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Major Article

Association between carbapenem-resistant Enterobacteriaceae and death: A systematic review and meta-analysis

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Key Words:
CRE
Antibacterial resistance
Mortality
Multiple drug resistance
MDR

Background: Carbapenem-resistant Enterobacteriaceae (CRE) has emerged in health care facilities around the world. Several studies demonstrated data regarding clinical outcomes for CRE infections including death. This systematic review and meta-analysis summarized literature discussing association between CRE and mortality.

Methods: A systematic literature review was performed by searching EMBASE, International Pharmaceutical Abstract databases, PubMed, and Scopus and to identify studies that assessed the association between CRE and death published from April 2012 to October 2017. A meta-analysis was performed using a random effect model. Heterogeneity was assessed using the I^2-statistic.

Results: Twenty-one studies were included in this meta-analysis. The underlying populations were moderately heterogeneous ($I^2 = 60\%$; $P = .01$). Pooled risk estimates from 9 studies revealed a significant association between CRE and death (pooled-adjusted odds ratio: 2.85; 95% confidence interval: 1.88, 4.30). The unadjusted variable pooled from 18 studies demonstrated a significant association between CRE and death (pooled-unadjusted odds ratio: 3.73; 95% confidence interval: 2.02, 6.88).

Discussion: The finding that CRE infection was positively associated with death agreed with the previous meta-analysis of studies published before April 2012.

Conclusions: This meta-analysis found that CRE was associated with increased risk of death. Our analysis implies a need for strict infection control measures.

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Enterobacteriaceae are ubiquitous and found worldwide in various environmental sources such as soil, water, vegetation, and animals. Enterobacteriaceae family currently represents a huge public health concern (eg, *Salmonella enterica* serotype Typhi, *Shigella* spp, *Escherichia coli*).[1] The treatment for Enterobacteriaceae infection includes the β-lactam group of antibiotics such as cephalosporins and carbapenems. However, the bacteria have become resistant to several antibacterial medications. Carbapenem-resistant Enterobacteriaceae (CRE) is a well-recognized problem. In the United States, CRE detection rate in 2012 has been confirmed in 48 states with a 5-fold increase from 2008.[2] The New York and New Jersey area is an epicenter for CRE. Data from 8 New York and New Jersey medical centers showed that the prevalence of carbapenem resistance among Enterobacteriaceae bloodstream isolates, *Klebsiella pneumoniae, Enterobacter* spp, and *E coli* bacteremia were 9.7%, 2.2%, and 0.1%, respectively.[3]

Several studies have shown the data on clinical consequences of CRE infections. A meta-analysis study, which evaluated the number of deaths attributable to CRE using studies published before April 2012, showed that mortality among CRE-infected patients was higher than the mortality among carbapenem-susceptible Enterobacteriaceae (CSE) infected counterparts.[4] Since 2012, studies still reported and showed that CRE infection was associated with a higher risk of mortality.[5-7] However, 2 studies reported that a 30-day mortality of patients infected with CRE and CSE were not significantly different.[8-9] Therefore, to update the prevalence and mortality data regarding CRE after April 2012, we attempted to investigate the association between CRE and mortality among hospitalized patients using studies published internationally between April 2012 and October 2017.

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METHODS

Search strategy

Search terms were developed by the first author (S.S.) and revised by the last author (N.L.). A systematic literature search was performed by the first author using EMBASE, International Pharmaceutical Abstract databases, MEDLINE/PubMed, and Scopus from April 2012 to October 2017 using the terms "carbapenem" AND "resist" AND ("mortality" OR "prevalence") without applying restrictions. The MEDLINE database was searched through PubMed by using Medical Subject Headings and Text Words. EMBASE was searched using Emtree terms and synonyms. The full search strategies are provided in the Supplementary Material. Potential pertinent studies were also searched for references of review articles, letters, and relevant excluded studies.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they were (1) human studies, and (2) studies that defined CRE according to the 2015 Centers for Disease Control and Prevention definition that are Enterobacteriaceae that resist imipenem, meropenem, doripenem, or ertapenem. Studies were excluded if they were (1) not observational or experimental studies, for example, review articles, case reports, or case series; (2) studies whose risk ratios (ie, odds ratio [OR], relative risk, and hazard ratio [HR]) were not able to be calculated or reported; and (3) studies that explicitly indicated mortality as an outcome. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis diagram of the systematic literature search and review process is shown in Figure 1.

Data extraction

A citation manager (EndNote X8, Thomson Reuters, New York, NY) was used to manage the retrieved articles and remove redundant articles. Titles and abstracts of the nonredundant articles were reviewed by both authors. For non-English articles, English abstracts and result sections in full texts were used to determine if any further translation would be necessary. Information on study design, location, patient demographics, CRE definition, CRE prevalence, mortality, and potential confounders were independently extracted. The number of patients provided in studies were used to calculate OR and their corresponding 95% confidence interval (CI) using the formula:

$$95\%\mathrm{CI} = \exp(\ln(\mathrm{OR}) - 1.96 \times \mathrm{SE}\{\ln(\mathrm{OR})\}) \text{to} \exp(\ln(\mathrm{OR}) + 1.96 \times \mathrm{SE}\{\ln(\mathrm{OR})\}).$$

In case of disagreement, is was resolved by consultation and consensus. Corresponding authors of selected articles were contacted when information was not provided or able to be accessed.

Assessment of study quality

Study quality was independently evaluated using the Newcastle-Ottawa Scale (NOS) for quality assessment. Disagreement was also resolved by consultation and consensus.

Statistical methods

Random effects models with inverse variance weighting were created using Review Manager (RevMan 5.3, The Nordic Cochrane Center, Copenhagen, Denmark). Q-statistic and I^2 statistic were used to assess the heterogeneity of the underlying population. I^2 of <25% was

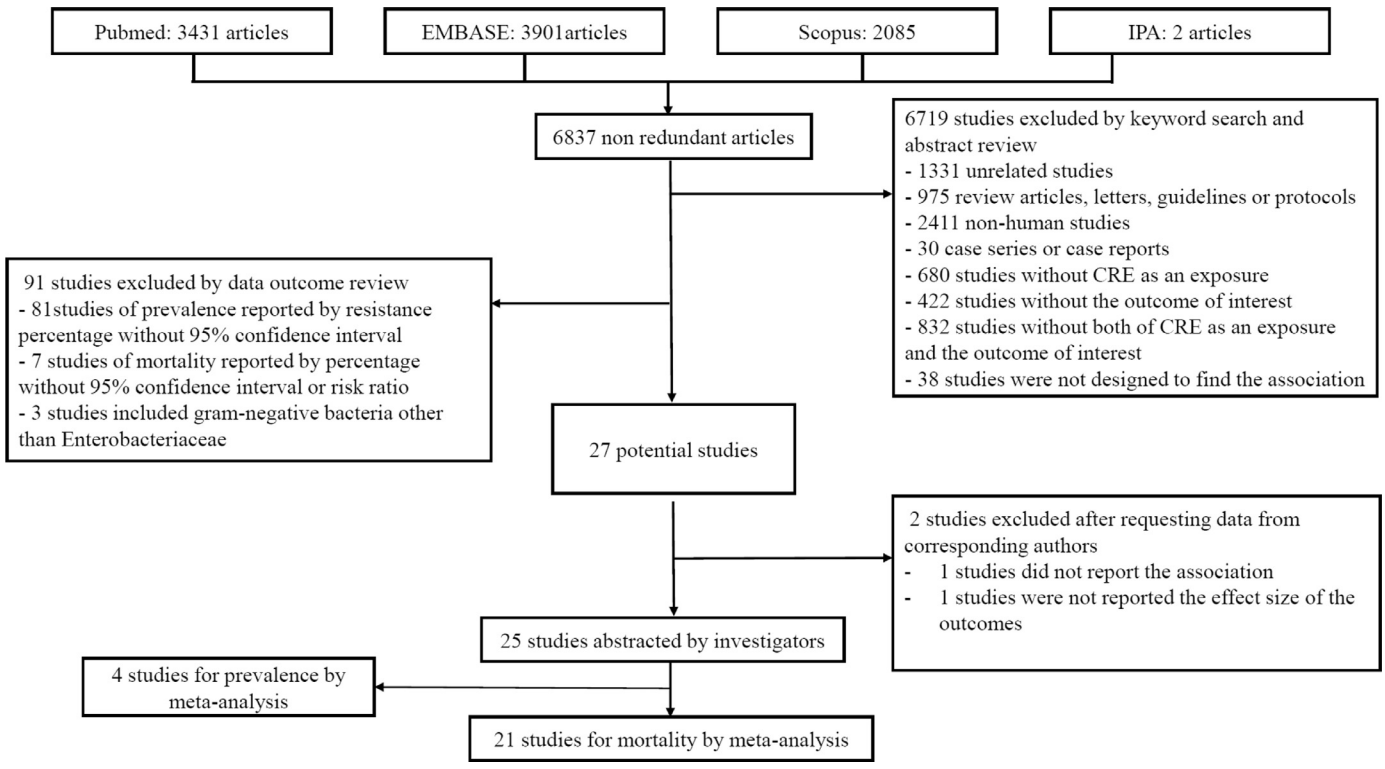

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis diagram for systematic review of the association between CRE and death. *CRE*, carbapenem-resistant Enterobacteriaceae; *IPA*, International Pharmaceutical Abstract databases.

negligible heterogeneity, whereas I^2 values >75% were heterogeneous.[10] Visual evaluation of a funnel plot was used to assess the publication bias.

RESULTS

Study characteristics

The systematic literature search retrieved 6,837 nonredundant articles. According to the inclusion and exclusion criteria, 21 articles were selected. All of them were cohort studies; 9 of which were retrospective and 2 of which were prospective (Fig 1). A description of the included studies is provided in Table 1. Of the 21 studies,[10-31] 12 of them were conducted in countries with Caucasian as a major population, for example, the United States and Europe (Table 1). Seventeen studies reported the mean age of patients ranging from age 50-79 years. There were 3 studies involving the pediatric population. All studies were conducted in hospitals. Among these 18 studies, 9 studies reported adjusted risk ratio and 18 studies reported unadjusted risk ratio. The NOS assessment of study quality is summarized in Table 2. According to the NOS quality assessment, 17 studies had medium quality (score 4-6 out of 9), and 4 had high quality (score 7-9 out of 9). Most of them had inadequate time for follow-up.

Publication bias was assessed by a funnel plot of the adjusted association between CRE and mortality. Adjusted OR from 9 studies were used to calculate the funnel plot as shown in Figure 2. The standard error of log OR were distributed heavily at the right top, implying that larger studies showing a negative association between CRE infection and mortality and smaller studies may not have been published. Asymmetry in the funnel plot indicated a potential for publication bias.

CRE and risk of mortality

The pooled risk ratio calculated from combined HR and OR from the included studies showed the association between CRE infection and death. In the unadjusted analysis, CRE increased the risk of mortality by 273% (OR: 3.73; 95% CI: 2.02, 6.88) (Fig 3). After adjusting the effect of known confounders, for example age, the association between CRE infection and mortality rate decreased (adjusted OR: 2.85 [95% CI: 1.88-4.30]) (Fig 4). Moderate heterogeneity was detected among the 9 included studies ($I^2 = 60\%$; $P = .01$). Post hoc analyses using either only HR or OR were not performed because of the limited sample size.

CRE and prevalence

The prevalence of CRE was meta-analyzed using data with 95% CI from four studies which involved 2,823 isolates from patients in acute care settings.[32-35] Three studies were conducted in Europe. Two of the 4 studies included CRE carriers or CRE colonization that were defined by the detection of CRE isolates from rectal or perianal swab samples. This meta-analysis found that CRE prevalence was 3.06% (95% CI: 1.65-4.47). Heterogeneity was detected among these studies ($I^2 = 98\%$; $P < .0001$).

DISCUSSION

Enterobacteriaceae are a family of bacteria including *Klebsiella* spp and *E coli*. CRE are Enterobacteriaceae that are resistant to carbapenem, whereas CSE are Enterobacteriaceae bacteria that are susceptible to carbapenem. Several studies have attempted to find an association between CRE infection and death. In this systematic review and meta-analysis of 21 studies, we found that CRE exposure was associated with a higher mortality rate. In those studies, 19 studies were CRE infections, 14 studies mainly defined Enterobacteriaceae as *K pneumoniae*, and 5 studies defined infection as septicemia as cause of infection. CRE-infected patients had an adjusted risk of deaths higher than CSE-infected patients (pooled risk ratio: 2.85 [95% CI: 1.88-4.30]). The finding that CRE was positively associated with risk of death was similar to a finding from the previous meta-analysis conducted in 2014,[4] in which the majority of studies (7 out of 8) included patients who also had septicemia caused by *K pneumoniae*. They reported that CRE infection doubled the unadjusted risk of death.

According to the NOS, studies included in our analysis were of moderate to high quality. The included studies contained minimal selection bias but had inadequate follow-up duration and incomparable cohort. Other potential biases were also identified. First, the difference in the definition of CRE exposure among the studies may influence the mortality outcome. Alicino et al,[11] Biehle et al,[12] Hussein et al,[20] Tamma et al,[28] and Trecarichi et al,[30] defined CRE exposure as bloodstream CRE infection, whereas Dautzenberg et al[17] and Jaiswal et al[21] defined CRE as a colonization of CRE in patients. Second, differences in the underlying population was also an issue. For example, the patients in studies from Jaiswal et al[21] and Trecarichi et al[30] were varied by hematologic malignancies, comorbidity, and severity status of the patients in the included studies (Table 1). The age of study populations was also diverse. In the studies by Chiotos et al,[15] Jaiswal et al,[21] and Meng et al[24] children were also included, whereas the other studies only included adults. Many other factors such as differences in the number and severity of underlying concurrent conditions or intensive care unit admission could have caused higher mortality among CRE-infected patients. Third, differences in the site of infection could be the source of bias. Bloodstream infections due to CRE are more common in patients with severe comorbidities and are associated with high hospital mortality rates.[36] Therefore, our meta-analysis, which contained 5 studies with bacteremia patients, might overestimate the association between CRE exposure and death. In addition, different species of bacteria within Enterobacteriaceae, that is *Escherichia, Klebsiella, Enterobacter, Proteus, Providencia*, and *Serratia*, have a different level of virulence[37,38] and may have affected the severity of the infection, thus affecting the mortality rate among patients. The difference in the species of Enterobacteriaceae may have also caused the heterogeneity among studies. Finally, multiple studies that could have been included were excluded because they did not report the number of patients for risk ratio calculation or calculated risk ratios although they mentioned a significant relationship between CRE exposure and death[18,39-41] and vice versa.[42-44] Had those studies reported the calculated risk ratios, the findings from this meta-analysis may have been different.

The Centers for Disease Control and Prevention modified its surveillance definition for CRE to the current definition that defined CRE in January 2015 as Enterobacteriaceae that resist imipenem, meropenem, doripenem, ertapenem, or Enterobacteriaceae that possess a carbapenemase.[45] Phenotypic definition of CRE requires that the bacteria must resist carbapenem antibiotics, for example meropenem. Moreover, CRE have high levels of resistance to other antibiotics including extended-spectrum cephalosporin-resistant.[45] The current standard treatment of CRE infection is the combination of antimicrobials such as colistin, tigecycline, or fosfomycin.[46] The data regarding CRE infection treatment regimen of studies in this meta-analysis were not able to be retrieved. It was possible that the included studies used older regimens that were not effective for the treatment and might not truly represent the true mortality rate of the CRE-infected patients.

Our secondary objective of this meta-analysis study was to study the prevalence of CRE. The meta-analysis of prevalence from 4 studies[32-35] that published during April 2012 and October 2017 showed that pooled prevalence was 3.06% (95% CI: 1.65-4.47). The prevalence

Table 1
Description of included studies

	Author	Study Design*	Study Population and Location	Country	Years of Study	Demographics	Definitions of CRE	Definition of Outcomes	Confounder Adjusted	Risk Ratio (CI)
1	Alicino et al, 2015[11]	Retrospective, cohort	A 1,300-bed tertiary adult acute care teaching hospital	Genoa, Italy	2007–2014	Patients, BSI **CRKP-positive** n = 349 Median age: 68 y (IQR 57-76) Sex: 62% male **CRKP-negative** n = 162 Age, Sex: No data	CRKP Lab: Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France), interpreted breakpoint was based on EUCAST criteria	Crude 30-day mortality		CRKP death (126/349), CSKP death (38/162)
2	Biehle et al, 2015[12]	Retrospective, cohort	An 880-bed tertiary care and university-affiliated hospital of Texas Medical Center and a 649-bed teaching hospital of Harvard Medical School	Texas, USA	2016–2012	Patients, BSI with *Klebsiella* spp n = 107 Mean age: 61.5 ± 15.4 y Sex: 53.3% male **Carbapenem non-susceptible group** No data in detail **Carbapenem- susceptible group** No data in detail	*Klebsiella* spp, *K pneumoniae* 93.5%, *K oxytoca* 6.5% Lab: Vitex 2 automated System, susceptible to imipenem/meropenem/doripenem if MIC <1mg/L, non-susceptible if MIC >1 mg/L	30-day all cause hospital mortality	-APACHE II at index culture -Hospital length of stay -Source of bacteremia -Comorbidities; eg, immunosuppression-organ transplantation, human immunodeficiency viral infection	aOR 9.08 (1.17-70.51) OR 9.96 (1.85-53.60)
3	Bleumin et al, 2012[13]	Prospective, cohort	A 1100-bed university medical center hospital	Jerusalem, Israel	2006–2009	Maintenance hemodialysis patients **CRKP-positive** n = 43 Age: 26% <65 y, 44% 65-75 y, and 30% >75 y Sex: 70% female **CRKP-negative** n = 150 Age: 40% <65 y, 32% 65-75 y, and 28% >75 y Sex: 36% female	CRKP colonized or infected after hemodialysis Lab: routine antibiotic susceptibilities determined by CLSI disk diffusion assay and interpreted using CLSI breakpoint	1-month all-cause mortality	- Age - Sex - Children - Diabetes - Vascular access - Hospitalized in 6 months - Antibiotic exposure - Time dialysis	aHR 5.9 (3.2-11) HR 12.7 (8.3-9.4)
4	Bogan et al, 2014[14]	Retrospective, cohort	The Detroit Medical Center health care system consists of 8 hospitals and a 2,200-bed tertiary referral facility for metropolitan Detroit and southeastern Michigan	Michigan, USA	2008–2009	Patients n = 364 Mean age 62 ± 16 y **CRE:** carbapenem-resistant Enterobacteriaceae group n = 23 Mean age: 63.4 ± 18.5 y Sex: no data **CSE**: carbapenem-susceptible Enterobacteriaceae group n = 10 Mean age: 59.5 ± 20.4 Sex: no data	CRE Lab: susceptibilities were determined to predefined antimicrobials, based on an automated broth microdilution system (MicroScan; Siemens AG, Munich, Germany), using standard American Type Culture Collection controls, and in accordance with CLSI criteria	In-hospital mortality	- Age >65 y - ICU stay in past 3 months - Charlson combined condition score - Dependent functional status - Body site of isolation: blood (infected only) - Permanent foreign devices - Pneumonia (infected only)	aOR 2.7 (0.8-9.4) OR 3.3 (1.5-7.5)
5	Chiotos et al, 2016[15]	Retrospective, cohort	Children's Hospital of Philadelphia and Boston Children's Hospital	Philadelphia and Boston, USA	2011–2015	Children patients 26 matched (2:1) group Total n = 78 n of infection = 42	CRE Lab: no data	30-day all-cause mortality		OR 7.22 (1.3-40.2)

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Table 1 (*Continued*)

	Author	Study Design*	Study Population and Location	Country	Years of Study	Demographics	Definitions of CRE	Definition of Outcomes	Confounder Adjusted	Risk Ratio (CI)
6	Correa et al, 2013[16]	Retrospective, cohort	The Hospital Israelita Albert Einstein, a 620-bed private tertiary hospital	São Paulo, Brazil	2006–2008	Patients infection with *K pneumoniae* **CRKP** n = 20 (urinary tract infections (9), central venous catheter-associated BSI (5), surgical site infections (4), and skin and soft tissue infections (2)) Mean age: 59.6 y Sex: 65% male **CSKP** n = 40 Mean age: 64.9 y Sex: 52.5% male There were no significant differences ($P > .05$) among cases and controls	CRKP Lab: imipenem and meropenem MICs were confirmed by CLSI broth microdilution (TREK Diagnostic Inc, Westlake, OH, USA.)	In-hospital mortality		OR 2.64 (0.86-8.07)
7	Dautzenberg et al, 2015[17]	Cohort study, post hoc analysis	Two Greek ICUs (Attikon University Hospital and Laikon General Hospital)	Greece	2008–2011	≥18 y, admit ICU 3 days or longer **CPE colonized** n = 132 Mean age: 65.9 ± 17.6 y Sex: 37.9% female **non-CPE colonized** n = 875 Mean age: 63.3 ± 17.4 y Sex: 41.8% female	CPE colonization, *K pneumoniae* 94.7% Lab: EUCAST criteria	ICU mortality		HR 1.79 (1.31-2.43)
8	Garbati et al, 2016[18]	Retrospective, cohort	King Fahad Medical City	Riyadh, Saudi Arabia	2012–2013	Adult patients with infection due to health care–associated infections **CRE**: n = 29 Mean age: 55.4 ± 3.8 y (range 17-85 y) Sex: 37.9% female **CSE**: n = 58 Mean age: 54.7 ± 2.6 y (range 15-94 y) Sex: 44.8% female	CRE (mainly *K pneumoniae, Escherichia coli, Enterobacter* spp, and *Citrobacter* spp) Lab: susceptibility testing for meropenem and imipenem were performed by both the disk diffusion method and Vitek 2 automated system) susceptibility was interpreted as per criteria according to CLSI guidelines	30-day mortality		CRE death (9/29), CSE death (7/58)

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Table 1 (*Continued*)

	Author	Study Design*	Study Population and Location	Country	Years of Study	Demographics	Definitions of CRE	Definition of Outcomes	Confounder Adjusted	Risk Ratio (CI)
9	Hoxha et al, 2016[19]	Retrospective, cohort	Ten Italian hospitals	Italy	2012–2013	Adult patients (≥18 y) *K pneumoniae* was isolated from blood or bronchoscopy specimens (bronchoalveolar lavage or protected bronchial brush) **CRKP** n = 49 Age >65 y: 63% Sex: 65% male **CSKP** n = 49 Age >65 y: 69% Sex: 65% male	CRKP Lab: specimens were analyzed by the microbiological laboratory of each hospital determined the MIC of meropenem for the *K pneumoniae* isolate. CRKP was defined as MIC >8 mg/mL for meropenem CSKP was defined as MIC 2 mg/mL for meropenem	30-day mortality	- Age >65 years - Male - ICU treatment - Hospitalized in previous 6 months - SAPS II score - Charlson comorbidity index 3 - Immunodeficiency (eg, organ or blood transplant, dialysis, surgery, invasive procedure)	adjusted mIRR 3.0 (1.3-7.1) mIRR 3.0 (1.5-6.1)
10	Hussein et al, 2013[20]	Retrospective, cohort	Rambam Health Care Campus, a 900-bed tertiary teaching hospital	Haifa, Israel	2006–2008	Adult inpatients (age ≥18 years) with health care-related *K pneumoniae* bacteremia **CRKP** n = 103 Mean age: 61.4 ± 17 y Sex: 70.9% male **CSKP** n = 214 Mean age: 63.2 ± 18 y Sex: 62.0% male	CRKP bacteremia Lab: blood cultures were performed with the automated Bactec 9240 system (Becton Dickinson, Franklin Lakes NJ), bacterial isolates were identified to the genus level by conventional biochemical methods. Antimicrobial susceptibility was determined by disk diffusion according to CLSI guidelines	30-day mortality	- Bedridden status - Chronic liver disease - Charlson comorbidity index 5 - Mechanical ventilation - Dialysis	aOR 1.3 (0.7-2.3) OR 1.9 (1.2-3.1)
11	Jaiswal et al, 2016[21]	Prospective, cohort	Dharamshila Narayana Superspeciality Hospital	New Delhi, India	2013–2016	Hematologic malignancy patients, Median age: 46 y Sex: 61% male **CRE-positive colonization in hospital** n = 46 Median age: 46.5 (2-74) y Sex: 71.7% male **CRE-negative colonization** n = 133 Median age: 45 (2-84) y Sex: 63.4% male	Gut colonization with CRE Lab: immediately rectal swabs samples, isolates were subjected to a series of biochemical tests for identification, both manually or using Vitek 2 automated system, susceptibility testing was performed by disk diffusion (Kirby-Bauer) method following CLSI guidelines	Infection-related mortality		CRE death (14/46), CSE death (0/131)
12	Kyaw et al, 2015[22]	Retrospective, cohort	Hospital infection control database, tertiary care hospital	Singapore	2011–2013	Patients CRE-positive isolates n = 382 Age: 67.4% >65 y Sex: 44% female	CRE	30-day all-cause mortality		OR 2.1 (1.21-3.74)

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Table 1 (*Continued*)

	Author	Study Design*	Study Population and Location	Country	Years of Study	Demographics	Definitions of CRE	Definition of Outcomes	Confounder Adjusted	Risk Ratio (CI)
13	Lee et al, 2016[23]	Retrospective, cohort	Bucheon St Mary's Hospital, a 607-bed, university-affiliated, community-based general hospital	Korea	2013–2014	Adult hospitalized patients (age ≥16 y) CRE was cultured from sputum (41.5%), urine (29.3%), surgical wound (17.1%), soft tissue (7.3%), and blood (4.9%) **CRE** n = 37 Median age: 68 (31-90) y Sex: 56.8% male **CSE** n = 37 Median age: 68 (42-88) y Sex: 56.8% male	CRE Lab: antimicrobial susceptibility profiles were determined using the Vitek 2 automated system in accordance with the manufacturer instructions. MIC for imipenem, meropenem, and ertapenem were determined by CLSI M100-S22 guidelines. Using current EUCAST breakpoints, imipenem MICs of CRKP isolates ranged from 2 to >32 μg/mL (breakpoint for resistance and intermediate susceptibility MIC ≥2 μg/mL); meropenem MICs from 4 to >32 μg/mL (breakpoint for resistance and intermediate susceptibility MIC ≥4 μg/mL); all the isolates had ertapenem MICs in the resistant range (breakpoint for resistance and intermediate susceptibility MIC ≥1 μg/mL)	28-day mortality		CRE death (10/37), CSE death (8/37)
14	Meng et al, 2017[24]	Retrospective, cohort	Xiangya Hospital, a 3500-bed general hospital in Changsha	Hunan Province, Central South China	2012–2015	Hospitalized patients with health care–associated infection **CREC** respiratory secretions (28.6%), followed by urine (24.5%), surgical wounds (20.4%), blood (12.2%), ascitic fluid (12.2%), and bile (2.0%) n = 49 Median age: 51 (0-82) y Sex: 41% male **CSEC** n = 96 Median age: 53 (0-91) y Sex: 41% male	CREC was defined as *E coli* resistant to at least 1 of the carbapenems (imipenem, meropenem, or ertapenem) Lab: an automated broth microdilution method (Vitek 2 automated system) was used to perform identification and susceptibility testing. Carbapenem resistance was determined using the disk diffusion method. Antimicrobial susceptibility was determined by disk diffusion according to CLSI guidelines M100-S22			CREC death (6/49), CSEC death (1/96)

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Table 1 (*Continued*)

	Author	Study Design*	Study Population and Location	Country	Years of Study	Demographics	Definitions of CRE	Definition of Outcomes	Confounder Adjusted	Risk Ratio (CI)
15	Nouvenne et al, 2014[25]	Retrospective, cohort	University Hospital of Italy, a 1218-bed tertiary referral facility hospital	Parma, Italy	August 2011 to May 2012	All patients with clinical signs of infection **CRKP-positive** n = 133 Mean age: 79 ± 12 y Sex: 56.4% male **CRKP-negative** n = 400 Mean age: 79 ± 10 y Sex: 44.7% male	CRKP Lab: no data			CRKP-positive death (29/133), CRKP-negative death (104/400)
16	Pouch et al, 2015[26]	Retrospective, cohort	Two academic medical centers; the Columbia University Medical Center, Weill Cornell Medical Center	New York, USA	2007–2010	Bacteriuria in kidney transplant recipients **CRKP** n = 20 Age, Sex: no data **CSKP** n = 80 Age, Sex: no data	CRKP Lab: carbapenem resistance was defined by imipenem, or meropenem resistance by Vitek 2 automated system or carbapenemase detection by MHT	Overall mortality		OR 3.0 (1.0-9.0)
17	Salsano et al, 2016[27]	Retrospective, cohort	IRCCS San Martino-IST teaching hospital, University of Genoa	Italy	2014	Patients undergoing open heart surgery **CRKP infection** n = 32 Median age: 74 (67-77) y Sex: 53% male **Non-CRKP infection** n = 521 Median age: 71 (63-77) y Sex: 69% male	CRKP Lab: Vitek 2 automated system was used for the identification, interpretative breakpoints for carbapenem resistance were based on EUCAST criteria	Overall crude in-hospital mortality		CRKP infection death (8/32), non-CRKP infection death (30/521)
18	Tamma et al, 2017[28]	Retrospective, cohort	Johns Hopkins Hospital	Maryland, USA	2013–2016	Hospitalized unique bacteremia patients **CP-CRE** n = 37 Median age: 58 (48-63) y Sex: 78% female **Non-CP-CRE** n = 46 Median age: 58 (43-62) y Sex: 71% female	CP-CRE, *Klebsiella* spp 76%, *Enterobacter* spp 19%, *E coli*, and others 3% Lab: matrix-assisted laser-desorption ionization time-of-flight mass spectrometry and the BD Phoenix automated system (Becton Dickinson, NJ, USA.)	30-day mortality after positive bacteremia, died of bacteremia	-Pitt bacteremia score >4 - Active empirical therapy - Active directed therapy - Day of combination antibiotic therapy - Diabetes and polymyxin therapy	aOR (30-day mortality) 3.19 (0.99-10.25) OR 3.20 (1.06-9.61)
19	Teo et al, 2012[29]	Retrospective, cohort	A tertiary care hospital	Singapore	2009	Adult patients (>18 y) Hospitalized infection patients **ERE** n = 29 Median age: 55 (22-91) y Sex: 58.6% female **ESE** n = 29, Median age: 75 (27-88) y Sex: 48.9% female	ERE, *Klebsiella* spp 55.2%, *Enterobacter* spp 27.6%, *E coli* 17.2% Lab: CLSI as per hospital's clinical microbiology laboratory protocol	In-hospital mortality (final end of hospitalization)		OR 5.55 (1.05-29.33)

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Table 1 (*Continued*)

	Author	Study Design*	Study Population and Location	Country	Years of Study	Demographics	Definitions of CRE	Definition of Outcomes	Confounder Adjusted	Risk Ratio (CI)
20	Trecarichi et al, 2015[30]	Prospective, Cohort	Multicenter, 13 Italian hematological units participating to HEMABIS registry-SEIFEM group	Italy	2010–2014	Onco-hematologic patients with *K pneumoniae* BSI **CRKP** n = 161 Age, Sex: no data **CSKP** n = 117 Age, Sex: no data	CRKP Lab: no data	30-day mortality after first positive blood culture	- Age - Corticosteroid therapy - Altered state of consciousness - Acute respiratory failure - Septic shock	aOR 4.21 (1.87-9.47)
21	Vardakas et al, 2015[31]	Retrospective, cohort	The ICU of Gennimatas General Hospital, a 350-bed tertiary center	Thessaloniki, Greece	2006–2009	Patients with *K pneumoniae*-acquired infections, ICU Mean age: 66.3 ± 14.3 y Sex: 49% male **CRKP** n = 80 Mean age: 66.3 ± 14.4 y Sex: 49.3% male **CSKP** n = 24 Mean age: 60.9 ± 15.6 y Sex: 38.9% male	CRKP Lab: identification of the isolates was performed using the Vitek 2 automated system	All cause ICU mortality		CRKP death (58/80), CSKP death (14/24)

aHR, adjusted hazard ratio; *aOR*, adjusted odds ratio; *BSI*, bloodstream infection; *CI*, confidence interval; *CLSI*, Clinical and Laboratory Standards Institute; *CP*, carbapenemase producing; *CPE*, carbapenemase-producing Enterobacteriaceae; *CRE*, carbapenem-resistant Enterobacteriaceae; *CREC*, carbapenem-resistant *Escherichia coli; CRKP*, carbapenem-resistant *Klebsiella pneumoniae; CSE*, carbapenem-susceptible Enterobacteriaceae; *CSKP*, carbapenem-susceptible *Klebsiella pneumoniae; ERE*, ertapenem-resistant Enterobacteriaceae; *ESE*, ertapenem-susceptible Enterobacteriaceae; *EUCAST*, European Committee on Antimicrobial Susceptibility Testing; *HR*, hazard ratio; *ICU*, intensive care unit; *IQR*, interquartile range; *MIC*, minimum inhibitory concentration; *OR*, odds ratio; *HEMABIS*, Hematological Malignancies Associated Bacterial Infections Surveillance; *SEIFEM*, Sorveglianza Epidemiologica Infeczioni Nelle EMioatie (Epidemiological Surveillance of Infections in Hematological Diseases) is a non-profit group consisting essentially of Italian Hematologists); *CSEC*, Carbapenem-susceptible E coli; *MHT*, modified Hodge testing; *mIRR*, matched incidence rate ratio.
*Study design was based on how the studies examined mortality outcome.

Table 2
Risk of bias assessment by Newcastle-Ottawa scale

	Cohort Studies								
	Selection (1 star for each)					Exposure (1 star for each)			
Author, Year	Representativeness of the Exposed Cohort	Selection of Non-Exposed Cohort	Ascertainment of Exposure	Outcome not Present at the Beginning	Comparability of Cohorts (*/2)	Assessment of Outcome	Follow-Up Duration	Adequacy of Follow-Up	Total (*/9)
Alicino et al, 2015[11]	*	*	*	*	-	*	*	-	6
Biehle et al, 2015[12]	*	*	*	*	*	-	*	-	6
Bleumin et al, 2012[13]	*	*	*	*	-	*	*	-	6
Bogan et al, 2014[14]	*	*	*	*	**	*	-	-	7
Chiotos et al, 2016[15]	*	-	-	*	*	-	*	-	4
Correa et al, 2013[16]	*	*	*	*	-	-	-	-	4
Dautzenberg et al, 2015[17]	-	*	*	*	-	*	-	*	5
Garbati et al, 2016[18]	*	*	*	*	-	-	-	-	4
Hoxha et al, 2016[19]	*	*	*	*	**	*	*	-	8
Hussein et al, 2013[20]	*	*	*	*	**	-	*	-	7
Jaiswal et al, 2016[21]	*	*	*	*	-	*	-	-	5
Kyaw et al, 2015[22]	*	*	-	*	-	-	*	-	4
Lee et al, 2016[23]	*	*	*	*	-	-	-	-	4
Meng et al, 2017[24]	*	*	*	*	-	-	-	-	4
Nouvenne et al, 2014[25]	*	*	*	*	-	-	-	-	4
Pouch et al, 2015[26]	*	*	*	*	-	*	*	-	6
Salsano et al, 2016[27]	*	*	*	*	-	-	*	-	5
Tamma et al, 2017[28]	*	*	*	*	*	*	*	-	7
Teo et al, 2012[29]	*	*	*	*	-	*	-	-	5
Trecarichi et al, 2015[30]	-	*	-	*	-	*	*	-	4
Vardakas et al, 2015[31]	*	*	*	*	-	*	-	-	5

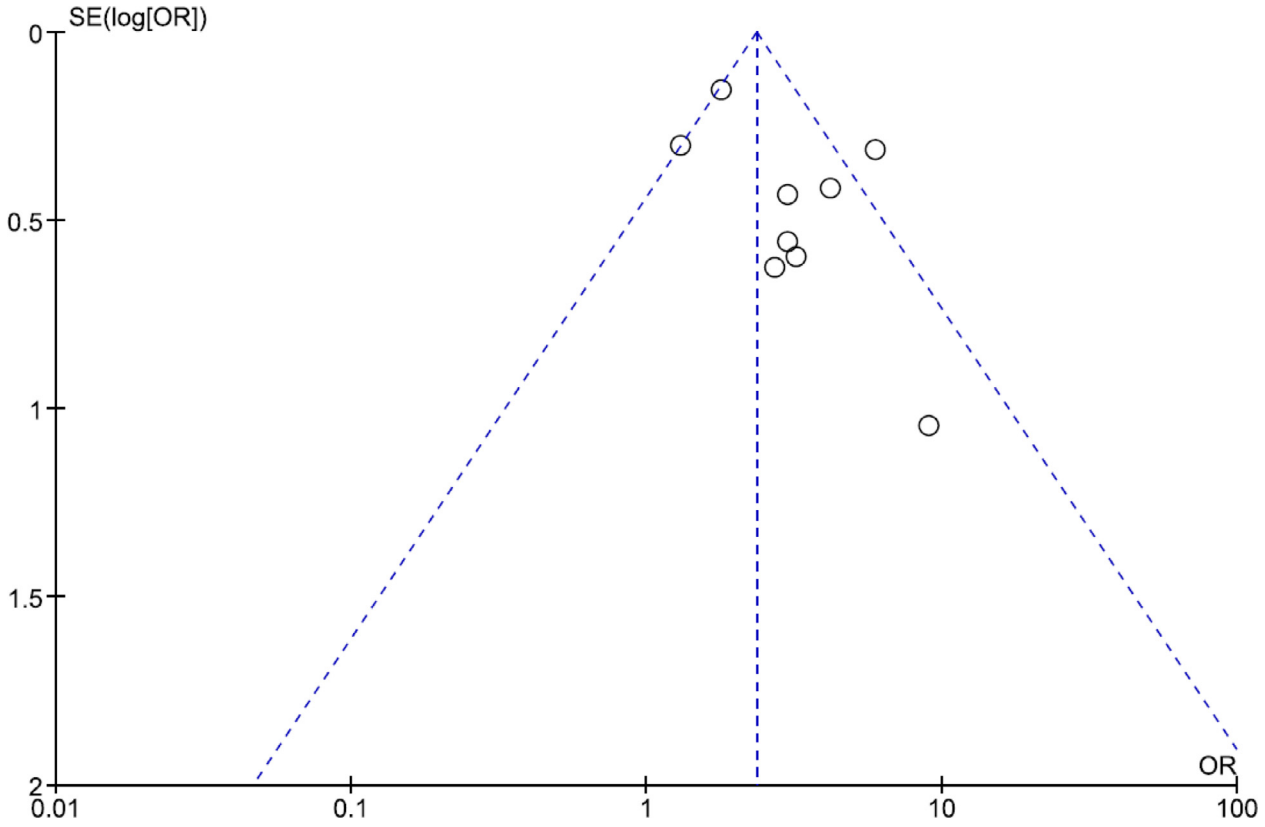

Fig 2. Funnel plot using data for 9 adjusted analysis trails of association between carbapenem-resistant Enterobacteriaceae and death. *OR*, odds ratio; *SE*, standard error.

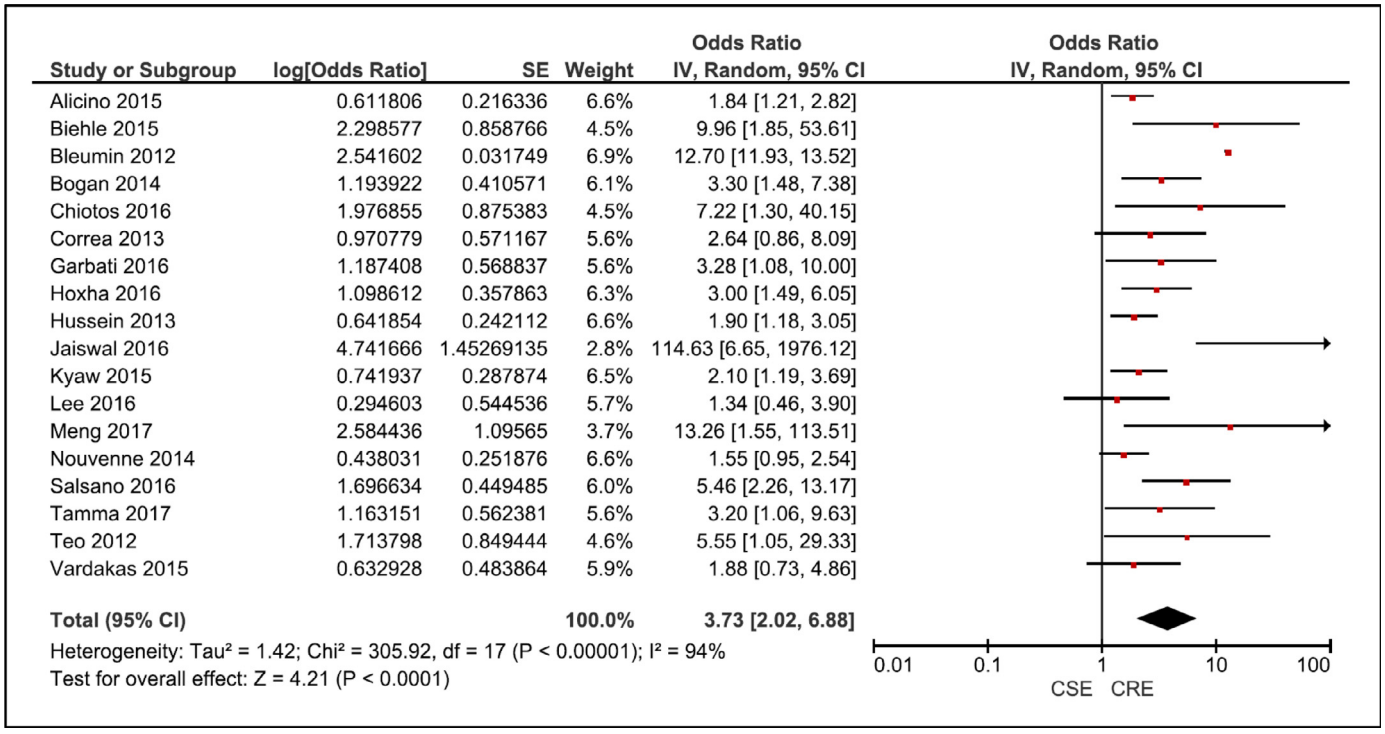

Fig 3. Forest plot of unadjusted analysis association between CRE and death. *CI*, confidence interval; *CRE*, carbapenem-resistant Enterobacteriaceae; *CSE*, carbapenem-susceptible Enterobacteriaceae; *IV*, inverse variance; *SE*, standard error.

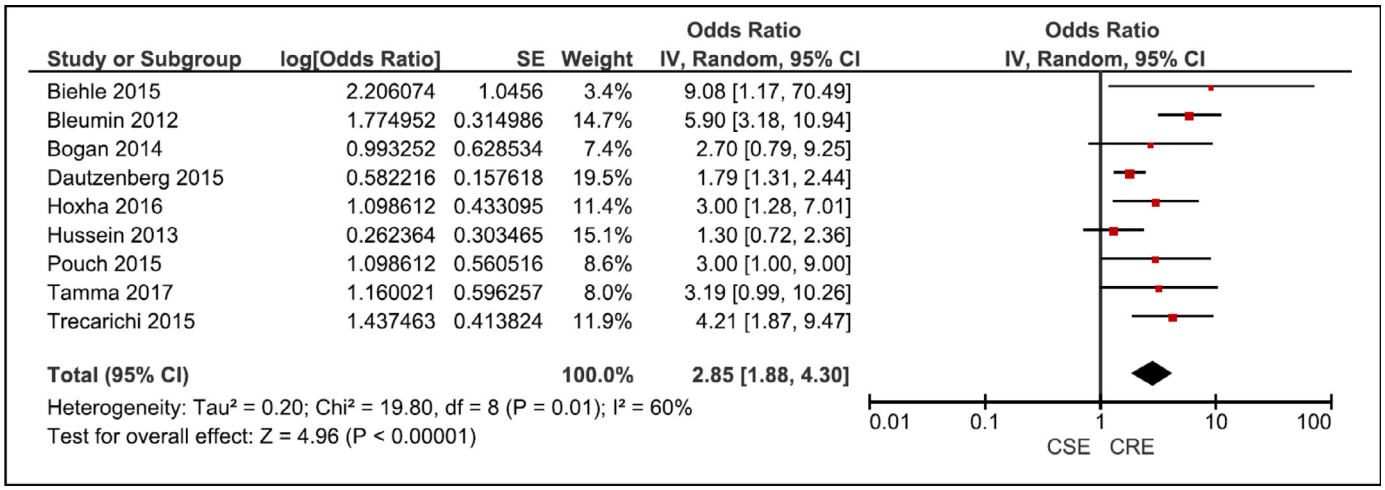

Fig 4. Forest plot of adjusted analysis association between CRE and death. *CI*, confidence interval; *CRE*, carbapenem-resistant Enterobacteriaceae; *CSE*, carbapenem-susceptible Enterobacteriaceae; *IV*, inverse variance; *SE*, standard error.

was 10-fold higher than the prevalence from the Doll et al[47] study, which reported that the prevalence of CRE was 0.3% (39 isolates out of 12,947 isolates), and the Livorsi et al[48] study reported that the incidence of CRE infections was 0.3-2.93 per 100,000 person per year in the United States. The higher prevalence from our meta-analysis may come from the difference in the definition of CRE exposure. This meta-analysis included 3 studies with CRE colonization (Ehrhard et al,[32] Poole et al,[33] and Reuben et al[34]) and 1 study with clinical CRE infection (Trepanier et al[35]), whereas Doll et al[47] reported only clinical CRE infection. Studies reported that CRE colonization rate was ranging from 12.2% -18%.[49,50] Although including CRE colonization to the analysis may have contributed to the higher prevalence of CRE, CRE colonization should be considered as CRE exposure and not be neglected because CRE colonization is associated with clinical infection and increased risk of mortality. Dickstein et al[51] reported that CRE colonization was associated with Enterobacteriaceae infection (HR: 3.32 [95% CI: 1.31-8.43]) and Zilberberg et al[52] reported that CRE infection was associated with an increased risk of receiving inappropriate empirical treatment, which in turn increased mortality because CRE patients were 3-fold more likely to receive inappropriate empirical treatment than non-CRE patients (46.5% vs 11.8%, $P < .001$). The results from these studies showed that a high prevalence of CRE colonization in the hospitals related to a potential risk of transmission and mortality.

CONCLUSIONS

Pooled risk estimates from this meta-analysis revealed that CRE was associated with an increased mortality risk. Our findings suggested that the risk of death caused by carbapenem resistance is significant among individuals with Enterobacteriaceae infection. Our analysis implies that strict infection control procedures in the hospital to control CRE colonization are necessary.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.ajic.2019.03.020.

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