airborne transmission [3-5]. Moreover, multidrug-resistant (MDR) *A. baumannii* is rapidly emerging due to its capability of acquiring resistance to multiple classes of antimicrobials [6-9]. The rapid

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increase and worldwide spread of carbapenem-resistant *A. baumannii* infection is a major threat. Rates of carbapenem resistance are generally higher in Latin America and Asia than in North America and Europe [2]. In recent studies, rates of resistance to carbapenem in *A. baumannii* infection ranged from 50% to 75% in Latin America [10,11].

The health and economic impacts of carbapenem resistance in patients with *A. baumannii* infection remain uncertain. There is ongoing controversy regarding whether patients infected with carbapenem-resistant *A. baumannii* (CRAB) are at greater risk of mortality than patients infected with carbapenem-susceptible *A. baumannii* (CSAB). Previous studies from North America, Europe and Asia have reported inconsistent results regarding a potential association between carbapenem resistance and mortality [12-24]. Furthermore, the literature on the economic impact of carbapenem resistance is limited, with a few studies suggesting that resistance may be associated with prolonged hospitalization and increased hospital costs in patients with *A. baumannii* infection [9, 14]. To our knowledge, no study has examined the impact of carbapenem resistance on clinical and economic outcomes in Latin America.

The objective of this study was to examine the associations of carbapenem resistance with mortality, length of hospital stay, and hospital costs among patients infected with *A. baumannii* in intensive care units (ICUs) in Colombia.

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METHODS

Study Design and Population

This prospective cohort study was conducted in the ICUs of three tertiary-care hospitals in Bogota, Colombia. The first hospital consisted of 214 beds (17 of which were in the ICU), the second one consisted of 398 beds (15 of which were in the ICU), and the third one consisted of 275 beds (10 of which were in the ICU). We included all adult patients diagnosed with *A. baumannii* infection between April 1st 2006 and April 1st 2010. Patients were included in the study if they had been hospitalized for more than 48 hours. The study was approved by the participating institutions and Universidad Nacional de Colombia through their respective research ethics committees.

Microbiological Examination

Microbiological and antimicrobial susceptibility of *A. baumannii* was determined using microbiological cultures processed in the microbiology laboratories using with automated systems. Testing was carried out according to the methods recommended by the National Committee for Clinical Laboratory Standards (CLSI) [25]. The species were identified at participating sites by the Vitek System® (bioMerieux Vitek) and MicroScan® (MicroScan Siemens). Isolates identified as intermediate or resistant to antibiotics were classified as resistant to the agents. Carbapenem resistance was defined as resistance to imipenem or meropenem.

Data Collection

We collected data regarding demographics, site of infection, Acute Physiology and Chronic Health Evaluation (APACHE) II score, comorbidities, and the dates of hospital and ICU

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admission. Patients were classified as having pneumonia (ventilator-associated pneumonia and healthcare associated pneumonia), primary bacteremia, central venous catheter–associated infection, surgical site infection, urinary tract infection, skin and soft tissue infection, and intra-abdominal infection [26]. The number of diagnoses was defined as the total number of comorbidities and complications present on the day of A. *baumannii* diagnosis [27]. We considered the empirical antibiotic treatment appropriate if the patient received at least one antibiotic that was susceptible to the isolated *A. baumannii in vitro*. Additionally, such a drug had to be administered within at least 72 hours from the time of culture collection.

Mortality was defined as a death occurring within 30 days after diagnosis of *A. baumannii*. The lengths of ICU and hospital stay after infection were defined as time from the day of culture collection until discharge from the ICU, hospital, or until death. We used an incidence-based approach to determine costs for individual patients (i.e., micro costing) during their ICU stay. Costs were analyzed from the perspective of a third party payer, because hospitals are responsible for funding infection control and quality improvement programs. The total cost of hospitalization included days of stay in the ICU, fees for health professionals, surgical procedures, laboratory tests, microbiological cultures, and radiological examinations, and antimicrobial therapy and other drugs used as a consequence of the infection. The total cost of hospitalization for each patient was obtained by multiplying the number of resource units consumed by unit cost. Because the study was conducted over 4 years, we adjusted costs to 2011 currency using the Consumer Price Index for Colombia. We initially measured costs in Colombian Pesos and then converted them to US dollars.

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Data Analysis

To compare the characteristics of patients with CRAB vs. CSAB, we used the chi-square tests or Fisher's exact tests for categorical variables, Student's t-test for normally distributed continuous variables, and the Wilcoxon rank sum test for non-normally distributed continuous variables. We employed the Kaplan-Meier method to construct survival curves. We used Cox proportional hazards models to investigate the association between carbapenem resistance and risk of mortality. The multivariate model was built using a backward selection procedure. We first considered variables with $p<0.05$ in the univariate analysis as candidates for multivariate model, and then, kept variables with $p<0.05$ and prior known risk factors in the final model.

To examine the associations of carbapenem resistance with the length of hospital stay and cost of hospitalization, we employed generalized linear models with a gamma distribution and a log link function. Univariate and multivariate analyses were conducted. We estimated predicted lengths of stay and cost based on average marginal effects from a generalized linear model. Non-parametric bootstrap estimation was used to construct 95% confidence intervals (CI) and p-values. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

The cohort consisted of a total of 165 patients, the majority of which were male (64%) and had CRAB infection (63%). The average age (± SD) was 50 years (± 19 years) and the average APACHE II score at onset of infection was 13 (± 6). Compare to patients with CSAB, patients with CRAB had higher APACHE II scores at onset of infection and lower albumin levels ($p<0.01$ and $p=0.04$, respectively; Table 1). Patients with CRAB were more likely to

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receive inappropriate empirical antibiotic treatment than patients with CSAB (38.5% vs. 16.4%; p = 0.003).

Within 30 days of the onset of infection, 55 patients died (33%). Patients with CRAB had significantly higher risk of 30-day mortality than patients with CSAB in the univariate analysis (40% vs. 21%; unadjusted hazard ratio (HR) = 2.12; 95% CI = 1.14, 3.95; p <0.05; Figure 1 and Table 2). However, after adjusting for age, gender, APACHE II score, number of diagnoses, and inappropriate empirical antimicrobial treatment in the multivariate model, carbapenem resistance was not significantly associated with risk of mortality (adjusted HR = 1.45; 95% CI = 0.74, 2.87; p = 0.28).

Patients with CRAB had longer ICU stays after the onset of infection than patients with CSAB in the univariate analysis (mean = 13.2 days vs. 10.1 days; p = 0.04; Table 3). However, the association was attenuated in the multivariate model (adjusted mean = 13.1 days vs. 10.5 days; p = 0.14). We did not find a significant difference in length of hospital stay after infection between the two groups (adjusted mean = 19.3 days vs. 16.2 days; p = 0.58).

The average total cost of hospitalization among patients with CRAB was significantly higher than that among patients with CSAB in both the univariate and multivariate analyses (adjusted US$11,359 vs. US$7,049; p<0.01; Table 4). Carbapenem resistance was associated with an additional treatment cost of US$4,309 (95% CI = US$2,819, US$5,645; p<0.01) after adjusting for age, gender, APACHE II score and site of infection. Patients with CRAB had

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significantly higher cost for hospital-related cost and for cost of antimicrobial drugs than patients with CSAB ($p<0.01$ and $p<0.01$, respectively).

DISCUSSION

In this prospective cohort study of patients with *A. baumannii* infection in Colombia, we found that carbapenem resistance was not significantly associated with risk of 30-day mortality after adjusting for severity of illness and other confounding factors. Our study demonstrated that the average total cost of hospitalization among patients infected with CRAB was significantly higher than that among patients infected with CSAB in the multivariate analysis.

Patients infected with CRAB are more likely to have severe illness and less likely to receive appropriate empirical antibiotic treatment than patients infected with CSAB. Therefore, in the unadjusted analysis, the higher mortality rate in patients with CRAB compared to patients with CSAB may be partly due to severe underlying disease status of patients with CRAB. Though the adjusted HR was attenuated and not statistically significant, it is possible that carbapenem resistance may have contributed to an increased risk of mortality; however, our study may not have enough statistical power to detect a statistically significant association. Previous studies have reported conflicting results as to whether high risk of death in patients with CRAB is due to carbapenem resistance or greater severity of underlying illness [12-24]. Among 13 prior studies of patients with *A. baumannii* infection, five studies found that carbapenem resistance may increase risk of mortality after adjusting for severity of illness and other confounding factors [13-17]. However, other studies did not find statistically significant association in the multivariate analysis and reported that higher crude mortality rates in patients

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with CRAB is due to severity of illness, inappropriate antimicrobial therapy, and/or primary source of infection [18-24]. Most studies had a limited sample size. It is also important to note substantial differences in the methodology, rates of carbapenem resistance, study population, and study country, which may have resulted in conflicting findings. Furthermore, previous studies have mostly examined patients with bacteremia who may be at greater risk of resistant infection.

We demonstrated that carbapenem resistance was significantly associated with higher average cost of hospitalization (adjusted cost for CRAB US$11,359 vs. CSAB US$7,049). Longer ICU stays and higher costs from antimicrobial drugs have contributed to higher cost in patients with CRAB. Similarly, Lautenbach et al. (2009) found that patients with CRAB compared to patients with CSAB have greater hospital charges in the U.S. (US$334,516 vs. US$276,059; p=0.03) [14]. Lee et al. also found that an average cost of patient infected with multidrug resistant (MDR) *A. baumannii* were higher than that of patients infected with non-MDR *A. baumannii* in Taiwan (US$9,349 vs. US$4,863; $p < 0.05$) [9]. Researchers have also found that antimicrobial resistance is associated with higher hospital cost in other gram-negative bacterial infections, such as *Pseudomonas aeruginosa* [28, 29].

Our study has several notable strengths. The present study is the first in Latin America to examine the clinical and economic impacts of carbapenem resistance among patients with *A. baumannii* infection. Furthermore, we prospectively collected clinical and cost data, which are not typically collected systematically in Colombia. We also carefully collected and adjusted for a number of important confounding factors.

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Several limitations are worth noting. Although we adjusted for many known risk factors for outcomes, as with any observational study, it is difficult to infer causation because of possible unmeasured factors, including hospital or individual level characteristics. Carbapenem resistance in *A. baumannii* may result from a number of mechanisms, including production of β-lactamases, overexpression of efflux pump, alterations in outer membrane proteins, or penicillin-binding protein modifications [30]. We did not conduct molecular level analysis to characterize mechanisms of carbapenem resistance. Another limitation is that our study may not have sufficient statistical power to detect a statistically significant difference in the mortality rate. Combining results from previous studies using meta-analysis technique may further elucidate whether such an association exists.

In conclusion, we observed a high rate of carbapenem resistance (63%) in patients with *A. baumannii* admitted ro the ICU. Carbapenem resistance was not significantly associated with risk of 30-day mortality, though we are unable to rule out an increased risk due to the limited sample size. Our study demonstrated that *A. baumannii* infection causes substantial hospital costs, with carbapenem resistance adding additional costs. In addition to prevention and control of healthcare-associated infections, timely and appropriate antimicrobial treatment is critical for patients with *A. baumannii* infection, particularly those with resistance to carbapenem.

Acknowledgements

We would like to thank Dra. Narda Olarte, Jefe Alberto Valderrama, and Jefe Karlo Reyes from Hospital el Tunal; Dr.Fabio Barrera, Jefe Ana Gilma, Sánchez de Parada, Dra. Blanca Arango, and Dra. Luz Dary Teheran from Hospital Occidente de Kennedy; and Dr. Edgar Ruiz Luengas,

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Dr. Fabio Corredor, Dr. Diego Villarraga, Dra. Norma Montoya, Dra. Martha Salinas from Clínica del Occidente, Dr Julio Cesar Castillo Inocencio, Dra Liliana Raquel Lemos Luengas from FUDASAI. We also thank Alison Tse Kawai for editorial assistance.

Funding

Professionals and research assistant's time involved in the present research was supported by the participating institutions. We did not receive any external funding.

Potential conflicts of interest

The authors declare no conflict of interest related to this article.

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Table 1 Baseline characteristics comparing patients with carbapenem-resistant *A. baumannii* and patients with carbapenem-susceptible *A. baumannii* (N=165).

Baseline Characteristics	**Carbapenem-resistant (n = 104)[1]**	**Carbapenem-susceptible (n = 61)[1]**	***p***
Age	51.2 ± 19.4	47.7 ± 19.0	0.006
Gender, male	63 (60.6%)	42 (68.9%)	0.29
APACHE II score[3]			
At admission to ICU	12.8 ± 5.4	10.1 ± 4.6	0.001
At onset of infection	14.2 ± 6.2	11.6 ± 5.2	0.006
Number of diagnoses			
< 5	62 (59.6%)	39 (63.9%)	0.58
≥ 5	42 (40.4%)	22 (36.1%)	
White blood cell count at onset of infection (/mm^3)	17800 ± 6100	19300 ± 5800	0.14
Albumin (mg/dl)	2.93 ± 0.78	3.20 ± 0.78	0.038
Acute respiratory distress syndrome	38 (36.5%)	25 (41.0%)	0.57
Length of hospital stay before infection (days)	20.2 ± 23.5	16.8 ± 14.5	0.44
Length of ICU stay before infection (days)	10.3 ± 8.3	10.1 ± 10.1	0.43
Inappropriate empirical antimicrobial treatment	40 (38.5%)	10 (16.4%)	0.003
Site of infection			
Pneumonia	30 (28.9%)	27 (44.3%)	0.044
Bacteremia	14 (13.5%)	10 (16.5%)	0.61
Central venous catheter-associated infection	13 (12.5%)	7 (11.5%)	0.85
Surgical infection	28 (26.9%)	12 (19.7%)	0.29
Urinary tract	10 (9.6%)	1 (1.6%)	0.06
Soft tissue	4 (3.9%)	3 (4.9%)	0.71
Intra-abdominal	5 (4.8%)	1 (1.6%)	0.41
Primary and secondary bacteremia	30 (28.9%)	17 (27.8%)	0.89
Diagnostic category			
Elective surgery	10 (9.6%)	7 (11.5%)	0.70
Emergency surgery	24 (23.1%)	21 (34.4%)	0.11
Medical	54 (51.9%)	20 (32.8%)	0.017
Trauma	16 (15.4%)	13 (21.3%)	0.33
Comorbidities			
Diabetes	7 (6.8%)	3 (4.9%)	0.75
Hypertension	17 (16.5%)	12 (19.7%)	0.38
Chronic obstructive pulmonary disease	12 (11.7%)	10 (16.4%)	0.59
Neoplasia	1 (1.0%)	1 (1.6%)	1.0

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Renal insufficiency	1 (1.0%)	0 (0%)	1.0

Footnotes

[1] Mean ± SD or n (%)

[2] Chi-squared or Fisher's exact test was used for categorical variables. Student's t-test was used for continuous variables. However, for lengths of hospital and ICU stays, we used Wilcoxon rank sums test.

[3] APACHE II = Acute Physiology and Chronic Health Evaluation II.

Table 2. Carbapenem-resistance and other risk factors associated with 30-day mortality among patients infected with *A. baumannii*.

Risk factors	**n/N**[1]	**Unadjusted HR (95% CI)** [2]	***p***	**Adjusted HR (95% CI)** [2]	***p***
Carbapenem					
Resistant	42/104	2.12 (1.14, 3.95)	0.018	1.45 (0.74, 2.87)	0.28
Susceptible	13/61	1.0		1.0	
Age					
< 65 years	34/123	1.0		1.0	
≥ 65 years	21/42	2.27 (1.32, 3.92)	0.003	1.89 (1.07, 3.35)	0.03
Gender					
Male	31/105	1.0		1.0	
Female	24/60	1.49 (0.87, 2.53)	0.14	1.56 (0.88, 2.76)	0.13
APACHE II[3]					
< 10	2/52	1.0		1.0	
10 - 19	23/77	9.12 (2.15, 38.68)	0.003	9.32 (2.19, 39.70)	0.003
≥ 20	30/36	38.37 (9.12, 161.31)	<0.001	23.06 (5.31, 100.16)	<0.001
Number of diagnoses					
< 5	19/101	1.0		1.0	
≥ 5	36/64	3.60 (2.06, 6.29)	<0.001	2.22 (1.18, 4.18)	0.01
Empirical antimicrobial treatment					
Inappropriate	21/50	1.48 (0.86, 2.56)	0.15	1.39 (0.78, 2.46)	0.26
Appropriate	34/115	1.0		1.0	
Length of hospital stay before infection					
< 10 days	14/48	1.0		-	
10 - 19 days	23/67	1.13 (0.59, 2.16)	0.72		
≥ 20 days	17/48	1.12 (0.56, 2.24)	0.75		
Length of ICU stays before infection					

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< 10 days	33/108	1.0		-
≥ 10 days	22/57	1.25 (0.73, 2.15)	0.41	
Albumin				
≥ 2.5 mg/dl	37/125	1.0		-
< 2.5 mg/dl	17/39	1.67 (0.94, 2.96)	0.08	
Acute respiratory distress syndrome				
Presence	19/63	0.90 (0.52, 1.56)	0.70	-
Absence	36/102	1.0		
Primary and secondary bacteremia				
Presence	16/47	1.07 (0.60, 1.92)	0.81	
Absence	39/118	1.0		
Site of infection				
Pneumonia	17/57	1.0		-
Bacteremia	8/24	1.15 (0.50, 2.67)	0.74	
Catheter-associated	7/20	1.15 (0.48, 2.78)	0.75	
Surgery infection	14/40	1.11 (0.55, 2.26)	0.77	
Urinary tract	7/11	2.36 (0.98, 5.69)	0.06	
Soft tissue or skin	1/7	0.40 (0.05, 2.99)	0.37	
Intra-abdominal	1/6	0.52 (0.07, 3.89)	0.52	
Diagnostic category				
Emergency surgery	12/45	1.00		-
Elective surgery	7/17	1.73 (0.68, 4.39)	0.25	
Medical	28/74	1.45 (0.74, 2.85)	0.28	
Trauma	8/29	0.99 (0.40, 2.41)	0.97	

[1]Number who died (n) / Number at risk (N)

[2] Unadjusted and adjusted Hazard Ratios (HRs) and 95% CIs were estimated from Cox proportional hazards model.

[3] APACHE II = Acute Physiology and Chronic Health Evaluation II.

Table 3 Length of hospital and ICU stays comparing patients with carbapenem-resistant *A. baumannii* and patients with carbapenem-susceptible *A. baumannii*

	Unadjusted			**Adjusted[2]**		
Length of stay after infection	**Carbapenem-resistant, Mean ± SD**	**Carbapenem-susceptible, Mean ± SD**	***p*[1]**	**Carbapenem-resistant, Mean (95% CI)**	**Carbapenem-susceptible, Mean (95% CI)**	***p***
Hospital	19.0 ± 17.2	16.2 ± 18.0	0.20	19.3 (16.0,	16.2 (11.5,	0.58

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days				22.5)	19.9)	
Intensive care unit days	13.2 ± 13.8	10.1 ± 8.7	0.04	13.1 (10.8, 15.4)	10.5 (8.2, 12.8)	0.14

[1] Based on Wilcoxon rank sums test

[2]Predicted lengths of stay based on average marginal effects from a generalized linear model with a log link function and gamma distribution that adjusted for age, gender, APACHE II score, and site of infection. 95% CIs and p-values were estimated by non-parametric bootstrapping.

Table 4 Cost of hospitalization (US$) comparing patients with carbapenem-resistant *A. baumannii* and patients with carbapenem-susceptible *A. baumannii*

Cost (US$)	**Unadjusted**			**Adjusted[2]**			
	Carbapenem-resistant, Mean ± SD	**Carbapenem-susceptible, Mean ± SD**	***p*[1]**	**Carbapenem-resistant, Mean (95% CI)**	**Carbapenem-susceptible, Mean (95% CI)**	**Mean difference (95% CI)**	***p***
Total cost	11822 ± 7334	7178 ± 3938	<0.001	11359 (10053, 12483)	7049 (6206, 8021)	4309 (2819, 5645)	<0.001
Hospital-related cost	7726 ± 4458	4704 ± 3287	<0.001	7596 (6736, 8440)	4539 (3824, 5291)	3057 (1943, 4134)	<0.001
Cost of antimicrobials	4096 ± 4026	2475 ± 2042	0.002	3657 (3069, 4159)	2520 (2009, 3073)	1137 (386, 1894)	0.002

[1]P-value based on Wilcoxon rank sums test.

[2]Predicted cost based on average marginal effects from a generalized linear model with a log link function and gamma distribution that adjusted for age, gender, APACHE II score, and site of infection. 95% CIs and p-values were estimated by non-parametric bootstrapping.

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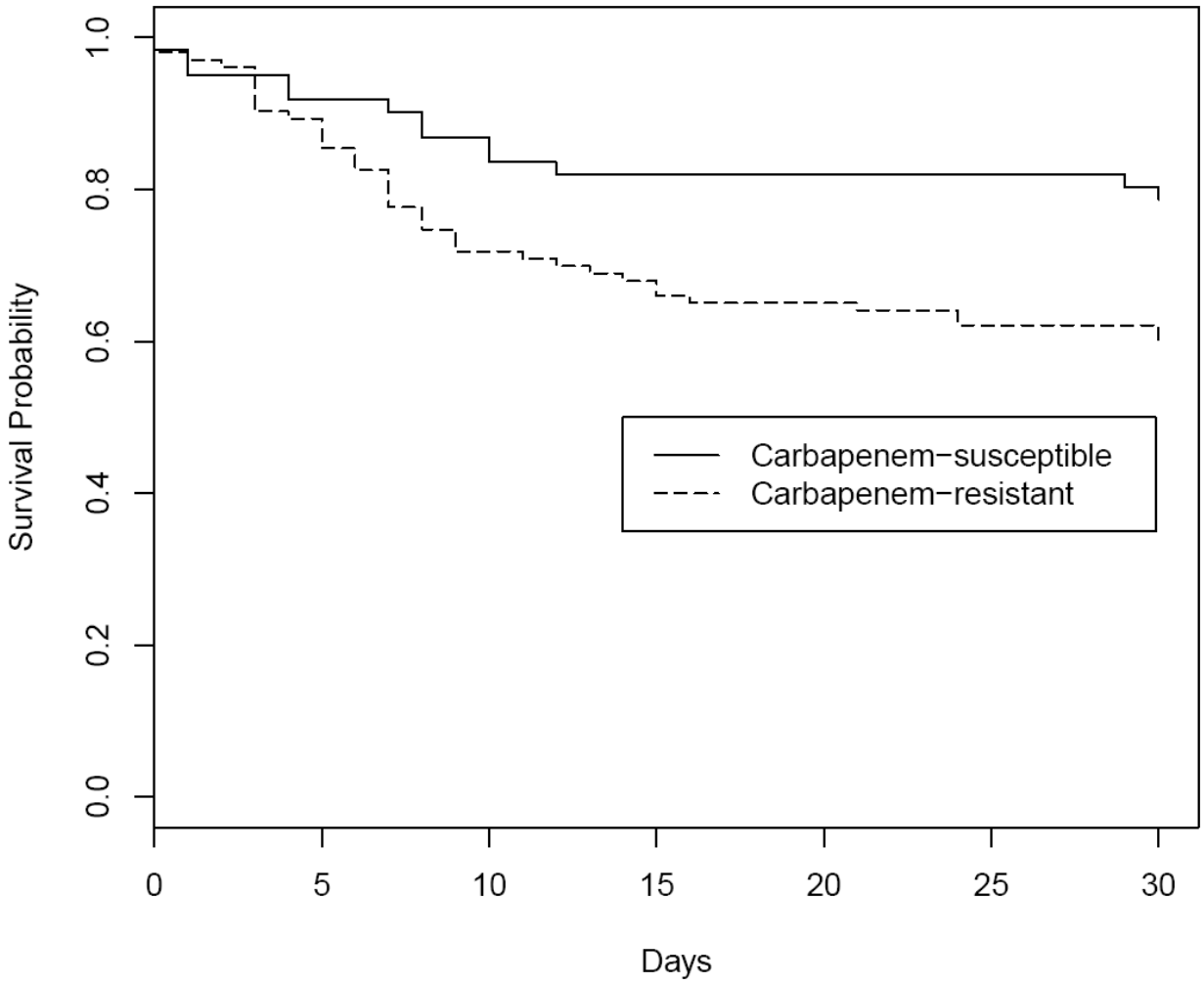
Figure 1 Risk of 30-day mortality comparing patients with carbapenem-resistant *A.baumannii* and patients with carbapenem-susceptible *A. baumannii* (log rank test, p = 0.02).



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