Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant *Klebsiella pneumoniae*

Liangfei Xu, Xiaoxi Sun and Xiaoling Ma*

**Abstract**

**Purpose:** Carbapenem resistant *K. pneumoniae* (CRKP) has aroused widespread attention owing to its very limited therapeutic options, and this strain has increased rapidly in recent years. Although it is accepted that drug resistance is associated with increased mortality in general, some other studies found no such relationship. To estimate mortality of patients infected with CRKP in general and analyze factors for mortality of this infection, thus, we conducted this systematic review and meta-analysis.

**Methods:** A systematic literature review of relevant studies published until December 2015 was conducted. We selected and assessed articles reporting mortality of patients infected with CRKP.

**Results:** Pooled mortality was 42.14% among 2462 patients infected with CRKP versus 21.16% in those infected with carbapenem-susceptible *K. pneumoniae* (CSKP). The mortality of patients with bloodstream infection (BSI) or urinary tract infection was 54.30 and 13.52%, respectively, and 48.9 and 43.13% in patients admitted to the intensive care unit (ICU) or who underwent solid organ transplantation (SOT). Mortality was 47.66% in patients infected with *K. pneumoniae* carbapenemase-producing *K. pneumoniae* and 46.71% in those infected with VIM-producing *K. pneumoniae*. Geographically, mortality reported in studies from North America, South America, Europe, and Asia was 33.24, 46.71, 50.06, and 44.82%, respectively.

**Conclusions:** Our study suggests that patients infected with CRKP have higher mortality than those infected with CSKP, especially in association with BSI, ICU admission, or SOT. We also considered that patients’ survival has a close relationship with their physical condition. Our results imply that attention should be paid to CRKP infection, and that strict infection control measures and new antibiotics are required to protect against CRKP infection.

**Keywords:** CRKP, Carbapenem-resistant, *K. pneumoniae*, Mortality

**Background**

It is well known that *Klebsiella pneumoniae* is ubiquitous in nature, one of the most relevant opportunistic pathogens, and causes various human infections such as bloodstream infection (BSI), urinary tract infection (UTI), surgical-site infection, and pneumonia [1–3]. Resistance can develop in *K. pneumoniae* isolates, notably producing extended-spectrum β-lactamases (ESBLs). ESBL-producing strains of *K. pneumoniae* are currently found throughout the world and have caused numerous outbreaks of infection [4, 5]. Carbapenems represent the first-line therapy for severe infection by ESBL-producing *K. pneumoniae* [6]. However, since Yigit et al. [7, 8] reported the first *K. pneumoniae* carbapenem (KPC)-producing *K. pneumoniae* isolate in North Carolina in 1996, carbapenem-resistant strains have increased rapidly, rising from 1.6 to 10.4% associated with central line bloodstream infections between 2001 and 2011 in the...
United States, and have aroused widespread attention, presenting a challenge because the antimicrobial treatment options remain very restricted [7, 9].

Carbapenem-resistant *K. pneumoniae* (CRKP) deactivates the carbapenems through two main mechanisms: (1) acquisition of carbapenemase genes that encode for enzymes capable of hydrolyzing carbapenems—the three most important carbapenemase types being KPC-type enzymes, metallo-β-lactamases (VIM, IMP, NDM), and OXA-48 type enzymes; and (2) reduction in the accumulation of antibiotics by a quantitative and/or qualitative deficiency of porin expression in combination with over-expression of β-lactamases that possess weak affinity for carbapenems [10].

Most researchers reported higher mortality rates among persons infected with CRKP isolates [11–30] while others reported contrary results [31, 32]. In recent years, many studies from single medical centers or individual countries have reported mortality rates in patients infected with CRKP, but until now there has been no systematic review focusing on mortality resulting from carbapenem-resistant infections in general. Although in a recent meta-analysis Falagas et al. [33] reported a higher all-cause mortality among patients infected with carbapenem-resistant Enterobacteriaceae than in those with carbapenem-susceptible infections, but their research included only nine studies. Considering this scenario, we conducted a systematic review and meta-analysis to estimate the mortality of patients infected with CRKP, and analyzed mortality resulting from multiple infection types and patients conditions.

**Methods**

**Search strategy**

Two independent examiners (LF.X. and XX.S.) searched entries in the PubMed and EMBASE databases from their inception until December 22, 2015 to identify potentially relevant studies. The search terms included “Klebsiella pneumoniae” AND resistance AND (“carbapenem” OR “imipenem” OR “meropenem” OR “ertapenem”). The language was restricted to English.

**Inclusion and exclusion criteria**

Studies were considered in accordance with inclusion criteria if articles reported mortality of patients infected with CRKP. Research that focused on children, did not differentiate mortality between infection and colonization, did not define the strains that were carbapenem resistant, and did not present the exact death toll were excluded. In this analysis, carbapenem resistance was defined as resistance to carbapenems such as imipenem, meropenem, and ertapenem, irrespective of susceptibility to other antibiotics.

**Assessment of study quality**

The articles were assessed for quality of the cohort or case–control studies included in the systematic analysis according to the Newcastle-Ottawa scale (NOS) score [34], ranging from 0 to 9. Studies with a NOS score of 5 or greater were included in this analysis.

**Data extraction**

Two independent investigators (LF.X. and XX.S.) extracted information from eligible articles. Divergences were solved by discussion and consultation of the relevant literature. The information extracted from original publications included title, first author, year of publication and experiment, type of study, sample size, characteristics of the study population (mean age, sex, type of infection, mean severity of underlying disease), and crude mortality rates in patients infected with CRKP and carbapenem-susceptible *K. pneumoniae* (CSKP). If articles reported mortality from both infection and colonization, we extracted information only regarding infections.

**Statistical analysis**

We calculated the pooled odds ratio (OR) and 95% confidence interval (CI) by comparing crude mortality in patients with CRKP with that in patients with CSKP. Between-study heterogeneity was assessed by the χ² test ($p < 0.10$ was selected to indicate the presence of heterogeneity, in which case a random-effects model was adopted; otherwise a fixed-effects model was applied) and $I^2$ test (to assess the degree of heterogeneity) [35, 36]. We then calculated pooled rates of mortality in patients infected with CRKP, and stratified analyses with respect to geographic location, infection types, carbapenemase types, and patients conditions performed. Freeman–Tukey arc sine transformations were used to stabilize the variances, and after the meta-analysis we transformed the summary estimates and the CI boundaries back to proportions using the sine function [37]. We used Stata version 12.0 software for all statistical calculations.

**Results**

**Results of the systematic literature search**

We identified and screened 3168 articles. After exclusion by title and abstract, the remaining 87 articles were subjected to full-text assessment for eligibility. Among these articles, 12 were duplicates, seven did not differentiate between infection- and colonization-related mortality, and six did not report valid data. Ultimately, 62 studies were analyzed based on the inclusion and exclusion criteria (Fig. 1).

The basic characteristics of these 62 studies are summarized in Table 1 [11–32, 38–77]. These articles were published from 1999 to 2015 and the sample size varied...
across studies, ranging from 7 to 1022. The total number of patients in this systematic review was 4701, of whom 2462 had CRKP infection and the remainder CSKP infection. Among these patients, the reported death was 1018 among the CRKP patients and 398 among the CSKP patients. In the pooled analysis, the overall mortality was 42.14% (95% CI 37.06–47.31) in patients infected with CRKP and 21.16% (95% CI 16.07–26.79) in CSKP patients (Table 2).

Comparison of mortality in CRKP and CSKP patients
Among the included articles, 22 compared mortality between patients infected with CRKP and CSKP. The summary estimate of these studies from the random-effects model suggested that patients with CRKP had a significantly higher mortality than those with CSKP in the univariate analysis (pooled crude OR 2.80; 95% CI 2.15–3.65) with a moderate heterogeneity $I^2$ of 33.9% ($p = 0.031$) (Fig. 2).

Mortality in multiple patient conditions
As shown in Table 2, 722 patients had BSI and 284 had UTI, 479 were in an intensive care unit (ICU), and 362 underwent solid organ transplantation (SOT). In the pooled analysis, the mortality was 54.30% (95% CI 47.51–61.02), 13.52% (95% CI 7.50–20.92), 48.9% (95% CI 44.47–53.46), and 43.13% (95% CI 32.40–54.16) in BSI, UTI, ICU-admission, and SOT patients, respectively.

Mortality in multiple carbapenemase types
In this subgroup analysis, we mainly analyzed the mortality of patients infected with KPC-producing $K. pneumoniae$ and VIM-producing $K. pneumoniae$. In the articles included, 302 patients were infected with KPC-producing $K. pneumoniae$ and 73 were infected with VIM-producing $K. pneumoniae$. The mortality among these two types of carbapenemases was 47.66% (95% CI 38.61–56.79) and 46.71% (95% CI 35.81–57.73), respectively (Table 2).

Mortality in different geographic locations
Twenty-three studies were carried out in North America, eight in South America, twenty-one in Europe, and ten in Asia. The rate of mortality was 33.24% (95% CI 25.08–42.00) of 980 patients in North America, 46.71% (95% CI 39.83–53.66) of 191 in South America, 50.06% (95% CI 41.45–58.62) of 860 in Europe, and 44.82% (95% CI 37.83–51.91) of 431 in Asia (Table 2).

Discussion
ESBL-producing $K. pneumoniae$ as an opportunistic pathogen is becoming more challenging to treat because of the emergence of carbapenem resistance, and has a significant influence on patient mortality. The primary result of this analysis was the pooled crude mortality of 42.14% among patients with CRKP, which is intimately connected with patients’ health and physical status.

Although it is accepted that drug resistance is associated with increased mortality because patients tend to receive inappropriate empiric therapy in general [4, 78], other studies have found no such relationship. Bhavnani et al. [79] reported that clinical success was similar between patients with ESBL and those with non-ESBL-producing $K. pneumoniae$, and ESBL production alone did not appear to be an independent risk factor for treatment failure. Kim et al. [80] also found that ESBL production was not significantly associated with death. In addition, García-Sureda et al. [81] reported that CRKP isolates are less virulent and fit than CSKP isolates in an antibiotic-free environment. We conducted this systematic review and meta-analysis to estimate the mortality of patients infected with CRKP in general and to study the factors related to mortality resulting from this infection. We found that patients infected with CRKP had significantly higher mortality in comparison with CSKP (crude OR 2.80). To identify risk factors associated with the higher mortality of CRKP infections, we conducted a stratified analysis of patient condition, carbapenemase types, and study location.

Based on multiple patient conditions, our analysis confirmed that patients with CRKP in association with BSI, ICU admission, or SOT have a higher mortality than the pooled mortality, although UTI patients have a lower mortality than the pooled overall mortality, even lower than that of CSKP patients. From this result, we assumed that patient survival has a close relationship with patients’ underlying illness and comorbidities. Mouloudi et al. [26] reported that BSI, ICU admission, and recent receipt of a
### Table 1 Characteristics of the eligible studies

| Author, year | Study type | Region/study year | Resistance | CRKP mortality (%) | CSKP mortality (%) | P value | Carbapenemases | Infection type | ICU | SOT |
|--------------|------------|-------------------|------------|--------------------|--------------------|---------|----------------|----------------|-----|-----|
| Vardakas (2015) [11] | Retrospective cohort study | Greece 2006.1–2009.10 | CLSI 2010 | 58/80 (72.5) | 14/24 (58.3) | 0.19 | NA | BSI:44/65 | 80 | 0 |
| Brizendine (2015) [16] | Retrospective cohort study | USA 2011.12–2013.10 | CLSI 2012 | 16/157 (10.2) | NA | NA | NA | UTI6/157 | 0 | 0 |
| Pouch (2015) [12] | Nested case–control study | USA 2007.1–2010.12 | CLSI 2009 | 6/20 (30) | 8/80 (10) | 0.03 | NA | UTI6/20 | 0 | 20 |
| Ny (2015) [13] | Retrospective cohort study | USA 2011.1–2013.12 | NA | 7/48 (14.6) | 5/48 (10.4) | 0.76 | NA | UTI2/27 | 0 | 0 |
| Girmenia (2015) [39] | Retrospective cohort study | Italy 2010.1–2013.7 | NA | 65/112 (58.1) | NA | NA | NA | Any infection:65/112 | 0 | 112 |
| Hoxha (2015) [14] | Prospective matched cohort study | Italy 2012.11–2013.7 | Eucast Guideline | 30/49 (61) | 10/49 (20) | NA | NA | Any infection:30/49 | 0 | 0 |
| Cubero (2015) [15] | Retrospective cohort study | Spain 2010.10–2012.12 | EUCAST 2015 | 8/20 (40) | 1/9 (11.1) | NA | NA | Any infection:8/20 | 0 | 0 |
| Chang (2015) [40] | Retrospective study | Taiwan 2012.1–2012.12 | CLSI 2012 | 21/41 (51.2) | NA | NA | KPC:6/8 | Any infection:21/41 | 41 | 0 |
| Chen (2015) [58] | Retrospective study | Taiwan 2014–2015 | NA | 12/41 (29.3) | NA | NA | NA | Any infection:12/41 | 0 | 0 |
| Madrigal (2015) [66] | Retrospective study | Spain 2014.5–9 | NA | 2/5 (40) | NA | NA | NA | Any infection:2/5 | 0 | 0 |
| Bias (2015) [70] | Retrospective, observational cohort study | USA –2014.8 | NA | 5/30 (16.7) | NA | NA | NA | Any infection:5/30 | 0 | 30 |
| Katsiaro (2015) [67] | Prospective, observational study | Greece 2010.4–2012.3 | CLSI 2012 | 14/32 (43.8) | NA | NA | KPC:11/28VIM:3/5 | BSI:9/16 | 32 | 0 |
| Maristela Freire (2015) [69] | Retrospective cohort study | Brazil 2009.1–2013.3 | CLSI 2012 | 13/31 (41.9) | NA | NA | KPC:13/31 | BSI:7/11 | 0 | 31 |
| Brizendine (2015) [16] | Retrospective cohort study | USA 2006–2012 | NA | 4/22 (18) | 1/64 (1.5) | NA | NA | UTI4/22 | 0 | 22 |
| Sarah Welch (2015) [65] | Retrospective cohort study | USA | NA | 19/51 (37.3) | NA | NA | NA | Pneumonia19/51 | 0 | 0 |
| van Duin (2014) [16] | Prospective, multi-center, observational study | USA 2011.12–2013.3 | CLSI 2012 | 26/114 (22.8) | NA | NA | NA | BSI:5/26 | 0 | 0 |
| Simkins (2014) [17] | Retrospective case–control study | USA 2006.1–2010.12 | NA | 6/13 (46.2) | 3/39 (7.7) | 0.005 | NA | Any infection 6/13 | 0 | 13 |
| Viviana Gómez Rueda (2014) [18] | Case–case–control study | Colombia 2008.1–2011 | CLSI 2012 | 31/61 (50.8) | 20/61 (32.8) | NA | NA | Any infection 31/61 | 0 | 0 |
| Christoph Lübbert (2014) [71] | Retrospective study | Germany 2010.9–2011 | NA | 7/8 (87.5) | NA | NA | KPC:7/8 | Any infection 7/8 | 0 | 8 |
| Qureshi (2014) [42] | Retrospective cohort study | USA 2009.1–2012.10 | NA | 0/21 (0.00) | NA | NA | NA | UTI0/21 | 0 | 0 |
| Author, year | Study type | Region/study year | Resistance | CRKP mortality (%) | CSKP mortality (%) | P value | Carbapenemases | Infection type | ICU | SOT |
|-------------|------------|------------------|------------|-------------------|-------------------|---------|----------------|---------------|-----|-----|
| Mouloudi (2014) [43] | Retrospective cohort study | Greece 2008.1–2011.12 | EUCAST 2012 | 14/17 (82.4) | NA | NA | NA | CRKP:14/17 | 17 | 17 |
| Bulent Aydinli (2014) [72] | Retrospective analysis | Turkey 2012.1–2013.11 | NA | 2/5 (40) | NA | NA | NA | Any infection:2/5 | 0 | 5 |
| Gallagher (2014) [44] | Retrospective case–control study | USA 2005.6–2010.10 | CLSI 2009 | 19/43 (44.2) | NA | NA | NA | CRKP:19/43 | 0 | 0 |
| Grazia Hanna Pereira (2013) [47] | Retrospective cohort study | Brazil 2008.10–2010.10 | CLSI 2010 | 16/33 (48) | NA | NA | NA | CRKP:16/33 | 0 | 0 |
| Orsi (2013) [19] | Case–case–control study | Italy 2008.7–2011.6 | EUCAST | 25/65 (38.5) | 12/43 (27.9) | NA | KPC:14/36 | Any infection:25/65 | 0 | 0 |
| Kontopidou (2013) [48] | Retrospective cohort study | Greece 2009.9–2010.6 | CLSI 2010 | 29/127 (22.8) | NA | NA | NA | Any infection:29/127 | 0 | 0 |
| Hussein (2013) [20] | Retrospective case–control study | Israel 2006.1–2008.12 | CLSI 2006 | 45/103 (43.7) | 62/214 (29) | NA | NA | Any infection:45/103 | 0 | 0 |
| Correa (2013) [22] | Matched case–control study | Brazil 2006.1–2008.8 | CLSI 2009 | 10/20 (50) | 11/40 (27.5) | 0.085 | NA | Any infection:10/20 | 0 | 0 |
| Clancy (2013) [49] | Single-center, retrospective study | USA 2008.8–2011.7 | CLSI 2012 | 3/17 (17.6) | NA | NA | NA | BSI:3/17 | 0 | 17 |
| Cober (2013) [21] | Retrospective cohort study | USA 2006–2009 | NA | 8/19 (42.1) | 7/46 | 0.005 | NA | BSI:8/19 | 0 | 19 |
| Grassi (2013) [73] | Retrospective cohort study | Italy 2009.1–2012.10 | NA | 11/36 (30.6) | NA | NA | NA | Any infection:11/36 | 0 | 36 |
| Cicora (2013) [50] | Observational, retrospective study | Argentina 2011.4–2012.6 | CLSI 2010 | 2/6 (33.3) | NA | NA | KPC:2/6 | UTI:2/6 | 0 | 6 |
| Paola Di Carlo (2013) [46] | Prospective case series study | Italy 2011.8–2012.8 | EUCAST | 12/30 (40) | NA | NA | KPC1:2/30 | Any infection:12/30 | 30 | 0 |
| Fligou (2013) [88] | Retrospective cohort study | Greece | CLSI | 21/48 (43.8) | NA | NA | KPC2:14/48 | BSI:21/48 | 48 | 0 |
| Rose (2012) [74] | Retrospective, cohort study | USA 2006–2011 | NA | 20/44 (45.5) | NA | NA | NA | BSI:20/44 | 0 | 0 |
| Sanchez-Romero (2012) [51] | Retrospective cohort study | Spain 2009.1–2009.12 | CLSI 2011 | 13/28 (46.4) | NA | NA | VIM:13/28 | Any infection:13/28 | 28 | 0 |
| Liu (2012) [23] | Matched case–control study | Taiwan 2007.1–2009.12 | CLSI 2009 | 15/25 (60) | 20/50 | 0.102 | NA | BSI:15/25 | 0 | 0 |
| Kalpoes (2012) [52] | Retrospective cohort study | USA 2005.1–2006.10 | NA | 10/14 (71.4) | NA | NA | NA | Any infection:10/14 | 0 | 14 |
| Borer (2012) [53] | Retrospective case control study | Israel 2007.5–2010.1 | CLSI 2006 | 13/42 (31) | NA | NA | NA | Any infection:13/42 | 0 | 0 |
| Bergamasco (2012) [54] | Retrospective cohort study | Brazil 2009.7–2010.2 | CLSI 2009 | 5/12 (41.7) | NA | NA | KPC2:12/48 | Any infection:5/12 | 0 | 12 |
| Author, year        | Study type                                      | Region/study year | Resistance | CRKP mortality (%) | CSKP mortality (%) | P value | Carbapenemases | Infection type | ICU | SOT |
|---------------------|------------------------------------------------|-------------------|------------|--------------------|--------------------|---------|----------------|----------------|-----|-----|
| Ben-David (2012)    | Retrospective cohort study                      | Israel 2006.1–2006.12 | CLSI 2006  | 29/42 (69.1)       | 45/150 (30)        | <0.001  | NA             | BSI:29/42      | 0   | 0   |
| Balkhy (2012)       | Retrospective/prospective surveillance study     | Saudi Arabia 2009–2010 | CLSI 2009  | 8/20 (40)         | NA                 | NA      | NA             | Any infection 8/20 | 0   | 0   |
| Jason Gallagher     | A retrospective, cohort study                   | USA 2006–2011     | NA         | 24/44 (54.5)       | NA                 | NA      | NA             | BSI:24/44      | 0   | 0   |
| Pereira (2011)      | Retrospective cohort study                      | Brazil 2008.10–2010 | CLSI 2010  | 9/22 (40.9)        | NA                 | NA      | NA             | Any infection 9/22 | 0   | 0   |
| Orsi (2011)         | Retrospective case control study                | Italy 2008.7–2009.12 | EUCAST    | 11/28 (39.3)       | 12/43              | NA      | NA             | Any infection 11/28 | 0   | 0   |
| Neuner (2011)       | Retrospective cohort study                      | USA 2007.1–2009.5 | CLSI 2009  | 35/60 (58.3)       | NA                 | NA      | NA             | BSI:35/60      | 0   | 0   |
| Diana Gaviria       | Retrospective matched case–control study        | USA 2009.4–2011.12 | CLSI      | 1/19 (5.3)         | 3/38 (7.9)         | NA      | NA             | Any infection 1/19 | 0   | 0   |
| Cuzon (2011)        | Retrospective cohort study                      | France 2010.4–2010.6 | CLSI 2010 | 5/7 (71.4)         | NA                 | NA      | NA             | Any infection 5/7 | 0   | 0   |
| Elisa Maria Beirão  | Retrospective cohort study                      | Brazil 2008.1–2008.12 | CLSI 2009 | 3/6 (50)         | NA                 | NA      | KPC:3/6        | Any infection 3/6 | 0   | 0   |
| Nguyen (2010)       | Retrospective cohort study                      | USA 2004.1–2008.9 | CLSI      | 29/48 (60.4)       | NA                 | NA      | NA             | BSI:29/48      | 0   | 0   |
| Vardakas (2010)     | Retrospective cohort study                      | Greece 2006.1–2009.9 | NA       | 42/56 (75)        | NA                 | NA      | NA             | Any infection 42/56 | 56  | 0   |
| Mouloudi (2010)     | Retrospective nested case–control study         | Greece 2007.1–2008.12 | CLSI 2007 | 25/37 (67.6)       | 9/22 (40.9)        | 0.03    | KPC:15/19 VIM:10/18 | BSI:25/37     | 0   | 0   |
| Gregory (2010)      | Retrospective case–control study                | Puerto Rico 2008.2–2008.9 | CLSI 2009 | 7/19 (36.8)       | NA                 | NA      | NA             | Any infection 7/19 | 0   | 0   |
| Balandin Moreino (2010) | Retrospective cohort study                   | Spain 2009.7–2010.4 | NA       | 2/8 (25)          | NA                 | NA      | VIM:2/8        | Any infection 2/8 | 8   | 0   |
| Gasink (2009)       | Case–control study                              | USA 2006.10–2008.4 | NA       | 18/56 (32.1)      | 85/863 (9.8)       | NA      | KPC:18/56      | Any infection 18/56 | 0   | 0   |
| Daikos (2009)       | Prospective observational study                 | Greece 2005.2–2006.3 | CLSI 2004 | 6/14 (42.9)       | 25/148 (16.9)      | NA      | VIM:6/14       | BSI:6/14       | 0   | 0   |
| Borer (2009)        | Matched retrospective, historical cohort study   | Israel 2005.10–2008.10 | CLSI 2006 | 30/64 (46.9)      | NA                 | NA      | NA             | BSI:23/32      | 0   | 0   |
| Schwaber (2008)     | Retrospective cohort study                      | Israel 2003–2006   | CLSI 2005  | 21/48 (43.8)      | 7/56 (12.5)        | NA      | NA             | Any infection 21/48 | 0   | 0   |
| Patel (2008)        | Retrospective matched case–control              | USA 2004.7–2006.6 | CLSI 2006  | 48/99 (48.5)      | 20/99 (20.2)       | <0.001  | NA             | Any infection 48/99 | 0   | 0   |
| Author, year | Study type | Region/study year | Resistance | CRKP mortality (%) | CSKP mortality (%) | P value | Carbapenemases | Infection type | ICU | SOT |
|-------------|------------|-------------------|------------|--------------------|--------------------|---------|----------------|----------------|-----|-----|
| Falagas (2007) [32] | Retrospective matched case–control study | Greece 2000.10–2006.5 | NA | 16/53 (30.2) | 18/53 (34) | 0.83 | NA | Any infection:16/53 | 0 | 0 |
| Woodford (2004) [63] | Retrospective cohort study | USA 2000.4–2001.4 | CLSI | 8/14 (57.1) | NA | NA | KPC8/14 | Any infection:8/14 | 14 | 0 |
| Muhammad Ahmad (1999) [64] | Retrospective cohort study | USA 1994.12–1995.11 | CLSI 1994 | 6/8 (75) | NA | NA | NA | Any infection:6/8 | 8 | 0 |

*CLSI Clinical and Laboratory Standards Institute, CRKP carbapenem-resistant *K. pneumonia*, CSKP carbapenem-susceptible *K. pneumonia*, BSI bloodstream infection, UTI urinary tract infection*
### Table 2  Mortality of patients based on patient condition, carbapenemases type, study region

| Subgroup                      | Number of studies | Sample size | Mortality Rate % (95% CI) | Statistical model |
|-------------------------------|-------------------|-------------|---------------------------|-------------------|
| **Pooled mortality**          |                   |             |                           |                   |
| CRKP                          | 62                | 2462        | 42.14 (37.06–47.31)       | Random            |
| CSKP                          | 22                | 2239        | 21.12 (16.07–26.79)       | Random            |
| **Patient conditions**        |                   |             |                           |                   |
| Bloodstream infections        | 20                | 722         | 54.30 (47.51–61.02)       | Random            |
| Urinary tract infections      | 8                 | 284         | 13.52 (7.50–20.92)        | Random            |
| Intensive care unit           | 12                | 479         | 53.90 (39.44–68.00)       | Random            |
| Solid organ transplantation   | 15                | 362         | 43.13 (32.40–54.16)       | Random            |
| **Carbapenemases type**       |                   |             |                           |                   |
| KPC-producing *K. pneumoniae* | 13                | 302         | 47.66 (38.61–49.51)       | Random            |
| VIM-producing *K. pneumoniae* | 5                 | 73          | 46.71 (35.81–57.73)       | Random            |
| **Region**                    |                   |             |                           |                   |
| North America                 | 23                | 980         | 33.24 (25.08–42.00)       | Random            |
| South America                 | 8                 | 191         | 46.71 (39.83–53.66)       | Fixed             |
| Europe                        | 21                | 860         | 50.06 (41.45–58.62)       | Random            |
| Asia                          | 10                | 431         | 44.82 (37.83–51.91)       | Random            |

CRKP Carbapenem-resistant *K. pneumoniae*, CSKP carbapenem-susceptible *K. pneumoniae*

**Fig. 2**  Crude odds ratio (OR) for the association between carbapenem resistance and mortality of patients with *K. pneumoniae* infection
aminoglycosides and fluoroquinolones. In this system—also frequently other classes of antimicrobials, such as are resistant to not only all β-lactam antimicrobials but isolates reported that KPC-producing spread, causing nosocomial outbreaks. Bratu et al. [84] successful pathogen because of its ability to persist and addition, KPC-producing is considered a K. pneumoniae in independent risk factor in patient mortality [26, 27]. In mortality, we analyzed only crude mortality among patients with CRKP. Second, most studies may have lacked power in differentiating death caused by CRKP from any other factors, and it is difficult to draw definitive conclusions from current evidence because of the residual confounding factors and small sample sizes in many studies. Third, some studies included in our meta-analysis did not define a cutoff value to judge the susceptibility of K. pneumoniae to carbapenems, and when defined the cutoff value varied among studies owing to different reference criteria. Thus, there exists the potential for heterogeneity. Fourth, most studies were retrospective in nature and thus susceptible to selection bias. Last, we selected only English-language articles, thus limiting the scope of our analysis.

Conclusions
Our study suggests that patients infected with CRKP have a higher mortality than those infected with CSKP, especially patients with BSI, ICU admission, or SOT intervention. We suggest that the survival of patients has a close relationship with their physical condition. Thus, our results imply that attention should be paid to CRKP infection in patients in a poor state of health, and that strict infection control measures and new antibiotics are required to protect against CRKP infection.

Abbreviations
CRKP: carbapenem-resistant Klebsiella pneumoniae; CSKP: carbapenem-susceptible Klebsiella pneumoniae; BSI: bloodstream infection; UTI: urinary tract infection; ICU: intensive care unit; SOT: solid organ transplantation.

Authors’ contributions
LX and XS designed the study, performed the articles search and screen. LX wrote the paper. LX and XS performed the Statistical analysis. XM reviewed the manuscript. All authors read and approved the final manuscript.

References
1. Podschun R, Ullmann U. Klebsiella spp. as nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors. Clin Microbiol Rev. 1998;11:589–603.
2. Daikos GL, Markogiannakis A, Souli M, Tzouvelekis LS. Bloodstream infections caused by carbapenemase-producing Klebsiella pneumoniae: a clinical perspective. Expert Rev Anti Infect Ther. 2012;10(12):1393–404.

3. Broberg CA, Palacios M, Miller VL. Klebsiella: a long way to go towards understanding this enigmatic clinical isolate. Curr Opin Infect Dis. 2012;25(1):1–6.

4. Tumbarello M, Spata T, Sanguinetti M, Citton R, Montuori E, Leone F, Fadda G, Gauda R. Bloodstream infections caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae: risk factors, molecular epidemiology, and clinical outcome. Antimicrob Agents Chemother. 2006;50(2):498–504.

5. Paterson DL, Yu VL. Editorial response: extended-spectrum beta-lactamas: a call for improved detection and control. Clin Infect Dis. 1999;29:1419–22.

6. Pitout JDD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public health concern. Lancet Infect Dis. 2008;8(3):159–66.

7. Yigit H, Queenan AM, Anderson GJ, Domenech-Sanchez A, Biddle JW, Steward CD, Albetti S, Bush K, Tenover FC. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of Klebsiella pneumoniae. Antimicrob Agents Chemother. 2001;45(4):1151–61.

8. Jacob JT, Klein E, Laxminarayan R, Beldavs Z, Lynfield R, Kallen AJ, Ricks P, Edwards J, Sindwani A, Fridkin S, et al. Vital signs: carbapenem-resistant Enterobacteriaceae. Morb Mortal Wkly Rep. 2013;62(9):165–70.

9. Nordmann P, Gunzon G, Naas T. The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria. Lancet Infect Dis. 2009;9(4):228–36.

10. Nordmann P, Doret P, Poirer L. Carbapenem resistance in Enterobacteriaceae: here is the storm! Trends Mol Med. 2012;18(5):263–72.

11. Vardakas KZ, Matthaiou DK, Falagas ME, Antypa E, Kotelis A, Antoniadou E. Characteristics, risk factors and outcomes of carbapenem-resistant Klebsiella pneumoniae infections in the intensive care unit. J Infect. 2015;70(6):592–9.

12. Pouch SM, Kubin CJ, Satlin MJ, Tsapepas DS, Lee JR, Dube G, Pereira MR. Epidemiology and outcomes of carbapenem-resistant Klebsiella pneumoniae bacteremia in kidney transplant recipients. Transpl Infect Dis. 2015;17(6):800–9.

13. Ny P, Nieberg P, Wong-Beninger A. Impact of carbapenem resistance on epidemiology and outcomes of nonbacteremic Klebsiella pneumoniae infections. Am J Infect Control. 2015;43(10):1076–80.

14. Hoxha A, Karli T, Gimbic B, Montano C, Sisto A, Bella D, A’Donofa F, Study Working G. Attributable mortality of carbapenem-resistant Klebsiella pneumoniae infections in a prospective matched cohort study in Italy, 2012–2013. J Hosp Infect. 2015;92(1):61–6.

15. Cubero M, Cuervo G, Dominguez MA, Tubau F, Marti S, Sevillano E, Gallego L, Ayats J, Perich P, Pujol M, et al. Carbapenem-resistant and carbapenem-susceptible isolates of Klebsiella pneumoniae ST101 causing infection in a tertiary hospital. BMC Microbiol. 2015;15:177.

16. Brizendine KD, Richter SS, Cober ED, van Duin D. Carbapenem-resistant Klebsiella pneumoniae urinary tract infection following solid organ transplantation. Antimicrob Agents Chemother. 2015;59(1):553–7.

17. Simkins J, Muggia JS, Mohnow GY, Humphrey JS, Chassam EN. Carbapenem-resistant Klebsiella pneumoniae infections in kidney transplant recipients: a case-control study. Transpl Infect Dis. 2014;16(5):775–82.

18. Rueda VG. Risk factors for infection with carbapenem-resistant Klebsiella pneumoniae: a case–case–control study. Colombo Med. 2014;45(2):54–60.

19. Orsi GB, Bencardino A, Giordano V, Venditti M, Bencardino D, Gianfreda R, Falcone M, Carattoli A, Venditti M. Risk factors and clinical significance of etrampenem-resistant Klebsiella pneumoniae in hospitalised patients. J Hosp Infect. 2011;78(1):54–8.

20. Moulooudi E, Potronotanou E, Zagoniakou A, Kastrouli A, Karapanagiotou A, Giasnetsova T, Tsikou S, Roilides E, Sofianou D, Gritsio-Gerogianni N. Bloodstream infections caused by metallo-beta-lactamase/Klebsiella pneumoniae carbapenemase-producing K. pneumoniae among intensive care unit patients in Greece: risk factors for infection and impact of type of resistance on outcomes. Infect Control Hosp Epidemiol. 2010;31(12):1250–6.
42. Qureshi ZA, Syed A, Clarke LG, Doi Y, Shields RK. Epidemiology and clinical outcomes of patients with carbapenem-resistant Klebsiella pneumoniae bacteremia. Antimicrob Agents Chemother. 2014;58(6):3100–4.

43. Mouloudi E, Massa E, Papadopoulos S, Josifidis E, Rolides I, Theodoridou T, Piperidou M, Orphanou A, Passalkiotou M, Iamvros G, et al. Broad-spectrum carbapenemase-induced infections caused by carbapenemase-producing Klebsiella pneumoniae among intensive care unit patients after orthotopic liver transplantation: risk factors for infection and impact of resistance on outcomes. Transplant Proc. 2014;46(9):3216–8.

44. Gallagher JC, Kuriakose S, Haynes K, Axello P. Case-control study of patients with carbapenem-resistant and third-generation cephalosporin-resistant Klebsiella pneumoniae bloodstream infections. Antimicrob Agents Chemother. 2014;58(10):5732–5.

45. Shilo S, Assous MV, Lachish T, Kopuit P, Bdolah-Abram T, Yinnon AM, Weinler-Yell W. Risk factors for bacteremia with carbapenem-resistant Klebsiella pneumoniae and its impact on mortality: a case-control study. Infection. 2013;41(2):503–9.

46. Di Carlo P, Gulotta G, Casuccio A, Pantuso G, Raineri M, Farulla CA, Bonotto CA, et al. Sa1016 lessons learned from excess mortality due to kpc-producing Klebsiella pneumoniae bloodstream infections. J Glob Antimicrob Resist. 2015;3:1–8.

47. Pereira GH, Garcia DO, Mostardeiro M, Fanti KS, Levin AS. Outbreak of carbapenemase-producing Klebsiella pneumoniae due to carbapenem-resistant Klebsiella pneumoniae ST258 clone in postoperative abdominal surgery patients in an intensive care setting: analysis of a case series of 30 patients. BMC Anesthesiol. 2013;13(1):13.

48. Pereira GH, Garcia DO, Mostardeiro M, Fanti KS, Levin AS. Outbreak of carbapenem-resistant Klebsiella pneumoniae in patients with severe acute pancreatitis. J Hosp Infect. 2011;79(2):182–3.

49. Kontopidou F, Giamarellou H, Katerelos P, Maragos A, Kioumis I, Trikka-Anggelidou O, et al. Ann Clin Microbiol Antimicrob (2017) 16:18

50. Lübbert C, Rodloff AC, Laudi S, Simon P, Busch T, Mössner J, Bartels M, et al. Infections with metallo-b-lactamase (MBL)-producing Klebsiella pneumoniae: clinical features of a multilocus sequence type 15: molecular basis, clinical risk factors, and outcome. Antimicrob Agents Chemother. 2012;56(1):420–7.

51. Balarini Moreno B, Isidoro Fernandez B, Vazquez Grande G, Ortega MA, Paredes J, Najera C, et al. Infection and colonization with carbapenem-resistant Klebsiella pneumoniae in haematology patients. Haematologica. 2015;100(SUPPL 1):471.
nosocomial outbreak in a Spanish intensive care unit. Intensive Care Med. 2010;36(SUPPL 2):S256.

78. Cordery RJ, Roberts CH, Cooper SJ, Bellinghan G, Shetty N. Evaluation of risk factors for the acquisition of bloodstream infections with extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in the intensive care unit: antibiotic management and clinical outcome. J Hosp Infect. 2008;68(2):108–15.

79. Bhavnani SM, Ambrose PG, Craig WA, Dudley MN, Jones RN, Program SAS. Outcomes evaluation of patients with ESBL- and non-ESBL-producing Escherichia coli and Klebsiella species as defined by CLSI reference methods: report from the SENTRY Antimicrobial Surveillance Program. Diagn Microbiol Infect Dis. 2006;54(3):231–6.

80. Kim BN, Woo JH, Kim MN, Ryu J, Kim YS. Clinical implications of extended-spectrum β-lactamase-producing Klebsiella pneumoniae bacteraemia. J Hosp Infect. 2002;52(2):99–106.

81. Garcia-Sureda L, Domenech-Sanchez A, Barbier M, Juan C, Gasco J, Alberti S. OmpK26, a novel porin associated with carbapenem resistance in Klebsiella pneumoniae. Antimicrob Agents Chemother. 2011;55(10):4742–7.

82. Vardakas KZ, Rafaillidis PI, Konstantelias AA, Falagas ME. Predictors of mortality in patients with infections due to multi-drug resistant Gram negative bacteria: the study, the patient, the bug or the drug? J Infect. 2013;66(5):401–14.

83. Villegas MV, Lolans K, Correa A, Kattan JN, Lopez JA, Quinn JP. Colombian Nosocomial Resistance Study G. First identification of Pseudomonas aeruginosa isolates producing a KPC-type carbapenem-hydrolyzing beta-lactamase. Antimicrob Agents Chemother. 2007;51(4):1553–5.

84. Bratu S, Landman D, Haag R, Recco R, Eramo A, Alam M, Quale J. Rapid spread of carbapenem-resistant Klebsiella pneumoniae in New York City: a new threat to our antibiotic armamentarium. Arch Intern Med. 2005;165(12):1430–5.

85. Bratu S, Tolaney P, Karumudi U, Quale J, Mooty M, Nichani S, Landman D. Carbapenemase-producing Klebsiella pneumoniae in Brooklyn, NY: molecular epidemiology and in vitro activity of polymyxins B and other agents. J Antimicrob Chemother. 2005;56(1):129–32.

86. Karabinis A, Paramythiotou E, Mylona-Petrosioulou D. Colistin for Klebsiella pneumoniae—associated sepsis. Clin Infect Dis. 2004;38(1):e7–9.

87. Daly MW, Riddle DJ, Ledeboer NA, Dunne WM, Ritchie DJ. Tigecycline for the treatment of pneumonia and empyema caused by carbapenemase producing Klebsiella pneumoniae. Pharmacotherapy. 2007;27(7):1052–7.

88. Fligou F, Papadimitriou-Olivegeris M, Sklavou C, Anastassiou ED, Marangos M, Filos K. Risk factors and predictors of mortality for KPC-producing Klebsiella pneumoniae bacteraemia during intensive care unit stay. Eur J Anaesthesiol. 2013;30(suppl 51):187.