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The impact of carbapenem resistance on mortality in patients infected with *Enterobacteriaceae*: a global systematic review and meta-analysis

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ABSTRACT

Objective To provide a comprehensive assessment of the impact of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae* and explore the source of heterogeneity between studies.

Methods We conducted a systematic review and meta-analysis of all observational studies published between 1 January 1994 and 30 August 2020 which reported mortality outcomes of hospitalized patients infected with carbapenem-resistant *Enterobacteriaceae* (CRE) and carbapenem-susceptible *Enterobacteriaceae* (CSE). Stratified analysis and meta-regression were further performed to investigate the heterogeneity between studies.

Results Of 10304 identified studies, 50 studies were included. The results showed that carbapenem resistance has doubled the mortality rate of patients infected with CRE compared to patients infected with CSE (RR, 2.14, 95% CI, 1.85-2.48), and in absolute terms, CRE infection can increase the risk of mortality by 22% (RD, 0.22, 95%CI, 0.18-0.26). The results of the stratified analysis and meta-regression suggested the effect of carbapenem resistance on mortality varied by infection type, geographic region, sample size and year of publication.

Conclusion CRE infections were associated with a higher risk of death compared with CSE infection. The magnitude of the effect of carbapenem resistance on mortality may be influenced by infection type, geographic region, sample size and publication year. In further research, more studies need to be conducted in low-income countries and other regions to provide more evidence to draw resources to fight against CRE.

Keywords: *Enterobacteriaceae*; carbapenems; meta-analysis; mortality; resistance

Article summary

Strengths and limitations of this study

- This study provided a comprehensive meta-analysis to assess the impact of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae*, including nearly 20 new published studies in recent three years that were not included in previous relevant reviews.
- This is the first review to explore the source of heterogeneity between studies through meta-regression analysis in consideration of country economic status and geographic region when assessing the association between carbapenem resistance and mortality among patients infected with *Enterobacteriaceae*.
- This review reported effect measures in both relative and absolute terms, providing a complete picture of the effect of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae.*
- Publication bias may exist due to a lack of studies from low-income countries and other regions.

INTRODUCTION

The *Enterobacteriaceae* species, mainly *Klebsiella pneumoniae* and *Escherichia coli*, can cause infections such as bloodstream infections, ventilator-associated pneumonia, intra-abdominal infections and urinary tract infections both in healthcare and community settings. [1] The treatment of these infections is becoming increasingly challenging because of the increasing prevalence of multi-drug-resistant *Enterobacteriaceae*, such as extended-spectrum β-lactamases (ESBLs)-producing *Enterobacteriaceae*. To counter this, carbapenems were introduced in the 1980s[2] and proved efficacious in the clinical treatment of infections caused by ESBLs-producing *Enterobacteriaceae*.[3] However, since the carbapenem-resistant *Enterobacteriaceae* (CRE) emerged in the early 1990s,[4] CRE has been increasingly reported worldwide.[5,6] The prevalence of CRE is mostly driven by the spread of carbapenemases, a group of β-lactamases hydrolyzing carbapenems.[7] The CRE strains producing diverse types of carbapenemases are endemic in different areas of the world.[8] Some countries have high overall rates of CRE, including Greece, Italy, Brazil, China, the United States, and Colombia.[7] For example, the rate of carbapenem resistance in *Klebsiella pneumoniae* isolates was as high as 63.9% in Greece in 2018.[9] The increasing prevalence of CRE has posed a serious threat to public health due to reduced efficacy of carbapenem and limited available therapy options, it was therefore categorized as the most critical group of multidrug-resistant pathogens with the highest urgency of the need for new antibiotics.[10]

The mortality of CRE infections is a research hotspot. Recently, some systematic reviews have conducted meta-analyses to assess the association between CRE infections and mortality by comparing with the mortality outcome of patients infected with carbapenem-susceptible *Enterobacteriaceae*(CSE), [12-17] and the results showed that CRE infections could lead to increased mortality. The latest systematic review on this topic included studies published until 2017. [13] However, nearly 20 relevant articles have

been published since 2018. A timely and comprehensive summary of the results in published articles will be helpful to understand the excess health burden attributable to carbapenem-resistant *Enterobacteriaceae* (CRE) infections. Moreover, although previous systematic reviews have identified heterogeneity between studies and discussed some confounding factors of mortality including patient-, infection-, organism-, and therapy-related factors,[13,14,16] few of them examined whether the effect of carbapenem resistance on mortality varies by these factors through a formal statistical approach or meta-regression analysis. Besides, the differences in economic status and geographic region were not considered in previous reviews. The development of antibiotic resistance resulted in decreasing effectiveness of first-line antibiotics, and more expensive second and third-line antibiotic treatments need to be used, but these treatments may be not obtained or afforded by patients in developing countries with a resistant infection, [18] which might result in worse prognostic outcomes. The effect of carbapenem resistance on mortality may exist regional differences because the CRE strains with different types of carbapenemases and virulence characteristics[1] are predominant in different regions worldwide.[8] Two previous reviews have shown that the mortality rate of patients with CRE infections differs by geographic region.[11,15] However, without data from control groups, whether the impact of carbapenem resistance on mortality differs in the region is still unknown.

Therefore, we aim to provide a comprehensive systematic review of the impact of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae* and explore the source of heterogeneity between studies in consideration of the differences in country income and geographic regions to help policy-makers to develop strategies and policies to combat CRE worldwide.

METHODS

This systematic review is conducted following the guidelines of Cochrane Guidance[19] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (see Supplementary Material Appendix 1).[20] The protocol was registered with PROSPERO on July 5, 2020(CRD42020176808). The initial protocol was designed with a broad scope including many research contents, but in consideration of the limitation of maximum length, we decided to divide our work into two parts: the first (this study) focused on mortality, and the second will focus on morbidity and the economic outcomes.

Search strategy

We conducted a systematic literature search on the databases of PubMed, Embase, Web of Science, and the Cochrane Library to select relevant studies published between 1 January 1994, and 30 August 2020 to identify eligible studies. This period was chosen because carbapenem-resistant *Enterobacteriaceae* were first reported in the 1990s. Specifically, the strains producing Metallo-β-lactamase(MBL)IMP-1, which is a type of carbapenemase that can hydrolyze carbapenems, were first identified in Japan from a study published in 1994.[4]

The search strategy was designed by combining the terms of bacteria and carbapenem resistance (see Supplementary Material Appendix 2). The search terms for the bacteria include "*Enterobacteriaceae*" and also *"Klebsiella pneumoniae"* and *"Escherichia coli"*, which are the two most clinically important pathogens within the *Enterobacteriaceae* family, to ensure comprehensive identification of relevant studies. The search terms for carbapenem resistance include "carbapenem-resistant" or "carbapenem resistance" or "carbapenem non-susceptible" or "carbapenemase-producing" because CRE can be generally divided into carbapenemase-producing CRE (CP-CRE) and non-carbapenemase-producing CRE (non-CP-CRE).[21]

Selection criteria

We included studies fulfilling the following criteria: (1) primary observational studies (i.e., case-control study, cohort studies); (2) published from 1 January 1994 to 30 August 2020; (3) published in English; (4) studies that assessed the mortality for hospitalized patients with confirmed infections due to CRE and the mortality of patients in control group infected with CSE.

Exclusion criteria were as follows: (1) studies that designed patients colonized with CRE or with unconfirmed CRE infection as exposed groups; (2) studies that mainly focused on the resistance of other antibiotics instead of carbapenem antibiotics; (3) studies without a control group, or with a control group not infected with *Enterobacteriaceae* pathogens; (4) studies including less than 10 patients in case or control group; (5) studies on animals; (6) publications such as editorials and letters. The list of excluded studies with reasons for exclusion is provided in Supplementary Material Appendix 3.

Two reviewers independently screened all titles and abstracts of identified studies and then reviewed the full text of studies satisfying the inclusion criteria. Disagreements were resolved through consensus or discussion with a third senior reviewer.

Data extraction

Data were extracted from each selected study into a data extraction form in Excel. The extracted data include first author, year of publication, study period, country, region, country income level classified by the World Bank,[22] study design, infection type, specific pathogen, sample size, number of deaths in CRE and CSE groups. Notably, we will choose the income status of the country based on the period when the study was conducted because the income status of some countries may have changed between 1994 and 2020. For example, there are 15 studies conducted in China from 2006 to 2018 in this meta-analysis, but

the income status of China changed from lower-income level to upper-income level since 2010. Therefore, two studies conducted between 2006 and 2009 were classified as lower middle income, and the other 13 studies conducted after 2010 were classified as upper middle income. All kinds of measurements of mortality outcomes in each included study were extracted including all-cause in-hospital mortality, all-cause mortality at 6-30 days (6 days, 7 days, 14 days, 21 days, 28 days, 30 days) after diagnosis, mortality in ICU, and mortality attributable to infection (usually defined as the death of a patient with clinical and laboratory evidence of ongoing infection in absence of other feasible reasons). If mortality outcomes at multiple time points were reported in one study, only one mortality outcome will be analyzed in the subsequent calculation of the pooled overall mortality, with a priority of in-hospital mortality and the latest time point of mortality.

Data extraction was conducted by two reviewers independently and disagreements were resolved through consensus or discussion with a third senior reviewer.

Data synthesis and analysis

We calculated the pooled relative risk (RR) and risk difference (RD) by comparing the mortality in patients with CRE infection with that in patients with CSE infection. The reason that we choose RR as the measure of relative risk rather than OR is that the latter was more difficult to interpret compared to RR[23,24] and usually misinterpreted as a RR which may overestimate the intervention effect when it is more than 1.[25] Besides, we also calculated RD to describe the absolute difference in the risk of mortality between the two groups because of the drawback of sole reporting the relative risk that it may conceal the underlying absolute risks and readers tend to overestimate the effect.[26] It was recommended that both relative risk and absolute risk should be reported to provide a complete picture of the effect.[27] The pooled estimates of RRs

and RDs with 95% confidence intervals were calculated using a random-effects model using the method of DerSimonian & Laird,[28] with the estimate of heterogeneity being taken from the Mantel-Haenszel model. An RR of 1 and RD of 0 indicate that the risk of mortality is identical regardless of carbapenem resistance. The heterogeneity across studies was assessed by Q-statistic and I^2 measures. The heterogeneity was considered statistically significant when I^2 values >50%. To identify the potential sources of heterogeneity, we conducted stratified analysis by bacterial species, different mortality endpoints, geographic region, economic status, source of infection, sample size, and resistance mechanism. F-test based on a one-way analysis of variance (ANOVA) was used to test the differences in the mean effect estimates between subgroups. We also conducted random-effects meta-regression based on restricted maximum likelihood using an iterative procedure to examine whether the effect estimates differ significantly by the above variables, and P <0.05 was considered statistically significant. A sensitivity analysis was also conducted, in which the pooled RRs were recalculated using random-effects meta-analysis after removing one study at a time to evaluate the stability of the results. Finally, we conducted a funnel plot to assess the publication bias. All the statistical analyses were conducted using the Stata version 15 software.

Risk of bias assessment

Two reviewers independently assessed the risk of bias of each included study using the Newcastle-Ottawa quality assessment Scale (NOS) for observational studies,[29] and disagreements were resolved through consensus or discussion with a third senior reviewer.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of

this systematic review.

RESULTS

We identified 10304 studies from the literature search, and 50 studies[30-79] were selected according to the inclusion and included in the final review (Figure.1). The characteristics of the included studies are provided in Table.1. The studies are conducted in 14 countries from four regions. Nearly half of the studies are conducted in Asia (n=24), followed by the region of America (n=15), Europe (n=9), and only one study was conducted in Africa. We also included a multi-region study including data from Asia, Africa and America.[79] The studies included are mainly conducted in high-income countries (n=27) and upper-middle-income countries (n=19), only three studies were conducted in lower-middle-income countries and no study in low-income countries was found that met the criteria. Most studies (n=39) reported mortality outcomes of infections due to *Klebsiella pneumoniae* pathogens, and two studies reported mortality outcomes of infections due to *Escherichia coli* and nine studies reported mortality outcomes of infections due to mixed *Enterobacteriaceae* pathogens. Half of the studies (n=24) evaluated infected patients regardless of specific infection type. Among the rest studies focused on specific sites of infection, bloodstream infection was the most frequent type (n=21), followed by urinary tract infection (n=3), and one study for neurosurgical infection and one for pneumonia. Among the 50 studies included, most were cohort studies(n=29). In the other 21 case-control studies, the mortality outcomes were measured using a cohort study design, therefore those studies were assessed as cohort studies in our quality appraisal. The NOS assessment for the risk of bias of all included studies was summarized in Supplementary Material Appendix 4. According to the NOS scores, 46 were categorized as low risk of bias (7 to 9) and only 4 studies were categorized as the moderate risk of bias (4 to 6).

Table.1 Characteristic of included studies

First Author	Year	study period	Country	Region	Economic status	Study design	Infection type	Pathogen	Sample size (n)		Mortality measurements	Mortality (%)	
									CRE	CSE		CRE	CSE
Alicino [30]	2015	2007.01-2014.12	Italy	Europe	High income	retrospective cohort study	bloodstream infection	Klebsiella pneumoniae	349	162	30d mortality	36.1	23.5
Balkhair[31]	2019	2007.01-2016.12	Oman	Asia	High income	retrospective cohort study	bloodstream infection	Klebsiella pneumoniae	69	305	30d mortality	63.8	24.3
Ben-David[32]	2012	2006.01-2006.12	Israel	Asia	High income	retrospective cohort study	bloodstream infection	Klebsiella pneumoniae(KPC)	42	85	inhospital mortality	69	24
											mortality attributable to infection	48	17
Brizendine[33]	2015	2006-2012	USA	America	High income	retrospective cohort study	urinary tract infection	Klebsiella pneumoniae	22	64	inhospital mortality	18	2
Chang[34]	2019	2014.01-2018.07	China	Asia	Upper middle income	retrospective cohort study	bloodstream infection	Klebsiella pneumoniae	46	239	28d mortality	50	14.6
											7d mortality	37	10.5
											inhospital mortality	58.7	15.9
Chang[35]	2011	2006.1-2008.12	China	Asia	Lower middle income	retrospective case control	bloodstream infection	Escherichia. coli	17	34	inhospital mortality	94.12	50
											28d hospital mortality	70.59	47.06
											14d hospital mortality	47.06	38.24
Chiotos[36]	2018	2011.1-2016.7	USA	America	High income	retrospective cohort study	mixed	Mixed Enterobacteriaceae	31	144	30d mortality	6.5	1.4

Cienfuegos-Gallet[37]	2019	2014.02-03; 2014.10-2015.09	Colombia	America	Upper middle income	prospective cohort study	mixed	Klebsiella pneumoniae(KPC)	49	289	30d mortality	32.65	15.92
Correa[38]	2013	2006.1-2008.8	Brazil	America	Upper middle income	retrospective case control	mixed	Klebsiella pneumoniae	20	40	inhospital mortality	50	27.5
Cubero[39]	2015	2010.10-2012.12	Spain	Europe	High income	retrospective case control	mixed	Klebsiella pneumoniae(OXA)	20	9	inhospital mortality	35	11.1
Daikos[40]	2009	2004.2-2006.3	Greece	Europe	High income	preospective cohort study	bloodstream infection	Klebsiella pneumoniae(VIM)	14	148	14d mortality	42.9	16.9
Fraenkel-Wandel[41]	2016	2006-2012	Israel	Asia	High income	retrospective case control	bloodstream infection	Klebsiella pneumoniae(KPC)	68	136	inhospital mortality	65	40
Gallagher[42]	2014	2005.6-2010.10	USA	America	High income	retrospective case control	bloodstream infection	Klebsiella pneumoniae	43	111	inhospital mortality	45	32
Garbati[43]	2016	2012.3-2013.12	Saudi Arabia	Asia	High income	prospective case control study	mixed	Mixed Enterobacteriaceae	29	58	inhospital mortality	31	12.1
Gomez Rueda[44]	2014	2008.1-2011.1	Colombia	America	Upper middle income	prospective case control study	mixed	Klebsiella pneumoniae	61	61	inhospital mortality	50.8	32.7
Hoxha[45]	2016	2012.11-2013.7	Italy	Europe	High income	prospective cohort study	mixed	Klebsiella pneumoniae	49	49	30d mortality	61	20
											6d mortality	24	8
Huang[46]	2018	2017.01-2017.12	China	Asia	Upper middle income	retrospective cohort study	mixed	Klebsiella pneumoniae	267	1328	inhospital mortality	14.61	5.65
Hussein[47]	2013	2006.1-2008.12	Israel	Asia	High income	retrospective case control study	bloodstream infection	Klebsiella pneumoniae	103	214	30d mortality	43.7	29

Kotb[48]	2020	2011-2017	Egypt	Africa	Lower middle income	retrospective cohort study	mixed	Mixed Enterobacteriaceae	871	727	mortality in ICU	61.1	51.7
Lee[49]	2016	2013.1-2014.2	Korea	Asia	High income	retrospective case control study	mixed	Mixed Enterobacteriaceae	37	37	inhospital mortality	10.8	10.8
											28d mortality	27	21.6
Li[50]	2019	2014.1-2018.6	China	Asia	Upper middle income	retrospective case control study	mixed	Klebsiella pneumoniae	244	263	30d mortality in ICU	28.9	11
Liu[51]	2019	2014.1-2018.9	China	Asia	Upper middle income	retrospective cohort study	bloodstream infection	Klebsiella pneumoniae	20	69	30d mortality	55	15.9
Liu[52]	2012	2007.1-2009.12	China	Asia	Lower middle incom	retrospective case control study	bloodstream infection	Klebsiella pneumoniae	25	50	inhospital mortality	60	40
											28d mortality	52	30
											14d mortality	44	22
Mclaughlin[53]	2014	2010.3-2011.12	USA	America	High income	retrospective case control study	bloodstream infection	Klebsiella pneumoniae(KPC)	15	60	inhospital mortality	33.3	11.7
Meng[54]	2017	2012.1-2015.12	China	Asia	Upper middle income	retrospective case control study	mixed	Escherichia. coli	49	96	inhospital mortality	12	1
Mouloudi[55]	2010	2007.1-2008.12	Greece	Europe	High income	retrospective case control study	bloodstream infection	Klebsiella pneumoniae(KPC)	37	22	inhospital mortality	67.8	41
											mortality in ICU	27	14
Ny[56]	2015	2011.1-2013.12	USA	America	High	retrospective	mixed	Klebsiella pneumoniae	48	48	inhospital	14.6	10.4

					income	cohort study					mortality		
Orsi[57]	2013	2008.7-2011.6	Italy	Europe	High income	retrospective case control study	mixed	Klebsiella pneumoniae(KPC)	36	43	inhospital mortality	38.9	27.9
Pan[58]	2019	2014	China	Asia	Upper middle income	retrospective case control study	mixed	Klebsiella pneumoniae(KPC)	66	132	inhospital mortality	57.6	18.2
											28d mortality	18.18	11.36
Patel[59]	2008	2004.7-2006.6	USA	America	High income	retrospective case control	mixed	Klebsiella pneumoniae	99	99	inhospital mortality	48	20
											mortality attributable to infection	38	12
Pereira[60]	2015	2010.1-2013.1	USA	America	High income	retrospective cohort study	mixed	Klebsiella pneumoniae	20	36	inhospital mortality	45	28
Pouch[61]	2015	2007.1-2010.12	USA	America	High income	retrospective case control study	urinary tract infection	Mixed Enterobacteriaceae	20	80	inhospital mortality	30	10
Qureshi[62]	2012	2011.1-2014.12	USA	America	High income	retrospective case control	bloodstream infection	Klebsiella pneumoniae	19	51	28d mortality	47.4	27.5
Sánchez-Romero[63]	2011	2009.1-2009.12	Spain	Europe	High income	retrospective case control	mixed	Klebsiella pneumoniae(VIM)	28	55	14d mortality	46.4	30.9
Schwaber[64]	2008	2003.9-2006.12	Israel	Asia	High income	retrospective cohort study	mixed	Klebsiella pneumoniae	48	56	inhospital mortality	44	12.5
Shilo[65]	2013	2006.1-2009.12	Israel	Asia	High income	retrospective case control study	urinary tract infection	Klebsiella pneumoniae	135	127	inhospital mortality	29	25

Simkins[66]	2014	2006.1-2010.12	USA	America	High income	retrospective case control study	mixed	Klebsiella pneumoniae	13	39	inhospital mortality	46	8
Tian[67]	2016	2011.1-2015.12	China	Asia	Upper middle income	retrospective cohort study	bloodstream infection	Klebsiella pneumoniae	33	81	inhospital mortality	42.4	19.8
											mortality attributable to infection	42.4	24.6
											28d mortality	33.3	18.5
Torres-Gonzalez[68]	2016	2013.11-2015.7	Mexico	America	Upper middle income	retrospective case control study	mixed	Mixed Enterobacteriaceae(OXA)	27	108	mortality attributable to infection	11.1	7.4
Trecarichi[69]	2016	2010.1-2014.6	Italy	Europe	High income	prospective cohort study	bloodstream infection	Klebsiella pneumoniae	161	117	21d mortality	52.2	14.5
Ulu[70]	2015	2012.1-2012.12	Turkey	Asia	Upper middle income	retrospective cohort study	mixed	Klebsiella pneumoniae	47	51	mortality in ICU	44.7	51
Vardakas[71]	2015	2006.1-2009.10	Greece	Europe	High income	retrospective cohort study	mixed	Klebsiella pneumoniae	80	24	mortality in ICU	72.5	58.3
Wang [72]	2018	2010.1-2014.12	China	Asia	Upper middle income	retrospective case control study	mixed	Klebsiella pneumoniae	48	48	inhospital mortality	47.9	4.2
Xiao[73]	2018	2013.1-2015.12	China	Asia	Upper middle income	retrospective cohort study	bloodstream infection	Klebsiella pneumoniae	135	293	30d mortality	58.5	15.4
Zhang[74]	2018	2011.1-2014.12	China	Asia	Upper middle	retrospective case control	bloodstream infection	Klebsiella pneumoniae	54	84	inhospital mortality	18.5	8.3

					income	study					7d mortality	16.7	1.2
											28d mortality	18.5	2.4
Zheng[75]	2018	2014.1-2016.12	China	Asia	Upper middle income	retrospective cohort study	bloodstream infection	Klebsiella pneumoniae	59	230	28d mortality	54.2	19.6
Zheng[76]	2020	2012-2017	China	Asia	Upper middle income	retrospective cohort study	neurosurgical infection	Mixed Enterobacteriaceae	26	107	mortality attributable to infection	69.2	12.1
Zuo[77]	2020	2015-2017	China	Asia	Upper middle income	retrospectivecase control	pneumonia	Klebsiella pneumoniae	74	74	inhospital mortality	35.1	20.3
											mortality attributable to infection	25.7	9.5
Villegas[78]	2016	2013.7-2014.11	7 countries in Latin America	America	Upper middle income	retrospective cohort study	bloodstream infection	Mixed Enterobacteriaceae	53	202	inhospital mortality	64	30
											mortality attributable to infection	85	43
Stewardson[79]	2019	2014.8-2015.6	10 countries	Asia, Africa, America	low and middle income countries	prospective cohort study	bloodstream infection	Mixed Enterobacteriaceae	123	174	inhospital mortality	35	20

Meta-analysis results

In the 50 studies identified, a total of 11190 patients were analyzed, 4031 patients infected with resistant pathogens, and 7159 patients infected with susceptible pathogens. Most studies reported higher mortality in patients infected with CRE than in patients with CSE infections, however, the difference is not statistically significant (p>0.1) in 12 studies, one study[49] reported the same in-hospital mortality outcome between the two groups and one study[70] observed lower mortality in patients infected with CRE. The reported mortality rates ranged from 6.5%[36] to 94.12%[35] in patients with CRE infections and ranged from 1%[54] to 58.3%[71] in patients with CSE infections. The unweighted means of the mortality of CRE patients and CSE patients reported in each study were 43.99% and 21.33% (Table.2). The result of the meta-analysis based on the outcome measure of risk ratio (RR) suggested that carbapenem resistance has doubled the risk of death (RR, 2.16; 95%CI, 1.85-2.52) in patients infected with *Enterobacteriaceae*. However, high heterogeneity was detected (I^2=80.6%; P<0.001, Figure.2). In terms of the absolute risk, the meta-analysis results base on the outcome measure of risk difference (RD, 0.22, 95%CI, 0.18-0.26) suggested that CRE infection contributed 22% excess risk of overall mortality compared with CSE infection, but the heterogeneity between studies was also high (I^2=78.0%; P<0.001, Figure.3).

Stratified analysis

To explore the heterogeneity between studies and assess the robustness of our findings, we conducted the stratified analysis to evaluate the potential sources of heterogeneity including pathogens, geographic region, economic status of the country, source of infection, resistance mechanism type, sample size, and publication year. One study[79] was not included in our subgroup analysis by geographic region and country income level, because it was conducted in 10 countries with different economic status from three

continents. As seen in Table.2, the carbapenem resistance has a significant positive effect on the mortality for patients infected with *Enterobacteriaceae* in most subgroups, however, it was not significantly different in mortality between CRE infection and CSE infection in studies focusing on patients infected with *Escherichia. coli* pathogens (RR, 3.83, 95%CI, 0.46-31.78, p=0.214; RD, 0.27, 95%CI, -0.06-0.59, p=0.115) as well as studies focusing on patients infected with OXA-producing *Enterobacteriaceae* (RR, 1.87, 95%CI, 0.65-5.37, p=0.246; RD, 0.09, 95%CI, -0.09-0.28, p=0.306) in both relative and absolute terms. In the subgroup analysis by infection type, no significant difference in pooled RR of mortality was observed for studies focusing on patients with urinary tract infections (RR, 2.40, 95%CI, 0.82-7.03, p=0.110).

The results of the statistical test based on RD showed that the effect of carbapenem resistance on mortality is significantly different for patients with different infection types (p=0.006). For patients with neurosurgical infection, carbapenem resistance had a greater effect on mortality compared to other types of infection (Table.2).

Meta-regression

To further explore whether the effect of carbapenem resistance on mortality differs by the above variables, we conducted a univariate meta-regression. In the case of RR (Table.3), the meta-regression results showed that infection type, publication year might contribute to the heterogeneity between included studies. Specifically, carbapenem resistance had a significantly greater effect on mortality in studies focusing on patients with neurosurgical infection compared to studies focusing on bloodstream infection (coefficient=-0.95, p=0.042), urinary tract infection (coefficient=-1.16, p=0.039), and studies without focusing on a specific type of infection (coefficient=-1.065, p=0.024). Meta-regression using the year of

publication range as a categorical variable showed that compared to studies published between 2017-2020, the influence of carbapenem resistance on mortality is significantly smaller in studies published between 2011 to 2013 (coefficient=-0.476, p=0.007) and 2014 to 2016 (coefficient=-0.366, p=0.015). However, the results from statistical analysis (p-value between groups) showed no significant difference in risk ratio between groups of sub-categories. In the case of RD (Table.4), the meta-regression results showed geographic region and sample size might be the source of heterogeneity between studies. Compared to studies conducted in Asia, the effect of carbapenem resistance on mortality is significantly smaller in studies in Africa (coefficient=-0.187, p=0.005), but the effect has no difference between studies in other regions and Asia. Moreover, it was found the effect of carbapenem resistance trend to decrease with the increase of sample size (coefficient=-0.0001, p=0.006).

Sensitivity analysis

A sensitivity analysis was performed by removing one study at a time and recalculated the pooled RRs of remaining studies using random-effects meta-analysis to assess the influence of individual studies on the results. We found that the direction of the effect did not change when any one study was excluded, which means the stability of the results of the meta-analysis.

Publication bias

Publication bias was assessed by a funnel plot (Figure.4). Slight asymmetrical was observed in the funnel plots and the points were heavily distributed at the right top, implying a lack of smaller studies that show a negative association between carbapenem resistance and mortality.

Table.2 Subgroup analysis of the effect of carbapenem resistance on mortality in patients infected with Enterobacteriaceae

Sub-groups	No. of studies	mortality among CRE patients (unweighted means)	mortality among CSE patients (unweighted means)	RR(95%CI)	*P*-value (significance tests of RR=1)	I^2(%)	*P*-value beteen groups	RD(95%CI)	*P*-value (significance tests of RD=0)	I^2(%)	*P*-value beteen groups
Pathogens											
Klebsiella pneumoniae	39	45.51%	22.05%	2.12(1.84, 2.45)	0.000	68.1		0.23(0.19, 0.28)	0.000	75.7	
Mixed Enterobacteriaceae pathogens	9	35.41%	17.28%	2.13(1.41, 3.22)	0.000	84.3	**0.073**	0.17(0.08, 0.25)	0.000	80.4	**0.526**
Escherichia. coli	2	53.06%	25.50%	3.83(0.46, 31.78)	0.214	76.2		0.27(-0.06, 0.59)	0.115	88.6	
Geographical region											
America	15	36.16%	17.63%	1.96(1.68, 2.28)	0.000	0.0		0.17(0.11, 0.23)	0.000	50.9	
Europe	9	50.38%	27.11%	1.89 (1.43, 2.51)	0.000	58.9	**0.636**	0.24(0.14, 0.33)	0.000	61.3	**0.338**
Asia	24	46.16%	20.25%	2.37(1.95,2.88)	0.000	76.2		0.25(0.19, 0.32)	0.000	85.5	
Africa	1	61.10%	51.70%	1.18(1.08, 1.29)	0.000	NA		0.09(0.05, 0.14)	0.000	NA	
Economic status											
High income	27	42.35%	21.21%	1.97(1.68, 2.30)	0.000	52.5		0.21(0.15, 0.26)	0.000	68.4	
Upper middle income	19	42.41%	17.47%	2.52(2.03, 3.13)	0.000	71.8	**0.329**	0.25(0.17, 0.32)	0.000	85.7	**0.662**
Lower middle income	3	71.74%	47.23%	1.44(1.04, 1.98)	0.027	71.5		0.23(0.01, 0.45)	0.041	82.5	
Infection type											
Bloodstream infections	21	52.72%	24.72%	2.20(1.88, 2.57)	0.000	65.8		0.28(0.22, 0.34)	0.000	70.7	
Urinary tract infection	3	25.67%	12.33%	2.40(0.82, 7.03)	0.110	72.5		0.11(0.003, 0.21)	0.044	29.7	
pneumonia	1	35.10%	20.30%	1.73(1.00, 3.00)	0.049	NA	**0.255**	0.15(0.006, 0.29)	0.040	NA	**0.006**
Neurosurgical infection	1	69.20%	12.10%	5.70(3.22, 10.08)	0.000	NA		0.57(0.38, 0.76)	0.000	NA	
Mixed	24	37.96%	19.90%	2.02(1.60, 2.55)	0.000	78.0		0.17(0.12, 0.22)	0.000	70.2	
Resistance type											

KPC-producing Enterobacteriaceae	7	52.12%	25.52%	2.12(1.64, 2.75)	0.000	49.9		0.28(0.18, 0.37)	0.000	52.0	
OXA-producing Enterobacteriaceae	2	23.05%	9.25%	1.87(0.65, 5.37)	0.246	0.0		0.09(-0.09, 0.28)	0.306	36.4	
VIM- producing Enterobacteriaceae	2	44.65%	23.90%	1.87(1.12, 3.11)	0.016	24.6	**0.766**	0.20(0.03, 0.37)	0.023	0.0	**0.717**
include non-carbapenemase-producing strains or multiple resistance types	39	43.57%	21.06%	2.17(1.83, 2.58)	0.000	83.1		0.22(0.17, 0.26)	0.000	80.5	
Sample size											
<100	19	44.61%	22.63%	1.94(1.53, 2.46)	0.000	51.5		0.21(0.14, 0.29)	0.000	60.8	
100-200	16	40.91%	18.43%	2.33(1.82, 2.98)	0.000	61.1	**0.521**	0.22(0.14, 0.30)	0.000	76.9	**0.942**
>200	15	46.50%	22.76%	2.13(1.67, 2.72)	0.000	90.9		0.23(0.16, 0.30)	0.000	87.8	
Range of publication year											
2008-2010	4	50.83%	22.58%	2.34(1.75, 3.14)	0.000	0.0		0.29(0.20, 0.38)	0.000	0.0	
2011-2013	9	53.17%	31.31%	1.66(1.38, 2.00)	0.000	31.2	**0.143**	0.21(0.11, 0.32)	0.000	67.7	**0.343**
2014-2016	20	40.43%	21.67%	1.84(1.51, 2.24)	0.000	55.7		0.18(0.12, 0.24)	0.000	64.3	
2017-2020	17	41.72%	15.35%	2.83(2.06, 3.88)	0.000	91.3		0.25(0.18, 0.32)	0.000	88.5	
Total	**50**	**43.99%**	**21.33%**	**2.14(1.85, 2.48)**	**0.000**	**80.0**	**-**	**0.22(0.18, 0.26)**	**0.000**	**78.0**	**-**

OXA, oxacillinase; KPC, Klebsiella pneumoniae carbapenemase; VIM, Verona integron-encoded MBL

Table.3 Univariate meta-regression and statistical analysis for the potential variables between studies (Outcome measure=risk ratio)

Variables	Sub-categories	No. of studies	coefficient	standard error	95% confidence interval		*P* value from meta-regression
Pathogen type	Klebsiella pneumoniae	39	-0.087	0.389	-0.870	0.696	0.824
	Mixed Enterobacteriaceae pathogens	9	-0.109	0.418	-0.950	0.731	0.795
	Escherichia. coli	2	reference	-	-	-	-
Geographical region	America	15	-0.149	0.160	-0.471	0.173	0.357
	Europe	9	-0.215	0.176	-0.570	0.139	0.228
	Asia	24	reference	-	-	-	-
	Africa	1	-0.690	0.355	-1.405	0.024	0.058
Economic status	High income	27	reference	-	-	-	-
	Upper middle income	19	0.235	0.134	-0.034	0.504	0.085
	Lower middle income	3	-0.306	0.228	-0.765	0.153	0.186
Infection type	Bloodstream infections	21	-0.950	0.454	-1.865	-0.036	0.042
	Urinary tract infection	3	-1.160	0.545	-2.258	-0.063	0.039
	pneumonia	1	-1.190	0.624	-2.447	0.067	0.063
	Neurosurgical infection	1	reference	-	-	-	-
	Mixed	24	-1.065	0.456	-1.984	-0.146	0.024
Resistance type	KPC-producing Enterobacteriaceae	7	-0.008	0.188	-0.387	0.372	0.968
	OXA-producing Enterobacteriaceae	2	-0.112	0.617	-1.354	1.130	0.857
	VIM- producing Enterobacteriaceae	2	-0.118	0.354	-0.831	0.596	0.741
	include non-carbapenemase-producing strains or multiple resistance types	39	reference	-	-	-	-
Sample size group	<100	19	-0.091	0.159	-0.412	0.230	0.571
	100-200	16	0.090	0.160	-0.232	0.412	0.577
	>200	15	reference	-	-	-	-
Year of publication range	2008-2010	4	-0.114	0.243	-0.604	0.376	0.642
	2011-2013	9	-0.476	0.167	-0.813	-0.139	0.007
	2014-2016	20	-0.366	0.144	-0.657	-0.075	0.015
	2017-2020	17	reference	-	-	-	-
Sample size	-	50	-0.0001	0.0002	-0.0005	0.0003	0.554
Year of publication	-	50	0.034	0.020	-0.006	0.073	0.094

OXA, oxacillinase; KPC, Klebsiella pneumoniae carbapenemase; VIM, Verona integron-encoded MBL

Table.4 Univariate meta-regression and statistical analysis for the potential variables between studies (Outcome measure=risk difference)

Variables	Sub-categories	No. of studies	coefficient	standard error	95% confidence interval		*P* value from meta-regression
Pathogen type	Klebsiella pneumoniae	39	-0.191	0.183	-0.559	0.178	0.303
	Mixed Enterobacteriaceae pathogens	9	-0.307	0.184	-0.677	0.063	0.102
	Escherichia. coli	2	reference	-	-	-	-
Geographical region	America	15	-0.052	0.089	-0.232	0.128	0.566
	Europe	9	-0.075	0.096	-0.268	0.118	0.437
	Asia	24	reference	-	-	-	-
	Africa	1	-0.187	0.063	-0.314	-0.059	0.005
Economic status	High income	27	reference	-	-	-	-
	Upper middle income	19	0.045	0.073	-0.102	0.192	0.541
	Lower middle income	3	-0.114	0.065	-0.245	0.017	0.086
Infection type	Bloodstream infections	21	-0.275	0.294	-0.867	0.318	0.355
	Urinary tract infection	3	-0.506	0.345	-1.200	0.189	0.149
	pneumonia	1	-0.422	0.403	-1.235	0.390	0.301
	Neurosurgical infection	1	reference	-	-	-	-
	Mixed	24	-0.448	0.293	-1.039	0.143	0.134
Resistance type	KPC-producing Enterobacteriaceae	7	0.073	0.097	-0.122	0.268	0.46
	OXA-producing Enterobacteriaceae	2	-0.116	0.542	-1.206	0.975	0.832
	VIM- producing Enterobacteriaceae	2	-0.017	0.230	-0.480	0.447	0.943
	include non-carbapenemase-producing strains or multiple resistance types	39	reference	-	-	-	-
Sample size group	<100	19	0.019	0.089	-0.160	0.198	0.831
	100-200	16	0.051	0.084	-0.119	0.220	0.551
	>200	15	reference	-	-	-	-
Year of publication range	2008-2010	4	0.048	0.161	-0.275	0.372	0.765
	2011-2013	9	-0.003	0.094	-0.192	0.186	0.974
	2014-2016	20	-0.031	0.078	-0.189	0.127	0.693
	2017-2020	17	reference	-	-	-	-
Sample size	-	50	-0.0001	0.00004	-0.0002	-0.00003	0.006
Year of publication	-	50	-0.005	0.010	-0.025	0.015	0.648

OXA, oxacillinase; KPC, Klebsiella pneumoniae carbapenemase; VIM, Verona integron-encoded MBL

DISCUSSION

This study systematically reviewed 50 studies and provided a comprehensive analysis of the impact of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae*. Our analysis suggests that carbapenem resistance has doubled the mortality rate of patients infected with CRE compared to patients infected with CSE, and CRE infection can increase the risk of mortality by 22%. The results were consistent with the direction of the previous meta-analysis of the association between carbapenem resistance and mortality among patients infected with *Enterobacteriaceae*.[13,14]

It is necessary to identify the risk factors for worse mortality outcomes in patients with CRE infections. In previous studies, higher mortality among patients with CRE infection was usually explained by patient-, infection-, treatment-, and organism-related factors.[13,14,16,80] Overall, 20 studies included in this review conducted the multivariable analysis to identify risk factors of mortality among patients infected with *Enterobacteriaceae*. After controlling patient-related factors such as age, sex, the severity of underlying illness and comorbidities, three studies[47,51,67] found carbapenem resistance was not associated with increased mortality risk, however, 14 studies found that carbapenem resistance remained an independent predictor of mortality. Besides, therapeutic interventions were also considered as important risk factors for the explanation of the increased mortality in CRE infection. Patients with CRE infection are more likely to receive a delayed administration of initial antibiotic therapy with in-vitro activity[32,33,40,59,62,67,74], which might lead to a worse outcome. It has been suggested that the effect of carbapenem resistance was probably mediated by inappropriate initial therapy in several studies included in this meta-analysis.[40,51,37] This finding was supported by a recent review, in which a significant association between the differences in the proportion of the patients receiving appropriate initial antibiotic therapy and mortality was identified through a meta-regression analysis including 11 studies.[16] However,

nine studies included in our review[32,38,41,47,62,67,71,73,74] did not identify an association between early appropriate antibiotic therapy and mortality after adjustment for some confounding factors. Instead, other treatment methods were addressed as important risk factors of mortality in some studies. For example, a recent meta-analysis including seven studies showed that monotherapy treatment was associated with significantly higher mortality compared with combination therapy for patients with CRE infections[14]. Additionally, some studies[72,73] suggested other therapies, such as adjunctive therapy, tigecycline therapy and the use of aminoglycoside may be associated with mortality among patients infected with *Klebsiella pneumoniae*. The increased mortality among patients with CRE infections might also be related to the increased virulence of carbapenemase-producing strains. Two studies included in this meta-analysis showed that isolation of KPC-positive strain was a predictor of mortality among patients infected with Klebsiella pneumoniae independent of the appropriateness of initial treatment and patient characteristics,[41,55] while another study[47] found KPC-positive status was not associated with mortality when the virulence score was included in the multivariate analysis. In our subgroup analysis, we identified an increased risk of mortality associated with KPC- and VIM-producing strains but not with OXA-producing strains, which may be explained by the different virulence characteristics of the carbapenem-resistant isolates with different types of carbapenemases.[17] As most of the included studies did not provide the mortality outcomes after adjustment for confounding factors, we did not calculate the pooled adjusted effect measures.

To investigate the heterogeneity between studies, stratified analysis and meta-regression were performed. We found that the effect of carbapenem resistance on mortality differs by infection type, geographic region, sample size and year of publication. The results of the statistical test and meta-regression analysis identified a significant difference in effect between different infection types. For

patients with neurosurgical infection, carbapenem resistance had a significantly greater effect on mortality compared to other types of infection. The possible explanation could be that CRE meningitis/encephalitis in neurosurgery can result in more severe morbidity and mortality because of difficulties in treatment.[74] In addition, we found that the effect of carbapenem resistance on mortality in Africa is significantly smaller compared with studies in Asia in the case of RD, but no significant difference was identified between studies in America, Europe and Asia. This could be due to both high mortality rates in patients (61.1%) and CSE patients (51.7%) reported in only one study in Africa, which might be related to the low level of medical care and poor hygiene. We also found that with the increase of sample size, the RD had a decreasing trend, indicating that the absolute risk difference of mortality between CRE and CSE infection tends to be stable with larger sample size. Moreover, it should be noted that the effect of carbapenem resistance on mortality is greater in studies published from 2017-2020 compared to previous studies in relative terms. On the one hand, the mortality of CRE infection remains high as it is a therapeutic challenge due to limited effective antibiotics. What's worse, carbapenem-resistant *Enterobacteriaceae* have started to develop resistance against some key antibiotics such as colistin,[81] resulting in increased difficulties for treatment for CRE infection. As shown in a previous study, [16] the proportion of CRKP patients receiving appropriate initial antibiotic therapy did not change over time. In addition, another study[11] observed higher mortality of CRE infection from studies published from 2014 to 2016 than those published from 2009 to 2013. On the other hand, the mortality of CSE infection tends to decrease in recent years and the unweighted mean of mortality among CSE patients in studies conducted from 2017-2020 is 15.35%, lower than that of other ranges of publication year (Table.2). This could be due to the increasing treatment success rate with the development of medical technology and medical treatment, which may enlarge the differences in mortality between CRE and CSE infections.

To our knowledge, this is the most comprehensive meta-analysis so far to assess the impact of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae.* Nearly 20 new studies published in recent three years that have been included in our study. Although high heterogeneity was observed between studies, sensitivity analysis suggested that no single study influenced the pooled RR, indicating the stability of the results of the meta-analysis. This is the first review to explore the source of heterogeneity between studies through statistical tests and meta-regression analysis of potential variables in consideration of country economic status and geographic region.

Our study also has several limitations. Firstly, we only include two clinically important *Enterobacteriaceae* species, *Klebsiella pneumoniae* and *Escherichia coli*. and only included studies published in English. Secondly, we only calculated the unadjusted results, many confounding factors such as the health condition of patients, therapy options are not adjusted in the analysis because of data limitation. At last, minor publication bias was observed, possibly due to the lack of smaller studies from low-income countries. Therefore, more studies that quantifying the attributable mortality of CRE in low-income countries are needed to provide reliable data for the decision-makers about the great threat of CRE to promote interventions to reduce its consequences.

CONCLUSIONS

The results of this meta-analysis suggested that carbapenem resistance was associated with an increased risk of mortality for patients infected with *Enterobacteriaceae.* The subgroup analysis and meta-regression showed the effect of carbapenem resistance differs by infection type, geographic region, sample size and publication year. In further research, more studies need to be conducted in low-income countries to provide

sound evidence to draw resources to fight against CRE and suggest the way forward for alleviating the implications.

Contributors All authors were involved in the design and development of the study. The review was designed by XF, RZ, RZ, JL, JS, TRW, and YW. The literature search in electronic databases was conducted by JZ, SS, SC and XZ. RZ and JZ screened all studies for inclusion into the systematic review and performed the assessments of risk bias for all studies. RY and JZ performed data extraction. All authors contributed to data interpretation and data analysis. RZ drafted the manuscript and all authors revised it critically for content. All authors have reviewed the results and approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The corresponding author (XF) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing interests None declared

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Figure legends

Figure.1 Flow chart of the study selection process for the meta-analysis

Figure.2 Forest plot of overall mortality in patients with carbapenem-resistant Enterobacteriaceae (CRE) versus carbapenem-susceptible Enterobacteriaceae (CSE) infections (outcome measure = relative risk).

Figure.3 Forest plot of overall mortality in patients with carbapenem-resistant Enterobacteriaceae (CRE) versus carbapenem-susceptible Enterobacteriaceae (CSE) infections (outcome measure = risk difference).

Figure.4 Funnel plot of studies evaluating mortality of patients with infections due to carbapenem-resistant compared to carbapenem-susceptible *Enterobacteriaceae*.

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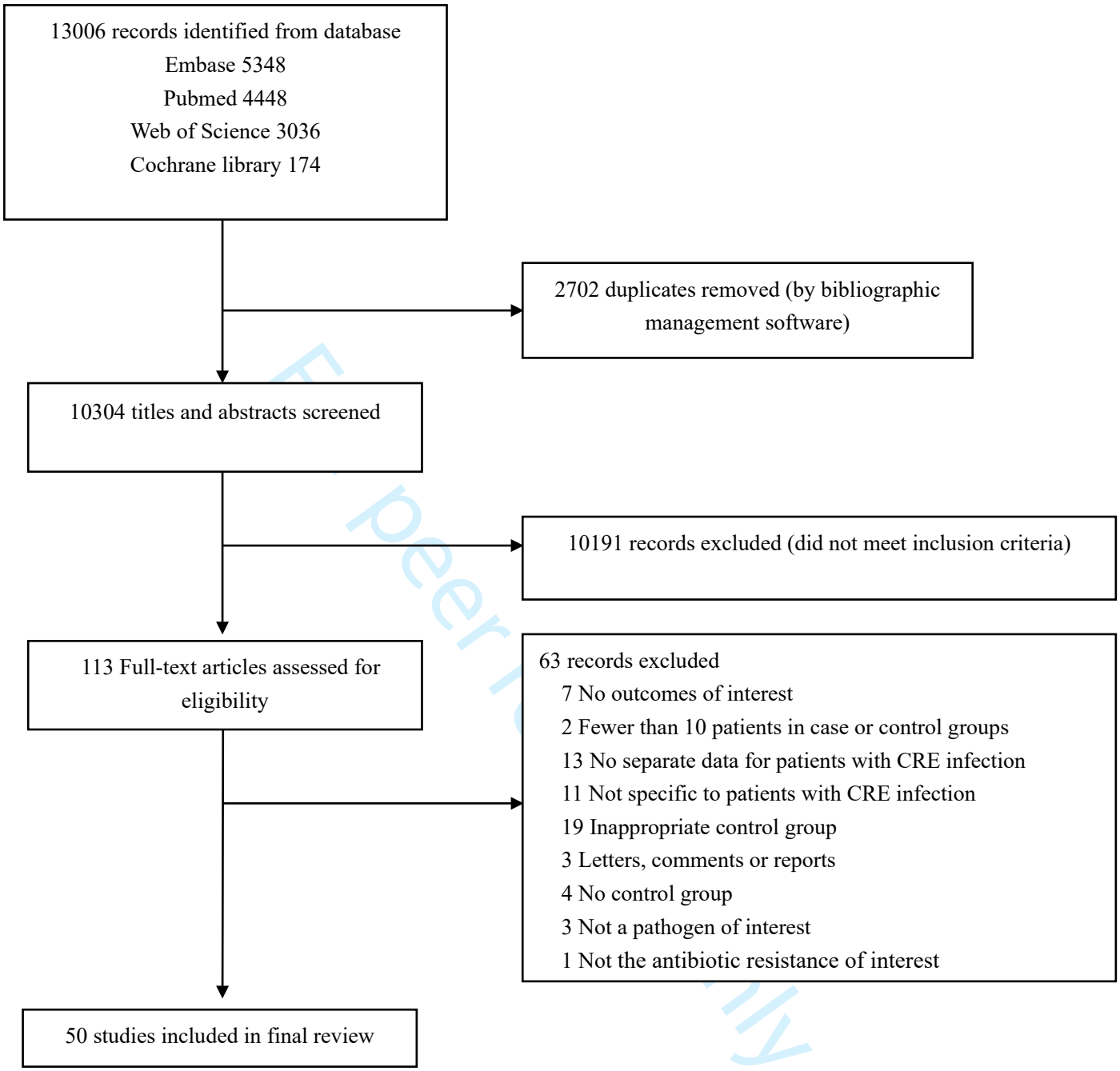

author	year	country	RR (95% CI)	% Weight
Patel	2008	USA	2.40 (1.54, 3.73)	2.43
Schwaber	2008	Israel	3.50 (1.63, 7.51)	1.68
Daikos	2009	Greece	2.54 (1.26, 5.12)	1.81
Mouloudi	2010	Greece	1.67 (0.93, 3.01)	2.07
Chang	2011	China	1.88 (1.32, 2.69)	2.64
Sánchez-Romero	2011	Spain	1.50 (0.86, 2.63)	2.14
Ben-David	2012	Israel	2.93 (1.90, 4.53)	2.45
Liu	2012	China	1.50 (0.94, 2.39)	2.37
Qureshi	2012	USA	1.73 (0.90, 3.31)	1.92
Correa	2013	Brazil	1.82 (0.93, 3.54)	1.89
HUSAsein	2013	Israel	1.51 (1.11, 2.04)	2.76
Orsi	2013	Italy	1.39 (0.74, 2.62)	1.97
Shilo	2013	Israel	1.15 (0.77, 1.71)	2.54
Gallagher	2014	USA	1.36 (0.89, 2.09)	2.46
Gomez Rueda	2014	Colombia	1.55 (1.00, 2.40)	2.45
Mclaughlin	2014	USA	2.86 (1.05, 7.75)	1.26
Simkins	2014	USA	6.00 (1.74, 20.64)	0.96
Alicino	2015	Italy	1.54 (1.13, 2.10)	2.75
Brizendine	2015	USA	11.64 (1.37, 98.62)	0.40
Cubero	2015	Spain	3.15 (0.45, 21.96)	0.47
Ny	2015	USA	1.40 (0.48, 4.10)	1.15
Pereira	2015	USA	1.62 (0.79, 3.31)	1.78
Pouch	2015	USA	3.00 (1.17, 7.67)	1.36
Ulu	2015	Turkey	0.88 (0.58, 1.33)	2.50
Vardakas	2015	Greece	1.24 (0.86, 1.79)	2.62
Fraenkel-Wandel	2016	Israel	1.63 (1.24, 2.14)	2.83
Garbati	2016	Saudi Arabia	2.57 (1.07, 6.21)	1.45
Hoxha	2016	Italy	3.00 (1.65, 5.45)	2.05
Lee	2016	Korea	1.00 (0.27, 3.70)	0.88
Tian	2016	China	2.15 (1.19, 3.88)	2.06
Torres-Gonzalez	2016	Mexico	1.50 (0.43, 5.28)	0.93
Trecarichi	2016	Italy	3.59 (2.26, 5.71)	2.38
Villegas	2016	multiple countries	2.12 (1.59, 2.84)	2.79
Meng	2017	China	11.76 (1.46, 94.93)	0.42
Chiotos	2018	USA	4.65 (0.68, 31.72)	0.48
Huang	2018	China	2.59 (1.80, 3.72)	2.62
Wang	2018	China	11.50 (2.87, 46.10)	0.81
Xiao	2018	China	3.81 (2.81, 5.16)	2.76
Zhang	2018	China	2.22 (0.90, 5.48)	1.41
Zheng	2018	China	2.77 (1.95, 3.94)	2.65
Balkhair	2019	Oman	2.63 (2.01, 3.43)	2.84
Chang	2019	China	3.79 (2.59, 5.56)	2.58
Cienfuegos-Gallet	2019	Colombia	2.05 (1.27, 3.32)	2.33
Li	2019	China	2.60 (1.75, 3.87)	2.55
Liu	2019	China	3.45 (1.76, 6.75)	1.88
Pan	2019	China	3.17 (2.09, 4.80)	2.49
Stewardson	2019	multiple countries	1.74 (1.19, 2.55)	2.58
Kotb	2020	Egypt	1.18 (1.08, 1.29)	3.11
Zheng	2020	China	5.70 (3.22, 10.08)	2.11
Zuo	2020	China	1.73 (1.00, 3.00)	2.17
Overall (I-squared = 80.0%, p = 0.000)			2.14 (1.85, 2.48)	100.00

NOTE: Weights are from random effects analysis

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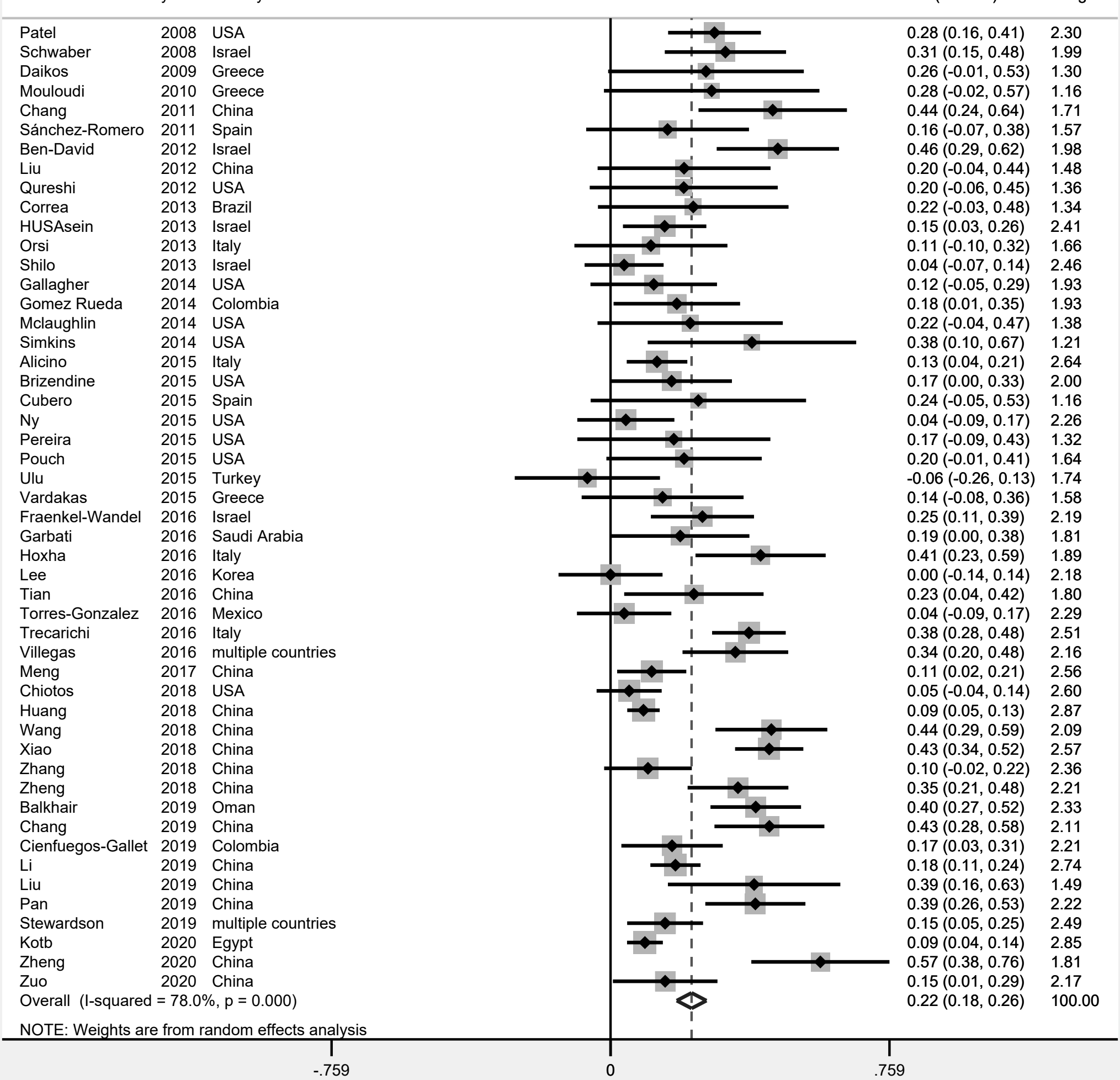
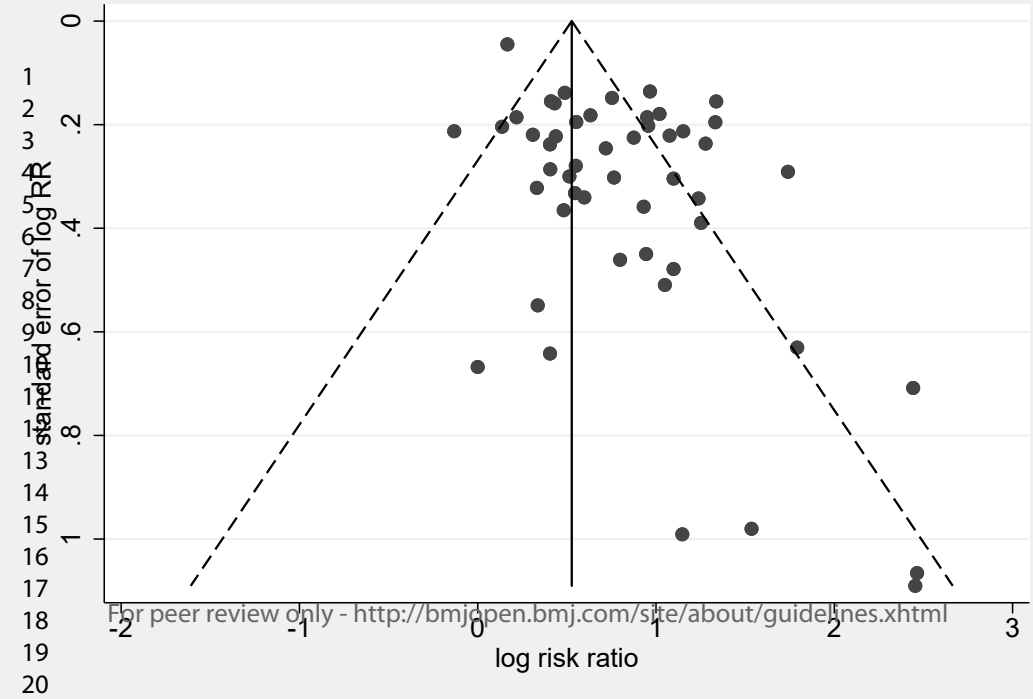
author	year	country	RD (95% CI)	% Weight
Patel	2008	USA	0.28 (0.16, 0.41)	2.30
Schwaber	2008	Israel	0.31 (0.15, 0.48)	1.99
Daikos	2009	Greece	0.26 (-0.01, 0.53)	1.30
Mouloudi	2010	Greece	0.28 (-0.02, 0.57)	1.16
Chang	2011	China	0.44 (0.24, 0.64)	1.71
Sánchez-Romero	2011	Spain	0.16 (-0.07, 0.38)	1.57
Ben-David	2012	Israel	0.46 (0.29, 0.62)	1.98
Liu	2012	China	0.20 (-0.04, 0.44)	1.48
Qureshi	2012	USA	0.20 (-0.06, 0.45)	1.36
Correa	2013	Brazil	0.22 (-0.03, 0.48)	1.34
HUSAsein	2013	Israel	0.15 (0.03, 0.26)	2.41
Orsi	2013	Italy	0.11 (-0.10, 0.32)	1.66
Shilo	2013	Israel	0.04 (-0.07, 0.14)	2.46
Gallagher	2014	USA	0.12 (-0.05, 0.29)	1.93
Gomez Rueda	2014	Colombia	0.18 (0.01, 0.35)	1.93
Mclaughlin	2014	USA	0.22 (-0.04, 0.47)	1.38
Simkins	2014	USA	0.38 (0.10, 0.67)	1.21
Alicino	2015	Italy	0.13 (0.04, 0.21)	2.64
Brizendine	2015	USA	0.17 (0.00, 0.33)	2.00
Cubero	2015	Spain	0.24 (-0.05, 0.53)	1.16
Ny	2015	USA	0.04 (-0.09, 0.17)	2.26
Pereira	2015	USA	0.17 (-0.09, 0.43)	1.32
Pouch	2015	USA	0.20 (-0.01, 0.41)	1.64
Ulu	2015	Turkey	-0.06 (-0.26, 0.13)	1.74
Vardakas	2015	Greece	0.14 (-0.08, 0.36)	1.58
Fraenkel-Wandel	2016	Israel	0.25 (0.11, 0.39)	2.19
Garbati	2016	Saudi Arabia	0.19 (0.00, 0.38)	1.81
Hoxha	2016	Italy	0.41 (0.23, 0.59)	1.89
Lee	2016	Korea	0.00 (-0.14, 0.14)	2.18
Tian	2016	China	0.23 (0.04, 0.42)	1.80
Torres-Gonzalez	2016	Mexico	0.04 (-0.09, 0.17)	2.29
Trecarichi	2016	Italy	0.38 (0.28, 0.48)	2.51
Villegas	2016	multiple countries	0.34 (0.20, 0.48)	2.16
Meng	2017	China	0.11 (0.02, 0.21)	2.56
Chiotos	2018	USA	0.05 (-0.04, 0.14)	2.60
Huang	2018	China	0.09 (0.05, 0.13)	2.87
Wang	2018	China	0.44 (0.29, 0.59)	2.09
Xiao	2018	China	0.43 (0.34, 0.52)	2.57
Zhang	2018	China	0.10 (-0.02, 0.22)	2.36
Zheng	2018	China	0.35 (0.21, 0.48)	2.21
Balkhair	2019	Oman	0.40 (0.27, 0.52)	2.33
Chang	2019	China	0.43 (0.28, 0.58)	2.11
Cienfuegos-Gallet	2019	Colombia	0.17 (0.03, 0.31)	2.21
Li	2019	China	0.18 (0.11, 0.24)	2.74
Liu	2019	China	0.39 (0.16, 0.63)	1.49
Pan	2019	China	0.39 (0.26, 0.53)	2.22
Stewardson	2019	multiple countries	0.15 (0.05, 0.25)	2.49
Kotb	2020	Egypt	0.09 (0.04, 0.14)	2.85
Zheng	2020	China	0.57 (0.38, 0.76)	1.81
Zuo	2020	China	0.15 (0.01, 0.29)	2.17
Overall (I-squared = 78.0%, p = 0.000)			0.22 (0.18, 0.26)	100.00

NOTE: Weights are from random effects analysis





Supplementary Materials

Appendix 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors	6

sources		to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Figure.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10,Table.1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, Appendix.4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10,Table.1,Figure.2,Figure.3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	17, Figure.2, Figure.3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	19, Figure.4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	18-19
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24-27
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	27
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	27-28
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	28

Appendix 2. Search terms and search strategies

1.Pubmed (4448)

Search	Query	Items found
#1	Search: ((enterobacteriaceae[MeSH Terms]) OR klebsiella pneumoniae[MeSH Terms]) OR escherichia coli[MeSH Terms]	399348
#2	Search: (((carbapenem resistant) OR (carbapenem resistance)) OR (carbapenem nonsusceptible)) OR (carbapenemase producing)	15576
#3	Search: (((enterobacteriaceae[MeSH Terms]) OR (klebsiella pneumoniae[MeSH Terms])) OR (escherichia coli[MeSH Terms])) AND ((((carbapenem resistant) OR (carbapenem resistance)) OR (carbapenem nonsusceptible)) OR (carbapenemase producing))	5776
#4	Search: (((enterobacteriaceae[MeSH Terms]) OR (klebsiella pneumoniae[MeSH Terms])) OR (escherichia coli[MeSH Terms])) AND ((((carbapenem resistant) OR (carbapenem resistance)) OR (carbapenem nonsusceptible)) OR (carbapenemase producing)) Filters: Humans	4761
#5	Search: (((enterobacteriaceae[MeSH Terms]) OR (klebsiella pneumoniae[MeSH Terms])) OR (escherichia coli[MeSH Terms])) AND ((((carbapenem resistant) OR (carbapenem resistance)) OR (carbapenem nonsusceptible)) OR (carbapenemase producing)) Filters: Humans, from 1994 - 2020	4716
#6	Search: (((enterobacteriaceae[MeSH Terms]) OR (klebsiella pneumoniae[MeSH Terms])) OR (escherichia coli[MeSH Terms])) AND ((((carbapenem resistant) OR (carbapenem resistance)) OR (carbapenem nonsusceptible)) OR (carbapenemase producing)) Filters: Humans, English, from 1994 - 2020	4448

2.Embase(5348)

#	**searches**	**results**
1	Enterobacteriaceae.af.	38034
2	Klebsiella pneumoniae.af.	47767
3	Escherichia coli.af.	425764
4	1 or 2 or 3	470290
5	carbapenem resistant.af.	7442
6	carbapenem resistance.af.	3418
7	carbapenem nonsusceptible.af.	139
8	carbapenemase producing.af.	3413
9	5 or 6 or 7 or 8	11419
10	4 and 9	8235
11	limit 10 to (human and english language and yr="1994 -Current")	5348

3.Web of Science(3036)

#	searches	results
1	TI=(Enterobacteriaceae) Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	6685
2	TI=(Klebsiella pneumoniae) Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	10759
3	TI=(Escherichia coli) Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	102497
4	#3 OR #2 OR #1 Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	118551
5	TI=(carbapenem resistance OR carbapenem resistant OR carbapenem nonsusceptible OR carbapenemase producing) Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	5926
6	#5 AND #4 Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	3036

4.Cochrane library

ID	Search	Hits
#1	(carbapenem) AND (Enterobacteriaceae) (Limits: Word variations have been searched)	137
#2	(carbapenem) AND (Klebsiella pneumoniae) (Limits: Word variations have been searched)	71
#3	(carbapenem) AND (Escherichia coli) (Limits: Word variations have been searched)	67
#4	#1 OR #2 OR #3 with Cochrane Library publication date Between Jan 1994 and Sep 2020	174

Appendix 3. List of excluded studies with reason for exclusion

First author	Year	Reason for exclusion
Adams[1]	2019	inappropriate control group
Ahn[2]	2014	Not specific to patients with CRE infection
Akgul[3]	2016	Not specific to patients with CRE infection
Balkan[4]	2014	inappropriate control group
Biehle[5]	2015	not a pathogen of interest
Bleumin[6]	2012	No separate data for patients with CRE infection
Bogan[7]	2014	No separate data for patients with CRE infection
Chang[8]	2015	no control group
Cristina[9]	2016	no control group
Dautzenberg[10]	2015	Not specific to patients with CRE infection
de Maio Carrilho[11]	2016	no control group
Debby[12]	2012	Not specific to patients with CRE infection
Diaz[13]	2016	Not specific to patients with CRE infection
Dizbay[14]	2014	not a pathogen of interest
Eser[15]	2019	Not specific to patients with CRE infection
Falcone[16]	2009	not a pathogen of interest
Fang[17]	2019	No separate data for patients with CRE infection
Forde[18]	2017	No separate data for patients with CRE infection
Freire[19]	2015	inappropriate control group
Gao[20]	2019	inappropriate control group
Gasink[21]	2009	No separate data for patients with CRE infection
Gaviria[22]	2011	Letters, comments or reports
Giacobbe[23]	2015	Not the antibiotic resistance of interest
Giannella[24]	2014	Not specific to patients with CRE infection
Girmenia[25]	2015	inappropriate control group
Girometti[26]	2014	no outcomes of interest
Gowda[27]	2014	no outcomes of interest
Grabowsk[28]	2017	No separate data for patients with CRE infection
Hauck[29]	2016	inappropriate control group
Hu[30]	2016	Not specific to patients with CRE infection
Jiao[31]	2015	No separate data for patients with CRE infection
Kang[32]	2019	Not specific to patients with CRE infection
Kofteridis[33]	2014	No separate data for patients with CRE infection
Lai[34]	2013	inappropriate control group
Lee[35]	2013	no outcomes of interest
Lee[36]	2012	inappropriate control group
López-González[37]	2017	inappropriate control group
Lubbert[38]	2014	No separate data for patients with CRE infection
Mantzarlis[39]	2013	inappropriate control group
Marimuthu[40]	2013	Letters, comments or reports

Mazza[41]	2017	Fewer than10 patients in case or control groups
Miller[42]	2016	no outcomes of interest
Mouloudi[43]	2014	inappropriate control group
Muggeo[44]	2017	No separate data for patients with CRE infection
Nouvenne[45]	2014	No separate data for patients with CRE infection
Orsi[46]	2011	Fewer than10 patients in case or control groups
Papadimitriou-Olivgeris[47]	2013	Not specific to patients with CRE infection
Patel[48]	2015	inappropriate control group
Porwal[49]	2014	Letters, comments or reports
Qureshi[50]	2014	inappropriate control group
Rodrigues[51]	2016	inappropriate control group
Salsano[52]	2016	inappropriate control group
Segagni Lusignani[53]	2020	No separate data for patients with CRE infection
Shankar[54]	2018	no control group
Taminato[55]	2019	inappropriate control group
Tamma[56]	2017	inappropriate control group
Tascini[57]	2015	Not specific to patients with CRE infection
Tsereteli[58]	2018	no outcomes of interest
Tumbarello[59]	2015	inappropriate control group
Tumbarello[60]	2014	inappropriate control group
Tuon[61]	2017	no outcomes of interest
Jamal[62]	2016	no outcomes of interest
Wang[63]	2016	No separate data for patients with CRE infection

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Appendix 4. Risk of bias assessed with the Newcastle-Ottawa Assessment Scale.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. In this version of NOS, we define the exposure as carbapenem resistance and the outcome as death in hospital and the target population is patients infected with *Enterobacteriaceae*.

Selection: (Maximum 4 stars)

1) Representativeness of the exposed cohort
   a) truly representative of the average carbapenem resistance in patients infected with *Enterobacteriaceae*. ✸
   b) somewhat representative of the average carbapenem resistance in patients infected with *Enterobacteriaceae* ✸
   c) selected group of users (e.g. organ transplant recipients, onco-hematological patients)
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (e.g. medical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes ✹

b) no

Comparability: (Maximum 2 stars)

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for age✹

b) study controls for comorbidity✹

Outcome: (Maximum 3 stars)

1) Assessment of outcome

a) independent blind assessment ✹

b) record linkage ✹

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (adequate if >14 days) ✹

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for ✹

b) subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % follow up, or description provided of those lost ✹

c) follow up rate < 80% and no description of those lost

d) no statement

First Author	Year	selection(1)	selection(2)	selection(3)	selection(4)	comparability(1)	outcome(1)	outcome(2)	outcome(3)	Total score	Risk of bias
Alicino,C	2015	1	1	1	1	0	1	1	1	7	Low
Balkhair, A.	2019	1	1	1	1	0	1	1	1	7	Low
Ben-David, D.	2012	1	1	1	1	1	1	1	1	8	Low
Brizendine, K. D	2015	0	1	1	1	1	1	1	1	7	Low
Chang, H	2019	1	1	1	1	0	1	1	1	7	Low
Chang, H. J	2011	1	1	1	1	1	1	1	1	8	Low
Chiotos, K.	2018	0	1	1	1	1	1	1	1	7	Low
Cienfuegos-Gallet, A. V.	2019	1	1	1	1	1	1	1	1	8	Low
Correa, L.	2013	1	1	1	1	1	1	1	1	8	Low
Cubero,M	2015	1	1	1	1	0	1	1	1	7	Low
Daikos	2009	1	1	1	1	0	1	0	1	6	Moderate
Fraenkel-Wandel,Y.	2016	1	1	1	1	1	1	1	1	8	Low
Gallagher	2014	1	1	1	1	0	1	1	1	7	Low
Garbati, M. A.	2016	1	1	1	1	0	1	1	1	7	Low
Gomez Rueda, V.	2014	1	1	1	1	0	1	1	1	7	Low
Hoxha, A.	2016	1	1	1	1	1	1	1	0	7	Low
Huang, W.	2018	1	1	1	1	2	1	1	1	9	Low
Hussein, K.	2013	1	1	1	1	1	1	1	1	8	Low
Kotb, Sara	2020	1	1	1	1	0	1	1	1	7	Low
Lee, H. J.	2016	1	1	1	1	1	1	1	1	8	Low
Li, Yi	2019	0	1	1	1	1	1	1	1	7	Low
Liu, Jianling	2019	0	1	1	1	1	1	1	1	7	Low

Liu, S. W.	2012	1	1	1	1	1	1	1	1	8	Low
Mclaughlin	2014	1	1	1	1	1	1	1	1	8	Low
Meng, Xiujuan	2017	1	1	1	1	1	1	1	1	8	Low
Mouloudi, Eleni	2010	0	1	1	1	1	1	1	1	7	Low
Ny, P.	2015	1	1	1	1	1	1	1	1	8	Low
Orsi,G.B.	2013	1	1	1	1	1	1	1	1	8	Low
Pan, H.	2019	1	1	1	1	1	1	1	1	8	Low
Patel	2008	1	1	1	1	1	1	1	1	8	Low
Pereira, M. R.	2015	0	1	1	1	1	1	1	1	7	Low
Pouch, S. M.	2015	0	1	1	1	1	1	1	1	7	Low
Qureshi	2012	1	1	1	1	0	1	1	1	7	Low
Sánchez-Romero	2011	1	1	1	1	0	1	0	1	6	Moderate
Schwaber	2008	1	1	1	1	0	1	1	1	7	Low
Shilo, S.	2013	1	1	1	1	1	1	1	1	8	Low
Simkins, J.	2014	0	1	1	1	1	1	1	1	7	Low
Stewardson	2019	1	1	1	1	2	1	1	1	9	Low
Tian, Lijun	2016	1	1	1	1	1	1	1	1	8	Low
Torres-Gonzalez, P.	2016	1	1	1	1	0	1	1	1	7	Low
Trecarichi, Enrico Maria	2016	0	1	1	1	0	1	1	1	6	Moderate
Ulu, Aslıhan Candevir	2015	0	1	1	1	1	1	1	1	7	Low
Vardakas, Konstantinos Z.	2015	0	1	1	1	1	1	1	1	7	Low
Villegas	2016	1	1	1	1	1	1	1	1	8	Low
Wang, Z.	2018	1	1	1	1	1	1	1	1	8	Low
Xiao, Tingting	2018	1	1	1	1	1	1	1	1	8	Low

Zhang, Y.	2018	0	1	1	1	0	1	1	1	6	Mod
Zheng, Si-Han	2018	1	1	1	1	1	1	1	1	8	Low
Zheng,Guanghui	2020	0	1	1	1	1	1	1	1	7	Low
Zuo	2020	1	1	1	1	1	1	1	1	8	Low

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Figure.1

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10,Table.1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, Appendix.4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10,Table.1,Figure.2,Figure.3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	17, Figure.2, Figure.3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	19, Figure.4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	18-19
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24-27
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	27
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	27-28
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	28

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The impact of carbapenem resistance on mortality in patients infected with Enterobacteriaceae: a systematic review and meta-analysis

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The impact of carbapenem resistance on mortality in patients infected with *Enterobacteriaceae*: a systematic review and meta-analysis

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ABSTRACT

Objectives To provide a comprehensive assessment of the impact of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae* and to explore the source of heterogeneity across studies.

Design This systematic review was conducted following the guidelines of Cochrane Guidance and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Data sources We conducted a systematic literature search of the PubMed, Embase, Web of Science, and Cochrane Library databases to identify relevant studies published between 1 January 1994 and 30 August 2020.

Eligibility criteria We included primary observational studies published in English that reported the mortality outcomes for hospitalized patients with confirmed infections due to carbapenem-resistant *Enterobacteriaceae* (CRE) and carbapenem-susceptible *Enterobacteriaceae* (CSE). Studies with no comparison group or with a comparison group of patients infected with unconfirmed CSE were excluded.

Data extraction and synthesis Data extraction and assessment of risk bias were conducted independently by two reviewers. The pooled relative risk (RR) and risk difference (RD) were calculated as effect measures with 95% confidence intervals using a random-effects model. The heterogeneity across studies was assessed by Q-statistic and I^2 measures.

Results Of 10,304 studies initially identified, 50 studies were included in the meta-analyses. The results of the meta-analyses showed that carbapenem resistance has a significant positive effect on the probability of death for patients infected with *Enterobacteriaceae* for any type of mortality outcome. The results of the stratified analysis and meta-regression suggested that the effect of carbapenem resistance on the risk of death varied by infection type, sample size, and year of publication.

Conclusions Our results suggested that patients with CRE infection still face a greater risk of death than

patients with CSE infection do, and an urgent need to develop new antibiotics and appropriate treatments to reduce the risk of death.

Strengths and limitations of this study

- This study provided a comprehensive meta-analysis to assess the impact of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae*, including nearly 20 new published studies in the last three years that were not included in previous relevant reviews.
- The statistical test and meta-regression analysis in this study was conducted for different groups of mortality outcome type, which may help to address the potential heterogeneity caused by the factor of mortality measurements.
- This review is the first to explore the source of heterogeneity across studies through meta-regression analysis and to consider the country's economic status and geographical region in assessing the association between carbapenem resistance and mortality among patients infected with *Enterobacteriaceae*.
- This review includes effect measures in both relative and absolute terms, thus providing a complete picture of the effect of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae.*
- The comparison in our research is currently limited to high-income and upper-middle-income countries from the Americas, Asia, and Europe due to insufficient data from elsewhere; more studies from different countries, especially low-income countries and other regions, are needed to provide comprehensive data for further analysis stratified by geographical region and economic status.

INTRODUCTION

The *Enterobacteriaceae* species, mainly *Klebsiella pneumoniae* and *Escherichia coli*, can cause infections like bloodstream infections, ventilator-associated pneumonia, intra-abdominal infections, and urinary tract infections in both healthcare and community settings.[1] The treatment of these infections is becoming increasingly challenging because of the increasing prevalence of multi-drug-resistant *Enterobacteriaceae*, such as extended-spectrum β-lactamases (ESBLs)-producing *Enterobacteriaceae*. To counter this challenge, carbapenems were introduced in the 1980s[2] and proved efficacious in the clinical treatment of infections caused by ESBLs-producing *Enterobacteriaceae*.[3] However, since the carbapenem-resistant *Enterobacteriaceae* (CRE) emerged in the early 1990s,[4] CRE has been increasingly reported worldwide.[5,6] The prevalence of CRE is driven primarily by the spread of carbapenemases, a group of β-lactamases hydrolyzing carbapenems.[7] The CRE strains that produce diverse types of carbapenemases are endemic in different areas of the world.[8] Countries that have high overall rates of CRE include Greece, Italy, Brazil, China, the United States, and Colombia.[7] For example, the rate of carbapenem resistance in *Klebsiella pneumoniae* isolates was as high as 63.9% in Greece in 2018.[9] The increasing prevalence of CRE has posed a serious threat to public health because of the reduced efficacy of carbapenem and limited available therapy options, so CRE has been categorized as the most critical group of multidrug-resistant pathogens with the most urgent need for new antibiotics.[10]

The mortality of CRE infections is a research hotspot. Recently, some systematic reviews have included meta-analyses to assess the association between CRE infections and mortality by comparing with the mortality outcome of patients infected with carbapenem-susceptible *Enterobacteriaceae*(CSE).[11-16] The results showed that CRE infections could lead to increased mortality. The latest systematic review on this topic included studies published until 2017,[12]but nearly 20 relevant articles have been published since

then. A timely and comprehensive summary of the results of these articles can help explain the excess health burden that is attributable to carbapenem-resistant *Enterobacteriaceae* (CRE) infections. Moreover, although previous systematic reviews have identified heterogeneity across studies and discussed some confounding factors of mortality, including patient-, infection-, organism-, and therapy-related factors,[12,13,15] few used a formal statistical approach or meta-regression analysis to examine whether the effect of carbapenem resistance on mortality varies by these factors. In addition, these earlier reviews have not considered differences in economic status and geographical region. The development of antibiotic resistance has resulted in decreasing effectiveness of first-line antibiotics, such that more expensive second- and third-line antibiotic treatments must be used. However, these treatments may be unobtainable or unaffordable for patients with resistant infections in developing countries, [17] which would result in worse prognostic outcomes. The effect of carbapenem resistance on mortality may have regional differences because the CRE strains with different types of carbapenemases and virulence characteristics[1] are predominant in different regions worldwide.[8] Two previous reviews have shown that the mortality rate of patients with CRE infections differs by geographical region.[14,18] However, without data from control groups, whether the impact of carbapenem resistance on mortality differs between the region will remain unknown.

Therefore, we aim to provide a comprehensive systematic review of the impact of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae* and explore the source of heterogeneity among studies to help policymakers to develop strategies and policies to combat CRE worldwide.

METHODS

This systematic review was conducted following the guidelines of Cochrane Guidance[19] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[20] The protocol was registered with PROSPERO on July 5, 2020(CRD42020176808). The initial protocol was designed with a broad scope, but we divided our work into two parts to limit its length: the first (this study) focuses on mortality, and the second will focus on morbidity and the economic outcomes.

Search strategy

We conducted a systematic literature search of the databases of PubMed, Embase, Web of Science, and the Cochrane Library for relevant studies published between 1 January 1994, and 30 August 2020 to identify eligible studies. This period was chosen because carbapenem-resistant *Enterobacteriaceae* were first reported in the 1990s. Specifically, the strains producing Metallo-β-lactamase(MBL)IMP-1, which is a type of carbapenemase that can hydrolyze carbapenems, were first identified in Japan in a study published in 1994.[4]

The search strategy was designed by combining the terms for bacteria and carbapenem resistance (See Supplementary Material Appendix 1). The search terms for the bacteria were "*Enterobacteriaceae,*" along with *"Klebsiella pneumoniae"* and *"Escherichia coli,"*(the two most clinically important pathogens within the *Enterobacteriaceae* family). The search terms for carbapenem resistance were "carbapenem-resistant," "carbapenem resistance," "carbapenem non-susceptible," and "carbapenemase-producing" because CRE can be generally divided into carbapenemase-producing CRE (CP-CRE) and non-carbapenemase-producing CRE (non-CP-CRE).[21]

Selection criteria

We included studies that fulfilled all of the following criteria: (1) primary observational studies (i.e., case-control study, cohort study); (2) studies published between 1 January 1994 and 30 August 2020; (3) studies published in English; and (4) studies that assessed the mortality of hospitalized patients with confirmed infections due to CRE and CSE.

Studies that met any of the following criteria were excluded: (1) studies that could not provide the mortality data for patients with confirmed CRE infection; (2) studies that focused on the resistance of other antibiotics instead of carbapenem antibiotics; (3) Studies with no comparison group or with a comparison group of patients infected with unconfirmed CSE; (4) studies on animals; or (5) publications like editorials and letters. The list of excluded studies with reasons for exclusion is provided in Supplementary Material Appendix 2.

Two reviewers independently screened all titles and abstracts of the initially identified studies and then reviewed the full text of studies that met all of the inclusion criteria and none of the exclusion criteria. Disagreements were resolved through consensus or discussion with a third senior reviewer.

Data extraction

Data were extracted from each selected study into a data extraction form in Excel. The extracted data included the first author, year of publication, study period, country, region, country income level classified by the World Bank,[22] study design, infection type, specific pathogen, sample size, and the number of deaths in CRE and CSE groups. Notably, we assigned the income status of the country based on the period when the study was conducted because the income status of some countries may have changed between

1994 and 2020. For example, there were 15 studies conducted in China between 2006 and 2018 included in this meta-analysis, but since the income status of China changed from the lower-income level to the upper-income level in 2010, the two studies conducted between 2006 and 2009 were classified as lower middle income, and the other 13 studies conducted after 2010 were classified as upper middle income. The kinds of measurements of mortality outcomes that were extracted from included studies were all-cause in-hospital mortality, all-cause mortality at 6-30 days (6 days, 7 days, 14 days, 21 days, 28 days, 30 days) after diagnosis, mortality in ICU, 30d mortality in ICU, and mortality attributable to infection, which is usually defined as the death of a patient with clinical and laboratory evidence of ongoing infection in the absence of other feasible reasons.

Data extraction was conducted by two reviewers independently and disagreements were resolved through consensus or discussion with a third senior reviewer.

Data synthesis and analysis

We calculated the pooled relative risk (RR) and risk difference (RD) by comparing the mortality of patients with CRE infection with that of patients with CSE infection. We choose RR as the relative measure rather than the odds ratio (OR) because the latter was more difficult to interpret than RR[23,24] and is usually misinterpreted as RR, which may overestimate the intervention effect when RR is more than 1.[25] We also calculated RD to describe the absolute difference in the risk of mortality between the two groups because reporting only the relative risk may conceal the underlying absolute risks, resulting in readers' overestimating the effect.[26] It has been recommended that both relative risk and absolute risk should be reported to provide a complete picture of the effect.[27] We calculated the pooled estimates of RRs and RDs with 95% confidence intervals were calculated using a random-effects model based on the method of

DerSimonian & Laird,[28] with the estimate of heterogeneity being taken from the Mantel-Haenszel model. An RR of 1 and an RD of 0 indicate that the risk of mortality is identical regardless of carbapenem resistance. When RR>1 or RD>0, it means carbapenem resistance has a positive effect on the risk of death for patients infected with *Enterobacteriaceae*; in other words, the risk of death from CRE infection is higher than that from CSE infection. The heterogeneity across studies was assessed by Q-statistic and I^2 measures. The heterogeneity was considered substantial when I^2 >50%.

In the primary analysis, we calculated the pooled estimates of the overall mortality using one mortality outcome in each study with a priority given to in-hospital mortality and the latest time point of mortality if mortality outcomes at multiple time points were reported in a study. Then we categorized the mortality measurements into eight groups and conducted meta-analysis for each type of mortality outcome. In further analysis, to identify the potential sources of heterogeneity, we conducted stratified analysis by bacterial species, geographical region, economic status, source of infection, sample size, and resistance mechanism in the mortality outcome groups in which substantial heterogeneity was detected. An F-test based on a one-way analysis of variance (ANOVA) was used to test the differences in the mean effect estimates between subgroups. We also conducted a random-effects meta-regression analysis in the group of mortality outcome type with more than then studies. The meta-regression analysis was based on restricted maximum likelihood using an iterative procedure to determine whether the effect estimates differ significantly by the above variables, and P <0.1 was considered statistically significant. A sensitivity analysis was conducted for the overall mortality, with the pooled RRs recalculated using random-effects meta-analysis after removing one study at a time to evaluate the stability of the results. Finally, we conducted a funnel plot for the overall mortality to assess the publication bias. All the statistical analyses were conducted using the Stata version 15 software.

Risk of bias assessment

Two reviewers independently assessed the risk of bias for each included study using the Newcastle-Ottawa quality assessment scale (NOS) for observational studies,[29] and disagreements were resolved through consensus or discussion with a third senior reviewer.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this systematic review.

RESULTS

We identified 10,304 studies from the literature search, among which 50 studies[30-79] were selected for final review based on the inclusion and exclusion criteria (Figure1). The basic characteristics of the included studies are provided in Table.1, and Table S1 in Supplementary Material Appendix 3 shows the details of the studies. The studies were conducted in 14 countries from four regions. Nearly half of the studies were conducted in Asia (n=24), followed by the Americas (n=15) and Europe (n=9), with only one study conducted in Africa. We also included a multi-region study that contained data from Asia, Africa, and South America.[79] Most of the studies were conducted in high-income countries (n=27) and upper-middle-income countries (n=19), only three studies were conducted in lower-middle-income countries and no study conducted in a low-income country met the criteria. Most studies (n=39) reported mortality outcomes of infections that were due to *Klebsiella pneumoniae* pathogens, while two studies reported mortality outcomes of infections that were due to *Escherichia coli*, and nine studies reported

mortality outcomes regardless of the specific species of *Enterobacteriaceae*. Nearly half of the studies (n=24) evaluated infected patients regardless of specific infection type. Among the studies that focused on specific sites of infection, bloodstream infection was the most frequent type (n=21), followed by urinary tract infection (n=3), and one study each for neurosurgical infection and pneumonia. Among the 50 studies included, most were cohort studies (n=29). In the other 21 case-control studies, the mortality outcomes were measured using a cohort study design, so these studies were assessed as cohort studies in our quality appraisal. The NOS assessment for the risk of bias of all included studies is summarized in Supplementary Material Appendix 4. According to the NOS scores, 46 were categorized as having a low risk of bias (scoring7 to 9) and only 4 studies were categorized as having the moderate risk of bias (scoring 4 to 6).

Table 1 Characteristics of included studies

First Author (Year)	Study period	Country	Infection type	Pathogen	Mortality outcomes
Alicino (2015) [30]	2007.01-2014.12	Italy	BSI	K. pneumoniae	30d mortality
Balkhair (2019)[31]	2007.01-2016.12	Oman	BSI	K. pneumoniae	30d mortality
Ben-David (2012) [32]	2006.01-2006.12	Israel	BSI	K. pneumoniae	in-hospital mortality ， mortality attributable to infection
Brizendine (2015)[33]	2006-2012	USA	UTI	K. pneumoniae	in-hospital mortality
Chang (2019)[34]	2014.01-2018.07	China	BSI	K. pneumoniae	7d mortality，28d mortality，in-hospital mortality
Chang (2011)[35]	2006.1-2008.12	China	BSI	E. coli	14d hospital mortality，28d hospital mortality，in-hospital mortality
Chiotos (2018)[36]	2011.1-2016.7	USA	Mixed	Enterobacteriaceae	30d mortality
Cienfuegos-Gallet (2019)[37]	2014.02-03; 2014.10-2015.09	Colombia	Mixed	K. pneumoniae	30d mortality
Correa (2013)[38]	2006.1-2008.8	Brazil	Mixed	K. pneumoniae	in-hospital mortality
Cubero (2015)[39]	2010.10-2012.12	Spain	Mixed	K. pneumoniae	in-hospital mortality
Daikos (2009)[40]	2004.2-2006.3	Greece	BSI	K. pneumoniae	14d mortality
Fraenkel-Wandel (2016)[41]	2006-2012	Israel	BSI	K. pneumoniae	in-hospital mortality
Gallagher (2014)[42]	2005.6-2010.10	USA	BSI	K. pneumoniae	in-hospital mortality
Garbati (2016)[43]	2012.3-2013.12	Saudi Arabia	Mixed	Enterobacteriaceae	in-hospital mortality
Gomez Rueda (2014)[44]	2008.1-2011.1	Colombia	Mixed	K. pneumoniae	in-hospital mortality
Hoxha (2016)[45]	2012.11-2013.7	Italy	Mixed	K. pneumoniae	6d mortality，30d mortality
Huang (2018)[46]	2017.01-2017.12	China	Mixed	K. pneumoniae	in-hospital mortality
Hussein (2013)[47]	2006.1-2008.12	Israel	BSI	K. pneumoniae	30d mortality
Kotb (2020)[48]	2011-2017	Egypt	Mixed	Enterobacteriaceae	mortality in ICU
Lee (2016)[49]	2013.1-2014.2	Korea	Mixed	Enterobacteriaceae	28d mortality，in-hospital mortality
Li (2019)[50]	2014.1-2018.6	China	Mixed	K. pneumoniae	30d mortality in ICU
Liu (2019)[51]	2014.1-2018.9	China	BSI	K. pneumoniae	30d mortality
Liu (2012)[52]	2007.1-2009.12	China	BSI	K. pneumoniae	14d mortality，28d mortality，in-hospital mortality
Mclaughlin (2014)[53]	2010.3-2011.12	USA	BSI	K. pneumoniae	in-hospital mortality
Meng (2017)[54]	2012.1-2015.12	China	Mixed	Escherichia. coli	in-hospital mortality
Mouloudi (2010)[55]	2007.1-2008.12	Greece	BSI	K. pneumoniae	in-hospital mortality ， mortality in ICU，mortality attributable to infection
Ny (2015)[56]	2011.1-2013.12	USA	Mixed	K. pneumoniae	in-hospital mortality
Orsi (2013)[57]	2008.7-2011.6	Italy	Mixed	K. pneumoniae	in-hospital mortality
Pan (2019)[58]	2014	China	Mixed	K. pneumoniae	in-hospital mortality
Patel (2008)[59]	2004.7-2006.6	USA	Mixed	K. pneumoniae	in-hospital mortality ， mortality attributable to infection
Pereira (2015)[60]	2010.1-2013.1	USA	Mixed	K. pneumoniae	in-hospital mortality
Pouch (2015)[61]	2007.1-2010.12	USA	UTI	Enterobacteriaceae	in-hospital mortality
Qureshi (2012)[62]	2011.1-2014.12	USA	BSI	K. pneumoniae	28d mortality
Sánchez-Romero (2011)[63]	2009.1-2009.12	Spain	Mixed	K. pneumoniae	14d mortality
Schwaber (2008)[64]	2003.9-2006.12	Israel	Mixed	K. pneumoniae	in-hospital mortality
Shilo (2013)[65]	2006.1-2009.12	Israel	UTI	K. pneumoniae	in-hospital mortality
Simkins (2014)[66]	2006.1-2010.12	USA	Mixed	K. pneumoniae	in-hospital mortality
Tian (2016)[67]	2011.1-2015.12	China	BSI	K. pneumoniae	in-hospital mortality ， mortality attributable to infection，28d mortality
Torres-Gonzalez (2016)[68]	2013.11-2015.7	Mexico	Mixed	Enterobacteriaceae	mortality attributable to infection
Trecarich (2016)i[69]	2010.1-2014.6	Italy	BSI	K. pneumoniae	21d mortality
Ulu (2015)[70]	2012.1-2012.12	Turkey	Mixed	K. pneumoniae	mortality in ICU
Vardakas (2015)[71]	2006.1-2009.10	Greece	Mixed	K. pneumoniae	mortality in ICU

Wang (2018)[72]	2010.1-2014.12	China	Mixed	K. pneumoniae	in-hospital mortality
Xiao (2018)[73]	2013.1-2015.12	China	BSI	K. pneumoniae	30d mortality
Zhang (2018)[74]	2011.1-2014.12	China	BSI	K. pneumoniae	7d mortality，28d mortality，in-hospital mortality
Zheng (2018)[75]	2014.1-2016.12	China	BSI	K. pneumoniae	28d mortality
Zheng (2020)[76]	2012-2017	China	Neurosurgical infection	Enterobacteriaceae	mortality attributable to infection
Zuo (2020)[77]	2015-2017	China	Pneumonia	K. pneumoniae	in-hospital mortality ， mortality attributable to infection
Villegas (2016)[78]	2013.7-2014.11	7 countries	BSI	Enterobacteriaceae	in-hospital mortality ， mortality attributable to infection
Stewardson (2019)[79]	2014.8-2015.6	10 countries	BSI	Enterobacteriaceae	in-hospital mortality

BSI, bloodstream infection; UTI, urinary tract infection; K.pneumoniae, Klebsiella pneumoniae; E.coli, Escherichia. coli

Meta-analysis results

Among the 50 studies included, 10 different measures of mortality were reported. In-hospital mortality(n=31) was most frequently reported, followed by 28-day mortality (n=9), 30-day mortality (n=8), mortality attributable to infection (n=8), 14-day mortality (n=4), and mortality in ICU (n=4). The mortality rates that were not commonly reported were 7-day mortality (n=2), 6-day mortality (n=1), 21-day mortality (n=1), and 30-day mortality in the ICU (n=1). The meta-analysis result for the overall mortality based on the measure of relative risk (RR, 2.14, 95% CI, 1.85-2.48; I^2=80.0%) (Figure 2) and risk difference (RD, 0.22, 95% CI, 0.18-0.26, I^2=78.0%) (Figure 3) suggested that carbapenem resistance was associated with increased risk of overall mortality, although a high level of heterogeneity was detected in these results.

The results of meta-analyses for different mortality outcome types showed that the I^2 for the pooled RR and RD was 0 in the studies that reported 14-day mortality, 6-day or 7-day mortality, and mortality in ICU, demonstrating low heterogeneity (Table 2). Among these three groups, the lowest pooled RR (1.17, 95% CI, 1.08-1.28) and RD (0.09, 95% CI, 0.04-0.14) was from the studies that reported mortality in the ICU. Although the pooled RR for 6-day or 7-day mortality (RR, 3.68, 95% CI, 2.32-5.83) was higher than that for 14-day mortality (RR, 1.70, 95% CI, 1.24-2.35), the pooled RD for both groups was 0.18. However, substantial heterogeneity was detected in the groups of studies that reported in-hospital mortality, 28-day or 30-day mortality, or mortality that was attributable to infection, which suggests other sources of heterogeneity.

Stratified analysis

To explore the source of heterogeneity between studies, we conducted a stratified analysis for each type of mortality outcome that had substantial heterogeneity. The potential sources of heterogeneity we explored

were pathogens, geographical region, economic status of the country, source of infection, resistance mechanism type, sample size, and publication year. One study[79] was not included in our subgroup analysis by geographical region and country income level, because it was conducted in 10 countries with different economic status from three continents.

For in-hospital mortality, carbapenem resistance had a significant positive effect on the risk of death for patients infected with *Enterobacteriaceae* in most subgroups. However, in-hospital mortality was not significantly different in either relative or absolute terms between CRE infection and CSE infection in studies that focused on patients infected with *Escherichia. coli* pathogens (RR, 3.83, 95% CI, 0.46-31.78, p=0.214; RD, 0.27, 95% CI, -0.06-0.59, p=0.115) or OXA-producing *Enterobacteriaceae* (RR, 3.15, 95% CI, 0.45-21.96, p=0.247; RD, 0.24, 95% CI, -0.05-0.53, p=0.110). In addition, no significant difference in pooled RR for in-hospital mortality was observed in studies that focused on patients with urinary tract infections (RR, 2.40, 95% CI, 0.82-7.03, p=0.110). The statistical test based on RR and RD showed that the effect of carbapenem resistance on mortality was not significantly different between the subgroups (Table S2 in Supplementary Material Appendix 5).

For 28-day or 30-day mortality, the subgroup analysis showed no significant difference in the mortality for CRE and CSE infections that were due to mixed *Enterobacteriaceae* pathogens (RR, 1.78, 95% CI, 0.57-5.60, p=0.321; RD, 0.05, 95% CI, -0.03-0.13, p=0.213). The results of the statistical tests based on RR showed that the later studies, those that were published from 2017 to 2020, reported higher RR for 28-day or 30-day mortality for patients who were infected with CRE versus CSE patients (p=0.006) than did studies that were published earlier. The statistical test results for 28-day or 30-day mortality showed that the pooled RD in studies with fewer than 100 patients was higher than that in studies with 100-200 patients. Although the pooled RD in studies with more than 200 patients was highest, the

heterogeneity in this group was high and should be interpreted with caution (Table S3 in Supplementary Material Appendix 5).

For mortality attributable to infection, the one study conducted in Europe with a sample size of fewer than 100 has found no significant difference in the risk of death for CRE and CSE infection (RR, 1.98, 95% CI, 0.61-6.43, p=0.255; RD, 0.13, 95% CI, -0.07-0.34, p=0.195), nor the study that focused on patients infected with OXA-producing *Enterobacteriaceae* (RR, 1.50, 95% CI, 0.43-5.28, p=0.528; RD, 0.04, 95% CI, -0.09-0.17, p=0.572). The results of statistical tests based on RD indicate that the effect of carbapenem resistance on attributable mortality is varied by the type of infection (p=0.075). Patients with neurosurgical infection were at greater risk of attributable death that was due to CRE infection than other types of infection (Table S4 in Supplementary Material Appendix 5).

Meta-regression

To further explore whether the effect of carbapenem resistance on mortality differs by the variables of pathogens, geographical region, economic status of the country, source of infection, resistance mechanism type, sample size, and publication year, we conducted the univariate meta-regression in the groups of mortality outcome type with more than 10 studies. The meta-regression results based on RD showed that the effect of carbapenem resistance on mortality was not influenced significantly by all the variables(Table S5, S6 in Supplementary Material Appendix 5). However, in terms of relative risk, the meta-regression for in-hospital mortality suggested that the influence of carbapenem resistance on in-hospital mortality in studies published between 2017 and 2020 was significantly greater than that in studies published between 2011 and 2013 (coefficient=-0.447, p=0.027) and in studies published from 2014 to 2016 (coefficient=-0.343, p=0.061) (Table S7 in Supplementary Material Appendix 5). The results of the

meta-regression for 28-day or 30-day mortality based on RR were similar to the results for in-hospital mortality. Moreover, the effect of carbapenem resistance on mortality at 28-day or 30-day tends to increase with the year of publication (coefficient=-0.0001, p=0.006) (Table S8 in Supplementary Material Appendix 5).

Sensitivity analysis

To assess the influence of individual studies on the results, we performed a sensitivity analysis by removing one study at a time and recalculated the pooled RRs of the overall mortality among the remaining studies using random-effects meta-analysis. We found that the direction of the effect did not change when any one study was excluded, which indicates the stability of the results of the meta-analysis.

Publication bias

Publication bias was assessed by a funnel plot (Figure 4). Slight asymmetricity was observed in the funnel plots and the points were heavily distributed at the top right, implying a lack of smaller studies that showed a negative association between carbapenem resistance and mortality.

Table 2 Pooled estimated results for different type of mortality outcome

Mortality outcome type	No. of studies	No. of CRE patients	No. of CSE patients	Unweighted means of mortality among CRE patients	Unweighted means of mortality among CSE patients	RR (95%CI)	*P* value (significance tests of RR=1)	I^2 (%)	RD (95%CI)	*P* value (significance tests of RD=0)	I^2 (%)
In-hospital mortality	31	1668	3753	42.30%	20.00%	2.09 (1.81, 2.42)	0.000	49.8	0.21 (0.17, 0.26)	0.000	71.0
28d or 30d mortality	17	1161	2463	42.85%	19.88%	2.23 (1.83, 2.72)	0.000	63.6	0.23 (0.15, 0.30)	0.000	79.1
21d mortality	1	161	117	52.20%	14.50%	3.59 (2.26, 5.71)	0.000	-	0.38 (0.28, 0.48)	0.000	-
14d mortality	4	84	287	45.09%	27.01%	1.70 (1.24, 2.35)	0.001	0.0	0.18 (0.06, 0.31)	0.003	0.0
6d or 7d mortality	3	149	372	25.90%	6.57%	3.68 (2.32, 5.83)	0.000	0.0	0.18 (0.11, 0.26)	0.000	0.0
Mortality attributable to infection	8	391	778	43.30%	17.45%	2.74 (1.97, 3.81)	0.000	58.3	0.27 (0.15, 0.38)	0.000	79.5
Mortality in ICU	4	1035	824	58.83%	50.50%	1.17 (1.08, 1.28)	0.000	0.0	0.09 (0.04, 0.14)	0.000	0.0
30d mortality in ICU	1	244	263	28.90%	11.00%	2.60 (1.75, 3.87)	0.000	-	0.18 (0.11, 0.25)	0.000	-

DISCUSSION

This study systematically reviewed 50 studies and provides a comprehensive analysis of the impact of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae*. Our analysis suggests that, for any type of mortality outcome, carbapenem resistance was associated with a greater probability of death for patients infected with CRE than that for patients infected with CSE. The results are consistent with the direction of previous meta-analyses of the association between carbapenem resistance and mortality among patients infected with *Enterobacteriaceae*.[13,14]

As for the risk factors for worse mortality outcomes in patients with CRE infections, previous studies usually explained higher mortality among patients with CRE infection as being due to patient-, infection-, treatment-, and organism-related factors.[13,14,16,80] Twenty studies included in this review conducted multivariate analyses to identify the risk factors for mortality among patients infected with *Enterobacteriaceae*. After controlling for patient-related factors like age, sex, the severity of underlying illness, and comorbidities, three studies[47,51,67] found that carbapenem resistance was not associated with increased mortality risk; however, 14 studies found that carbapenem resistance remained an independent predictor of mortality. Previous studies also considered therapeutic interventions as important risk factors for increased mortality in CRE infection, as administration of initial antibiotic therapy with in-vitro activity is more likely to be delayed in patients with CRE infection.[32,33,40,59,62,67,74] Several studies included in this research have suggested that the effect of carbapenem resistance was probably mediated by inappropriate initial therapy.[40,51,37] This finding was supported by a recent review of 11 studies that used a meta-regression analysis to identify a significant association between the proportion of patients who received appropriate initial antibiotic therapy and mortality.[16] However, nine studies included in our review[32,38,41,47,62,67,71,73,74] did not identify an association between early appropriate antibiotic therapy and

mortality after adjustment for some confounding factors. Instead, some studies found that other treatment methods were important risk factors of mortality. For example, a recent meta-analysis including seven studies showed that monotherapy treatment was associated with significantly higher mortality than combination therapy for patients with CRE infections.[14] In addition, some studies[72,73] have suggested that other therapies, such as adjunctive therapy, tigecycline therapy, and the use of aminoglycoside, may be associated with mortality among patients infected with *Klebsiella pneumoniae*. The increased mortality among patients with CRE infections might also be related to the increased virulence of carbapenemase-producing strains. Two studies included in this meta-analysis showed that isolation of the KPC-positive strain was a predictor of mortality among patients infected with *Klebsiella pneumoniae* independent of the appropriateness of initial treatment and patient characteristics,[41,55] while another study[47] found that KPC-positive status was not associated with mortality when the virulence score was included in the multivariate analysis. As most of the included studies we reviewed did not provide the mortality outcomes after adjusting for confounding factors, we did not calculate the pooled adjusted effect measures.

To investigate the heterogeneity across the studies, we performed stratified analysis and meta-regression based on the type of mortality outcome. In terms of RR, the meta-regression analysis for in-hospital mortality showed that the effect of carbapenem resistance on in-hospital mortality was greater in studies published in 2017-2020 than it was in studies published in 2011-2013 and 2014-2016. The statistical test and meta-regression analyses for 28-day and 30-day mortality showed similar results. The increasing effect of carbapenem resistance on mortality with the publication year could be explained by the increasingly limited availability of effective antibiotics and the development of carbapenem-resistant *Enterobacteriaceae* against some key antibiotics, such as colistin,[81] resulting in increasing difficulty in treating CRE infection. As one study showed, [16] the proportion of CRKP patients who received appropriate

initial antibiotic therapy did not change over time. In contrast, mortality from CSE infection has tended to decrease in recent years, and the unweighted mean of in-hospital mortality and 28-day and 30-day mortality among CSE patients in studies conducted from 2017-2020 is 11.69% and 13.43% respectively, the lowest of the studies we reviewed. This change could be due to the development of medical technology and medical treatment, which may enlarge the relative differences in mortality between CRE and CSE infections. In addition, the statistical test for mortality attributable to infection identified a significant difference between infection types, as carbapenem resistance in patients with neurosurgical infection had a significantly greater effect on mortality compared to other types of infection, perhaps because of difficulty in treating CRE meningitis/encephalitis in neurosurgery.[74] In terms of the RR, the statistical test showed that, compared with studies with fewer than 100 patients, carbapenem resistance had a greater effect on 28-day and 30-day mortality in studies with 100-200 patients, indicating that the absolute risk difference of mortality between CRE and CSE infection tends to be more stable with larger sample size.

To our knowledge, this study offers the most comprehensive meta-analysis so far of the impact of carbapenem resistance on mortality among patients infected with *Enterobacteriaceae.* Nearly 20 new studies published in the last three years have been included in our study. In addition, the meta-analysis was conducted in different groups of mortality outcomes, which may help address the potential heterogeneity caused by mortality measurements. Moreover, this review is the first to explore the source of heterogeneity among studies using statistical tests and meta-regression analyses of variables related to countries' economic status and geographical region. Moreover, this is the first review to explore the source of heterogeneity across studies using statistical tests and meta-regression analysis of potential variables and to consider the country's economic status and geographical region in assessing the association between carbapenem resistance and mortality among patients infected with *Enterobacteriaceae*

Our study also has several limitations. Firstly, among studies focusing on specific pathogens, we only included studies that focused on two clinically important *Enterobacteriaceae* species, *Klebsiella pneumoniae* and *Escherichia coli*. Secondly, we only included studies published in English. Thirdly, we only calculated the unadjusted results, so many confounding factors, such as patients' health conditions and therapy options, were not adjusted in the analysis because of data limitations. In addition, we were unable to conduct the stratified analysis and meta-regression for all kinds of mortality measurements because of insufficient data. Finally, the comparison in our research is currently limited to high-income and upper-middle-income countries from the Americas, Asia, and Europe due to insufficient data. More studies from different countries, especially low-income countries and other regions, are needed to provide comprehensive data for further analysis stratified by geographical region and economic status.

Our findings reinforced previous results regarding the positive effect of carbapenem resistance on mortality for patients infected with *Enterobacteriaceae*. These findings implied that patients with CRE infection still face a greater risk of death compared with patients with CSE infection. Furthermore, this study has identified an increasing effect of carbapenem resistance on mortality over time especially for 28d-30d mortality, which may reflect the difficulty of the CRE infection treatment in clinical practice and emphasizes the urgent need to develop new antibiotics and appropriate treatment to reduce the death risk. Our results also suggested that patients with neurosurgical infection were at greater risk of attributable death that was due to CRE infection than other types of infection. Thus, more attention should be paid to CRE infection in patients with neurosurgery in clinical practice. In addition, no significant differences in the effect of carbapenem resistance on mortality for different geographical regions and economic status were observed in our study, which may result from the limited data. The comparison in our research is currently limited to high-income and upper-middle-income countries from the Americas, Asia, and Europe

due to insufficient data. More studies from different countries, especially low-income countries, are needed to provide comprehensive data for further analysis stratified by geographical region and economic status.

CONCLUSIONS

Our results indicate that patients with CRE infection still face a greater risk of death than patients with CSE infection do, and an urgent need to develop new antibiotics and appropriate treatment to reduce the death risk. Future studies should address additional countries to provide comprehensive data and sound evidence from which to draw resources to fight CRE-related mortality and suggest the way forward to alleviate its implications.

Contributors All authors were involved in the design and development of the study. The review was designed by XF, RZ (Rong Zhang), RZ (Ruyin Zhou), JL, JS, TRW, and YW. The literature search in electronic databases was conducted by JZ, SS, SC and XZ. RZ (Ruyin Zhou) and JZ screened all studies for inclusion into the systematic review and performed the assessments of risk bias for all studies with the assistance of XZ, SS, SC, and XF. RZ (Ruyin Zhou) and JZ performed data extraction. RZ (Ruyin Zhou) and JZ conducted data analysis and interpretation with assistance of XZ, SS, SC, and XF. RZ (Ruyin Zhou) drafted the manuscript and YS, ZL, JL, RZ (Rong Zhang), JS, TRW, YW, XF revised it critically for important intellectual content. All authors contributed to drafting and revision of the article and have reviewed the results and approved the final version of the manuscript.

Competing interests None declared.

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Ethics Statement This study does not involve human participants or animal subjects.

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Figure legends

Figure 1. Flow chart of the study selection process for the meta-analysis

Figure 2. Forest plot of overall mortality in patients with carbapenem-resistant *Enterobacteriaceae* (CRE) versus carbapenem-susceptible *Enterobacteriaceae* (CSE) infections (outcome measure = relative risk).

Figure 3. Forest plot of overall mortality in patients with carbapenem-resistant *Enterobacteriaceae* (CRE) versus carbapenem-susceptible *Enterobacteriaceae* (CSE) infections (outcome measure = risk difference).

Figure 4. Funnel plot of studies evaluating mortality of patients with infections due to carbapenem-resistant compared to carbapenem-susceptible *Enterobacteriaceae*.

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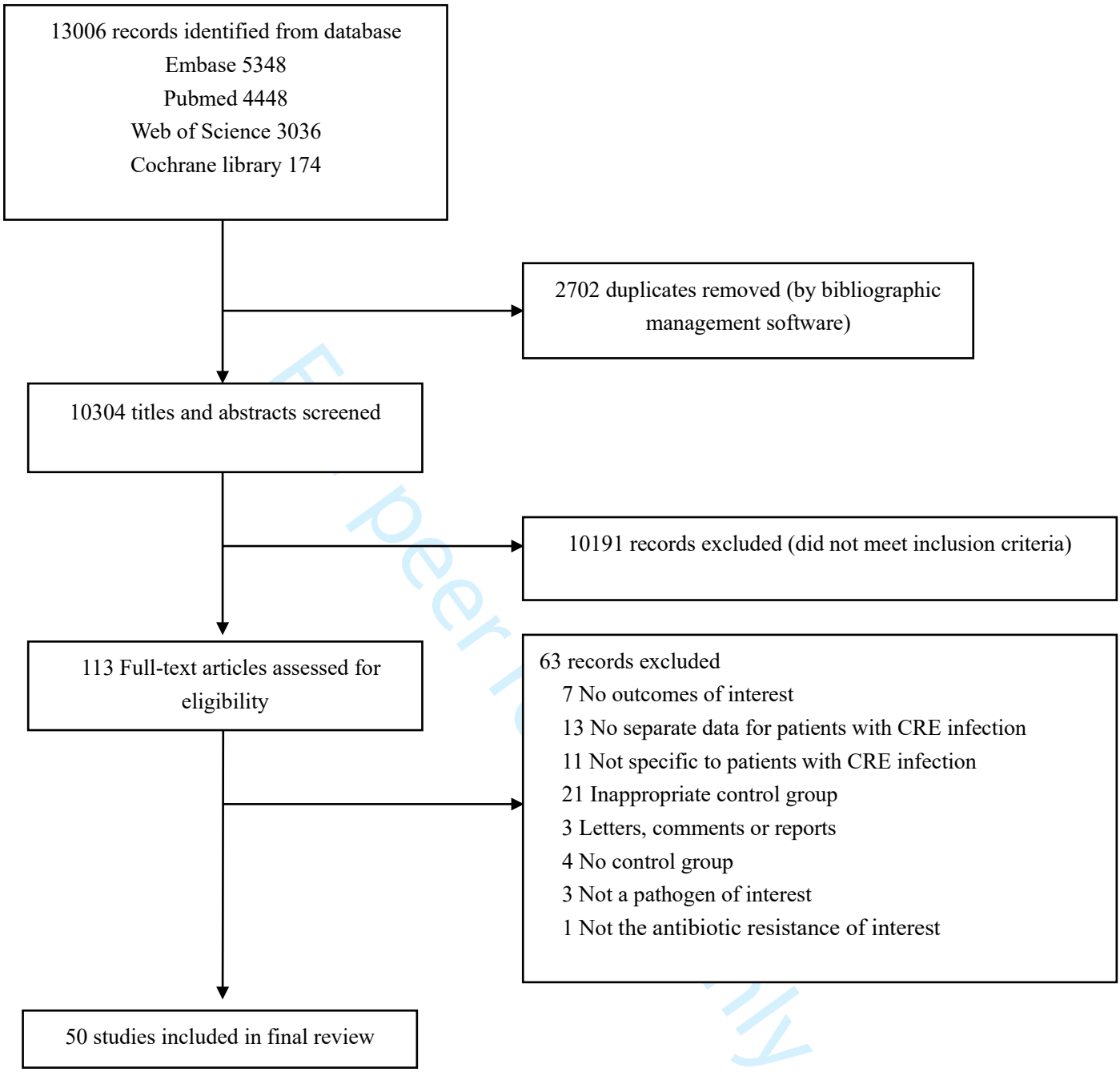
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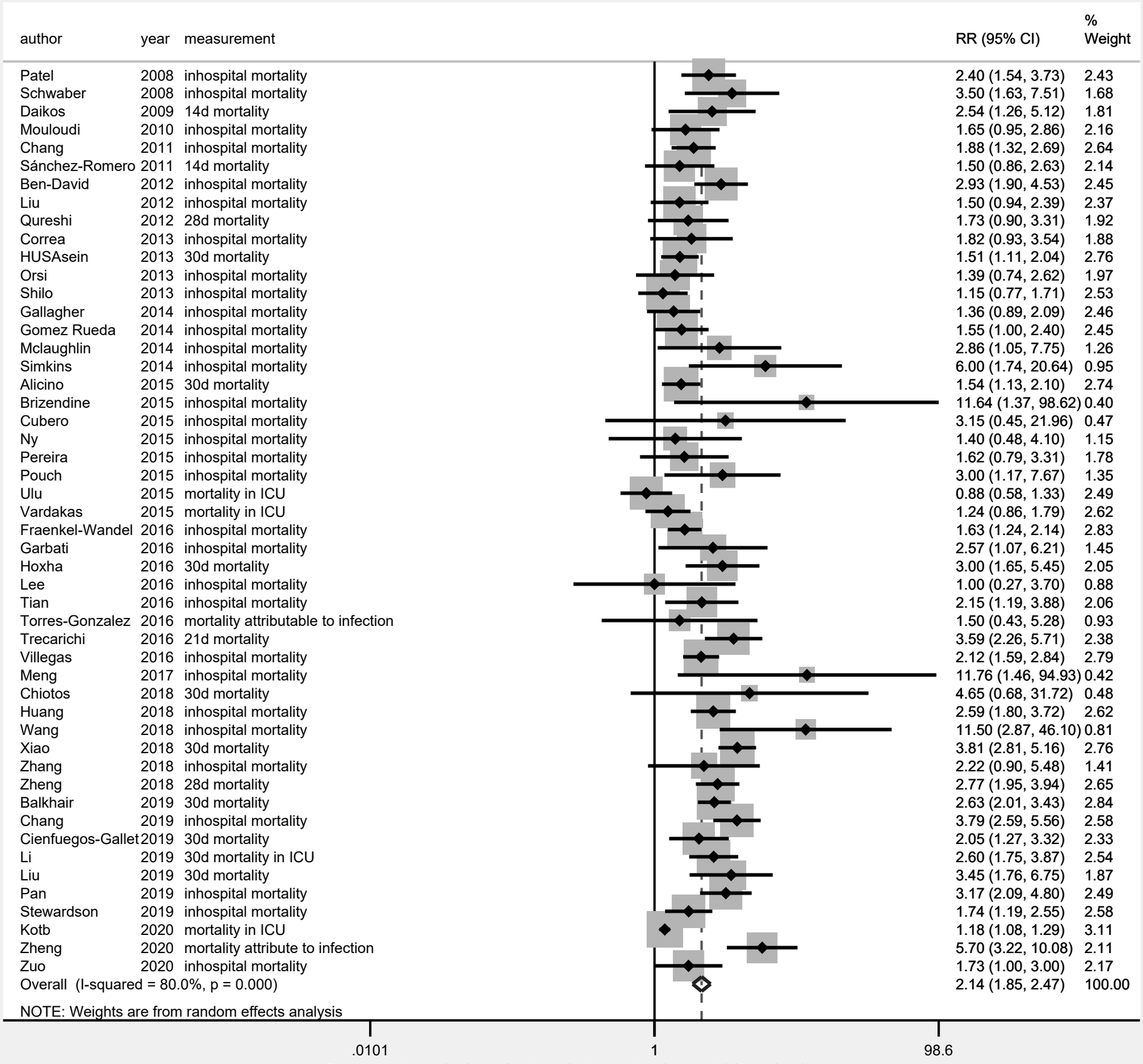
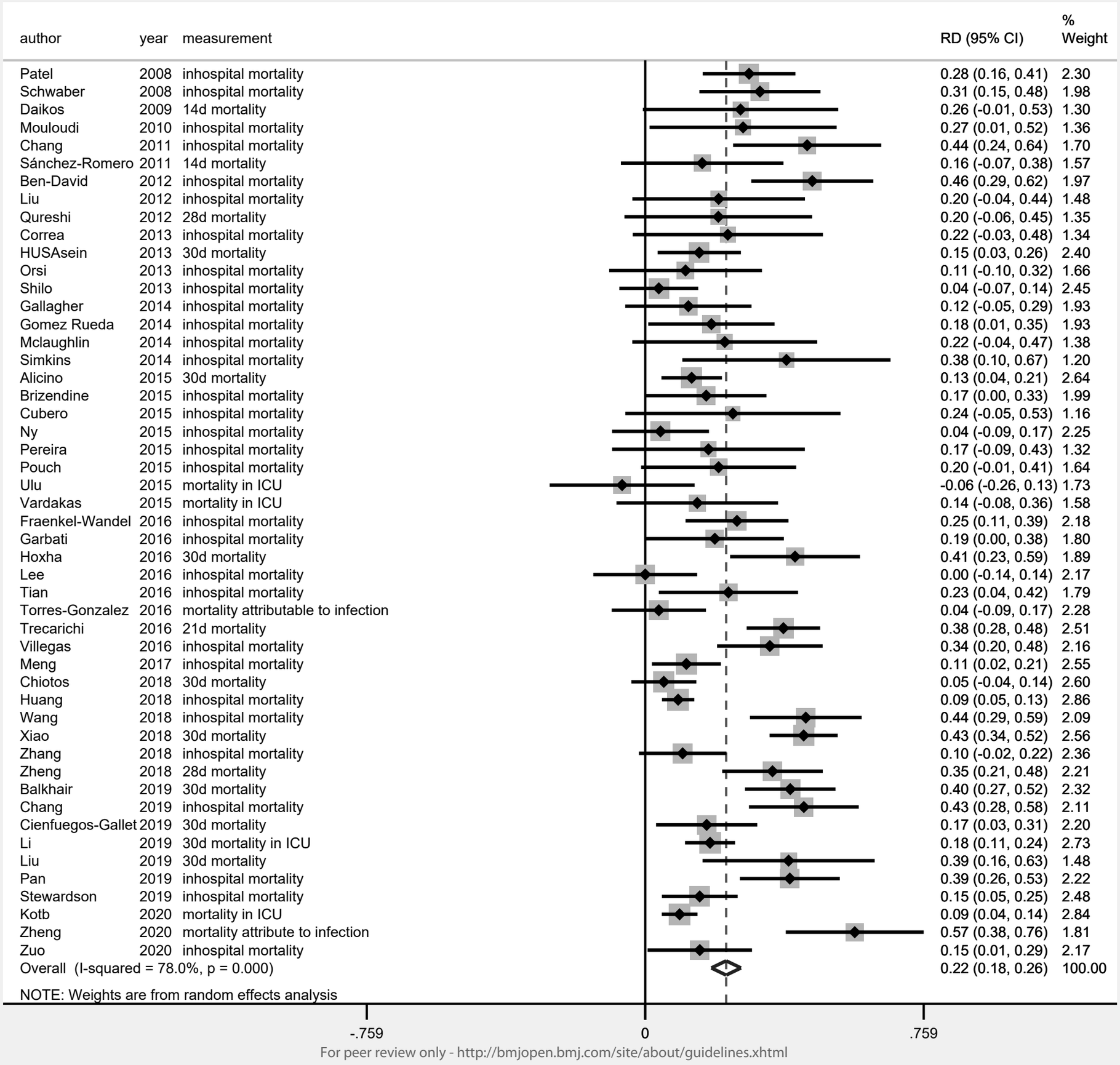
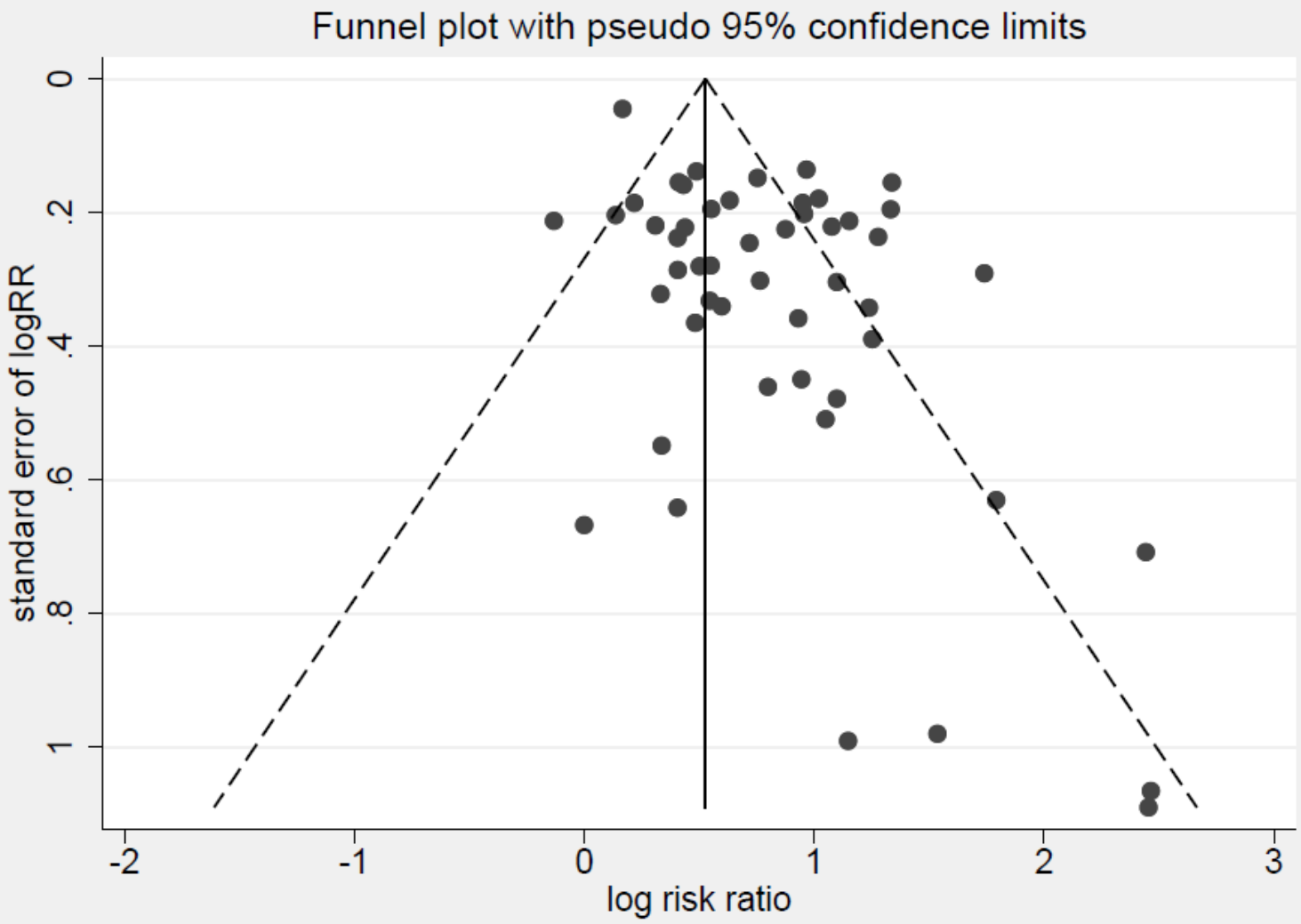
113 Full-text articles assessed for eligibility
63 records excluded
7 No outcomes of interest
13 No separate data for patients with CRE infection
11 Not specific to patients with CRE infection
21 Inappropriate control group
3 Letters, comments or reports
4 No control group
3 Not a pathogen of interest
1 Not the antibiotic resistance of interest
50 studies included in final review


author
year
measurement
RR (95% CI)
% Weight
Patel 2008 inhospital mortality 2.40 (1.54, 3.73) 2.43
Schwaber 2008 inhospital mortality 3.50 (1.63, 7.51) 1.68
Daikos 2009 14d mortality 2.54 (1.26, 5.12) 1.81
Mouloudi 2010 inhospital mortality 1.65 (0.95, 2.86) 2.16
Chang 2011 inhospital mortality 1.88 (1.32, 2.69) 2.64
Sánchez-Romero 2011 14d mortality 1.50 (0.86, 2.63) 2.14
Ben-David 2012 inhospital mortality 2.93 (1.90, 4.53) 2.45
Liu 2012 inhospital mortality 1.50 (0.94, 2.39) 2.37
Qureshi 2012 28d mortality 1.73 (0.90, 3.31) 1.92
Correa 2013 inhospital mortality 1.82 (0.93, 3.54) 1.88
HUSAsein 2013 30d mortality 1.51 (1.11, 2.04) 2.76
Orsi 2013 inhospital mortality 1.39 (0.74, 2.62) 1.97
Shilo 2013 inhospital mortality 1.15 (0.77, 1.71) 2.53
Gallagher 2014 inhospital mortality 1.36 (0.89, 2.09) 2.46
Gomez Rueda 2014 inhospital mortality 1.55 (1.00, 2.40) 2.45
Mclaughlin 2014 inhospital mortality 2.86 (1.05, 7.75) 1.26
Simkins 2014 inhospital mortality 6.00 (1.74, 20.64) 0.95
Alicino 2015 30d mortality 1.54 (1.13, 2.10) 2.74
Brizendine 2015 inhospital mortality 11.64 (1.37, 98.62) 0.40
Cubero 2015 inhospital mortality 3.15 (0.45, 21.96) 0.47
Ny 2015 inhospital mortality 1.40 (0.48, 4.10) 1.15
Pereira 2015 inhospital mortality 1.62 (0.79, 3.31) 1.78
Pouch 2015 inhospital mortality 3.00 (1.17, 7.67) 1.35
Ulu 2015 mortality in ICU 0.88 (0.58, 1.33) 2.49
Vardakas 2015 mortality in ICU 1.24 (0.86, 1.79) 2.62
Fraenkel-Wandel 2016 inhospital mortality 1.63 (1.24, 2.14) 2.83
Garbati 2016 inhospital mortality 2.57 (1.07, 6.21) 1.45
Hoxha 2016 30d mortality 3.00 (1.65, 5.45) 2.05
Lee 2016 inhospital mortality 1.00 (0.27, 3.70) 0.88
Tian 2016 inhospital mortality 2.15 (1.19, 3.88) 2.06
Torres-Gonzalez 2016 mortality attributable to infection 1.50 (0.43, 5.28) 0.93
Trecarichi 2016 21d mortality 3.59 (2.26, 5.71) 2.38
Villegas 2016 inhospital mortality 2.12 (1.59, 2.84) 2.79
Meng 2017 inhospital mortality 11.76 (1.46, 94.93) 0.42
Chiotos 2018 30d mortality 4.65 (0.68, 31.72) 0.48
Huang 2018 inhospital mortality 2.59 (1.80, 3.72) 2.62
Wang 2018 inhospital mortality 11.50 (2.87, 46.10) 0.81
Xiao 2018 30d mortality 3.81 (2.81, 5.16) 2.76
Zhang 2018 inhospital mortality 2.22 (0.90, 5.48) 1.41
Zheng 2018 28d mortality 2.77 (1.95, 3.94) 2.65
Balkhair 2019 30d mortality 2.63 (2.01, 3.43) 2.84
Chang 2019 inhospital mortality 3.79 (2.59, 5.56) 2.58
Cienfuegos-Gallet 2019 30d mortality 2.05 (1.27, 3.32) 2.33
Li 2019 30d mortality in ICU 2.60 (1.75, 3.87) 2.54
Liu 2019 30d mortality 3.45 (1.76, 6.75) 1.87
Pan 2019 inhospital mortality 3.17 (2.09, 4.80) 2.49
Stewardson 2019 inhospital mortality 1.74 (1.19, 2.55) 2.58
Kotb 2020 mortality in ICU 1.18 (1.08, 1.29) 3.11
Zheng 2020 mortality attribute to infection 5.70 (3.22, 10.08) 2.11
Zuo 2020 inhospital mortality 1.73 (1.00, 3.00) 2.17
Overall (I-squared = 80.0%, p = 0.000) 2.14 (1.85, 2.47) 100.00
NOTE: Weights are from random effects analysis
.0101
1
98.6


author year measurement RD (95% CI) % Weight
Patel 2008 inhospital mortality 0.28 (0.16, 0.41) 2.30
Schwaber 2008 inhospital mortality 0.31 (0.15, 0.48) 1.98
Daikos 2009 14d mortality 0.26 (-0.01, 0.53) 1.30
Mouloudi 2010 inhospital mortality 0.27 (0.01, 0.52) 1.36
Chang 2011 inhospital mortality 0.44 (0.24, 0.64) 1.70
Sánchez-Romero 2011 14d mortality 0.16 (-0.07, 0.38) 1.57
Ben-David 2012 inhospital mortality 0.46 (0.29, 0.62) 1.97
Liu 2012 inhospital mortality 0.20 (-0.04, 0.44) 1.48
Qureshi 2012 28d mortality 0.20 (-0.06, 0.45) 1.35
Correa 2013 inhospital mortality 0.22 (-0.03, 0.48) 1.34
HUSAsein 2013 30d mortality 0.15 (0.03, 0.26) 2.40
Orsi 2013 inhospital mortality 0.11 (-0.10, 0.32) 1.66
Shilo 2013 inhospital mortality 0.04 (-0.07, 0.14) 2.45
Gallagher 2014 inhospital mortality 0.12 (-0.05, 0.29) 1.93
Gomez Rueda 2014 inhospital mortality 0.18 (0.01, 0.35) 1.93
Mclaughlin 2014 inhospital mortality 0.22 (-0.04, 0.47) 1.38
Simkins 2014 inhospital mortality 0.38 (0.10, 0.67) 1.20
Alicino 2015 30d mortality 0.13 (0.04, 0.21) 2.64
Brizendine 2015 inhospital mortality 0.17 (0.00, 0.33) 1.99
Cubero 2015 inhospital mortality 0.24 (-0.05, 0.53) 1.16
Ny 2015 inhospital mortality 0.04 (-0.09, 0.17) 2.25
Pereira 2015 inhospital mortality 0.17 (-0.09, 0.43) 1.32
Pouch 2015 inhospital mortality 0.20 (-0.01, 0.41) 1.64
Ulu 2015 mortality in ICU -0.06 (-0.26, 0.13) 1.73
Vardakas 2015 mortality in ICU 0.14 (-0.08, 0.36) 1.58
Fraenkel-Wandel 2016 inhospital mortality 0.25 (0.11, 0.39) 2.18
Garbati 2016 inhospital mortality 0.19 (0.00, 0.38) 1.80
Hoxha 2016 30d mortality 0.41 (0.23, 0.59) 1.89
Lee 2016 inhospital mortality 0.00 (-0.14, 0.14) 2.17
Tian 2016 inhospital mortality 0.23 (0.04, 0.42) 1.79
Torres-Gonzalez 2016 mortality attributable to infection 0.04 (-0.09, 0.17) 2.28
Trecarichi 2016 21d mortality 0.38 (0.28, 0.48) 2.51
Villegas 2016 inhospital mortality 0.34 (0.20, 0.48) 2.16
Meng 2017 inhospital mortality 0.11 (0.02, 0.21) 2.55
Chiotos 2018 30d mortality 0.05 (-0.04, 0.14) 2.60
Huang 2018 inhospital mortality 0.09 (0.05, 0.13) 2.86
Wang 2018 inhospital mortality 0.44 (0.29, 0.59) 2.09
Xiao 2018 30d mortality 0.43 (0.34, 0.52) 2.56
Zhang 2018 inhospital mortality 0.10 (-0.02, 0.22) 2.36
Zheng 2018 28d mortality 0.35 (0.21, 0.48) 2.21
Balkhair 2019 30d mortality 0.40 (0.27, 0.52) 2.32
Chang 2019 inhospital mortality 0.43 (0.28, 0.58) 2.11
Cienfuegos-Gallet 2019 30d mortality 0.17 (0.03, 0.31) 2.20
Li 2019 30d mortality in ICU 0.18 (0.11, 0.24) 2.73
Liu 2019 30d mortality 0.39 (0.16, 0.63) 1.48
Pan 2019 inhospital mortality 0.39 (0.26, 0.53) 2.22
Stewardson 2019 inhospital mortality 0.15 (0.05, 0.25) 2.48
Kotb 2020 mortality in ICU 0.09 (0.04, 0.14) 2.84
Zheng 2020 mortality attribute to infection 0.57 (0.38, 0.76) 1.81
Zuo 2020 inhospital mortality 0.15 (0.01, 0.29) 2.17
Overall (I-squared = 78.0%, p = 0.000) 0.22 (0.18, 0.26) 100.00
NOTE: Weights are from random effects analysis
-.759
0
.759


Funnel plot with pseudo 95% confidence limits
standard error of logRR
0
.2
.4
.6
.8
1
-2
-1
0
1
2
3
log risk ratio

Supplementary Materials

Appendix 1. Search terms and search strategies

1.Pubmed (4448)

Search	Query	Items found
#1	Search: ((enterobacteriaceae[MeSH Terms]) OR klebsiella pneumoniae[MeSH Terms]) OR escherichia coli[MeSH Terms]	399348
#2	Search: (((carbapenem resistant) OR (carbapenem resistance)) OR (carbapenem nonsusceptible)) OR (carbapenemase producing)	15576
#3	Search: (((enterobacteriaceae[MeSH Terms]) OR (klebsiella pneumoniae[MeSH Terms])) OR (escherichia coli[MeSH Terms])) AND ((((carbapenem resistant) OR (carbapenem resistance)) OR (carbapenem nonsusceptible)) OR (carbapenemase producing))	5776
#4	Search: (((enterobacteriaceae[MeSH Terms]) OR (klebsiella pneumoniae[MeSH Terms])) OR (escherichia coli[MeSH Terms])) AND ((((carbapenem resistant) OR (carbapenem resistance)) OR (carbapenem nonsusceptible)) OR (carbapenemase producing)) Filters: Humans	4761
#5	Search: (((enterobacteriaceae[MeSH Terms]) OR (klebsiella pneumoniae[MeSH Terms])) OR (escherichia coli[MeSH Terms])) AND ((((carbapenem resistant) OR (carbapenem resistance)) OR (carbapenem nonsusceptible)) OR (carbapenemase producing)) Filters: Humans, from 1994 - 2020	4716
#6	Search: (((enterobacteriaceae[MeSH Terms]) OR (klebsiella pneumoniae[MeSH Terms])) OR (escherichia coli[MeSH Terms])) AND ((((carbapenem resistant) OR (carbapenem resistance)) OR (carbapenem nonsusceptible)) OR (carbapenemase producing)) Filters: Humans, English, from 1994 - 2020	4448

2.Embase(5348)

#	**searches**	**results**
1	Enterobacteriaceae.af.	38034
2	Klebsiella pneumoniae.af.	47767
3	Escherichia coli.af.	425764
4	1 or 2 or 3	470290
5	carbapenem resistant.af.	7442
6	carbapenem resistance.af.	3418
7	carbapenem nonsusceptible.af.	139
8	carbapenemase producing.af.	3413
9	5 or 6 or 7 or 8	11419
10	4 and 9	8235
11	limit 10 to (human and english language and yr="1994 -Current")	5348

3.Web of Science(3036)

#	searches	results
1	TI=(Enterobacteriaceae) Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	6685
2	TI=(Klebsiella pneumoniae) Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	10759
3	TI=(Escherichia coli) Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	102497
4	#3 OR #2 OR #1 Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	118551
5	TI=(carbapenem resistance OR carbapenem resistant OR carbapenem nonsusceptible OR carbapenemase producing) Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	5926
6	#5 AND #4 Databases= WOS, BCI, BIOSIS, CABI, CSCD, DIIDW, INSPEC, KJD, MEDLINE, RSCI, SCIELO, ZOOREC Timespan=1994-2020 Search language=English	3036

4.Cochrane library

ID	Search	Hits
#1	(carbapenem) AND (Enterobacteriaceae) (Limits: Word variations have been searched)	137
#2	(carbapenem) AND (Klebsiella pneumoniae) (Limits: Word variations have been searched)	71
#3	(carbapenem) AND (Escherichia coli) (Limits: Word variations have been searched)	67
#4	#1 OR #2 OR #3 with Cochrane Library publication date Between Jan 1994 and Sep 2020	174

Appendix 2. List of excluded studies with reason for exclusion

First author	Year	Reason for exclusion
Adams[1]	2019	inappropriate control group
Ahn[2]	2014	Not specific to patients with CRE infection
Akgul[3]	2016	Not specific to patients with CRE infection
Balkan[4]	2014	inappropriate control group
Biehle[5]	2015	not a pathogen of interest
Bleumin[6]	2012	No separate data for patients with CRE infection
Bogan[7]	2014	No separate data for patients with CRE infection
Chang[8]	2015	no control group
Cristina[9]	2016	no control group
Dautzenberg[10]	2015	Not specific to patients with CRE infection
de Maio Carrilho[11]	2016	no control group
Debby[12]	2012	Not specific to patients with CRE infection
Diaz[13]	2016	Not specific to patients with CRE infection
Dizbay[14]	2014	not a pathogen of interest
Eser[15]	2019	Not specific to patients with CRE infection
Falcone[16]	2009	not a pathogen of interest
Fang[17]	2019	No separate data for patients with CRE infection
Forde[18]	2017	No separate data for patients with CRE infection
Freire[19]	2015	inappropriate control group
Gao[20]	2019	inappropriate control group
Gasink[21]	2009	No separate data for patients with CRE infection
Gaviria[22]	2011	Letters, comments or reports
Giacobbe[23]	2015	Not the antibiotic resistance of interest
Giannella[24]	2014	Not specific to patients with CRE infection
Girmenia[25]	2015	inappropriate control group
Girometti[26]	2014	no outcomes of interest
Gowda[27]	2014	no outcomes of interest
Grabowsk[28]	2017	No separate data for patients with CRE infection
Hauck[29]	2016	inappropriate control group
Hu[30]	2016	Not specific to patients with CRE infection
Jiao[31]	2015	No separate data for patients with CRE infection
Kang[32]	2019	Not specific to patients with CRE infection
Kofteridis[33]	2014	No separate data for patients with CRE infection
Lai[34]	2013	inappropriate control group
Lee[35]	2013	no outcomes of interest
Lee[36]	2012	inappropriate control group
López-González[37]	2017	inappropriate control group
Lubbert[38]	2014	No separate data for patients with CRE infection
Mantzarlis[39]	2013	inappropriate control group

Marimuthu[40]	2013	Letters, comments or reports
Mazza[41]	2017	inappropriate control group
Miller[42]	2016	no outcomes of interest
Mouloudi[43]	2014	inappropriate control group
Muggeo[44]	2017	No separate data for patients with CRE infection
Nouvenne[45]	2014	No separate data for patients with CRE infection
Orsi[46]	2011	inappropriate control group
Papadimitriou-Olivgeris[47]	2013	Not specific to patients with CRE infection
Patel[48]	2015	inappropriate control group
Porwal[49]	2014	Letters, comments or reports
Qureshi[50]	2014	inappropriate control group
Rodrigues[51]	2016	inappropriate control group
Salsano[52]	2016	inappropriate control group
Segagni Lusignani[53]	2020	No separate data for patients with CRE infection
Shankar[54]	2018	no control group
Taminato[55]	2019	inappropriate control group
Tamma[56]	2017	inappropriate control group
Tascini[57]	2015	Not specific to patients with CRE infection
Tsereteli[58]	2018	no outcomes of interest
Tumbarello[59]	2015	inappropriate control group
Tumbarello[60]	2014	inappropriate control group
Tuon[61]	2017	no outcomes of interest
Jamal[62]	2016	no outcomes of interest
Wang[63]	2016	No separate data for patients with CRE infection

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Appendix 3. Descriptive details of the 50 included studies

Table S1 Descriptive details of the 50 included studies

First Author	Year	Country	Region	Economic status	Infection type	Pathogen	Resistance type	Sample size (n)		Mortality measurements	Mortality (%)	
								CRE	CSE		CRE	CSE
Alicino	2015	Italy	Europe	High income	bloodstream infection	Klebsiella pneumoniae	NA	349	162	30d mortality	36.1	23.5
Balkhair	2019	Oman	Asia	High income	bloodstream infection	Klebsiella pneumoniae	NA	69	305	30d mortality	63.8	24.3
Ben-David	2012	Israel	Asia	High income	bloodstream infection	Klebsiella pneumoniae	KPC-producing	42	85	in-hospital mortality	69	24
										mortality attributable to infection	48	17
Brizendine	2015	USA	America	High income	urinary tract infection	Klebsiella pneumoniae	NA	22	64	in-hospital mortality	18	2
Chang	2019	China	Asia	Upper middle income	bloodstream infection	Klebsiella pneumoniae	NA	46	239	28d mortality	50	14.6
										7d mortality	37	10.5
										in-hospital mortality	58.7	15.9
Chang	2011	China	Asia	Lower middle income	bloodstream infection	Escherichia. coli	NA	17	34	in-hospital mortality	94.12	50
										28d hospital mortality	70.59	47.06
										14d hospital mortality	47.06	38.24
Chiotos	2018	USA	America	High income	mixed	Mixed Enterobacteriaceae	NA	31	144	30d mortality	6.5	1.4

Cienfuegos-Gallet	2019	Colombia	America	Upper middle income	mixed	Klebsiella pneumoniae	KPC-producing	49	289	30d mortality	32.65	15.92
Correa	2013	Brazil	America	Upper middle income	mixed	Klebsiella pneumoniae	NA	20	40	in-hospital mortality	50	27.5
Cubero	2015	Spain	Europe	High income	mixed	Klebsiella pneumoniae	OXA-producing	20	9	in-hospital mortality	35	11.1
Daikos	2009	Greece	Europe	High income	bloodstream infection	Klebsiella pneumoniae	VIM-producing	14	148	14d mortality	42.9	16.9
Fraenkel-Wandel	2016	Israel	Asia	High income	bloodstream infection	Klebsiella pneumoniae	KPC-producing	68	136	in-hospital mortality	65	40
Gallagher	2014	USA	America	High income	bloodstream infection	Klebsiella pneumoniae	NA	43	111	in-hospital mortality	45	32
Garbati	2016	Saudi Arabia	Asia	High income	mixed	Mixed Enterobacteriaceae	NA	29	58	in-hospital mortality	31	12.1
Gomez Rueda	2014	Colombia	America	Upper middle income	mixed	Klebsiella pneumoniae	NA	61	61	in-hospital mortality	50.8	32.7
Hoxha	2016	Italy	Europe	High income	mixed	Klebsiella pneumoniae	NA	49	49	30d mortality	61	20
										6d mortality	24	8
Huang	2018	China	Asia	Upper middle income	mixed	Klebsiella pneumoniae	NA	267	1328	in-hospital mortality	14.61	5.65

Hussein	2013	Israel	Asia	High income	bloodstream infection	Klebsiella pneumoniae	NA	103	214	30d mortality	43.7	29
Kotb	2020	Egypt	Africa	Lower middle income	mixed	Mixed Enterobacteriaceae	NA	871	727	mortality in ICU	61.1	51.7
Lee	2016	Korea	Asia	High income	mixed	Mixed Enterobacteriaceae	NA	37	37	in-hospital mortality	10.8	10.8
										28d mortality	27	21.6
Li	2019	China	Asia	Upper middle income	mixed	Klebsiella pneumoniae	NA	244	263	30d mortality in ICU	28.9	11
Liu	2019	China	Asia	Upper middle income	bloodstream infection	Klebsiella pneumoniae	NA	20	69	30d mortality	55	15.9
Liu	2012	China	Asia	Lower middle incom	bloodstream infection	Klebsiella pneumoniae	NA	25	50	in-hospital mortality	60	40
										28d mortality	52	30
										14d mortality	44	22
Mclaughlin	2014	USA	America	High income	bloodstream infection	Klebsiella pneumoniae	KPC-producing	15	60	in-hospital mortality	33.3	11.7
Meng	2017	China	Asia	Upper middle income	mixed	Escherichia. coli	not focusing on a particular type of carbapenemase-producing strains	49	96	in-hospital mortality	12	1
Mouloudi	2010	Greece	Europe	High income	bloodstream infection	Klebsiella pneumoniae	KPC-producing	37	22	in-hospital mortality	68	41
										mortality attributable to infection	27	14

										mortality in ICU	57	41
Ny	2015	USA	America	High income	mixed	Klebsiella pneumoniae	NA	48	48	in-hospital mortality	14.6	10.4
Orsi	2013	Italy	Europe	High income	mixed	Klebsiella pneumoniae	KPC-producing	36	43	in-hospital mortality	38.9	27.9
Pan	2019	China	Asia	Upper middle income	mixed	Klebsiella pneumoniae	KPC-producing	66	132	in-hospital mortality	57.6	18.2
										28d mortality	18.18	11.36
Patel	2008	USA	America	High income	mixed	Klebsiella pneumoniae	NA	99	99	in-hospital mortality	48	20
										mortality attributable to infection	38	12
Pereira	2015	USA	America	High income	mixed	Klebsiella pneumoniae	NA	20	36	in-hospital mortality	45	28
Pouch	2015	USA	America	High income	urinary tract infection	Mixed Enterobacteriaceae	NA	20	80	in-hospital mortality	30	10
Qureshi	2012	USA	America	High income	bloodstream infection	Klebsiella pneumoniae	NA	19	51	28d mortality	47.4	27.5
Sánchez-Romero	2011	Spain	Europe	High income	mixed	Klebsiella pneumoniae	VIM-producing	28	55	14d mortality	46.4	30.9
Schwaber	2008	Israel	Asia	High income	mixed	Klebsiella pneumoniae	NA	48	56	in-hospital mortality	44	12.5

Shilo	2013	Israel	Asia	High income	urinary tract infection	Klebsiella pneumoniae	NA	135	127	in-hospital mortality	29	25
Simkins	2014	USA	America	High income	mixed	Klebsiella pneumoniae	NA	13	39	in-hospital mortality	46	8
Tian	2016	China	Asia	Upper middle income	bloodstream infection	Klebsiella pneumoniae	NA	33	81	in-hospital mortality	42.4	19.8
										mortality attributable to infection	42.4	24.6
										28d mortality	33.3	18.5
Torres-Gonzalez	2016	Mexico	America	Upper middle income	mixed	Mixed Enterobacteriaceae	OXA-producing	27	108	mortality attributable to infection	11.1	7.4
Trecarichi	2016	Italy	Europe	High income	bloodstream infection	Klebsiella pneumoniae	NA	161	117	21d mortality	52.2	14.5
Ulu	2015	Turkey	Asia	Upper middle income	mixed	Klebsiella pneumoniae	NA	47	51	mortality in ICU	44.7	51
Vardakas	2015	Greece	Europe	High income	mixed	Klebsiella pneumoniae	NA	80	24	mortality in ICU	72.5	58.3
Wang	2018	China	Asia	Upper middle income	mixed	Klebsiella pneumoniae	NA	48	48	in-hospital mortality	47.9	4.2
Xiao	2018	China	Asia	Upper middle income	bloodstream infection	Klebsiella pneumoniae	NA	135	293	30d mortality	58.5	15.4

Zhang	2018	China	Asia	Upper middle income	bloodstream infection	Klebsiella pneumoniae	NA	54	84	in-hospital mortality	18.5	8.3
										7d mortality	16.7	1.2
										28d mortality	18.5	2.4
Zheng	2018	China	Asia	Upper middle income	bloodstream infection	Klebsiella pneumoniae	NA	59	230	28d mortality	54.2	19.6
Zheng	2020	China	Asia	Upper middle income	neurosurgical infection	Mixed Enterobacteriaceae	NA	26	107	mortality attributable to infection	69.2	12.1
Zuo	2020	China	Asia	Upper middle income	pneumonia	Klebsiella pneumoniae	NA	74	74	in-hospital mortality	35.1	20.3
										mortality attributable to infection	25.7	9.5
Villegas	2016	7 countries in Latin America	America	Upper middle income	bloodstream infection	Mixed Enterobacteriaceae	NA	53	202	in-hospital mortality	64	30
										mortality attributable to infection	85	43
Stewardson	2019	10 countries	Asia, Africa, America	low and middle income countries	bloodstream infection	Mixed Enterobacteriaceae	NA	123	174	in-hospital mortality	35	20

OXA,oxacillinase; KPC, Klebsiella pneumoniae carbapenemase; VIM, Verona integron-encoded MBL; NA, Not Applicable i.e. include non-carbapenemase-producing strains or not focusing on a particular type of carbapenemase-producing strains

Appendix 4. Risk of bias assessed with the Newcastle-Ottawa Assessment Scale.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. In this version of NOS, we define the exposure as carbapenem resistance and the outcome as death in hospital and the target population is patients infected with *Enterobacteriaceae*.

Selection: (Maximum 4 stars)

1) Representativeness of the exposed cohort
   a) truly representative of the average carbapenem resistance in patients infected with *Enterobacteriaceae*. ✸
   b) somewhat representative of the average carbapenem resistance in patients infected with *Enterobacteriaceae* ✸
   c) selected group of users (e.g. organ transplant recipients, onco-hematological patients)
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (e.g. medical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes ✵

b) no

Comparability: (Maximum 2 stars)

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for age✵

b) study controls for comorbidity✵

Outcome: (Maximum 3 stars)

1) Assessment of outcome

a) independent blind assessment ✵

b) record linkage ✵

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (adequate if >14 days) ✵

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for ✵

b) subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % follow up, or description provided of those lost ✵

c) follow up rate < 80% and no description of those lost

d) no statement

First Author	Year	selection(1)	selection(2)	selection(3)	selection(4)	comparability(1)	outcome(1)	outcome(2)	outcome(3)	Total score	Risk of bias
Alicino	2015	1	1	1	1	0	1	1	1	7	Low
Balkhair	2019	1	1	1	1	0	1	1	1	7	Low
Ben-David	2012	1	1	1	1	1	1	1	1	8	Low
Brizendine	2015	0	1	1	1	1	1	1	1	7	Low
Chang	2019	1	1	1	1	0	1	1	1	7	Low
Chang	2011	1	1	1	1	1	1	1	1	8	Low
Chiotos	2018	0	1	1	1	1	1	1	1	7	Low
Cienfuegos-Gallet	2019	1	1	1	1	1	1	1	1	8	Low
Correa	2013	1	1	1	1	1	1	1	1	8	Low
Cubero	2015	1	1	1	1	0	1	1	1	7	Low
Daikos	2009	1	1	1	1	0	1	0	1	6	Moderate
Fraenkel-Wandel	2016	1	1	1	1	1	1	1	1	8	Low
Gallagher	2014	1	1	1	1	0	1	1	1	7	Low
Garbati	2016	1	1	1	1	0	1	1	1	7	Low
Gomez Rueda	2014	1	1	1	1	0	1	1	1	7	Low
Hoxha	2016	1	1	1	1	1	1	1	0	7	Low
Huang	2018	1	1	1	1	2	1	1	1	9	Low
Hussein	2013	1	1	1	1	1	1	1	1	8	Low
Kotb	2020	1	1	1	1	0	1	1	1	7	Low
Lee	2016	1	1	1	1	1	1	1	1	8	Low
Li	2019	0	1	1	1	1	1	1	1	7	Low
Liu	2019	0	1	1	1	1	1	1	1	7	Low

Liu	2012	1	1	1	1	1	1	1	1	8	Low
Mclaughlin	2014	1	1	1	1	1	1	1	1	8	Low
Meng	2017	1	1	1	1	1	1	1	1	8	Low
Mouloudi	2010	0	1	1	1	1	1	1	1	7	Low
Ny	2015	1	1	1	1	1	1	1	1	8	Low
Orsi	2013	1	1	1	1	1	1	1	1	8	Low
Pan	2019	1	1	1	1	1	1	1	1	8	Low
Patel	2008	1	1	1	1	1	1	1	1	8	Low
Pereira	2015	0	1	1	1	1	1	1	1	7	Low
Pouch	2015	0	1	1	1	1	1	1	1	7	Low
Qureshi	2012	1	1	1	1	0	1	1	1	7	Low
Sánchez-Romero	2011	1	1	1	1	0	1	0	1	6	Moderate
Schwaber	2008	1	1	1	1	0	1	1	1	7	Low
Shilo	2013	1	1	1	1	1	1	1	1	8	Low
Simkins	2014	0	1	1	1	1	1	1	1	7	Low
Tian	2016	1	1	1	1	1	1	1	1	8	Low
Torres-Gonzalez	2016	1	1	1	1	0	1	1	1	7	Low
Trecarichi	2016	0	1	1	1	0	1	1	1	6	Moderate
Ulu	2015	0	1	1	1	1	1	1	1	7	Low
Vardakas	2015	0	1	1	1	1	1	1	1	7	Low
Wang	2018	1	1	1	1	1	1	1	1	8	Low
Xiao	2018	1	1	1	1	1	1	1	1	8	Low
Zhang, Y.	2018	0	1	1	1	0	1	1	1	6	Mod
Zheng, Si-Han	2018	1	1	1	1	1	1	1	1	8	Low
Zheng,Guanghui	2020	0	1	1	1	1	1	1	1	7	Low

Zuo	2020	1	1	1	1	1	1	1	1	8	Low
Villegas	2016	1	1	1	1	1	1	1	1	8	Low
Stewardson	2019	1	1	1	1	2	1	1	1	9	Low

Appendix 5. The results from stratified analysis and meta-regression for different mortality outcome type

Table S2 Subgroup analysis of the effect of carbapenem resistance on in-hospital mortality for patients infected with Enterobacteriaceae

Sub-groups	No. of studies	No. of CRE patients	No. of CSE patients	unweighted means of mortality among CRE patients	unweighted means of mortality among CSE patients	RR(95%CI)	*P* value (significance tests of RR=1)	I^2(%)	*P* value between groups	RD(95%CI)	*P* value (significance tests of RD=0)	I^2(%)	*P* value beteen groups
Pathogens													
Klebsiella pneumoniae	24	1340	3072	43.10%	20.26%	2.12(1.77, 2.53)	0.000	57.4		0.22(0.16, 0.28)	0.000	72.3	
Mixed Enterobacteriaceae pathogens	5	262	551	34.16%	16.58%	2.01(1.62, 2.49)	0.000	0.0	**0.161**	0.17(0.06, 0.29)	0.003	65.8	**0.591**
Escherichia. coli	2	66	130	53.06%	25.50%	3.83(0.46, 31.78)	0.214	76.2		0.27(-0.06, 0.59)	0.115	88.6	
Geographical region													
America	11	414	840	40.43%	19.30%	1.97(1.60, 2.43)	0.000	22.2		0.20(0.14, 0.27)	0.000	28.2	
Europe	3	93	74	47.30%	26.67%	1.58(1.06, 2.38)	0.026	0.0	**0.781**	0.19(0.05, 0.33)	0.009	0.0	**0.832**
Asia	16	1038	2665	43.11%	19.23%	2.28(1.81, 2.85)	0.000	65.4		0.23(0.15, 0.31)	0.000	82.7	
Economic status													
High income	17	732	1110	39.45%	19.21%	1.94(1.57, 2.40)	0.000	42.5		0.19(0.13, 0.26)	0.000	57.8	
Upper middle income	13	813	2469	46.59%	21.04%	2.29(1.85, 2.82)	0.000	55.2	**0.494**	0.25(0.16, 0.34)	0.000	81.8	**0.263**
Infection type													
Bloodstream infections	12	556	1278	54.42%	27.73%	2.01(1.68, 2.41)	0.000	50.7	**0.323**	0.26(0.19, 0.34)	0.000	61.7	**0.355**

Urinary tract infection	3	177	271	25.67%	12.33%	2.40(0.82, 7.03)	0.110	72.5		0.11(0.00, 0.21)	0.044	29.7	
Pneumonia	1	74	74	35.10%	20.30%	1.73(1.00, 3.00)	0.049	NA		0.15(0.01, 0.29)	0.040	NA	
Mixed	15	861	2130	36.41%	15.34%	2.34(1.83, 2.97)	0.000	40.8		0.20(0.13, 0.28)	0.000	74.7	
Resistance type													
KPC-producing Enterobacteriaceae	6	264	478	55.30%	27.13%	2.13(1.56, 2.89)	0.000	58.7		0.30(0.20, 0.40)	0.000	46.2	
OXA-producing Enterobacteriaceae include non-carbapenemase-producing strains or multiple resistance types	1	20	9	35.00%	11.10%	3.15(0.45, 21.96)	0.247	NA	**0.716**	0.24(-0.05, 0.53)	0.110	NA	**0.450**
	24	1384	3266	39.36%	18.59%	2.08(1.75, 2.47)	0.000	51.5		0.20(0.14, 0.25)	0.000	69.8	
Sample size													
<100	14	387	588	42.33%	20.34%	1.96(1.52, 2.53)	0.000	30.6		0.21(0.13, 0.30)	0.000	58.3	
100-200	11	589	959	41.13%	18.07%	2.26(1.80, 2.84)	0.000	41.7	**0.641**	0.23(0.15, 0.30)	0.000	64.8	**0.974**
>200	6	692	2206	44.39%	22.76%	2.02(1.49, 2.72)	0.000	78.4		0.21(0.09, 0.32)	0.000	85.5	
Range of publication year													
2008-2010	3	184	177	53.33%	24.50%	2.28(1.57, 3.31)	0.000	24.7		0.29(0.20, 0.38)	0.000	0.0	
2011-2013	6	275	379	56.84%	32.40%	1.71(1.29, 2.28)	0.000	54.7	**0.278**	0.24(0.08, 0.41)	0.004	79.3	**0.658**
2014-2016	14	482	1022	37.92%	18.47%	1.86(1.57, 2.20)	0.000	11.5		0.18(0.12, 0.24)	0.000	35.1	
2017-2020	8	727	2175	34.93%	11.69%	2.74(2.00, 3.75)	0.000	60.0		0.22(0.12, 0.32)	0.000	86.1	
Total	**31**	1668	3753	42.30%	20.00%	2.09(1.81, 2.42)	0.000	49.8		**0.22(0.17, 0.26)**	0.000	**71.0**	

OXA,oxacillinase; KPC, Klebsiella pneumoniae carbapenemase

Table S3 Subgroup analysis of the effect of carbapenem resistance on 28d or 30d mortality for patients infected with Enterobacteriaceae

Sub-groups	No. of studies	No. of CRE patients	No. of CSE patients	unweighted means of mortality among CRE patients	unweighted means of mortality among CSE patients	RR(95%CI)	*P* value (significance tests of RR=1)	I^2(%)	*P* value between groups	RD(95%CI)	*P* value (significance tests of RD=0)	I^2(%)	*P* value beteen groups
Pathogens													
Klebsiella pneumoniae	14	1076	2248	44.60%	19.14%	2.34(1.90, 2.88)	0.000	65.9	**0.761**	0.25(0.18, 0.32)	0.000	76.9	**0.124**
Mixed Enterobacteriacea e pathogens	2	68	181	16.75%	11.50%	1.78(0.57, 5.60)	0.321	34.3		0.05(-0.03, 0.13)	0.213	0.0	
Escherichia. coli	1	17	34	70.59%	47.06%	1.50(0.94, 2.40)	0.091	NA		0.24(-0.04, 0.51)	0.092	NA	
Geographical region													
America	3	99	484	28.85%	14.94%	2.00(1.37, 2.92)	0.000	0.0	**0.927**	0.12(-0.00, 0.23)	0.055	50.1	**0.441**
Europe	2	398	211	48.55%	21.75%	2.04(1.07, 3.90)	0.030	73.6		0.26(-0.02, 0.53)	0.068	87.5	
Asia	12	664	1768	45.40%	20.81%	2.31(1.81, 2.94)	0.000	68.4		0.25(0.16, 0.34)	0.000	77.0	
Economic status													
High income	7	657	962	40.79%	21.04%	1.92(1.46, 2.52)	0.000	57.6	**0.427**	0.19(0.08, 0.30)	0.001	80.6	**0.414**
Upper middle income	10	504	1501	44.29%	19.07%	2.48(1.92, 3.20)	0.000	58.9		0.25(0.16, 0.35)	0.000	75.7	
Infection type													
Bloodstream infections	12	929	1812	48.59%	22.31%	2.29(1.81, 2.90)	0.000	72.0	**0.746**	0.26(0.18, 0.34)	0.000	73.2	**0.108**
Mixed	5	232	651	29.07%	14.06%	2.05(1.50, 2.81)	0.000	4.2		0.14(0.02, 0.26)	0.019	74.5	

Resistance type													
KPC-producing Enterobacteriacea e include non-carbapenema se-producing strains or multiple resistance types	2	115	421	25.42%	13.64%	1.89(1.27, 2.82)	0.002	0.0	**0.428**	0.11(0.01, 0.21)	0.030	22.9	**0.211**
	15	1046	2042	45.17%	20.72%	2.29(1.84, 2.84)	0.000	67.2		0.24(0.16, 0.32)	0.000	79.5	
Sample size													
<100	6	167	290	52.17%	27.01%	1.97(1.45, 2.67)	0.000	33.6		0.25(0.14, 0.37)	0.000	41.3	
100-200	4	184	441	19.12%	8.42%	2.30(1.25, 4.24)	0.008	34.6	**0.207**	0.09(0.04, 0.15)	0.001	3.7	**0.088**
>200	7	810	1732	48.42%	20.33%	2.39(1.80, 3.18)	0.000	80.1		0.28(0.17, 0.39)	0.000	83.5	
Range of publication year													
2011-2013	4	164	329	53.42%	33.39%	1.56(1.25, 1.94)	0.000	0.0		0.17(0.08, 0.26)	0.000	0.0	
2014-2016	4	468	349	39.35%	20.90%	1.79(1.28, 2.49)	0.001	32.6	**0.060**	0.18(0.05, 0.32)	0.009	67.9	**0.568**
2017-2020	9	529	1785	39.70%	13.43%	2.91(2.41, 3.51)	0.000	29.1		0.26(0.14, 0.37)	0.000	88.0	
Total	**17**	1161	2463	42.85%	19.88%	**2.23(1.83, 2.72)**	**0.000**	**63.6**		**0.23(0.15, 0.30)**	**0.000**	**79.1**	

KPC, Klebsiella pneumoniae carbapenemase

Table S4 Subgroup analysis of the effect of carbapenem resistance on mortality attributable to infection for patients infected with Enterobacteriaceae

Sub-groups	No. of studies	No. of CRE patients	No. of CSE patients	unweighted means of mortality among CRE patients	unweighted means of mortality among CSE patients	RR(95%CI)	*P* value (significance tests of RR=1)	I^2(%)	*P* value between groups	RD(95%CI)	*P* value (significance tests of RD=0)	I^2(%)	*P* value beteen groups
Pathogens													
Klebsiella pneumoniae	5	285	361	36.22%	15.42%	2.81(2.06, 3.82)	0.000	0.0		0.23(0.16, 0.29)	0.000	0.0	
Mixed									**0.739**				**0.388**
Enterobacteriaceae pathogens	3	106	417	55.10%	20.83%	2.72(1.17, 6.32)	0.020	84.6		0.34(0.02, 0.65)	0.036	93.3	
Geographical region													
America	3	179	409	44.70%	20.80%	2.27(1.41, 3.68)	0.001	52.4		0.24(0.03, 0.46)	0.026	89.5	
Europe	1	37	22	27.00%	14.00%	1.98(0.61, 6.43)	0.255	NA	**0.484**	0.13(-0.07, 0.34)	0.195	NA	**0.641**
Asia	4	175	347	46.33%	15.80%	3.32(2.22, 4.97)	0.000	38.8		0.32(0.14, 0.49)	0.000	77.4	
Economic status													
High income	3	178	206	37.67%	14.33%	2.99(2.01, 4.43)	0.000	0.0		0.26(0.17, 0.34)	0.000	0.0	
Upper middle income	5	213	572	46.68%	19.32%	2.68(1.66, 4.32)	0.000	70.4	**0.932**	0.28(0.10, 0.47)	0.002	87.7	**0.725**
Infection type													
Bloodstream infections	4	165	390	50.60%	24.65%	2.08(1.75, 2.48)	0.000	0.0		0.30(0.18, 0.42)	0.000	53.4	
Pneumonia	1	74	74	25.70%	9.50%	2.71(1.21, 6.07)	0.015	NA	**0.075**	0.16(0.04, 0.28)	0.008	NA	**0.203**
Neurosurgical infection	1	26	107	69.20%	12.10%	5.70(3.22, 10.08)	0.000	NA		0.57(0.38, 0.76)	0.000	NA	

Mixed	2	126	207	24.55%	9.70%	2.75(1.32, 5.71)	0.007	27.2		0.16(-0.08, 0.40)	0.200	87.2	
Resistance type													
KPC-producing Enterobacteriaceae	2	79	107	37.50%	15.50%	2.69(1.61, 4.51)	0.000	0.0		0.23(0.06, 0.41)	0.010	43.8	
OXA-producing Enterobacteriaceae	1	27	108	11.10%	7.40%	1.50(0.43, 5.28)	0.528	NA		0.04(-0.09, 0.17)	0.572	NA	
include non-carbapenemase-producing strains or multiple resistance types	5	285	563	52.06%	20.24%	2.96(1.87, 4.70)	0.000	75.4	**0.488**	0.33(0.20, 0.46)	0.000	76.9	**0.277**
Sample size													
<100	1	37	22	27.00%	14.00%	1.98(0.61, 6.43)	0.255	NA		0.13(-0.07, 0.34)	0.195	NA	
100-200	6	301	554	39.07%	13.77%	3.21(2.35, 4.39)	0.000	22.0	**0.641**	0.26(0.13, 0.39)	0.000	80.0	**0.566**
>200	1	53	202	85.00%	43.00%	1.97(1.62, 2.40)	0.000	NA		0.42(0.30, 0.54)	0.000	NA	
Range of publication year													
2008-2010	2	136	121	32.50%	13.00%	3.07(1.79, 5.28)	0.000	0.0		0.23(0.10, 0.36)	0.000	27.2	
2011-2013	1	42	85	48.00%	17.00%	2.89(1.63, 5.13)	0.000	NA		0.31(0.14, 0.48)	0.000	NA	
2014-2016	3	113	391	46.17%	25.00%	2.00(1.66, 2.40)	0.000	0.0	**0.380**	0.24(-0.02, 0.49)	0.067	89.5	**0.849**
2017-2020	2	100	181	47.45%	10.80%	4.14(1.94, 8.82)	0.000	58.4		0.36(-0.05, 0.77)	0.082	92.5	
Total		391	778	43.30%	17.45%	**2.74(1.97, 3.81)**	**0.000**	**58.3**		**0.27(0.15, 0.38)**	**0.000**	**79.5**	

OXA,oxacillinase;KPC, Klebsiella pneumoniae carbapenemase

Table S5 Univariate meta-regression of the potential variables on risk difference of in-hospital mortality for patients with CRE versus CSE

Variables	Sub-categories	No. of studies	No. of CRE patients	No. of CSE patients	coefficient	standard error	95% confidence interval		*P* value from meta-regression
Pathogens	Klebsiella pneumoniae	24	1340	3072	-0.199	0.187	-0.583	0.184	0.296
	Mixed Enterobacteriaceae pathogens	5	262	551	-0.178	0.210	-0.608	0.252	0.404
	Escherichia. coli	2	66	130	reference	-	-	-	-
Geographical region	America	11	414	840	-0.025	0.105	-0.241	0.190	0.810
	Europe	3	93	74	-0.067	0.216	-0.510	0.375	0.757
	Asia	16	1038	2665					
Economic status	High income	17	732	1110	-0.068	0.097	-0.267	0.131	0.490
	Upper middle income	13	813	2469	reference	-	-	-	-
Infection type	Bloodstream infections	12	556	1278	0.228	0.195	-0.171	0.627	0.252
	Urinary tract infection	3	177	271	reference	-	-	-	-
	pneumonia	1	74	74	0.084	0.335	-0.604	0.771	0.805
	Mixed	15	861	2130	0.150	0.203	-0.267	0.567	0.468
Resistance type	KPC-producing Enterobacteriaceae	6	264	478	0.062	0.995	-1.977	2.100	0.951
	OXA-producing Enterobacteriaceae	1	20	9	reference	-	-	-	-
	include non-carbapenemase-producing strains or multiple resistance types	24	1384	3266	-0.007	0.992	-2.040	2.025	0.994
Sample size	<100	14	387	588	0.006	0.128	-0.255	0.268	0.962
	100-200	11	589	959	reference	-	-	-	-
	>200	6	692	2206	-0.029	0.109	-0.253	0.194	0.789
Range of publication year	2008-2010	3	184	177	0.042	0.183	-0.335	0.418	0.823
	2011-2013	6	275	379	0.031	0.131	-0.238	0.299	0.816
	2014-2016	14	482	1022	-0.005	0.117	-0.245	0.234	0.964
	2017-2020	8	727	2175	reference	-	-	-	-
Sample size	-	31	1668	3753	-0.00012	0.00013	-0.00039	0.00015	0.380
Year of publication	-	31	1668	3753	-0.005	0.015	-0.035	0.025	0.751

OXA,oxacillinase;KPC, Klebsiella pneumoniae carbapenemase

Table S6 Univariate meta-regression of the potential variables on risk difference of 28d or 30d mortality for patients with CRE versus CSE

Variables	Sub-groups	No. of studies	No. of CRE patients	No. of CSE patients	coefficient	standard error	95% confidence interval		*P* value from meta-regression
Pathogens	Klebsiella pneumoniae	14	1076	2248	reference	-	-	-	-
	Mixed Enterobacteriaceae pathogens	2	68	181	-0.228	0.385	-1.055	0.598	0.563
	Escherichia. coli	1	17	34	-0.047	0.247	-0.576	0.483	0.853
Geographical region	America	3	99	484	-0.129	0.204	-0.566	0.307	0.536
	Europe	2	398	211	-0.116	0.154	-0.447	0.215	0.464
	Asia	12	664	1768	reference	-	-	-	-
Economic status	High income	7	657	962	-0.066	0.110	-0.301	0.169	0.558
	Upper middle income	10	504	1501	reference	-	-	-	-
Infection type	Bloodstream infections	12	929	1812	reference	-	-	-	-
	Mixed	5	232	651	-0.095	0.165	-0.446	0.257	0.575
Resistance type	KPC-producing Enterobacteriaceae include non-carbapenemase-producing strains or multiple resistance types	2	115	421	-0.150	0.210	-0.599	0.298	0.486
		15	1046	2042	reference	-	-	-	-
Sample size	<100	6	167	290	-0.030	0.141	-0.332	0.272	0.833
	100-200	4	184	441	-0.179	0.236	-0.686	0.327	0.460
	>200	7	810	1732	reference	-	-	-	-
Range of publication year	2011-2013	4	164	329	-0.168	0.134	-0.455	0.119	0.229
	2014-2016	4	468	349	-0.182	0.144	-0.491	0.128	0.228
	2017-2020	9	529	1785	reference	-	-	-	-
Sample size	-	17	1161	2463	0.00009	0.00039	-0.00075	0.00092	0.827
Year of publication	-	17	1161	2463	0.027	0.020	-0.017	0.070	0.207

KPC, Klebsiella pneumoniae carbapenemase

Table S7 Univariate meta-regression of the potential variables on risk ratio of in-hospital mortality for patients with CRE versus CSE

Variables	Sub-categories	No. of studies	No. of CRE patients	No. of CSE patients	coefficient	standard error	95% confidence interval		*P* value from meta-regression
Pathogens	Klebsiella pneumoniae	24	1340	3072	-0.040	0.344	-0.744	0.664	0.908
	Mixed Enterobacteriaceae pathogens	5	262	551	-0.080	0.387	-0.872	0.713	0.838
	Escherichia. coli	2	66	130	reference	-	-	-	-
Geographical region	America	11	414	840	-0.108	0.173	-0.463	0.247	0.537
	Europe	3	93	74	-0.334	0.306	-0.962	0.293	0.284
	Asia	16	1038	2665					
Economic status	High income	17	732	1110	-0.165	0.156	-0.485	0.154	0.299
	Upper middle income	13	813	2469	reference	-	-	-	-
Infection type	Bloodstream infections	12	556	1278	0.194	0.308	-0.437	0.825	0.533
	Urinary tract infection	3	177	271	reference	-	-	-	-
	pneumonia	1	74	74	0.044	0.495	-0.972	1.061	0.929
	Mixed	15	861	2130	0.339	0.315	-0.307	0.985	0.291
Resistance type	KPC-producing Enterobacteriaceae	6	264	478	-0.394	1.108	-2.664	1.875	0.725
	OXA-producing Enterobacteriaceae	1	20	9	reference	-	-	-	-
	include non-carbapenemase-producing strains or multiple resistance types	24	1384	3266	-0.419	1.100	-2.672	1.835	0.707
Sample size	<100	14	387	588	-0.142	0.189	-0.529	0.246	0.460
	100-200	11	589	959	reference	-	-	-	-
	>200	6	692	2206	-0.119	0.187	-0.502	0.265	0.532
Range of publication year	2008-2010	3	184	177	-0.157	0.254	-0.677	0.364	0.541
	2011-2013	6	275	379	-0.447	0.192	-0.840	-0.054	0.027
	2014-2016	14	482	1022	-0.343	0.175	-0.702	0.017	0.061
	2017-2020	8	727	2175	reference	-	-	-	-
Sample size	-	31	1668	3753	0.00016	0.00023	-0.00031	0.00062	0.503
Year of publication	-	31	1668	3753	0.023	0.023	-0.024	0.070	0.316

OXA,oxacillinase;KPC, Klebsiella pneumoniae carbapenemase

Table S8 Univariate meta-regression of the potential variables on risk ratio of 28-30d mortality for patients with CRE versus CSE

Variables	Sub-groups	No. of studies	No. of CRE patients	No. of CSE patients	coefficient	standard error	95% confidence interval		*P* value from meta-regression
Pathogens	Klebsiella pneumoniae	14	1076	2248	reference	-	-	-	-
	Mixed Enterobacteriaceae pathogens	2	68	181	-0.370	0.464	-1.364	0.625	0.439
	Escherichia. coli	1	17	34	-0.443	0.388	-1.275	0.389	0.272
Geographical region	America	3	99	484	-0.125	0.313	-0.796	0.545	0.695
	Europe	2	398	211	-0.146	0.299	-0.787	0.495	0.633
	Asia	12	664	1768	reference	-	-	-	-
Economic status	High income	7	657	962	-0.262	0.189	-0.664	0.141	0.186
	Upper middle income	10	504	1501	reference	-	-	-	-
Infection type	Bloodstream infections	12	929	1812	reference	-	-	-	-
	Mixed	5	232	651	-0.117	0.244	-0.636	0.402	0.637
Resistance type	KPC-producing Enterobacteriaceae	2	115	421	-0.209	0.316	-0.882	0.465	0.519
	include non-carbapenemase-producing strains or multiple resistance types	15	1046	2042	reference	-	-	-	-
Sample size	<100	6	167	290	-0.191	0.224	-0.672	0.290	0.408
	100-200	4	184	441	-0.064	0.322	-0.754	0.625	0.845
	>200	7	810	1732	reference	-	-	-	-
Range of publication year	2011-2013	4	164	329	-0.621	0.149	-0.939	-0.302	0.001
	2014-2016	4	468	349	-0.514	0.160	-0.856	-0.171	0.006
	2017-2020	9	529	1785	reference	-	-	-	-
Sample size	-	17	1161	2463	0.00039	0.00067	-0.00104	0.00182	0.572
Year of publication	-	17	1161	2463	0.093	0.025	0.038	0.147	0.002

KPC, Klebsiella pneumoniae carbapenemase

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table 1, Table S1 in Supplementary Material Appendix 3

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11, Supplementary Material Appendix 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14, Figure 2, Figure 3, Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14, Figure 2, Figure 3, Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	17, Figure 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-17
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22-23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24