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State of the Science Review

Predictors of mortality in patients infected with carbapenem-resistant *Acinetobacter baumannii*: A systematic review and meta-analysis

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Key Words:
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Risk factors
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Nosocomial pneumonia

Background: Carbapenem-resistant *Acinetobacter baumannii* (CRAB) tops the list of threats to human health. Studies exploring predictors of mortality in patients with CRAB infection produced conflicting results.
Methods: A systematic search of the PubMed, Embase, and the Cochrane Library databases was performed from inception to June 2018 to identify studies reporting mortality predictors in patients infected with CRAB. Two authors independently assessed trials for inclusion and data extraction.
Results: A total of 19 observational studies were enrolled in this study. Factors associated with mortality of patients infected with CRAB were inappropriate empirical antimicrobial treatment (odds ratio [OR], 5.04; 95% confidence interval [CI], 2.56-9.94), septic shock (OR, 5.65; 95% CI, 2.35-13.57), chronic liver disease (OR, 2.36; 95% CI, 1.33-4.16), chronic renal disease (OR, 2.02; 95% CI, 1.37-2.99), hypertension (OR, 1.74; 95% CI, 1.08-2.80), neutropenia (OR, 3.31; 95% CI, 1.25-8.77), immunosuppressant use (OR, 3.15; 95% CI, 1.94-5.11), total parenteral nutrition (OR, 1.66; 95% CI, 1.08-2.56), and intubation (OR, 5.03; 95% CI, 2.33-10.87). Acute Physiology and Chronic Health Evaluation II score at admission and Pitt bacteremia score at the onset of CRAB bacteremia were higher in nonsurvivors.
Conclusions: Our study suggests that severity of baseline condition and receiving inappropriate experience antibiotic therapy are major risk factors for higher mortality in patients with CRAB infections. These findings may help clinicians to take appropriate preventive measures and decrease mortality in such patients.

Acinetobacter baumannii is an important opportunistic pathogen that causes nosocomial infections, predominantly bloodstream and respiratory infections, including ventilator-associated pneumonia, especially among critically ill patients.[1,2] Carbapenems are commonly used for the treatment of serious infections caused by *A baumannii*. However, in recent decades, carbapenem-resistant *A baumannii* (CRAB) has emerged and permanently replaced the carbapenem-susceptible clones. Resistance is mainly due to overexpression of intrinsic and/or acquired β-lactamases, particularly carbapenem-hydrolyzing β-lactamases (carbapenemases).[3,4] Resistance could also result from overexpression of the efflux pump, which expels antibiotics, and from alterations in outer membrane porins, which block the entry of antibiotics.[4] In addition to the ability of acquiring multiple antibiotic resistances, *A baumannii* has a number of potential virulence factors, such as siderophore-mediated iron-acquisition systems and biofilm formation, which could possibly affect clinical outcomes.[5,6] The high rate of carbapenem resistance across the world has attracted widespread attention.[7-9] CRAB infection has become a serious clinical challenge owing to its very limited therapeutic options.[3]

A previous systematic review and meta-analysis including 16 observational studies reported that patients infected with CRAB have double the mortality rate compared with those with carbapenem-susceptible *A baumannii*.[10] Identification of risk factors for death

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caused by CRAB infection is crucial for early implementation of an appropriate therapy and improving patients' outcome. Many studies have attempted to identify all risk factors, which include the following: inappropriate antimicrobial therapy, intensive care unit stay, mechanical ventilation, accompanied by malignancy, Pitt bacteremia score, and Acute Physiology and Chronic Health Evaluation (APACHE) II score at onset of infection. However, studies investigating predictors of mortality in patients infected with CRAB produced inconsistent results. For instance, whereas most relevant studies report a positive correlation between mechanical ventilation and fatality,[11,12] others draw an opposite conclusion.[13] The impact of some underlying diseases (such as chronic renal disease) on the mortality caused by CRAB infection is also a matter of debate.[12,13]

Therefore, we conducted a systematic review and meta-analysis to evaluate the relation between possible risk factors and mortality in patients with CRAB infection. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14]

METHODS

Search strategy

To identify potentially relevant studies, 2 independent examiners (X.D. and X.X.) searched PubMed, Embase, and the Cochrane Library databases from inception to June 2018. The main search terms (Supplementary Table S1) were ('*Acinetobacter baumannii*" OR '*A baumannii* infection' OR '*Acinetobacter*') AND 'resistance' AND ('carbapenem' OR 'imipenem' OR 'meropenem' OR 'ertapenem' OR 'doripenem') AND ('mortality' OR 'fatality' OR 'lethality' OR 'prognosis' OR 'predictor' OR 'survival'). In addition, the references identified by this strategy were searched to select relevant articles. Grey literature or unpublished data were not searched for. The language was restricted to English.

Two authors (X.D. and X.X.) independently screened and reviewed each study for eligibility. Where relevant, we attempted to contact study authors for clarification if necessary.

Inclusion and exclusion criteria

Studies reporting risk factors of mortality in patients infected with CRAB were included in this meta-analysis. Carbapenem resistance was defined as resistance to carbapenems, such as imipenem, meropenem, ertapenem, or doripenem, irrespective of susceptibility to other antibiotics.[15] Appropriate empirical antibiotic therapy was defined as 1 or more agents active against *A baumannii*, administered with an adequate dosage and route, no later than 24 h after the culture was obtained.[16,17]

In contrast, articles that did not provide original data (eg, reviews, systematic reviews, meta-analyses, guidelines, editorials, letters, comments, and decision analysis studies), case reports, duplicate reports, animal research, in vitro studies, and research that focused on children were excluded. Research that did not differentiate between CRAB infection and colonization, or define whether the strains were carbapenem-resistant, were also excluded.

Assessment of study quality

Articles meeting the above criteria were assessed according to the Newcastle-Ottawa Scale score,[18] ranging from 0-9 for quality assurance. Studies with a Newcastle-Ottawa Scale score of ≥5 were included in this analysis.

Data extraction

Two investigators (X.D. and X.X.) independently extracted the relevant data from eligible articles. The following information was collected from each study: first author, year of publication, country, study period, study design, sample size, characteristics of the study population (eg, mean age, sex, type of infection, and mean severity of underlying disease), intensive care unit (ICU) admission, and length of hospital stay. To clarify the association between prognosis factors and mortality, the numbers of nonsurvivors for patients, with or without each factor, were collected. Prognosis factors previously considered to increase mortality in patients with CRAB were evaluated,[12,19,20] and only those examined in at least 2 eligible studies were presented. If mortalities from both infection and colonization were reported, only the information regarding infections was extracted.

To provide more specific guidance to clinicians, we also analyzed the prognostic risk factors of CRAB-related bacteremia and pneumonia, respectively. Relevant data, including only bacteremia or pneumonia, were separately extracted for further analysis.

Data analysis and statistical methods

Statistical analyses were performed using Stata (version 15.1 software; StataCorp LLC, College Station, TX). For controlled studies, the heterogeneity between studies was assessed using the I^2 test. Heterogeneity was considered as $I^2 > 50\%$. Binary outcome results of controlled studies were expressed as pooled odds ratios (OR) and 95% confidence intervals (CI), and continuous outcome results were expressed as weighted mean difference (WMD) and 95% CI. Either the Mantel-Haenszel fixed-effect method model or Mantel-Haenszel random-effects heterogeneity method model was used according to the heterogeneity result. For studies providing median and range (or interquartile range) only for continuous outcomes, the mean value and variance were estimated using the median and range.[21,22] To assess the possibility of publication bias, the funnel plot for asymmetry and the Egger test were performed. $P < .05$ was considered to be statistically significant.

RESULTS

Flow of included studies

A total of 1,597 publications were identified and screened, 1,499 of which were excluded after we reviewed the abstract and/or the title. The remaining 98 full-text articles were assessed for eligibility. Nineteen studies[11-13,19,20,23-36] were included in the systematic review based on the inclusion and exclusion criteria. The detailed process of search and selection is shown in Fig 1.

Study characteristics

The basic characteristics of these 19 studies are summarized in Table 1. These studies were published between 2005 and 2018, including 4 case-control, 2 prospective, and 13 retrospective studies. Studies were carried out in Asia (5 in South Korea, 4 in Taiwan, and 1 in Israel), Europe (3 in Spain, 1 in Greece, and 1 in Turkey), North America (2 in the United States), and South America (2 in Brazil).

The sample size ranged from 22-238. A total of 1,706 patients infected with CRAB were enrolled, including 899 (52.7%) reported deaths. Ten eligible studies were performed only on patients with bacteremia (923 patients in total), 3 studies only on patients with pneumonia (443 patients in total, including 1 study on patients with ventilator-associated pneumonia), 1 study only on patients with meningitis, and 5 studies on patients with all sources of infections.

Predictors of mortality in patients with CRAB

Prognosis factors previously considered to increase mortality in patients with CRAB were evaluated, and only those examined in at least

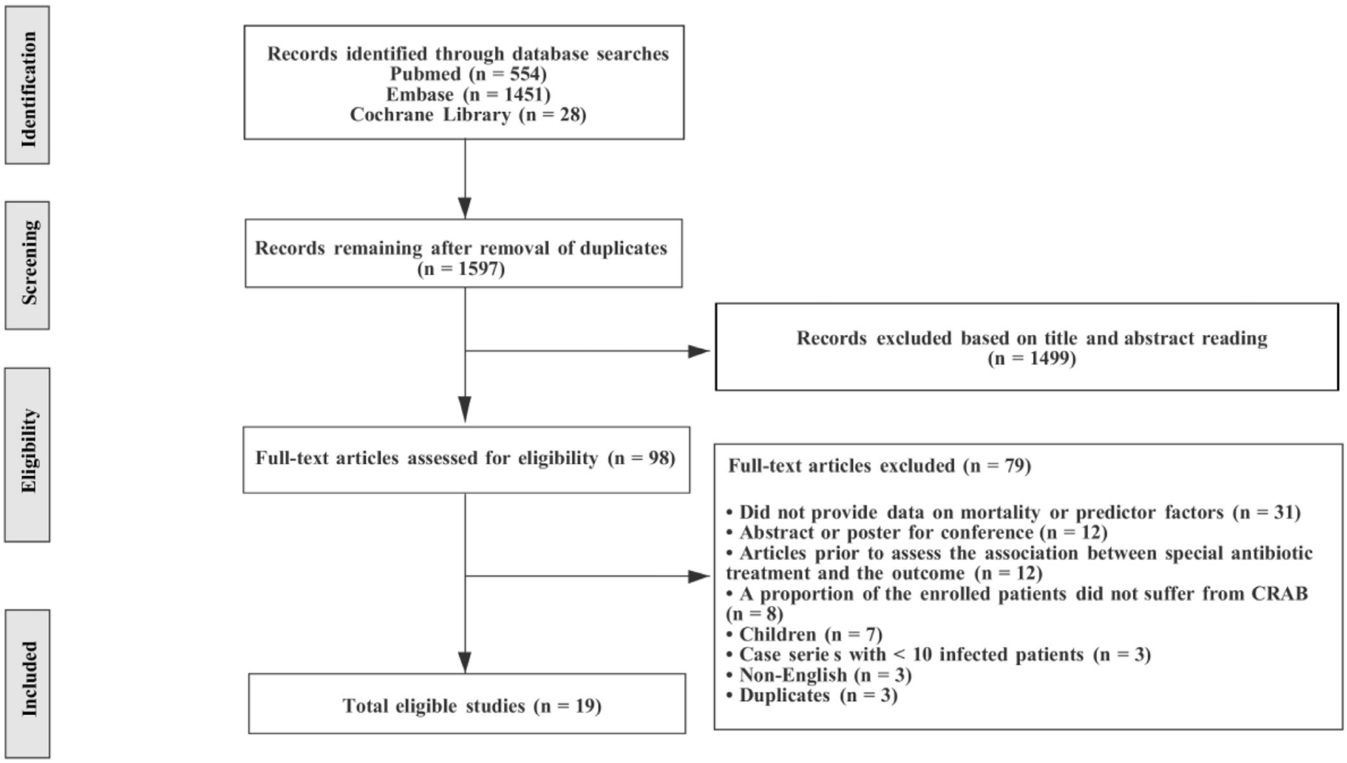

Fig 1. Flow diagram of included studies.

2 eligible studies were presented. Table 2 shows the comorbidities of patients at admission, such as chronic liver disease (OR, 2.36; 95% CI, 1.33-4.16), chronic renal disease (OR, 2.02; 95% CI, 1.37-2.99), hypertension (OR, 1.74; 95% CI, 1.08-2.80), septic shock (OR, 5.65; 95% CI, 2.35-13.57), and neutropenia (OR, 3.31; 95% CI, 1.25-8.77), were found to be associated with higher mortality. However, inappropriate empirical antimicrobial treatment (OR, 5.04; 95% CI, 2.56-9.94), steroid therapy (OR, 5.69; 95% CI, 1.82-17.75), immune-suppressant usage (OR, 3.15; 95% CI, 1.94-5.11), total parenteral nutrition (OR, 1.66; 95% CI, 1.08-2.56), and urinary catheter usage (OR, 2.91; 95% CI, 1.29-6.60) were also risk factors of higher mortality (Table 2, Supplementary Fig S1). To our surprise, ICU admission (OR, 1.69; 95% CI, 0.61-4.7) and mechanical ventilation (OR, 1.59; 95% CI, 0.86-2.95) were not risk factors of mortality.

Continuous variables as predictors of mortality in patients with CRAB

As shown in Table 3, the disease severity (14 studies; 10 studies assessed by APACHE II score, 2 studies by sepsis-related organ failure score, 1 study by Charlson's weighted index of comorbidity, and 1 study by Winston score) was observed to be associated with increased mortality in patients with CRAB. Quantitative analysis with fixed or random effects model indicated that elder age, higher APACHE II score, and higher Pitt bacteremia score at the onset day of *Acinetobacter* bacteremia were associated with higher mortality (Supplementary Fig S2).

Predictors of mortality among patients with CRAB bacteremia

Among the eligible articles, 10 studies[13,20,24-26,28,31,32,34,35] including 923 patients were performed on bacteremia, the pooled mortality of which was 56.3%. We assessed the risk factors previously considered to induce mortality among patients with CRAB bacteremia.

Supplementary Table S2 shows patients with baseline diseases at admission, such as chronic liver disease (OR, 2.75; 95% CI, 1.35-5.6) or chronic renal failure (OR, 5.28; 95% CI, 2.36-11.84), were found to be significantly associated with higher mortality. However, patients suffering from septic shock (OR, 4.36; 95% CI, 2.76-6.88), neutropenia (OR, 3.31; 95% CI, 1.25-8.77), steroid therapy (OR, 7.81; 95% CI, 2.13-28.67), immune-suppressant use (OR, 3.84; 95% CI, 2.09-7.06), as well as inappropriate empirical antimicrobial treatment (OR, 10.1; 95% CI, 4.06-25.14) were found to be associated with statistically significant risk factors of fatality.

We evaluated the association between several continuous variables present at hospital admission or at the day of bacteremia diagnosis and mortality (Supplementary Table S3). In this analysis, a random model resulted that the crude pooled Pitt bacteremia score at the day of bacteremia diagnosis was higher in the nonsurvival group than in the survival group (WMD, 1.46; 95% CI, 0.09-2.82).

Predictors of mortality among patients with CRAB pneumonia

In Supplementary Table S4, we summarized the reported risk factors of mortality of CRAB pneumonia included in 3 articles. We found that patients with chronic renal disease (OR, 4.82; 95% CI, 1.45-16.06) or septic shock (OR, 2.12; 95% CI, 1.41-3.19) at admission as well as inappropriate empirical antimicrobial treatment (OR, 1.86; 95% CI, 1.08-3.20) were related with higher mortality.

DISCUSSION

CRAB bacteremia tops the World Health Organization's threat list to human health and has emerged in recent decades as major causes of nosocomial infections.[8,37,38] Studies exploring predictors of mortality in patients infected with CRAB produced inconsistent results. Therefore, a comprehensive summary of the existing evidence is essential for health care providers and clinicians to make appropriate treatment decisions and to take appropriate preventive measures.

Table 1
General characteristics of the eligible studies

Study	Year	Country	Study period	Design	Definition of resistance	Resistance	Mortality day	Nonsurvivors/ CRAB patients (%)	Infection type
Tomas et al[23]	2005	Spain	October 2001 to August 2002	Case-contro / SC	NCCLS, 2003	Carbapenem	30 d	13/30 (43.3)	Any infection
Kwon et al[24]	2007	Korea	January 2000 to June 2005	R, matched / MC	CLSI 2005	Imipenem	30 d	23/40 (57.5)	BSI
Tseng et al[25]	2007	Taiwan	January 2001 to September 2004	R, cohort/ SC	CLSI 2000	XDR	30 d	27/56 (48.2)	BSI
Munoz Price et al[26]	2010	United States	January 2005 to April 2006	R, cohort/ MC	NA	Carbapenem	Over-all	35/86 (40.7)	BSI
Prates et al[27]	2011	Brazil	March 2006 to December 2008	R, cohort/ SC	CLSI 2006	Carbapenem	30 d	31/66 (47.0)	Any infection
Song et al[28]	2011	Korea	January 2005 to December 2010	R, cohort/ SC	CLSI 2006	Carbapenem	30 d	15/28 (53.6)	BSI
Aydemir et al[19]	2012	Turkey	January 2005 to December 2006	R, cohort/ SC	CLSI 2006	Carbapenem	NA	68/110 (61.8)	Any infection
Hernańdez-Torres et al[29]	2012	Spain	January 2007 to June 2008	P/SC	NA	Carbapenem	In-hospital	38/77 (49.4)	Any infection
Kim et al[20]	2012	Korea	January 2008 to December 2009	Case-control/ SC	CLSI 2008	Carbapenem	30 d	79/99 (79.8)	BSI
Shields et al[11]	2012	United States	November 2006to December 2011	R/SC	NA	XDR	28 d	22/41 (53.7)	Any infection
Moon et al[30]	2013	Korea	January 2005 to May 2011	R, cohort/ MC	CLSI 2012	Imipenem	Overall	13/22 (59.1)	PNSM
Nutman et al[31]	2014	Israel	July 2008 to July 2011	Case-control/ SC	CLSI 2011	Carbapenem	14 d	83/172 (48.3)	BSI
Lee et al[32]	2015	Taiwan	January 2010 to December 2010	R, cohort/ SC	CLSI 2013	Imipenem	NA	26/39 (66.7)	BSI
Alvarez-Marín et al[33]	2016	Spain	February 2010 to June 2011	P, cohort/ SC	CLSI 2007	Carbapenem	30 d	14/57 (24.6)	VAP
Freire et al[34]	2016	Brazil	July 2009 to July 2013	R/SC	NA	XDR	30 d	77/92 (83.7)	BSI
Liu et al[35]	2016	Taiwan	January 2009 to December 2012	R/SC	CLSI 2011	Imipenem	30 d	106/182(58.2)	BSI
Papadimitrious-Olivgeris et al[13]	2017	Greece	January 2010 to December 2015	Case-control/ SC	NA	Carbapenem	30 d	51/129 (39.5)	BSI
Liang et al[36]	2018	Taiwan	2010 to 2015	R/MC	NA	Carbapenem	In ICU	84/238 (35.3)	Pneumonia
Park et al[12]	2018	Korea	January 2012 to March 2015	R, cohort / MC	CLSI 2011	Carbapenem	30 d	103/146 (70.5)	Pneumonia

BSI, bloodstream infection; *CLSI*, Clinical and Laboratory Standards Institute; *CRAB*, carbapenem-resistant *Acinetobacter baumannii*; *MC*, multicenter; *NA*, not available/not applicable; *NOS*, Newcastle-Ottawa Scale; *P*, prospective; *PNSM*, post-neurosurgical meningitis; *R*, retrospective; *SC*, single center; *VAP*, ventilator-associated pneumonia; *XDR*, extensively drug resistance.

In the present study, inappropriate empirical therapy increased 5-fold of the pooled mortality of 1,169 patients (12 studies) with CRAB infection (OR, 5.04; 95% CI, 2.56-9.94; $P < .001$). Although 510 patients with CRAB bacteremia were included in 6 eligible studies, the mortality rate was 86.1% of patients who received inappropriate empirical antimicrobial therapy, which was significantly higher than that of 33.7% of patients who received appropriate antimicrobial treatment (OR, 10.1; 95% CI, 4.06-25.14). Our results clearly demonstrate that an inappropriate antimicrobial therapy can influence the survival rate in CRAB infections. Considerable studies have found that empirical therapy was more critical than definitive therapy in patients with CRAB infections and that alteration of therapy to an appropriate treatment after the available blood culture results did not have a significant effect on outcome.[12,39] All of these findings should be considered when choosing empirical antimicrobial therapy, and in hospitals with a high incidence of CRAB, use of more aggressive initial antimicrobial therapy, including colistin, may be an option.

The prognosis of patients with CRAB infection also depends on the host condition, such as severity of disease and immune status. CRAB typically affects critically ill patients. One included study reported approximately 80% of the infected patients were suffering from a variety of baseline diseases, particularly cardiopulmonary disease.[23] Our results demonstrate that the fatality rate of patients with underlying illnesses (eg, chronic liver disease, chronic renal disease, and hypertension) or immunosuppression status was higher in different degrees than in patients without these conditions (Table 2). Our study also suggested that invasive procedures (eg, urinary catheter and intubation) usage during hospital stay was associated with adverse outcome of patients with CRAB. In addition, we found that the presence of septic shock during CRAB infection was associated with higher mortality (OR, 5.65; 95% CI, 2.35-13.57). Septic shock is a sign of severe infection, which is often present in critically ill patients, who are more likely to die after critical strike.

Severity of illness of CRAB in most studies (10/14) were assessed with the APACHE II scoring system at admission. Mean APACHE II score was ranged from 15.77-25.0, varied among different source of infection and including criteria (Table 3). Quantitative analysis with a fixed random effects model indicated that APACHE II score at admission to ICU or hospital was much higher in the nonsurvival group than in those of survival group (WMD, 2.70; 95% CI, 2.21-3.18). Meanwhile, Pitt bacteremia score at the day of diagnosis of *Acinetobacter* bacteremia were also associated with higher mortality (WMD, 1.46; 95% CI, 0.09-2.82). Tseng et al[25] reported that Pitt bacteremia score ≥4 was an independent factor that predicted 30-day mortality from extensively resistant *Acinetobacter baumannii* bacteremia (OR, 18.53). The Pitt bacteremia score evaluated patients along 5 parameters, including body temperature, blood pressure and/or shock status, ventilator dependence, cardiac arrest, and consciousness at the onset of bacteremia. Scoring is easy and validated, and correlates well with clinical outcomes in studies of bloodstream infections, such as *Pseudomonas aeruginosa*, *Enterobacter*, *Klebsiella*, and *pneumococcus*.[40,41] APACHE II score is a very important and useful scoring system for clinicians to evaluate the severity of diseases and to predict the outcome of patients with CRAB.

Our study has several limitations. First, the heterogeneity in effect estimates could also depend on differences in study design or quality of the studies. Most studies employed retrospective study designs, which may be susceptible to selection bias through differential loss to follow up and misclassification of survival status. Second, most studies may have lacked power in differentiating death caused by CRAB from any other factors, and it is difficult to draw definitive conclusions from current evidence because of the residual confounding factors and small sample sizes in many studies. Last, we selected only English-language articles, thus limiting the scope of our analysis.

Table 2
Risk factors for mortality in patients with CRAB at admission

Type of factor	No. of studies	No. of patients in studies (nonsurvivors)	No. of patients in studies reporting specific data (nonsurvivors)	I^2 (%)	*P* value of Heterogeneity	Pooled OR (95% CI)	*P* value	*P* value of Egger test
Characteristics								
Sex, male	14	1384 (733)	867 (444)	7.3	.373	0.89 (0.71-1.12)	.330	.259
ICU admission	5	614 (345)	470 (277)	79.2	.001	1.69 (0.61-4.70)	.312	.668
Comorbidities								
Diabetes mellitus	9	893 (439)	242 (152)	33	.154	1.19 (0.86-1.64)	.302	.357
Chronic liver disease	7	618 (364)	69 (49)	0.0	.449	2.36 (1.33-4.16)	.003	.383
Chronic renal disease	11	1042 (609)	176 (116)	38.6	.092	2.02 (1.37-2.99)	.000	.242
Cerebrovascular diseases	7	582 (361)	110 (62)	41.9	.112	0.76 (0.49-1.18)	.218	.713
Chronic obstructive lung diseases	7	771 (460)	118 (74)	43.7	.100	1.02 (0.67-1.56)	.925	.871
Hypertension	4	468 (291)	126 (89)	5.7	.364	1.74 (1.08-2.80)	.022	.199
Hematologic malignancy	4	329 (239)	68 (58)	40.8	.167	1.55 (0.74-3.26)	.245	.458
Solid organ malignancy	10	985 (595)	212 (148)	0.0	.804	1.21 (0.85-1.72)	.300	.944
Transplantation	3	232 (144)	63 (35)	0.0	.598	2.28 (0.86-6.03)	.096	.920
Respiratory failure	3	414 (201)	210 (126)	88.2	.000	3.49 (0.56-21.61)	.180	.198
Congestive heart failure	6	509 (282)	109 (64)	14.2	.323	1.61 (0.97-5.78)	.064	.777
Renal failure	5	507 (298)	97 (79)	59.3	.044	3.40 (1.91-6.03)	.018	.766
Hepatic failure	3	232 (144)	29 (24)	0.0	.684	3.03 (1.09-8.40)	.033	.572
Septic shock	11	1172 (623)	517 (360)	85.2	.000	5.65 (2.35-13.57)	.000	.048
Neutropenia	4	429 (289)	50 (46)	42.9	.154	3.31 (1.25-8.77)	.016	.412
Chemotherapy	3	404 (179)	26 (13)	0.0	.894	0.89 (0.40-1.99)	.784	.430
Steroid therapy	2	166 (95)	24 (19)	0.0	.396	5.69 (1.82-17.75)	.003	NA
Immunosuppressant use	5	479 (266)	108 (80)	10.1	.348	3.15 (1.94-5.11)	.000	.374
Total parenteral nutrition	5	526 (278)	160 (88)	0.0	.601	1.66 (1.08-2.56)	.021	.080
Invasive procedures								
Nasogastric tube	4	271 (148)	176 (102)	0.0	.998	1.70 (1.01-2.87)	.048	.441
Urinary catheter usage	3	243 (133)	210 (123)	0.0	.447	2.91 (1.29-6.60)	.010	.074
Central venous catheter	4	440 (278)	317 (205)	0.0	.563	1.36 (0.87-2.12)	.182	.540
Peripheral catheter usage	2	166 (95)	87 (52)	0.0	.860	0.96 (0.48-1.95)	.918	NA
Intubation	2	166 (95)	124 (83)	0.0	.491	5.03 (2.33-10.87)	.000	NA
Tracheostomy	3	425 (190)	93 (40)	0.0	.578	0.82 (0.48-1.38)	.449	.798
Mechanical ventilation	7	837 (412)	684 (351)	50.3	.006	1.59 (0.86-2.95)	.141	.515
Hemodialysis	5	712 (365)	129 (79)	7.3	.365	1.34 (0.88-2.02)	.172	.626
Poly-microbial specimen	5	534 (275)	162 (82)	0.0	.804	0.94 (0.62-1.44)	.786	.053
Inappropriate empirical antimicrobial treatment	12	1169 (633)	684 (449)	76.0	.000	5.04 (2.56-9.94)	.000	.232

CI, confidence interval; *CRAB*, carbapenem-resistant *Acinetobacter baumannii*; *NA*, not available; *OR*, odds ratio.

CONCLUSIONS

Our prognosis of patients infected with CRAB is determined by 2 factors: the patients' condition, specifically underlying illnesses and severity of diseases, and receiving inappropriate initial antibiotic treatment. Our findings of mortality risk factors may help investigators to formulate reasonable predicting scores for patients with CRAB, which may further motivate clinicians to provide appropriate initial antibiotic treatment and to treat underlying illness and shock optimally in such patients.

Table 3
Continuous variables and risk for mortality in patients with CRAB

Continuous variable	No. of studies (total/ meta)	No. of patients in studies reporting specific data (nonsurvivors)	No. of studies reporting no difference between nonsurvivors and survivors (%)	No. of studies reporting worsen values for nonsurvivors than for survivors (%)	I^2 (%)	WMD (95% CI)	*P* value
Age, years	14/14	1,268 (643)	11 (78.6)	3 (21.4)	60.0	1.75 (0.55-3.55)	.002
ICU stay before infection (d)	3/3	186 (123)	3 (100.0)	0 (0.0)	0.0	0.21 (3.25-3.67)	.906
Hospital stay before infection (d)	6/6	681 (323)	4 (66.7)	2 (33.3)	74.2	1.78 (0.96-4.51)	.202
APACHE II score (at admission to ICU/ hospital)	10/7	665 (239)	4 (40.0)	6 (60.0)	44.4	2.70 (2.21-3.18)	.000
Pitt bacteremia score (on BSI d)	4/3	295 (149)	1 (25.0)	3 (75.0)	79.6	1.46 (0.09-2.82)	.036
*Disease severity (at admission to ICU/ hospital)	14/NA	1476 (702)	6 (42.9)	8 (57.1)	NA	NA	NA
**Disease severity (at day of diagnosis of infection)	6/NA	415 (246)	3 (50.0)	3 (50.0)	1.75 (-0.55-3.55)	0.21 (-3.25-3.67)	1.78 (-0.96-4.51)

APACHE II, Acute Physiology and Chronic Health Evaluation II score; *BSI*, blood stream infection; *CRAB*, carbapenem-resistant *Acinetobacter baumannii*; *ICU*, intensive care unit; *NA*, not available; *WMD*, weighted mean difference.
*Disease severity at ICU/hospital admission was assessed by means of APACHE II score (10 studies), Charlson's weighted index of comorbidity (2 studies), sequential organ failure assessment score (1 study), and Winston score (1 study).
**Disease severity at day of diagnosis of infection was assessed by means of APACHE II score (1 study), Charlson's weighted index of comorbidity (1 study), sequential organ failure assessment score (2 studies), and Glasgow Coma Scale score (2 studies).

SUPPLEMENTARY MATERIALS

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References

1. Potron A, Poirel L, Nordmann P. Emerging broad-spectrum resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: mechanisms and epidemiology. Int J Antimicrob Agents 2015;45:568-85.
2. Weinstein RA, Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis 2005;41:848-54.
3. Codjoe FS, Donkor ES. Carbapenem resistance: a review. Med Sci (Basel) 2017;6:1-28.
4. Mahamat A, Bertrand X, Moreau B, Hommel D, Couppie P, Simonnet C, et al. Clinical epidemiology and resistance mechanisms of carbapenem-resistant *Acinetobacter baumannii*, French Guiana, 2008-2014. Int J Antimicrob Agents 2016;48:51-5.
5. Munoz-Price LS, Weinstein RA. *Acinetobacter* infection. N Engl J Med 2008;358:1271-81.
6. Abbott I, Cerqueira GM, Bhuiyan S, Peleg AY. Carbapenem resistance in *Acinetobacter baumannii*: laboratory challenges, mechanistic insights and therapeutic strategies. Expert Rev Anti Infect Ther 2013;11:395-409.
7. Kuo SC, Chang SC, Wang HY, Lai JF, Chen PC, Shiau YR, et al. Emergence of extensively drug-resistant *Acinetobacter baumannii* complex over 10 years: nationwide data from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program. BMC Infect Dis 2012;12:200-8.
8. Willyard C. The drug-resistant bacteria that pose the greatest health threats. Nature 2017;543:15.
9. Choi JY, Kwak YG, Yoo H, Lee SO, Kim HB, Han SH, et al. Trends in the distribution and antimicrobial susceptibility of causative pathogens of device-associated infection in Korean intensive care units from 2006 to 2013: results from the Korean Nosocomial Infections Surveillance System (KONIS). J Hosp Infect 2016;92:363-71.
10. Lemos EV, de la Hoz FP, Einarson TR, McGhan WF, Quevedo E, Castaneda C, et al. Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis. Clin Microbiol Infect 2014;20:416-23.
11. Shields RK, Clancy CJ, Gillis LM, Kwak EJ, Silveira FP, Massih RC, et al. Epidemiology, clinical characteristics and outcomes of extensively drug-resistant *Acinetobacter baumannii* infections among solid organ transplant recipients. PLoS One 2012;7:e52349.
12. Park SY, Lee EJ, Kim T, Yu SN, Park KH, Lee MS, et al. Early administration of appropriate antimicrobial agents to improve the outcome of carbapenem-resistant *Acinetobacter baumannii* complex bacteraemic pneumonia. Int J Antimicrob Agents 2018;51:407-12.
13. Papadimitriou-Olivgeris M, Fligou F, Spiliopoulou A, Koutsileou K, Kolonitsiou F, Spyropoulou A, et al. Risk factors and predictors of carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* mortality in critically ill bacteraemic patients over a 6-year period (2010-15): antibiotics do matter. J Med Microbiol 2017;66:1092-101.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
15. Playford EG, Craig JC, Iredell JR. Carbapenem-resistant *Acinetobacter baumannii* in intensive care unit patients: risk factors for acquisition, infection and their consequences. J Hosp Infect 2007;65:204-11.
16. Prata-Rocha ML, Gontijo-Filho PP, Melo GB. Factors influencing survival in patients with multidrug-resistant *Acinetobacter baumannii* infection. Braz J Infect Dis 2012;16:237-41.
17. Retamar P, Portillo MM, Lopez-Prieto MD, Rodriguez-Lopez F, de Cueto M, Garcia MV, et al. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. Antimicrob Agents Chemother 2012;56:472-8.
18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
19. Aydemir H, Celebi G, Piskin N, Oztoprak N, Keskin AS, Aktas E, et al. Mortality attributable to carbapenem-resistant nosocomial *Acinetobacter baumannii* infections in a Turkish university hospital. Jpn J Infect Dis 2012;65:66-71.
20. Kim SY, Jung JY, Kang YA, Lim JE, Kim EY, Lee SK, et al. Risk factors for occurrence and 30-day mortality for carbapenem-resistant *Acinetobacter baumannii* bacteremia in an intensive care unit. J Korean Med Sci 2012;27:939-47.
21. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res 2018;27:1785-805.
22. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135-47.
23. del Mar Tomas M, Cartelle M, Pertega S, Beceiro A, Llinares P, Canle D, et al. Hospital outbreak caused by a carbapenem-resistant strain of *Acinetobacter baumannii*: patient prognosis and risk-factors for colonisation and infection. Clin Microbiol Infect 2005;11:540-6.
24. Kwon KT, Oh WS, Song JH, Chang HH, Jung SI, Kim SW, et al. Impact of imipenem resistance on mortality in patients with Acinetobacter bacteraemia. J Antimicrob Chemother 2007;59:525-30.
25. Tseng YC, Wang JT, Wu FL, Chen YC, Chie WC, Chang SC. Prognosis of adult patients with bacteremia caused by extensively resistant *Acinetobacter baumannii*. Diagn Microbiol Infect Dis 2007;59:181-90.
26. Munoz-Price LS, Zembower T, Penugonda S, Schreckenberger P, Lavin MA, Welbel S, et al. Clinical outcomes of carbapenem-resistant *Acinetobacter baumannii* bloodstream infections: study of a 2-state monoclonal outbreak. Infect Control Hosp Epidemiol 2010;31:1057-62.
27. Prates CG, Martins AF, Superti SV, Lopes FS, Ramos F, Cantarelli VV, et al. Risk factors for 30-day mortality in patients with carbapenem-resistant *Acinetobacter baumannii* during an outbreak in an intensive care unit. Epidemiol Infect 2011;139:411-8.
28. Song JY, Cheong HJ, Choi WS, Heo JY, Noh JY, Kim WJ. Clinical and microbiological characterization of carbapenem-resistant *Acinetobacter baumannii* bloodstream infections. J Med Microbiol 2011;60:605-11.
29. Hernandez-Torres A, Garcia-Vazquez E, Gomez J, Canteras M, Ruiz J, Yague G. Multidrug and carbapenem-resistant *Acinetobacter baumannii* infections: factors associated with mortality. Med Clin (Barc) 2012;138:650-5.
30. Moon C, Kwak YG, Kim BN, Kim ES, Lee CS. Implications of postneurosurgical meningitis caused by carbapenem-resistant *Acinetobacter baumannii*. J Infect Chemother 2013;19:916-9.
31. Nutman A, Glick R, Temkin E, Hoshen M, Edgar R, Braun T, et al. A case-control study to identify predictors of 14-day mortality following carbapenem-resistant *Acinetobacter baumannii* bacteraemia. Clin Microbiol Infect 2014;20:1028-34.
32. Lee HY, Huang CW, Chen CL, Wang YH, Chang CJ, Chiu CH. Emergence in Taiwan of novel imipenem-resistant *Acinetobacter baumannii* ST455 causing bloodstream infection in critical patients. J Microbiol Immunol Infect 2015;48:588-96.
33. Alvarez-Marin R, Lopez-Rojas R, Marquez JA, Gomez MJ, Molina J, Cisneros JM, et al. Colistin dosage without loading dose is efficacious when treating carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia caused by strains with high susceptibility to colistin. PLoS One 2016;11:e0168468.
34. Freire MP, de Oliveira Garcia D, Garcia CP, Campagnari Bueno MF, Camargo CH, Kono Magri ASG, et al. Bloodstream infection caused by extensively drug-resistant *Acinetobacter baumannii* in cancer patients: high mortality associated with delayed treatment rather than with the degree of neutropenia. Clin Microbiol Infect 2016;22:352-8.
35. Liu CP, Shih SC, Wang NY, Wu AY, Sun FJ, Chow SF, et al. Risk factors of mortality in patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia. J Microbiol Immunol Infect 2016;49:934-40.
36. Liang CA, Lin YC, Lu PL, Chen HC, Chang HL, Sheu CC. Antibiotic strategies and clinical outcomes in critically ill patients with pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*. Clin Microbiol Infect 2018;24, 908.e1-7.
37. Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. Clin Microbiol Rev 2008;21:538-82.
38. Santajit S, Indrawattana N. Mechanisms of antimicrobial resistance in ESKAPE pathogens. Biomed Res Int 2016;2016:2475067.
39. Erbay A, Idil A, Gozel MG, Mumcuoglu I, Balaban N. Impact of early appropriate antimicrobial therapy on survival in *Acinetobacter baumannii* bloodstream infections. Int J Antimicrob Agents 2009;34:575-9.
40. Yu VL, Chiou CC, Feldman C, Ortqvist A, Rello J, Morris AJ, et al. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. Clin Infect Dis 2003;37:230-7.
41. Hill PC, Birch M, Chambers S, Drinkovic D, Ellis-Pegler RB, Everts R, et al. Prospective study of 424 cases of *Staphylococcus aureus* bacteraemia: determination of factors affecting incidence and mortality. Intern Med J 2001;31:97-103.