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Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis

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Abstract

Acinetobacter baumannii has emerged as a major cause of healthcare-associated infections. Controversy exists as to whether antimicrobial resistance increases the risk of mortality. We conducted a systematic review and meta-analysis to examine this association. We searched MEDLINE and EMBASE databases up to May 2013 to identify studies comparing mortality in patients with carbapenem-resistant *A. baumannii* (CRAB) vs. carbapenem-susceptible *A. baumannii* (CSAB). A random-effects model was used to pool Odds Ratios (OR). Heterogeneity was examined using I^2. We included 16 observational studies. There were 850 reported deaths (33%) among the 2546 patients. Patients with CRAB had a significantly higher risk of mortality than patients with CSAB in the pooled analysis of crude effect estimates (crude OR = 2.22; 95% CI = 1.66, 2.98), although substantial heterogeneity was evident (heterogeneity I^2 = 55%). The association remained significant in the pooled adjusted OR of 10 studies. Studies reported that patients with CRAB compared to patients with CSAB were more likely to have severe underlying illness and also to receive inappropriate empirical antimicrobial treatment, which increases the risk of mortality. Our study suggests that carbapenem resistance may increase the risk of mortality in patients with *A. baumannii* infection. However, cautious interpretation is required because of the residual confounding factors and inadequate sample size in most studies.

Keywords: Acinetobacter, carbapenem, imipenem, meta-analysis, mortality, resistance
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Introduction

Acinetobacter baumannii causes healthcare-associated infections (HAI), often affecting critically ill patients [1–3]. HAIs due to *A. baumannii* have been associated with an increased risk of mortality by 8% to 40% [2–4]. Of particular concern are the prolonged survival of *A. baumannii* and the remarkable ability of this pathogen to acquire resistance to multiple antibiotics [2,5]. Rates of carbapenem resistance increased in the US from 9% in 1995 to 40% in 2004 and from 14% in 2003 to 46% in 2008 in Taiwan [1,6]. Recent studies have reported high rates of resistance across the world, particularly in Asia-Pacific and Latin America [1,2,7,8]. Limited treatment options are available for *A. baumannii* infection.

Antibiotic resistance may adversely affect clinical outcomes. There is ongoing controversy as to whether carbapenem resistance results in an increased risk of mortality in patients infected with *A. baumannii*. Previous studies have reported conflicting results. A comprehensive summary of the existing evidence is essential for healthcare providers and policy makers to make appropriate treatment decisions and recommendations and to take appropriate preventive measures. We therefore conducted a systematic review and meta-analysis to examine the association between carbapenem

resistance and risk of mortality in patients with *A. baumannii* infection.

Methods

Search strategy and study selection

Studies were included if the authors compared mortality in patients with carbapenem-resistant *A. baumannii* (CRAB) versus carbapenem-susceptible *A. baumannii* (CSAB). We excluded studies that examined only patients with either CRAB or CSAB. We included published articles written in English or Spanish. Letters or abstracts presented in conferences were not included.

We searched MEDLINE and EMBASE databases up to May 2013 to identify potentially relevant studies. In addition, we used the Cochrane library, Scielo, Cinah and Sumserach2. We also searched the references of the potentially relevant articles. The following search terms were used: 'Acinetobacter' AND ('mortality' or 'death') AND ('resistance' or 'carbapenem' or 'imipenem' or 'meropenem'). Two investigators (EVL and KK) independently performed systematic literature reviews, assessed study eligibility, and extracted information from included studies. Results for the two reviewers were compared, with discrepancies settled through consensus discussion.

Data extraction

We extracted information regarding study characteristics (authors, published year, journal, country, study period, study design and sample size), study population (mean age, mean severity of illness, sites of infection, definition of resistance, proportion of resistance and overall mortality rates), crude mortality rates in patients with CRAB and in patients with CSAB, reported crude and adjusted effect estimates, and variables included in confounder adjustment in multivariate analysis.

Data analysis

In the unadjusted analysis, we estimated odds ratios (OR) and corresponding standard errors by comparing crude mortality in patients with CRAB to that in patients with CSAB. For multivariate analysis, we calculated standard errors from adjusted OR and 95% confidence interval (95% CI). For studies that reported risk ratio (RR), we converted to OR. The natural logarithms of the ORs and their corresponding standard errors were used to pool the effect estimates across studies using the DerSimonian and Laird random effects model [9]. We estimated pooled crude and pooled adjusted effect estimates. In the primary analysis for pooled adjusted effect estimates, we included studies that reported adjusted ORs. Several studies found no statistically significant association in the univariate analysis and did not report adjusted effect estimates. Because exclusion of these studies in adjusted pooled effect estimates could bias the results, we included them, assuming a OR of 1 and using the standard error from the univariate analysis for a sensitivity analysis.

Heterogeneity of ORs across studies was assessed by the Higgins' I^2 statistic [10]. The I^2 statistic describes the percentage of variation among studies due to heterogeneity rather than chance. To identify the potential sources of heterogeneity, we conducted subgroup analysis. We examined the effect estimates by source of infection, geographic region and definition of resistance (carbapenem or imipenem). We conducted meta-regression analysis to examine whether effect estimates differ significantly by each variable. To assess the possibility of publication bias, we visually inspected the funnel plot for asymmetry and performed the Begg's test and Egger's test [11,12]. All analyses were performed using STATA version 11.

Results

We identified and screened 407 publications, 361 of which were excluded after we reviewed the abstract and/or title. We read the full text of the remaining 46 candidate articles. Thirty articles were excluded because they were review articles (n = 10) or duplicate publications (n = 1), did not evaluate the outcome of interests (n = 15), or enrolled patients who did not have CRAB or CSAB (n = 4) (Data S1). After exclusions, a total of 16 observational studies were included in this review.

Study characteristics of the 16 included studies are summarized in Tables 1 and 2 [13–28]. The sample size of studies ranged from 52 to 386. The total number of patients included in the meta-analysis was 2546, with 850 reported deaths (33%). All studies exclusively examined patients with *Acinetobacter baumannii* infections, with the exception of three studies that included other *Acinetobacter* species [14,15,18]. In cohort studies, the reported resistance to carbapenem varied across studies, ranging from 19% to 67% (Table 1). Ten studies examined patients with bacteraemia [14,15,17–21,23,25,26], four studies examined all sources of infections [13,16,24,27], and two studies examined pneumonia [22,28]. Studies were conducted in North America (three in the USA) [13,16,21], Asia (three in Taiwan, two in South Korea, one each in Malaysia, Thailand and China) [14,17,19,22,23,25,26,28], Europe (two studies in Turkey and one each in the UK and Greece) [15,18,20,24], and South America (one study in Colombia) [27]. Among 16 studies, 13 followed the Clinical

TABLE 1. Study characteristics

First author and Year	Country	Study years	Data collection	Source of infection	Sample size	Definition of resistance	Resistance	% Resistance
Cofsky 2002 [13]	US	1999	Retrospective case-control study	Any infection (59% pneumonia)	77	NA	Carbapenem	NA
Kwon 2007 [14]	South Korea	2000–2005	Retrospective matched-cohort study	Bacteremia (36% catheter related infection; 23% pneumonia)	80	CLSI guidelines 2005	Imipenem	NA
Wareham 2008 [15]	UK	1998–2006	Retrospective cohort study	Bacteremia (mostly catheter related infection)	298	NA	Carbapenem	18.5
Lautenbach 2009 [16]	US	2001–2006	Retrospective cohort study	Any infection or colonization	386	CLSI guidelines 2008	Imipenem	23.1
Jamulitrat 2009 [17]	Thailand	2004–2007	Retrospective cohort study	Bacteremia (45% catheter related infection; 17% pneumonia)	198	NA	Imipenem	33.8
Metan 2009 [18]	Turkey	2007–2008	Prospective cohort study	Bacteremia (29% pneumonia; 19% post-surgical wound)	100	CLSI guidelines 2005	Carbapenem	54.0
Sheng 2010 [19]	Taiwan	2004–2006	Retrospective cohort study	Bacteremia (70% catheter related infection)	123	CLSI guidelines 2007	Carbapenem	51.2
Routsi 2010 [20]	Greece	2004–2006	Prospective cohort study	Bacteremia (51% pneumonia; 16% catheter related infection)	96	CLSI guidelines 2007	Carbapenem	31.3
Esterly 2011 [21]	US	2005–2008	Retrospective cohort study	Bacteremia	79	CLSI guidelines 2009	Carbapenem	46.8
Chang 2011 [22]	Taiwan	2005–2007	Retrospective cohort study	Ventilator-associated pneumonia	180	CLSI guidelines	Imipenem	51.7
Deris 2011 [23]	Malaysia	N/A	Retrospective cohort study	Bacteremia (mostly catheter related infection)	56	CLSI guidelines	Imipenem	26.8
Aydemir 2012 [24]	Turkey	2005–2006	Retrospective cohort study	Any infection (70% pneumonia)	165	CLSI guidelines 2006	Carbapenem	66.7
Huang 2012 [25]	Taiwan	2002–2007	Retrospective cohort study	Bacteremia (42% pneumonia; 10% catheter related infection)	226	CLSI guidelines 2011	Carbapenem	27.4
Kim 2012 [26]	South Korea	2007–2010	Retrospective cohort study	Bacteremia (30% pneumonia; 25% catheter related infection)	95	CLSI guidelines 2008	Carbapenem	55.8
Lemos 2013 [27]	Colombia	2006–2010	Prospective cohort study	Any infection (35% pneumonia; 15% catheter related infection)	165	CLSI guidelines 2006	Carbapenem	63.0
Zheng 2013 [28]	China	2006–2011	Retrospective cohort study	Pneumonia	242	CLSI guidelines 2011	Carbapenem	40.1

Clinical and Laboratory Standard Institute (CLSI).

Laboratory Standards Institute breakpoints for *A. baumannii* of imipenem and meropenem (sensitive at $\leq$4 μg/ml and resistant at $\geq$16 μg/ml; Table 1).

The summary estimate of the 16 included studies from the random-effects model suggested that patients with CRAB had a significantly higher mortality than patients with CSAB in the univariate analysis (pooled crude OR = 2.22; 95% CI = 1.66, 2.98; Figure 1). However, effect estimates varied across studies, with a statistically significant heterogeneity I^2 of 55%.

Ten studies reported adjusted effect estimates and adjusted for confounding variables, such as severity of underlying disease, co-morbidities and appropriate antimicrobial therapy (Table 2). When we pooled the adjusted effect estimates, the association between carbapenem resistance and mortality remained statistically significant (pooled adjusted OR = 2.49; 95% CI = 1.61, 3.84; I^2 heterogeneity 32%; Fig. 2). Six other studies did not report adjusted ORs. It is important to note that four of these studies did not report adjusted RRs because they found no statistically significant association in the univariate analysis or the association did not remain significant in multivariate analysis. For sensitivity analysis, we pooled four of these studies (assuming adjusted OR = 1) and 10 studies that reported adjusted ORs and found a pooled adjusted OR = 1.77 (95% CI = 1.22, 2.55; I^2 heterogeneity 50%). For crude and adjusted effect estimates, we did not find evidence of publication bias in Begg's funnel plot test ($p > 0.20$) or Egger's test ($p > 0.20$).

Because inappropriate antimicrobial treatment and severity of underlying illness are potential confounding factors, we assessed these variables (Table 2). Seven studies reported that patients with CRAB were more likely to receive inappropriate empirical antibiotic treatment than patients with CSAB. Moreover, six studies reported that patients with CRAB were more likely to have severe underlying illness than patients with CSAB. As previously known, inappropriate empirical antibiotic treatment and APACHE II score were significant risk factors for mortality in most studies.

We also conducted subgroup analysis using the crude pooled estimates (Table 3). We did not observe any difference in pooled effect estimates by geographical regions, sources of infection or definitions of resistance.

Discussion

Acinetobacter baumannii causes healthcare-associated infections, often affecting critically ill patients. Our systematic review and meta-analysis suggests that patients infected with CRAB have higher mortality rates compared to patients with CSAB in the pooled crude effect estimate. We found that the

TABLE 2. Study results

First author and Year	Crude mortality rate CRAB vs. CSAB	Adjusted RR or OR (95% CI)	Variables adjusted in the multivariable model (Variables considered but not included in the final model)	Inappropriate antimicrobial treatment CRAB vs. CSAB	Inappropriate antimicrobial treatment and risk of mortality	Severity of disease CRAB vs. CSAB	Severity of disease and risk of mortality
Cofsky 2002 [13]	34% (15/44) vs. 27% (9/33)	NA	Not adjusted	NA	NA	NA	NA
Kwon 2007 [14]	58% (23/40) vs. 28% (11/40)	Adjusted OR = 3.90 (0.90, 16.89)	Age, Charlson comorbidity index, Pitt bacteremia score, immunosuppressive status, inappropriate antimicrobial treatment, acute renal failure, and pneumonia.	CRAB: 65% vs. CSAB: 20% (p <0.01)	Adjusted OR = 6.05 (1.34, 27.3)	Charlson co-morbidity CRAB 2.8 vs. CSAB 2.9 (no significant difference)	Charlson co-morbidity: Adjusted OR = 2.85 (0.23, 6.52)
Wareham 2008 [15]	16% (9/55) vs. 5% (13/243)	Adjusted OR = 2.27 (0.87, 5.93)	Intensive care treatment (Considered inappropriate antimicrobial treatment)	CRAB: 77% vs. CSAB: 41%	Crude OR = 1.59 (p 0.25)	NA	NA
Lautenbach 2009 [16]	18% (16/89) vs. 21% (63/297)	Adjusted OR = 5.30 (0.81, 34.59)	Patient location in an ICU, transfer from another healthcare facility, and duration of hospitalization (Considered: age, prior antibiotic use, diabetes).	NA	NA	NA	NA
Jamulitrat 2009 [17]	52% (35/67) vs. 20% (26/131)	Adjusted RR = 1.7 (0.9, 2.9)	Inappropriate antibiotic treatment, severity of underlying disease status (ASA and SOFA scores), and acquired bacteremia in ICU (Considered: age, gender, prior hospital stay, and pneumonia.)	CRAB: 39% vs. CSAB: 12% (p <0.01)	Adjusted RR = 3.3 (p <0.01)	Severity of illness ASA score CRAB 3.2 vs. CSAB 3.1 (no significant difference)	Severity of illness ASA score Adjusted RR = 2.7 (p <0.01)
Metan 2009 [18]	76% (41/54) vs. 48% (22/46)	Adjusted RR = 1.63 (1.19, 1.89)	Diabetes mellitus and septic shock (Considered: inappropriate antimicrobial treatment, underlying illness, Charlson comorbidity index, and site of infection.)	NA	Crude RR = 1.67 (1.13, 2.05)	NA	Charlson co-morbidity was not significant risk factor for mortality
Sheng 2010 [19]	46% (29/63) vs. 28% (17/60)	Adjusted RR = 5.31 (1.88, 13.25)	Central venous catheterization and ICU stay (Considered: age, gender, underlying disease, and prior invasive procedure.)	NA	NA	NA	NA
Routsi 2010 [20]	43% (13/30) vs. 47% (31/66)	NA. Not significant[a]	Not considered for multivariate analysis (Considered: age, gender, inappropriate antimicrobial treatment, APACHE II, comorbidities, severity of organ failure, and WBC count)	CRAB: 43% vs. CSAB: 24% (p 0.06)	NA	APACHE II score CRAB 17.8 vs. CSAB 18.0 (no significant difference)	APACHE II score was significant risk factor for mortality
Esterly 2011 [21]	57% (21/37) vs. 24% (10/42)	Adjusted OR = 0.73 (0.14, 3.84)	Inappropriate antimicrobial treatment, renal dysfunction, any transplant, residency in ICU at time of culture, number of sites of infection, and days of prior antibiotics (Considered: age, gender, and underlying disease)	CRAB: 24% vs. CSAB: 5% (p 0.02)	Adjusted OR = 16.7 (p 0.05)	NA	NA
Chang 2011 [22]	61% (57/93) vs. 46% (40/87)	NA. Not significant[a]	Not considered for multivariate analysis (Considered: age, gender, comorbidity, Charlson comorbidity index, diabetes mellitus, tracheostomy, and inappropriate antimicrobial treatment)	CRAB 79% vs. CSAB 76% (p 0.67)	Adjusted OR = 4.06 (1.39, 11.87)	Charlson co-morbidity CRAB 3.6 vs. CSAB 2.8 (p <0.01)	Charlson co-morbidity was not significant risk factor for mortality
Deris 2011 [23]	60% (9/15) vs. 37% (15/41)	NA	Not adjusted	CRAB 20% vs. CSAB 7% (p 0.19)	NA	NA	NA
Aydemir 2012 [24]	62% (68/110) vs. 53% (29/55)	NA. Not significant[a]	Not considered for multivariate analysis (Considered: inappropriate antimicrobial treatment, APACHE II, underlying disease status, and comorbidity)	CRAB 78% vs. CSAB 21%	Crude RR = 2.0 (1.3, 3.1)	APACHE II score CRAB 21.0 vs. CSAB 18.6 (p 0.02)	APACHE II score was significant risk factor for mortality
Huang 2012 [25]	35% (22/62) vs. 21% (34/164)	Adjusted OR = 1.03 (0.43, 2.2)	Inappropriate antimicrobial treatment, APACHE II, shock, hematological malignancy, and others (Considered: Age, gender, and comorbidity)	NA	Adjusted OR = 2.14 (1.01, 4.53)	APACHE II> 20 score CRAB 80% vs. CSAB 58% (p <0.01)	APACHE II >20 score Adjusted OR = 6.33 (2.32, 17.26)

Table 2 (*Continued*)

First author and Year	Crude mortality rate CRAB vs. CSAB	Adjusted RR or OR (95% CI)	Variables adjusted in the multivariable model (Variables considered but not included in the final model)	Inappropriate antimicrobial treatment CRAB vs. CSAB	Inappropriate antimicrobial treatment and risk of mortality	Severity of disease CRAB vs. CSAB	Severity of disease and risk of mortality
Kim 2012 [26]	49% (26/53) vs. 10% (4/42)	Adjusted OR = 7.29 (1.57, 33.8)	Inappropriate antimicrobial treatment, APACHE II, mechanical ventilator, central venous catheter, and septic shock (Considered: age, gender, underlying disease, and prior invasive procedure.)	NA	Adjusted OR = 8.05 (1.65, 39.2)	APACHE II score CRAB 14.4 vs. CSAB 10.4 ($p < 0.01$)	APACHE II >14 score Adjusted OR = 1.67 (0.36, 7.79)
Lemos 2013 [27]	40% (42/104) vs. 21% (13/61)	Adjusted RR = 1.47 (0.74, 2.89)	Inappropriate antimicrobial treatment, APACHE II, number of diagnosis, age, and sex (Considered: comorbidity)	CRAB 39% vs. CSAB 16% ($p < 0.01$)	Adjusted RR = 1.39 (0.78, 2.46)	APACHE II score CRAB 14.2 vs. CSAB 11.6 ($p < 0.01$)	APACHE II score was significant risk factor for mortality
Zheng 2013 [28]	46%(44/97) vs. 30%(43/145)	NA. Not significant[a]	Not considered for multivariate analysis (Considered: APACHE II, chronic respiratory disease, other infections, and inappropriate antimicrobial treatment)	NA	Adjusted OR = 6.92 (2.95, 16.22)	APACHE II score CRAB 22.2 vs. CSAB 16.3 ($p < 0.01$)	APACHE II >20 score Adjusted OR = 3.02 (1.30, 7.00)

CRAB, carbapenem-resistant *Acinetobacter baumannii*; CSAB, carbapenem-susceptible *Acinetobacter baumannii*; NA, not available; OR, odds ratio; RR, relative risk; CI, confidence interval.
aStudies did not report adjusted RR because they found no statistically significant association in the univariate analysis or did not remain significant in multivariate analysis.

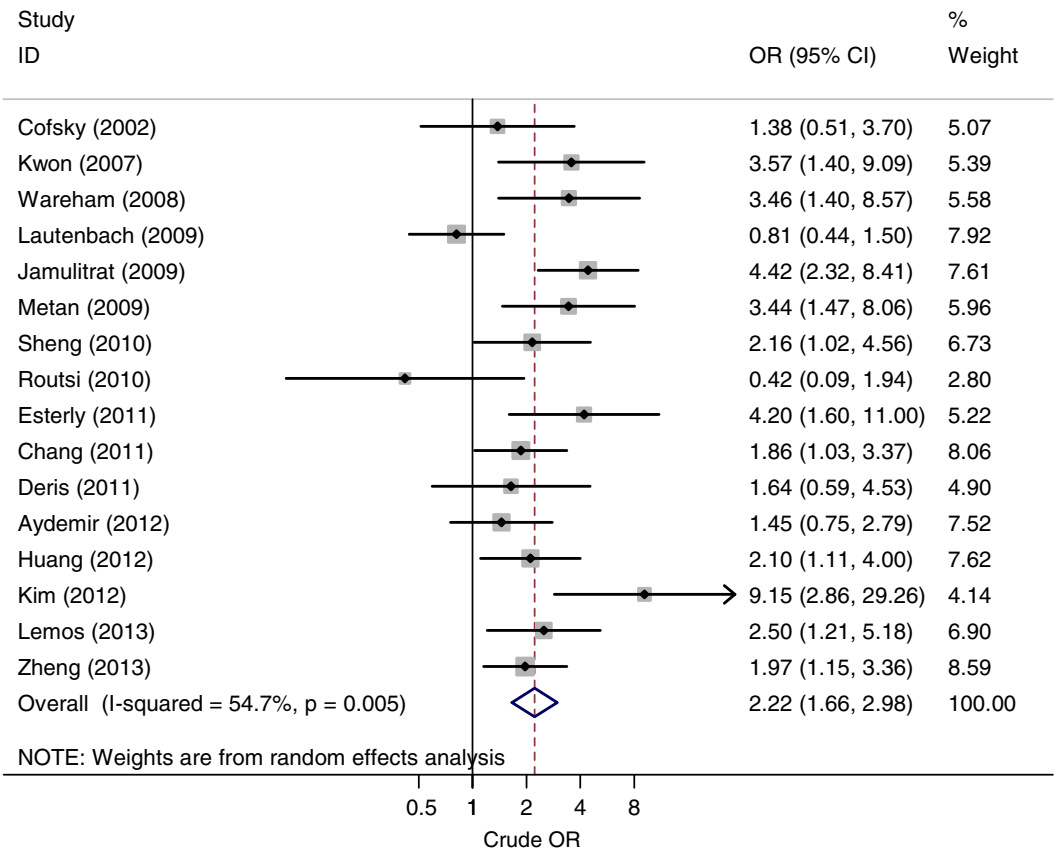

FIG. 1. Crude relative risks (RRs) of mortality in adult patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB) vs. carbapenem-susceptible *A. baumannii* (CSAB).

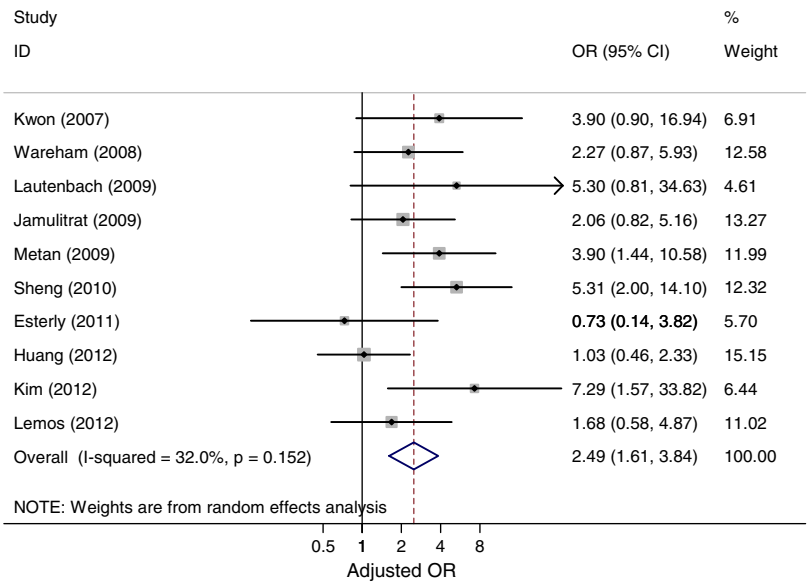

FIG. 2. Adjusted relative risk (RR or OR) for the association between carbapenem resistance and risk of mortality.

association remained significant in the pooled adjusted estimate, suggesting that higher risk of death may be due to carbapenem resistance. Similarly, previous studies of other infections such as methicillin-resistant *Staphylococcus aureus*, vancomysin-resistant Enteroccus and multidrug-resistant *Pseudomonas aeruginosa*, have also reported that drug resistance

TABLE 3. Subgroup analysis of association between carbapenem resistance and risk of mortality among patients infected with *Acinetobacter baumannii* infection

Variable	Sub-categories	No of studies	Pooled crude OR (95% CI)	Heterogeneity, I^2 (%)	p-value from meta-regression
Sources of infection	Bacteremia only	10	2.93 (2.03, 4.22)	41	Reference
	Included non-bacteremia	6	1.57 (1.14, 2.17)	30	0.11
Region	North America	3	1.60 (0.60, 4.23)	75	Reference
	Asia	8	2.58 (1.86, 3.58)	37	0.23
	Europe	4	1.90 (0.90, 4.02)	62	0.63
	South America	1	2.50 (1.21, 5.18)	NA	0.51
Resistance	Carbapenem	11	2.32 (1.69, 3.19)	40	Reference
	Imipenem	5	2.05 (1.07, 3.92)	75	0.69

OR, Odd Ratio; CI, confidence interval.

may lead to increased risk of death [30–32]. However, our findings should be interpreted with caution because of substantial heterogeneity in effect estimates across studies and other limitations.

Higher mortality rates found in patients with CRAB may be due to greater severity of illness and likelihood of receiving inappropriate empirical antibiotic treatment, which results in increased risk of mortality. Most studies reported that patients with CRAB were more likely to have severe underlying illness than patients with CSAB. Moreover, carbapenem resistance is often associated with resistance to several other classes of antibiotics; therefore, it is difficult to administer appropriate empirical antibiotic treatment to patients with CRAB. Studies reported that patients with CRAB were more likely to receive inappropriate empirical antibiotic treatment. Because a number of studies did not adequately adjust for such potential confounding factors, our findings should be interpreted with caution. Appropriate adjustment of these potential confounding factors is important in future research.

Acinetobacter baumannii has a wide spectrum of intrinsic and acquired antibiotic resistance mechanisms. Carbapenem resistance in *A. baumannii* frequently results from the production of β-lactamases, particularly carbapenem-hydrolyzing β-lactamases (carbapenemases) [1,2,29]. Resistance could also result from over-expression of the efflux pump that expels antibiotics and from alterations in outer membrane porins that block the entry of antibiotics. 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 [33,34].

Our study has several limitations. It is difficult to make definitive conclusions from current evidence due to residual confounding factors and small sample sizes in many studies. Most studies may have lacked power to detect significant differences in mortality rates. It is important to examine associations in adequately powered studies with appropriate adjustment of confounding factors in future research. 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. Heterogeneity in the results could be due to the small sample size in many studies included in this analysis. Because we searched for studies written in English or Spanish, we may have omitted studies written in other languages.

In conclusion, our study suggests that carbapenem resistance may increase risk of mortality in patients with *A. baumannii* infection. However, cautious interpretation is required because of the residual confounding factors by severity of illness and inappropriate empirical antimicrobial treatment and small sample size.

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Transparency Declarations

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Flow chart of the search strategy and results of mortality in adult patients with carbapenem-resistant *A.*

baumannii (CRAB) versus carbapenem-susceptible *A. baumannii* (CSAB) studies.

Data S2. References for excluded articles.

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