

# Adverse clinical outcomes associated with carbapenem-resistant *Acinetobacter* (CRA) infections: a systematic review and meta-analysis

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**Background:** Carbapenem-resistant *Acinetobacter* (CRA) infections have been associated with increased morbidity and mortality in hospitalized patients. This systematic review and meta-analysis aimed to quantify the association between CRA infections and adverse clinical outcomes.

**Methods:** Three databases (i.e. PubMed, EMBASE and Scopus) were searched for epidemiological studies that compared mortality, severe sepsis or shock, or bacteraemia among adult inpatients with CRA infections and those with carbapenem-susceptible *Acinetobacter* (CSA) infections. The pooled ORs for the three outcomes were estimated using the inverse variance heterogeneity model.

**Results:** Thirty-four studies were included. Patients with CRA infections had higher odds of mortality (31 studies, OR = 2.10, 95% CI: 1.58–2.79,  $I^2=60.6\%$ ) and severe sepsis or septic shock (7 studies, OR = 1.51, 95% CI: 1.09–2.09,  $I^2=0\%$ ) compared with CSA-infected patients. There was no difference in the odds of bacteraemia (four studies, OR = 1.39, 95% CI: 0.79–2.46,  $I^2=38.1\%$ ). CRA-infected patients presented with worse comorbidity at admission (e.g. APACHE score) (eight studies, standardized mean difference = 0.25, 95% CI: –0.01 to 0.52) and had lower frequency of appropriate antibiotic therapy. Results were consistent when pooling 16 study-adjusted risk estimates for mortality. There was no difference in risk of mortality from CRA infection when compared across geographical regions, country income, median year of enrolment and day of mortality from infection onset.

**Conclusions:** CRA-infected patients had worse clinical outcomes. This might be due to delay in appropriate antibiotic therapy, patients being sicker at admission and CRA strains potentially being more virulent than CSA strains. Improving appropriateness of antibiotic therapy in CRA-infected patients could reduce adverse clinical outcomes.

## Introduction

With widespread emergence and large scale hospital outbreaks of carbapenem-resistant *Acinetobacter* (CRA) infections in recent years,<sup>1–3</sup> CRA has been listed as urgent threat under the 2019 Antibiotic Resistance Threats Report.<sup>4</sup> Managing CRA outbreaks is highly challenging in healthcare facilities due to its ability to survive persistently in the environment and even on dry surfaces.<sup>5</sup> This increases the risk of nosocomial infections, more commonly pneumonia and bacteraemia, in hospital patients. *Acinetobacter* spp. strains circulating in hospitals are often MDR and commonly display resistance to carbapenems, attributed to both constitutive regulatory mechanisms and acquisition of various carbapenemases, such as OXA, NDM and VIM types.<sup>5,6</sup> With resistance to last-resort antibiotics such as tigecycline and polymyxins documented, viable treatment options for MDR *Acinetobacter* infections are limited among these patients.<sup>5,7</sup> The rise in CRA outbreaks and

the associated treatment complications have resultingly led to observations relating CRA infections and poor clinical outcomes.<sup>8</sup>

As research interest and CRA-related publications have been rising in the last decade, an updated review quantifying the association between CRA infection and clinical outcomes was warranted to supplement previous findings with greater degree of certainty. The last systematic review and meta-analysis by Lemos *et al.*<sup>8</sup> focused only on carbapenem-resistant *Acinetobacter baumannii* (CRAb), currently the most predominant and studied species,<sup>9</sup> and its association with mortality. While the study authors reported an increased risk of mortality in CRAb patients, there was the issue of study power in many small study samples out of the 16 studies included. Besides, investigations were also warranted to understand the risk of developing more invasive or severe infections, such as bacteraemia or septic shock, which are well-established risk factors for mortality. Therefore, this systematic review and meta-analysis aimed to summarize the risk of adverse clinical

outcomes (i.e. bacteraemia, sepsis or septic shock, and all-cause mortality) in adult patients with CRA infections compared with patients with carbapenem-susceptible *Acinetobacter* (CSA) infections.

## Methods

The protocol of this systematic review and meta-analysis is registered in PROSPERO (CRD42020184483). The report here follows the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA)<sup>10</sup> (Table S1, available as [Supplementary data](#) at JAC-AMR Online). The initial objective of the systematic review and meta-analysis was to estimate the risk of adverse clinical outcomes from infection caused by three MDR Gram-negative pathogens, identified as CRA, Enterobacterales producing ESBL (ESBL-E) and carbapenem-resistant Enterobacterales (CRE). The search strategy was constructed based on this objective and the subsequent search results pertained to these three pathogens. During the screening process, four existing systematic reviews and meta-analyses that estimated the risk of mortality from CRE infections were found,<sup>11–14</sup> with the latest database search conducted up till August 2016. As a result, a decision was made to remove CRE as our exposure of interest and to perform separate meta-analyses for the distinctly different CRA and ESBL-E pathogens. This systematic review and meta-analysis focused on estimating the risk of adverse clinical outcomes from CRA infections.

### Search strategy

The databases searched were PubMed, EMBASE and Scopus and this was conducted on 6 August 2020 with search terms constructed by a librarian. The search terms comprised of three categories: (i) antibiotic resistance profile of interest, namely carbapenem resistance and production of ESBL; (ii) bacteria of interest, namely Enterobacterales and *Acinetobacter* species; and (iii) outcomes of interest, namely bacteraemia, sepsis or septic shock and mortality. Other relevant and MeSH terms were also included in each category, and all categories were combined with appropriate Boolean functions. There was no restriction on year or language of publication that was imposed on the search. The details of the search strategy can be found in the [supplementary material](#) (Table S2). The search strategy was supplemented with backward and forward citation search of all included articles in the current systematic review and meta-analysis and the reference lists of relevant systematic reviews and meta-analyses were hand searched. Citations were imported into EndNote X9 to remove duplicates before exportation to Rayyan for the screening process.<sup>15</sup>

### Selection criteria and screening of studies

For this systematic review and meta-analysis, population was defined as adult hospital patients, exposure as CRA infection, comparator as patients with CSA infection and outcomes as bacteraemia, sepsis or septic shock, and all-cause mortality. Bacteraemia as an outcome could only be assessed in studies where study population was not restricted to bacteraemic patients. Definitions for sepsis, severe sepsis or septic shock were accepted as described in each study. Study selection was restricted to adults due to fundamental differences in antibiotic use, comorbidities and immune response between paediatric and adult patients. As such, the inclusion criteria were defined as (i) studies where patients were enrolled from healthcare facilities; (ii) studies where the risk of outcomes of interest from CRA infection is reported or where data are available to estimate this; and (iii) case-control or cohort study designs. The exclusion criteria were defined as (i) studies that only enrolled CRA-infected patients; (ii) studies where the comparator was not CSA-infected patients; (iii) studies where children aged less than 16 years were enrolled; (iv) case reports or case series; (v) publication without primary data; (vi) grey literature and conference abstracts/proceedings; and (viii) non-human studies.

Based on these criteria, two reviewers (W.L. and Y.E.) independently screened the studies. The reviewers met at two timepoints to discuss and resolve discrepancies in inclusion decisions: after screening based on abstract and title and after screening based on full text. If multiple studies reported on the same study population and there was an overlap in time, only the study reporting the largest sample size was included.

### Data extraction and quality assessment

The data items extracted included study authors; year of publication; study population; country where patients were enrolled; year of enrolment; definition of carbapenem resistance in *Acinetobacter* isolates; carbapenemase type; patient characteristics such as infection site, age, gender, Charlson comorbidity index (CCI) and APACHE II score; and appropriateness of antibiotic therapy and its associated definition. Other data items extracted included effect sizes (both crude and adjusted) for each outcome, confounders accounted for in the multivariable models and period of follow-up for mortality ascertainment. The quality of included studies was assessed using a modified version of the Newcastle-Ottawa Scale<sup>16</sup> (Table S3) for cohort studies. If multiple outcomes of interest were reported from one study, the quality was assessed using mortality as the outcome. A single study can score a maximum of four stars for selection, two stars for comparability and three stars for outcome.

### Data analysis

The pooled estimates (i.e. OR) for the three outcomes were estimated using the inverse variance heterogeneity (IVHet) model.<sup>17</sup> Heterogeneity of studies was determined as low if  $I^2$  was less than 25.0%, as moderate if between 25.0% and 50.0%, and as high if more than 50.0%.<sup>18</sup> Subgroup analyses were performed based on (i) median year of study enrolment (1999 to 2009 versus 2010 to 2017) due to differences in characteristics of circulating strains over the years; (ii) geographical regions (Asia versus Europe versus America versus Africa) due to differences in patient characteristics; (iii) income level of country (high versus middle) due to differences in treatment options; and (iv) 14 days versus 28–30 days from onset of infection to ascertain if risk of mortality differed over time. Subgroup analysis was only performed if there were at least three studies in each group.

Sensitivity analyses were performed by restricting study selection to (i) bacteraemic patients; (ii) studies reporting adjusted estimates; and (iii) *A. baumannii* infections to compare the results with the systematic review and meta-analysis.<sup>8</sup> Additional sensitivity analysis was also performed using studies where resistance of isolates was defined by CLSI guidelines to ensure standardization of carbapenem resistance level of isolates across the studies. Publication bias was assessed using the LFK index and visualization of Doi plot.<sup>19</sup>

As the association between CRA infection and adverse clinical outcomes may be confounded by patient's baseline risk, the differences between CRA- and CSA-infected patients were explored by pooling the standardized mean difference (SMD) of APACHE score, CCI and SOFA score at admission. If more than one index was reported in a study, APACHE score was selected and synthesized. In addition, as the clinical outcome of CRA infection may also be influenced by the appropriateness of antibiotic therapy, this characteristic was explored by (i) estimating mean delay to appropriate therapy in the CRA group and the correlation with effect estimates; and by (ii) examining subgroup effect estimates based on appropriateness of antibiotic therapy.

The statistical analyses were performed using the *admetan*<sup>20</sup> and *lflk*<sup>21</sup> modules in Stata/SE 16.1 (College Station, TX, USA). Statistical significance was set at 0.05.

## Results

A total of 2246 unique references were identified from the database search, of which 241 were screened by full text. The primary

reason for exclusion was that the study did not include CRA-infected patients or that the number of events in the CRA group was not reported. The backward and forward citation search further yielded another three studies for inclusion. The entire screening process and detailed reasons for full-text study exclusion are documented in Figure 1. All in all, a total of 34 studies were included for meta-analysis.<sup>22-55</sup> Excluding one study that did not report on number of patients per group, the pooled sample comprised at least 2488 CRA-infected patients and 2587 CSA-infected patients.

The study characteristics of the 34 studies are summarized in Table 1. The period of study enrolment ranged from 1998 to 2017, and the majority of studies (64.7%,  $n = 22$  studies) enrolled patients in Asia. Nineteen studies (55.9%) included only bacteraemic patients and six studies (17.6%) enrolled only ICU patients. Among studies that were not restricted to bacteraemic patients, respiratory-related infection was the most reported. Most of the studies (64.7%,  $n = 22$  studies) used CLSI guidelines to define resistance of isolates to carbapenems. There were four studies (11.8%) that performed molecular sequencing on the CRA isolates and only *bla*<sub>OXA-51</sub>, *bla*<sub>OXA-23</sub> and *bla*<sub>OXA-49</sub> were detected from a subset of *A. baumannii* strains. Interestingly, in 11 studies with available data, the proportion of appropriate antibiotic therapy was consistently lower in CRA-infected patients as compared with CSA-infected patients.

Using a modified version of the Newcastle-Ottawa Scale, 31 and 3 studies were assessed with mortality and severe sepsis or septic shock as outcome (Table S4), respectively. Most studies scored at least three stars for quality of study selection (70.6%,  $n = 24$  studies) and at least two stars for quality of outcome ascertainment (88.2%,  $n = 30$  studies). However, 22 studies (64.7%)

scored zero stars for comparability, mainly due to effect estimates not being adjusted for any confounders.

### Baseline characteristics at admission and appropriateness of antibiotic therapy

There were eight studies that reported mean APACHE score, CCI and/or SOFA score of CRA and CSA-infected patients at admission. The severity of underlying disease was higher in patients with CRA infection (eight studies, SMD = 0.25, 95% CI: -0.01 to 0.52) (Figure S1), although this was marginally not statistically significant. There were only two studies that reported effect estimates by appropriateness of antibiotic therapy and only three studies that reported mean or median delay in duration to appropriate therapy in CRA group. The effect of antibiotic therapy on outcome, hence, could not be explored due to the limited number of studies.

### Mortality

There were 31 studies reporting all-cause mortality as an outcome. The odds of mortality were 2.1 times higher in CRA-infected patients as compared with CSA-infected patients (OR = 2.10, 95% CI: 1.58–2.79) (Figure 2). Heterogeneity among the studies was high ( $I^2 = 60.6\%$ ). There was evidence of asymmetry (LFK index = 1.60) suggesting publication bias towards studies that reported higher odds of mortality among CRA-infected patients (Figure S2).

### Severe sepsis or septic shock

Seven studies reported data on sepsis or septic shock. All septic cases were observed as at least severe in the individual studies. The odds of severe sepsis or septic shock were 51% higher in

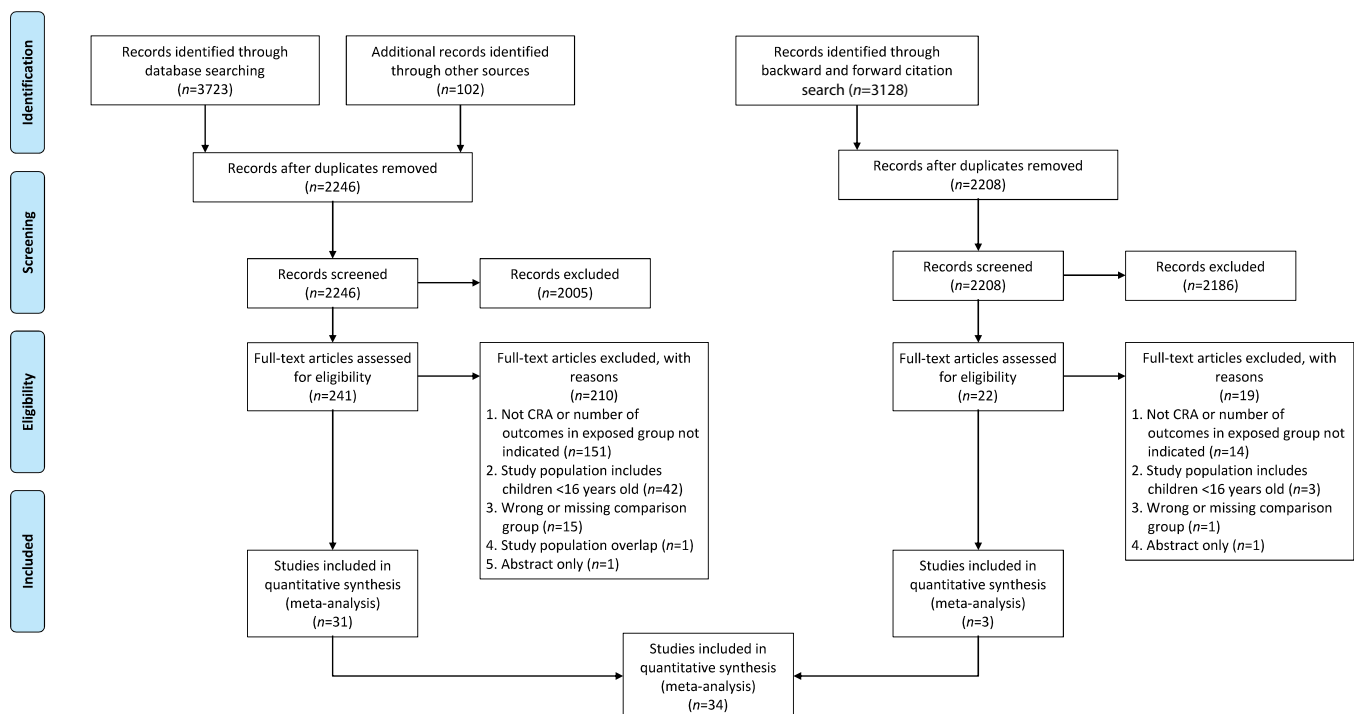


Figure 1. PRISMA diagram for study inclusion and exclusion.

**Table 1.** Summary characteristics of 34 included studies

First author and reference	Country	Study period	Study population and organism	Outcomes	Infection site <sup>a</sup>	Resistance definition	n	CRA group: CSA group			
								mean/median age, years	% male	mean/median APACHE <sup>b</sup>	% AIAT
Kopterides <sup>22</sup>	Greece	Jan 2002–Aug 2005	Inpatients with BSI caused by <i>A. baumannii</i> susceptible to colistin	mortality	blood	CLSI 2000	25:14	66.6:64	56:43	16.1:14.7	—
Wareham <sup>23</sup>	UK	Apr 1998–Sep 2006	Patients with BSI caused by <i>Acinetobacter</i> spp.	30 day mortality <sup>a</sup>	blood	—	55:243	—	—	—	23:—
Metan <sup>34</sup>	Turkey	Feb 2007–Mar 2008	Patients with BSI caused by <i>Acinetobacter</i> complex	14 day mortality <sup>b</sup>	blood	CLSI 2005	54:46	—	—	—	—
Lautenbach <sup>45</sup>	USA	Jan 2001–Dec 2006	Patients with <i>A. baumannii</i> infection	30 day mortality	respiratory, blood, wound	CLSI 2008	89:297	63:56	—	—	—
Routsis <sup>50</sup>	Greece	Sep 2004–Jan 2006	Patients with ICU-acquired BSI caused by <i>A. baumannii</i>	in-hospital mortality	blood	CLSI 2007	30:66	58.7:56.4	70:65	16.3:20	57:76
Esterly <sup>51</sup>	USA	Jan 2005–Dec 2008	Patients with BSI caused by <i>A. baumannii</i>	in-hospital mortality <sup>c</sup>	blood	CLSI 2009	37:42	56.3:49.2	70:36	—	76:95
Chang <sup>52</sup>	Taiwan	Jan 2005–Dec 2007	Patients with VAP caused by <i>A. baumannii</i>	BSI, 30 day mortality	respiratory	NCCS 2008	93:87	68.5:70.9	63:57	—	22:24
de Gouveia <sup>33</sup>	Brazil	Jan 2002–Jan 2009	Patients with kidney or liver transplant, and infection caused by <i>A. baumannii</i>	BSI, shock, 30 day mortality <sup>d</sup>	blood, respiratory, urinary tract	CLSI 2009	18:31	48:48	44:68	—	56:61
Kim <sup>54</sup>	South Korea	Jun 2007–Jun 2010	Patients with BSI caused by <i>A. baumannii</i>	14 day mortality <sup>e</sup>	BSI	CLSI 2008	53:42	59.4:57.1	62:43	14.4:10.4	—
Huang <sup>55</sup>	Taiwan	Jun 2002–Dec 2007	Patients with monomicrobial BSI caused by <i>A. baumannii</i>	shock, 14 day mortality <sup>f</sup>	blood	CLSI 2011	62:164	69.6:68.5	76:77	—	—
Aydemir <sup>24</sup>	Turkey	Jan 2005–Dec 2006	Inpatients with infection caused by <i>A. baumannii</i>	mortality	respiratory, other	CLSI 2006	110:55	64:59	51:60	—	58:89
Moon <sup>25</sup>	South Korea	Jan 2005–May 2011	Patients with nosocomial meningitis after neurosurgical procedure caused by <i>A. baumannii</i>	in-hospital mortality	meningitis	CLSI 2011	22:18	—	—	—	—
Zheng <sup>26</sup>	China	Jan 2006–Dec 2011	Patients with monomicrobial pneumonia caused by <i>A. baumannii</i>	28 day mortality	respiratory	CLSI 2011	97:145	62.2:60.9	54:56	20.3:17.9	—
Park <sup>27</sup>	South Korea	Jul 2003–Dec 2011	Patients with BSI caused by <i>A. baumannii</i>	30 day mortality <sup>g</sup>	blood	CLSI 2008	52:71	—	—	—	—
Vitkauskienė <sup>28</sup>	Lithuania	Aug 2010–Jan 2011	Inpatients with infection caused by <i>Acinetobacter</i> spp.	mortality	respiratory, wound, blood	CLSI 2008	40:59	—	73:59	—	—
Huang <sup>29</sup>	Taiwan	2000–08	Patients with BSI caused by <i>A. nosocomialis</i>	shock	blood	CLSI 2011	67:262	76:72	72:68	—	—
Lee <sup>30</sup>	Taiwan	2009–10	ICU patients with monomicrobial BSI caused by <i>A. baumannii</i>	30 day mortality	blood	CLSI 2010	68:151	—:62	—:56	—	28:67
Lemos <sup>31</sup>	Colombia	Apr 2006–Apr 2010	ICU patients with infection caused by <i>A. baumannii</i>	BSI, 30-day mortality <sup>h</sup>	respiratory, blood, surgical	CLSI 2006	104:61	51.2:47.7	61:69	12.8:10.1	62:84
Shorr <sup>32</sup>	USA	Jan 2002–Dec 2012	Patients with acute organ dysfunction (severe sepsis) and infection by <i>Acinetobacter</i> spp.	in-hospital mortality	blood	CLSI 2002–12	76:55	—	—	—	—
Chusri <sup>33</sup>	Thailand	Jan 2010–Dec 2011	Patients with nosocomial infection caused by <i>Acinetobacter</i> spp. belonging to Acb complex	BSI, 30 day mortality <sup>j</sup>	respiratory, skin and soft tissue, urinary tract	CLSI 2013	139:83	60:—	72:—	—	56:62
Tal-Jasper <sup>35</sup>	Israel	Jan 2007–Dec 2012	Patients with systemic inflammatory response syndrome and BSI caused by <i>A. baumannii</i>	30 day mortality <sup>k</sup>	blood	any group 2 carbapenem	149:91	—	—	—	53:68

Wang <sup>36</sup>	China	Jan 2014–Jun 2015	Patients with haematological malignancy and BSI caused by <i>A. baumannii</i>	shock, 30 day mortality <sup>m</sup>	blood	CLSI	13:27	42.7:54.6	62:57	—
Boykara <sup>37</sup>	Turkey	Jan 2016	All ICU patients	severe sepsis or shock	respiratory, blood, renal or urinary tract	—	173:58	—	—	—
Huang <sup>38</sup>	China	Jan 2013–Dec 2017	Inpatients with VAP	60 day mortality	respiratory	imipenem	55:17	—	—	—
Yang <sup>39</sup>	China	Jan 2011–Dec 2015	Inpatients with nosocomial BSI caused by <i>A. baumannii</i>	in-hospital mortality <sup>n</sup>	blood	CLSI	84:34	—	—	—
Balkhair <sup>40</sup>	Oman	Jan 2007–Dec 2016	Inpatients with BSI caused by <i>P. aeruginosa</i> , <i>A. baumannii</i> or <i>K. pneumoniae</i>	30 day mortality	blood	CLSI	117:49	49.6:44.2	67:27	—
Chusri <sup>41</sup>	Thailand	Jan 2012–Dec 2016	Inpatients with BSI caused by <i>A. baumannii</i>	30 day mortality <sup>o</sup>	blood	CLSI 2018	31:29	54:–	58:–	52:–
Nazer <sup>42</sup>	Jordan	Jan 2010–Dec 2013	ICU patients with infection	severe sepsis or shock	respiratory, blood, wound	—	143:18	—	—	—
Kwon <sup>43</sup>	South Korea	Jan 2000–Jun 2005	Inpatients with nosocomial BSI caused by <i>A. baumannii</i>	30 day mortality <sup>p</sup>	blood	CLSI 2005	40:40	47:47	70:73	35:80
Cofsky <sup>44</sup>	USA	1999	Inpatients with infection caused by <i>S. aureus</i> , <i>K. pneumoniae</i> , <i>A. baumannii</i> and <i>P. aeruginosa</i>	in-hospital mortality	respiratory, blood, urinary tract	—	44:33	—	—	—
Jamulitrat <sup>46</sup>	Thailand	Jul 2004–Sep 2007	Inpatients with BSI caused by <i>A. baumannii</i>	shock, in-hospital mortality <sup>q</sup>	blood	imipenem	67:131	56.1:50.8	45:60	61:88
Chaarri <sup>47</sup>	Tunisia	Aug 2010–Nov 2011	ICU patients with VAP caused by <i>A. baumannii</i>	in-hospital mortality	respiratory	imipenem	79:13	—	—	—
Liu <sup>48</sup>	China	2007–13	Patients with BSI caused by <i>A. baumannii</i>	30 day mortality <sup>r</sup>	blood	CLSI	202:84	59:59	74:56	—
Cai <sup>49</sup>	USA	2009–13	Patients with BSI caused by <i>A. baumannii</i> , <i>P. aeruginosa</i> , <i>E. coli</i> or <i>K. pneumoniae</i>	in-hospital mortality <sup>s</sup>	blood	doripenem, ertapenem, imipenem, meropenem	—	60.5:53.6	—	—

AIAT, appropriate initial antibiotic therapy; BSI, bloodstream infection; VAP, ventilator-associated pneumonia.

<sup>m</sup>Measured at admission as stated in study.

<sup>n</sup>Adjusted for ICU admission.

<sup>o</sup>Adjusted for diabetes mellitus, septic shock.

<sup>p</sup>Adjusted for active therapy, renal dysfunction, any transplant, ICU stay at BSI onset, *A. baumannii* isolated from at least two sites, prior antibiotic use.

<sup>q</sup>ICU-acquired infection.

<sup>r</sup>Adjusted for mechanical ventilator, central venous catheter, APACHE II  $\geq 14$ , septic shock, pneumonia as source of BSI, inappropriate antibiotic therapy.

<sup>s</sup>Adjusted for ICU stay, APACHE II  $> 20$ , pneumonia or urinary tract infection as source of BSI, haematological malignancies, shock, autoimmune disease, prior piperacillin/tazobactam or cefepime use, Foley catheter, mechanical ventilation, central venous catheter, total parenteral nutrition, femoral venous catheter.

<sup>t</sup>Adjusted for age  $\geq 65$  years, gender, APACHE II score, number of diagnoses, empirical antimicrobial treatment.

<sup>u</sup>Adjusted for age, APACHE II score, appropriate empirical antimicrobial therapy, infection with non-Acb complex.

<sup>v</sup>Adjusted for appropriate antimicrobials, age, CCI, Pitt bacteremia score, overall immunosuppression.

<sup>w</sup>APACHE score.

<sup>x</sup>Adjusted for multi-organ dysfunction syndrome, APACHE II score on admission and BSI onset, ICU, mechanical ventilation, central venous catheter, respiratory tract as source of infection, adequate empirical antibiotic therapy.

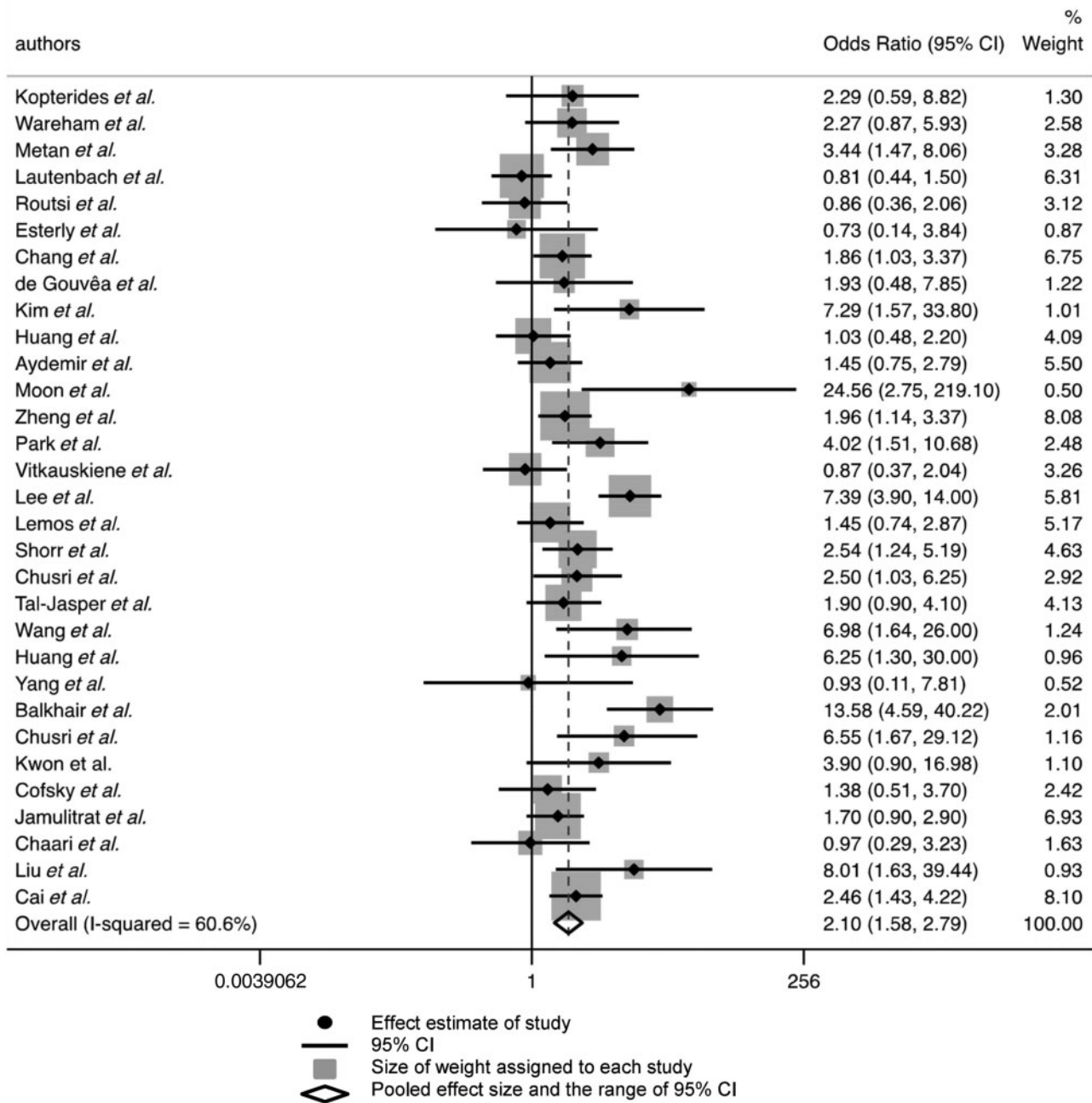
<sup>y</sup>Adjusted for community acquisition, APACHE II score, skin and soft tissue infection, appropriate empirical antimicrobial therapy.

<sup>z</sup>Adjusted for age, Pitt bacteremia score, acute renal failure, immunosuppressive status, pneumonia, CCI weighted  $\geq 3$ , discordant therapy.

<sup>aa</sup>Adjusted for medical patient, neutropenia, ASA score  $> 3$ , ICU acquisition, appropriate antibiotic treatment.

<sup>ab</sup>Adjusted for age, gender, race, ethnicity, various comorbid conditions, mechanical ventilation, renal impairment, geographic regions.





**Figure 2.** Forest plot of 31 studies estimating the association between CRA infection and all-cause mortality. Weights are from Doi’s IVHet model.

CRA-infected patients as compared with CSA-infected patients (OR = 1.51, 95% CI: 1.09–2.09) (Figure 3). Studies were homogenous ( $I^2=0\%$ ) and there was no evidence of publication bias (LFK index = -0.07, Figure S3).

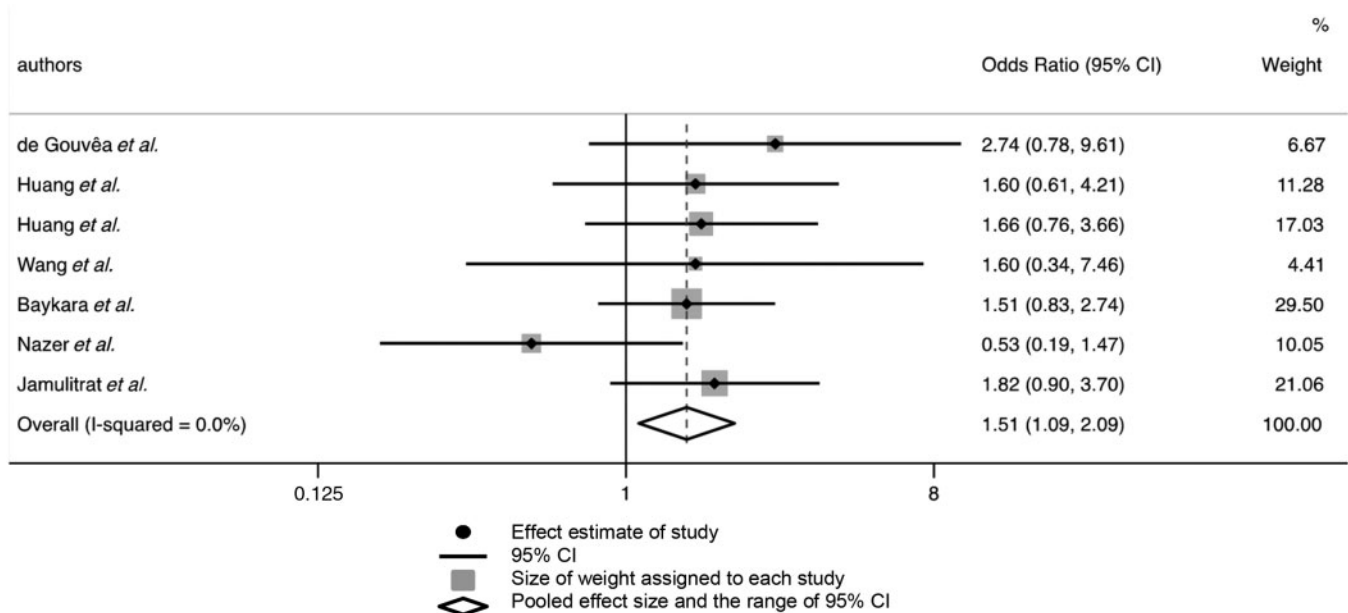
**Bacteraemia**

Four studies with data on bacteraemia were available for synthesis. There was no difference in odds of developing bacteraemia between those with CRA infection and those with CSA infection (OR = 1.39, 95% CI: 0.79–2.46) (Figure 4). There was moderate heterogeneity among the four studies ( $I^2=38.1\%$ ), and minor

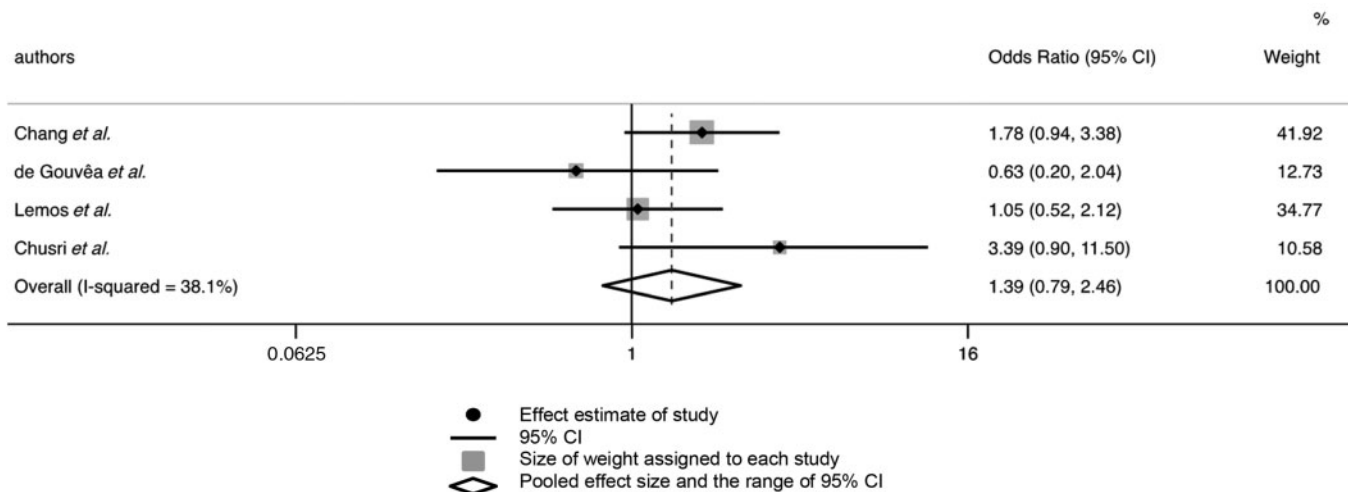
evidence of publication bias towards studies that reported lower odds of bacteraemia among CRA-infected patients (LFK index = -1.05, Figure S4).

**Subgroup analyses**

A summary of subgroup analyses can be found in Table 2. Although the odds of mortality from CRA infection was higher in studies where the median year of enrolment was from 2010 onwards (OR = 2.75, 95% CI: 1.36–5.55,  $I^2=64.4\%$ ), this was not significantly different from studies where median year of enrolment was before 2010 (OR = 1.94, 95% CI: 1.44–2.62,  $I^2=57.9\%$ ).



**Figure 3.** Forest plot of seven studies estimating the association between CRA infection and severe sepsis or septic shock. Weights are from Doi’s IVHet model.



**Figure 4.** Forest plot of four studies estimating the association between CRA infection and bacteraemia. Weights are from Doi’s IVHet model.

There was also no difference in the odds of mortality from CRA infection based on geographical regions and income levels of country where patients were enrolled. Lastly, although the odds of mortality were significantly higher in CRA-infected patients when mortality was ascertained 28 to 30 days from onset of infection (OR = 2.47, 95% CI: 1.58–3.85,  $I^2=69.1\%$ ), this was no different from when mortality was ascertained 14 days from onset of infection (OR = 2.09, 95% CI: 0.67–6.50,  $I^2=72.2\%$ ).

Subgroup analysis for risk of severe sepsis or septic shock was only performed based on median year of enrolment (Table 2). There was no difference in odds of severe sepsis or septic shock from CRA infection where median year of enrolment was prior to (OR = 1.81, 95% CI: 1.17–2.79,  $I^2=0\%$ ) and after 2010 (OR = 1.19,

95% CI: 0.58–2.47,  $I^2=36.7\%$ ). There was an insufficient number of studies to compare estimates based on geographical region of enrolment and income level of country. Subgroup analyses for bacteraemia as an outcome were also not performed due to unavailability of data.

**Sensitivity analyses**

Sensitivity analysis was performed by restricting study inclusion to bacteraemic patients. The odds of mortality (18 studies, OR = 2.71, 95% CI: 1.78–4.13,  $I^2=62.7\%$ ) and severe sepsis or shock (4 studies, OR = 1.70, 95% CI: 1.09–2.65,  $I^2=0\%$ ) in CRA-bacteraemic patients remained higher than that of CSA-bacteraemic patients. Similarly, when pooling only patients with *A. baumannii* infection,

**Table 2.** Subgroup analyses of summary effect sizes by median year of enrolment, geographical region of study, day of mortality ascertainment and income classification of country

	Sepsis/shock			Mortality		
	studies, n (patients, n)	OR (95% CI)	I <sup>2</sup> (%)	studies, n (patients, n)	OR (95% CI)	I <sup>2</sup> (%)
Overall	7 (1230)	<b>1.51 (1.09–2.09)</b>	0	31 (4383)	<b>2.10 (1.58–2.79)</b>	60.6
By median year of enrolment						
1999–2009	4 (802)	<b>1.81 (1.17–2.79)</b>	0	21 (3228)	<b>1.94 (1.44–2.62)</b>	57.9
2010–17	3 (428)	1.19 (0.58–2.47)	36.7	10 (1155)	<b>2.75 (1.36–5.55)</b>	64.4
By geographical region						
Asia	6 (1181)	1.44 (1.03–2.02)	93.3	19 (2872)	<b>2.68 (1.82–3.93)</b>	62.2
Europe	0	—	—	4 (532)	1.25 (0.73–2.13)	17.5
America	1 (49)	—	—	7 (887)	<b>1.60 (1.08–2.39)</b>	38.7
Africa	0	—	—	1 (92)	—	—
By mortality day from infection onset						
Day 14	—	—	—	3 (421)	2.09 (0.67–6.50)	72.2
Day 28 to 30	—	—	—	15 (2756)	<b>2.47 (1.58–3.85)</b>	69.1
By income classification of country						
high	2 (555)	—	—	18 (2574)	<b>2.12 (1.38–3.25)</b>	71.5
middle	5 (675)	1.46 (0.92–2.32)	71.7	13 (1809)	<b>2.07 (1.51–2.84)</b>	26.9

Bolded values indicate statistical significance.

the odds of mortality also reflected to be significantly higher in CRAB-infected patients as compared with CSAb-infected patients (24 studies, OR = 2.09, 95% CI: 1.45–3.00, I<sup>2</sup> = 67.0%).

When restricting the selection to studies that reported adjusted risk estimates, the odds of mortality persisted to be significantly higher in the CRA-infected group (16 studies, OR = 2.17, 95% CI: 1.61–2.92, I<sup>2</sup> = 27.1%). Appropriateness of antimicrobial therapy, age and APACHE scores were commonly adjusted for in these studies (Table 1). There was an insufficient number of studies reporting adjusted risk estimates for septic shock (one study) and bacteraemia (no studies).

Lastly, sensitivity analysis was performed by synthesizing studies where carbapenem resistance was defined by CLSI guidelines, regardless of year of CLSI publication. The results were consistent with the main analyses, where the odds of mortality (22 studies, OR = 2.28, 95% CI: 1.52–3.43, I<sup>2</sup> = 68.3%) and septic shock (4 studies, OR = 1.78, 95% CI: 1.06–2.99, I<sup>2</sup> = 0%) were significantly higher in CRA-infected patients than CSA-infected patients. There was no difference in odds of bacteraemia between the two groups (three studies, OR = 1.16, 95% CI: 0.50–2.72, I<sup>2</sup> = 48.0%).

## Discussion

The results from this systematic review and meta-analysis suggest that the odds of mortality and severe sepsis/septic shock were higher in CRA-infected patients compared with CSA-infected patients. However, no difference in odds of bacteraemia development between the two groups was observed. As such, while bloodstream is a common site of *Acinetobacter* infection, acquiring a carbapenem-resistant strain does not increase the likelihood of developing bacteraemia. The significantly higher odds of mortality in the CRA-infected group persisted in bacteraemic patients, when

pooling together study-adjusted risk estimates and when carbapenem resistance was defined by CLSI guidelines. There was no difference in odds of mortality between CRA- and CSA-infected patients when compared across median year of enrolment, geographical region of study enrolment, income level of country and period of follow-up for mortality ascertainment.

In general, *Acinetobacter* spp. have been reviewed in the literature for their pathogenic characteristics and virulence factors, causing nosocomial invasive infections such as pneumonia, meningitis, skin and soft tissue infection and bacteraemia.<sup>56–60</sup> However, highly virulent strains were not frequently observed with carriage of carbapenemases and remain susceptible to carbapenems.<sup>61</sup> Interestingly, the results from this systematic review and meta-analysis revealed an even higher odds of poor clinical outcomes in patients infected by the carbapenem-resistant strain. The worse prognosis in CRA-infected patients may be explained by several factors, including higher severity of underlying illness in those with CRA, delays in appropriate antibiotic therapy given the carbapenem resistance and virulence potential of CRA strains.

The effect modification by appropriateness of antibiotic therapy is strongly reflected in the consistently lower frequency of appropriate antibiotic therapy in the CRA-infected group as compared with the CSA-infected group. In addition, of the nine studies that adjusted for appropriateness of antibiotic therapy, five had reported no significant association between CRA infection and mortality. A previous systematic review and meta-analysis of 12 studies had reported five times increased odds of mortality in CRAB-infected patients with inappropriate empirical antibiotic therapy, as compared with those with appropriate therapy (pooled OR = 5.04, 95% CI: 2.56–9.94).<sup>62</sup> The turnaround time for antimicrobial susceptibility test results and the



increased likelihood of empirical treatment failure all suggest the potentially bigger role of inappropriate antibiotic therapy in the increased risk of mortality after CRA infection. Additionally, the possibility of confounding by severity of illness was explored using APACHE scores, CCI and SOFA scores at admission. We showed that severity of underlying illness was slightly higher in CRA-infected patients, suggesting that the higher risk of adverse clinical outcomes in CRA-infected patients could be confounded by sicker patients at admission.

Lastly, there is increasing evidence to suggest that *A. baumannii* strains, in particular, can possess both highly virulent and XDR characteristics.<sup>61,63–65</sup> An outbreak investigation of hospital-acquired *A. baumannii* infections by Jones *et al.*<sup>65</sup> had revealed XDR strains with substantial carriage of virulence genes. The virulence of these resistant strains was reflected in the high mortality counts observed in both their mouse models and hospital patients with low comorbidity score.<sup>65</sup> In this systematic review and meta-analysis, the significantly higher risk of mortality persisted when pooling together study-adjusted effect estimates, where the majority of these studies accounted for inappropriate antibiotic therapy and comorbidities. While this suggests the possibility of CRA strains being more virulent than CSA strains, the observation should be further validated with future comparative genomic and molecular studies of the bacteria.

The results from this systematic review and meta-analysis are consistent with the results reported by Lemos *et al.*,<sup>8</sup> which were that the odds of mortality were significantly higher in patients with CRAB infection than those with CSAb infection (pooled OR = 2.22, 95% CI: 1.66–2.98). The significance also similarly persisted when pooling together study-adjusted estimates only in both Lemos *et al.*'s<sup>8</sup> meta-analysis (pooled OR = 2.49, 95% CI: 1.61–3.84) and our results (not shown). However, in both instances, the estimates derived from our included studies were more conservative, likely due to the inclusion of additional studies and use of different models.

There are a few limitations to this systematic review and meta-analysis. Firstly, we found only four studies with data on bacteraemia presentation, of which only two clearly indicated subset of patients with bacteraemia as the primary site of *Acinetobacter* infection. Similarly, the ascertainment of severe sepsis or septic shock after positive *Acinetobacter* culture was observed in another two studies only. As a result, the directionality of the causal pathway between bacteraemia or septic shock and CRA infection could not be determined. Both directions are plausible, where use of antimicrobials during the course of infection would have increased the likelihood of the infecting pathogen acquiring a carbapenem resistance mechanism. In addition, several of the studies purposefully excluded CRA-colonized patients from the sample, which would have impeded the capability of the study to report the risk of bacteraemia development from CRA acquisition. As such, future well-designed longitudinal studies are still warranted to ascertain the development of bacteraemia and sepsis from CRA infection. Secondly, the heterogeneity of included studies for mortality is high. This is likely due to unadjusted and adjusted effect estimates being pooled in the meta-analysis and compounded by highly variable confounders that were accounted for in the adjusted effect estimates. The variability in confounder adjustment was also reflected in the poor score

for comparability in the quality assessment. In general, poor comparability scores among the studies would have reduced the precision of the pooled mortality estimates observed in this systematic review and meta-analysis. However, this should not significantly impair the statistical significance of higher mortality odds observed in CRA-infected patients, as supported by the sensitivity analysis of pooling adjusted effect estimates with moderate heterogeneity. Additionally, of the 16 studies with adjusted mortality risk estimates, at least 6 studies inappropriately adjusted for septic shock and severity of bacteraemia (measured using Pitt bacteraemia or APACHE score during infection) as confounders. The adjustment of these variables, which should be regarded as mediators along the causal pathway, would have underestimated the true association between CRA infection and mortality and should be avoided in future studies. Lastly, there was substantial presence of publication bias towards studies that reported higher effect sizes of mortality in CRA-infected patients. This suggests the possibility of unpublished studies, especially those of small sample sizes, that did not observe significant association between mortality and CRA infections and therefore could have biased the pooled estimates reported in this systematic review and meta-analysis.

Nonetheless, the results reported in this systematic review and meta-analysis are valuable in supplementing previous findings reported by Lemos *et al.*,<sup>8</sup> where an additional 15 studies have been included since the last search in 2013. This meta-analysis employed the IVHet model instead of the random effects model, as the former model allows proportional assignment of weightage based on individual study power.<sup>17</sup> This would have likely improved the precision of the study estimates reported here by assigning higher weightages to studies with better study power. In addition, this systematic review and meta-analysis also attempted to estimate the risk of developing other adverse clinical outcomes, including bacteraemia and septic shock, which are well-established risk factors for mortality. We also attempted to identify attributable factors for the higher risk of mortality observed in CRA-infected patients and observed that this may be attributed to treatment failure from inappropriateness of antibiotic therapy and to a smaller extent due to differences in severity of underlying illnesses. Although there was some evidence to suggest that CRA strains may be more virulent than CSA strains, this cannot be concluded with certainty due to confounding by sicker CRA-infected patients at baseline.

## Conclusions

In conclusion, this systematic review and meta-analysis reports higher odds of all-cause mortality and severe sepsis or septic shock in patients with CRA infection as compared with CSA infection. There are several postulations for this observation, including inappropriate antibiotic treatment given carbapenem resistance of the *Acinetobacter* strain, CRA-infected patients being sicker at baseline and higher virulence potential in CRA strains as compared with CSA strains, although this should be validated with further comparative genomic and molecular studies of the organism. It appears that acquiring CRA strains does not increase the likelihood of developing bacteraemia as compared with CSA strains, however, availability and quality of studies to support this observation

are very limited. Future well-designed longitudinal studies are still warranted to understand the risk of adverse clinical development from CRA infections. The evidence presented here further highlights the importance and need to rapidly detect CRA outbreaks in healthcare facilities, which have adverse implications on patient morbidity and mortality.

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## Author contributions

D.L.P., P.N.A.H. and W.L. conceived the aim of this systematic review and meta-analysis. W.L. performed the database search. W.L. and Y.E. were responsible for study screening and selection. W.L. did the data extraction and quality assessment. W.L. and L.F.-K. performed and checked the statistical analysis. W.L. drafted the manuscript. All authors reviewed and provided inputs for the manuscript. All authors approved the final version of the manuscript.

## Supplementary data

Tables S1 to S4 and Figures S1 to S4 are available as [Supplementary data](#) at [JAC-AMR Online](#).

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