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Data Article

# Mortality, clinical and microbiological response following antibiotic therapy among patients with carbapenem-resistant *Klebsiella pneumoniae* infections (a meta-analysis dataset)

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ABSTRACT

This meta-analysis was conducted to assess mortality, clinical and microbiological response following antibiotic therapy among patients with carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections. Fifty-four observational studies involving 3195 CRKP-infected patients who received antibiotic treatment were included. We found combination therapy to be associated with lower mortality than monotherapy, but no differences in clinical and microbiological response. Among the various combination therapies, no significant differences in mortality, clinical and microbiological response were found. Moreover, clinical outcomes did not differ significantly among various monotherapies. This report describes the data related to the article entitled: "A systematic review and meta-analysis of treatment outcomes following antibiotic therapy among patients with carbapenem-resistant *Klebsiella pneumoniae* infections".



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Specifications Table

| | |
|---|---|
| Subject | Infectious diseases |
| Specific subject area | Antibiotic efficacy against carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections. |
| Type of data | Table<br>Chart<br>Figure |
| How data were acquired | Systematic review and meta-analysis |
| Data format | Raw data and analyzed data |
| Parameters for data collection | Outcomes (mortality, clinical and microbiological response) among antibiotic-treated patients with carbapenem-resistant *Klebsiella pneumonia* (CRKP) infections. |
| Description of data collection | The data presented is based on fifty-five articles (54 studies) selected based on a systematic literature review that involved searches performed in Medline, Embase, Cochrane Central, and the International Pharmaceutical Abstracts databases from their inception to December 2018. |
| Data source location | Monash University, Melbourne, Australia |
| Data accessibility | Data are with this article |
| Related research article | Agyeman AA, Bergen PJ, Rao GG, Nation RL, Landersdorfer CB<br>A systematic review and meta-analysis of treatment outcomes following antibiotic therapy among patients with carbapenem-resistant *Klebsiella pneumoniae* infections<br>International Journal of Antimicrobial Agents. |

**Value of the Data**

- The data contained in this dataset are useful because they could be employed in further studies to investigate treatment outcomes following antibiotic treatment in patients with CRKP infections.
- The data contained in the present dataset are related to treatment outcomes (mortality, clinical and microbiological response) among antibiotic-treated CRKP-infected patients and has been obtained from multiple studies in different countries. Therefore, patients with infections caused by CRKP, and clinicians treating these patients can benefit from these data.
- This dataset can be used to generate further insights by informing future trials that seek to examine antibiotic treatment choices for CRKP infections.
- The method of data collection is systematic review and meta-analysis. Therefore, an additional value of the methods described and the data synthesized is that they can be useful for future systematic reviews and meta-analysis.

## 1. Data

Based on the inclusion criteria, out of 1863 articles initially screened, fifty-five articles (54 studies) reporting treatment outcomes among antibiotic-treated CRKP-infected patients were included in the meta-analysis (Fig. 1). The included studies were of good quality as per their quality appraisal scores (Table 1) which were evaluated using the Newcastle-Ottawa scale (NOS) for nonrandomized trials included in meta-analyses [1].

### 1.1. Mortality

The data showed that the overall pooled mortality rate among the CRKP-infected patients treated with antibiotics was 37.2% (95% CI 33.1–41.4%; $I^2$ = 76.8%) (Fig. 2). Sub-group analyses based on geographic region (North America: 30.4%, 95% CI 20.9–40.8%, $I^2$ = 80.4%; other: 39.5%, 95% CI 35.1–44.1%, $I^2$ = 74.7%), publication years (≤2012: 40.8%, 95% CI 31.4–50.6%; $I^2$ = 67.2%; 2013–2018: 36.1%, 95% CI 31.5–40.8%, $I^2$ = 79.8%) and study design (retrospective: 37.5%, 95% CI 32.6–42.5%, $I^2$ = 79.1%: prospective: 35.4%, 95% CI 28.2–42.9%; $I^2$ = 56.6%) did not result in significant reduction in heterogeneity levels for the pooled mortality rates. Moreover, funnel plot visualization showed no evidence of publication bias (Fig. 3).

Compared to combination therapy, monotherapy was associated with a higher likelihood of mortality (odds ratio [OR] 1.45, 95% CI 1.18–1.78; $I^2$ = 0.0%) (Fig. 4). However, there were no significant

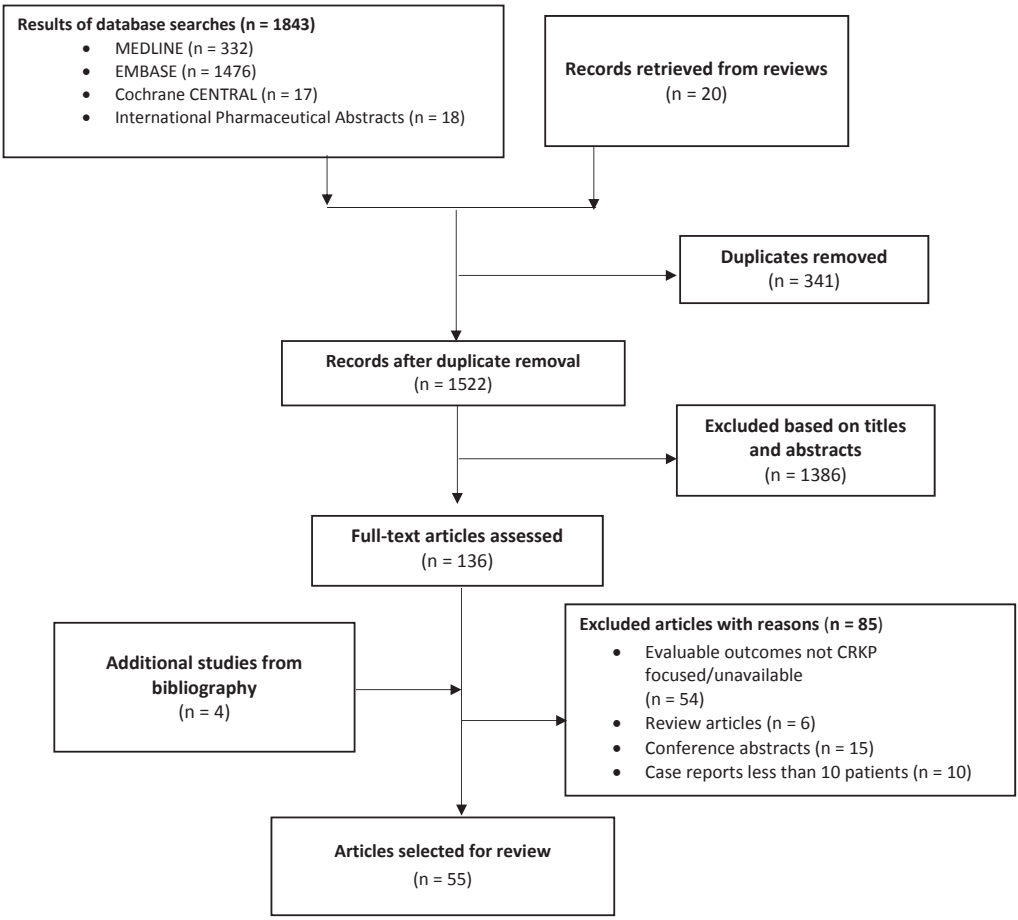


**Fig. 1.** Flow diagram of the systematic review process.

differences in the likelihood of mortality between CRKP-infected patients treated with 2-drug and ≥3-drug combination regimens (Fig. 5) or between the combination containing and sparing regimens of carbapenems (Fig. 6), polymyxins (Fig. 7), aminoglycosides (Fig. 8) and tigecycline (Fig. 9). Moreover, there were no significant differences in the likelihood of mortality between the various monotherapies (Table 2). The comparison of the mortality outcomes across the various antibiotic combination regimens did not change when the analysis was restricted to 14- and 30-day mortality (Table 3).

### *1.2. Clinical response*

The data showed that the overall pooled clinical response rate among the CRKP-infected patients treated with antibiotics was 69.0% (95% CI 60.1–78.2%; $I^2 = 82.8\%$) (Fig. 10). Sub-group analyses based on geographic region (North America: 64.9%, 95% CI 50.1–78.5%, $I^2 = 80.4$; other: 72.4%, 95% CI 60.0–83.4%; $I^2 = 85.4\%$), publication years (≤2012: 73.9%, 95% CI 57.1–88.0%; $I^2 = 82.5\%$; 2013–2018: 66.3%, 95% CI 54.9–76.9%, $I^2 = 83.6\%$) and study design (retrospective: 67.1%, 95% CI 55.5–77.7%, $I^2 = 84.4\%$: prospective: 79.7%, 95% CI 63.2–92.6%; $I^2 = 59.4\%$) did not result in significant reduction in heterogeneity levels for the pooled clinical response rate. Moreover, direct observation of the funnel plot did not show any obvious evidence of publication bias (Fig. 11).

**Table 1**
Newcastle-Ottawa Scale for quality assessment of included studies.

| Article No. | First author, year | Criteria for quality assessment | | | | | | | | Total quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Selection | | | | Comparability | Outcome/Exposure | | | |
| | | 1 | 2 | 3 | 4 | | 1 | 2 | 3 | |
| 1 | Alexander, 2012 [2] | * | n.a | * | * | n.a | * | * | * | 6 |
| 2 | Bergamasco, 2012 [3] | * | n.a | * | * | n.a | * | * | * | 7 |
| 3 | Brizendine, 2015 [4] | * | * | * | * | * * | * | * | * | 9 |
| 4 | Capone, 2013 [5] | * | n.a | * | * | n.a | * | * | - | 5 |
| 5 | Cprek, 2016 [6] | * | n.a | * | * | n.a | * | * | * | 6 |
| 6 | Daikos, 2009 [7] | * | * | * | * | ** | * | * | * | 9 |
| 7 | Daikos, 2014 [8] | * | n.a | * | * | n.a | * | * | * | 6 |
| 8 | Dubrovskaya, 2013 [9] | * | n.a | * | * | n.a | * | * | * | 6 |
| 9 | Gomez-Simmonds, 2016 [10] | * | n.a | * | * | n.a | * | * | * | 6 |
| 10 | Ji, 2015 [11] | * | n.a | * | * | n.a | * | * | * | 6 |
| 11 | Machuca, 2017 [12] | * | n.a | * | * | n.a | * | * | * | 6 |
| 12 | Michalopoulos, 2010 [13] | * | n.a | * | * | n.a | * | * | * | 6 |
| 13 | Mouloudi, 2010 [14] | * | * | - | - | ** | * | * | n.a | 6 |
| 14 | Nguyen, 2010 [15] | * | n.a | * | * | n.a | * | * | * | 6 |
| 15 | Qureshi, 2012 [16] | * | n.a | * | * | n.a | * | * | * | 6 |
| 16 | Qureshi, 2014 [17] | * | * | * | * | ** | * | * | * | 9 |
| 17 | Sanchez-Romero, 2012 [18] | * | * | * | * | ** | * | - | * | 8 |
| 18 | Satlin, 2011 [19] | * | n.a | * | * | n.a | * | * | * | 6 |
| 19 | Souli, 2008 [20] | * | n.a | * | * | n.a | * | * | * | 6 |
| 20 | Souli, 2010 [21] | * | n.a | * | * | n.a | * | * | * | 6 |
| 21 | Souli, 2017 [22] | * | n.a | * | * | n.a | * | * | * | 6 |
| 22 | Shields, 2016a [23] | * | n.a | * | * | n.a | * | * | * | 6 |
| 23 | Trecarichi, 2016 [24] | * | * | * | * | ** | * | * | * | 9 |
| 24 | Tumbarello, 2012 [25] | * | n.a | * | * | n.a | * | * | * | 6 |
| 25 | Tumbarello, 2015 [26] | * | n.a | * | * | n.a | * | * | * | 6 |
| 26 | Vardakas, 2015 [27] | * | n.a | * | * | n.a | * | * | * | 6 |
| 27 | Venugopalan, 2017 [28] | * | * | * | * | ** | * | * | n.a | 8 |
| 28 | Weisenberg, 2009 [29] | * | n.a | * | * | n.a | * | - | * | 5 |
| 29 | Daikos, 2007 [30] | * | * | - | - | ** | * | * | n.a | 6 |
| 30 | Maltezou, 2009 [31] | * | n.a | * | * | n.a | * | * | * | 6 |
| 31 | Navarro-San, 2013 [32] | * | n.a | * | * | n.a | * | * | * | 6 |
| 32 | Di Carlo, 2013 [33] | * | n.a | * | * | n.a | * | * | * | 6 |
| 33 | Balandin, 2014 [34] | * | n.a | * | * | n.a | * | * | * | 6 |
| 34 | Kontopidou, 2014 [35] | * | n.a | * | * | n.a | * | * | * | 6 |
| 35 | McLaughlin, 2014 [36] | * | * | - | * | ** | * | * | n.a | 7 |
| 36 | Pontikis, 2014 [37] | * | n.a | * | * | n.a | * | * | * | 6 |
| 37 | Mammina, 2010 [38] | * | n.a | * | * | n.a | * | * | * | 6 |
| 38 | Oliva, 2017 [39] | * | n.a | * | * | n.a | * | * | * | 6 |
| 39 | Gonzalez-Padilla, 2015 [40] | * | n.a | * | * | n.a | * | * | * | 6 |
| 40 | Neuner, 2011 [41] | * | n.a | * | * | n.a | * | * | * | 6 |
| 41 | Falagas, 2007 [42] | * | * | - | * | ** | * | * | n.a | 7 |
| 42 | Sbrana, 2013 [43] | * | n.a | * | * | n.a | * | * | * | 6 |
| 43 | Papadimitriou-Olivgeris, 2017 [44] | * | * | - | * | ** | * | * | n.a | 7 |
| 44 | Falcone, 2016 [45] | * | n.a | * | * | n.a | * | * | * | 6 |
| 45 | Liao, 2017 [46] | * | n.a | * | * | n.a | * | - | * | 5 |
| 46 | De Pascale, 2017 [47] | * | * | - | - | ** | * | * | n.a | 6 |
| 47 | Freire, 2015 [48] | * | * | * | * | ** | * | * | * | 9 |
| 48 | Hussein, 2013 [49] | * | * | - | * | ** | * | * | n.a | 7 |
| 49 | Simkins, 2014 [50] | * | * | - | * | ** | * | * | n.a | 7 |
| 50 | Shields, 2016b [51] | * | n.a | * | * | n.a | * | * | * | 6 |
| 51 | Russo, 2018 [52] | * | * | - | * | ** | * | * | n.a | 7 |
| 52 | Su, 2018 [53] | * | n.a | * | * | n.a | * | * | * | 6 |
| 53 | Varotti, 2017 [54] | * | * | - | * | ** | * | * | n.a | 7 |
| 54 | Pouch, 2015 [55] | * | * | - | * | ** | * | * | n.a | 7 |
| 55 | Duani, 2018 [56] | * | * | - | * | ** | * | * | n.a | 7 |

*Fulfillment of items within a section; n.a, not applicable.

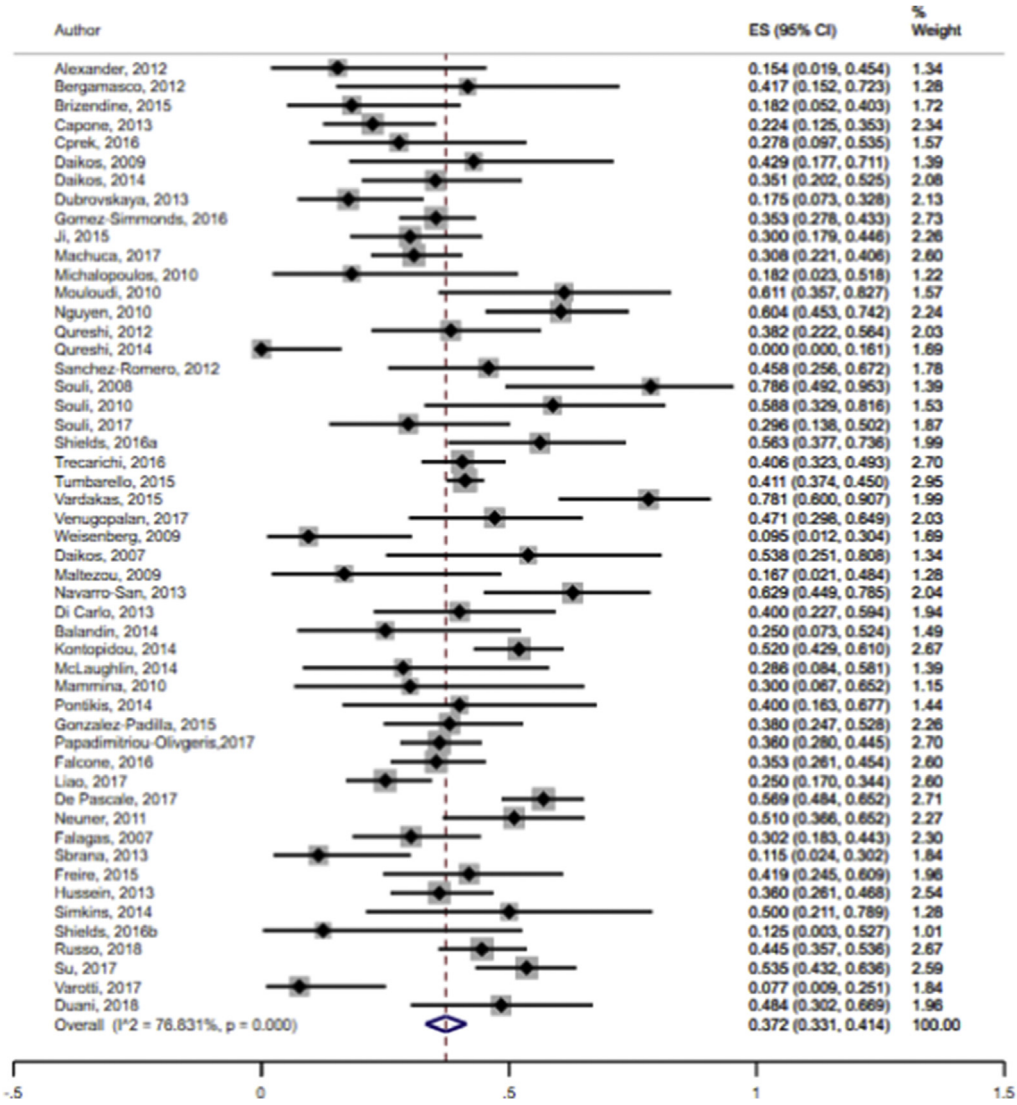


**Fig. 2.** Pooled mortality rates following antibiotic treatment among CRKP-infected patients in the included studies.

There was no significant difference in the clinical response rate between monotherapy and combination regimens (Fig. 12), nor between 2-drug and ≥3-drug combination regimens (Fig. 13). Furthermore, no significant differences were noted in the pooled clinical response between combination containing and sparing regimens of carbapenems (Fig. 14), polymyxins (Fig. 15), aminoglycosides (Fig. 16) and tigecycline (Fig. 17). Moreover, there were no significant differences in the likelihood of clinical response between the various monotherapies (Table 2).

### *1.3. Microbiological response*

The data showed that the overall pooled microbiological response rate among the CRKP-infected patients treated with antibiotics was 63.7% (95% CI 53.7−74.1%; $I^2$ = 82.1%) (Fig. 18). Sub-group

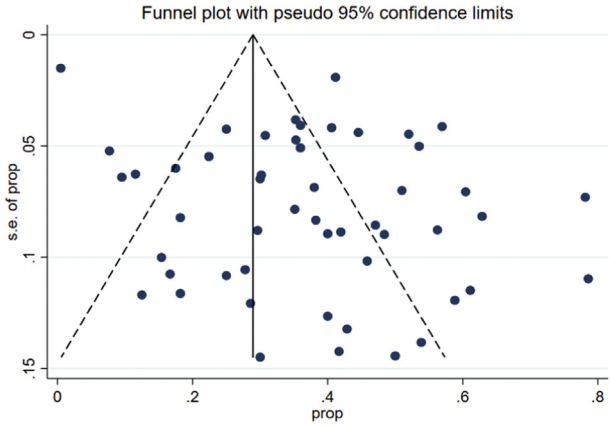


**Fig. 3.** Funnel plot depicting reported mortality rates following antibiotic therapy across included studies.

analyses based on geographic region (North America: 71.6%, 95% CI 63.6–79.1%, $I^2 = 48.7\%$; other: 53.9%, 95% CI 34.5–72.7%, $I^2 = 86.7\%$), publication years (≤2012: 67.8%, 95% CI 49.1–84.2%; $I^2 = 82.6\%$; 2013–2018: 62.2%, 95% CI 49.3–74.4%, $I^2 = 80.9\%$) and study design (retrospective: 63.2%, 95% CI 51.6–74.1%, $I^2 = 81.9\%$; prospective: 78.8%, 95% CI 60.6–92.9%; $I^2 = 68.0\%$) did not result in significant reduction in heterogeneity levels for the pooled microbiological response rate. Moreover, as per the funnel plot visualization, there was no obvious presence of publication bias (Fig. 19).

There was no significant difference in the microbiological response rate between monotherapy and combination regimens (Fig. 20), nor between 2-drug and ≥3-drug combination regimens (Fig. 21). Furthermore, no significant differences were noted in the pooled microbiological response between combination containing and sparing regimens of carbapenems (Fig. 22), polymyxins (Fig. 23), aminoglycosides (Fig. 24) and tigecycline (Fig. 25). Moreover, there were no significant differences in the likelihood of clinical response between the various monotherapies (Table 2).

## 2. Experimental design, materials and methods

### 2.1. Search strategy

In this article, treatment outcomes (mortality, clinical and microbiological response) among antibiotic-treated CRKP-infected patients were reviewed based on published literature. More specifically, a thorough systematic literature search was conducted in Medline, EMBASE, the Cochrane Central Register of Controlled Trials, and the International Pharmaceutical Abstracts databases from their inception to December 26 2018 using the using search terms such as *Klebsiella pneumoniae*, antibiotic therapy and carbapenem resistance. The full search strategy is presented in Table 4. The database searches were also supplemented by manual reference screening of the included articles.

## 3. Methodological quality assessment

All studies that met the selection criteria were assessed for quality via the Newcastle-Ottawa scale (NOS) for nonrandomized trials included in meta-analyses [1]. Studies achieving a NOS score of ≥5 were deemed to be of sufficient quality for inclusion in the review.

### 3.1. Inclusion and exclusion criteria

All studies addressing treatment outcomes for patients with infections caused by CRKP who received antibiotic therapy were eligible for inclusion. Studies involving both infected and colonized

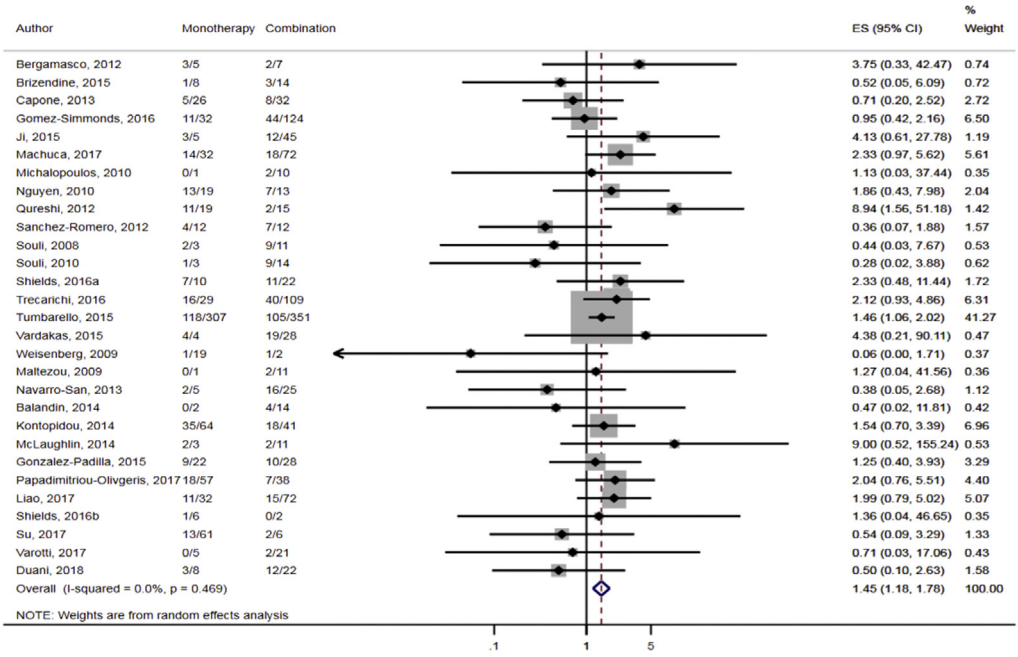


**Fig. 4.** Comparison of mortality between CRKP-infected patients treated with monotherapy and combination therapies.

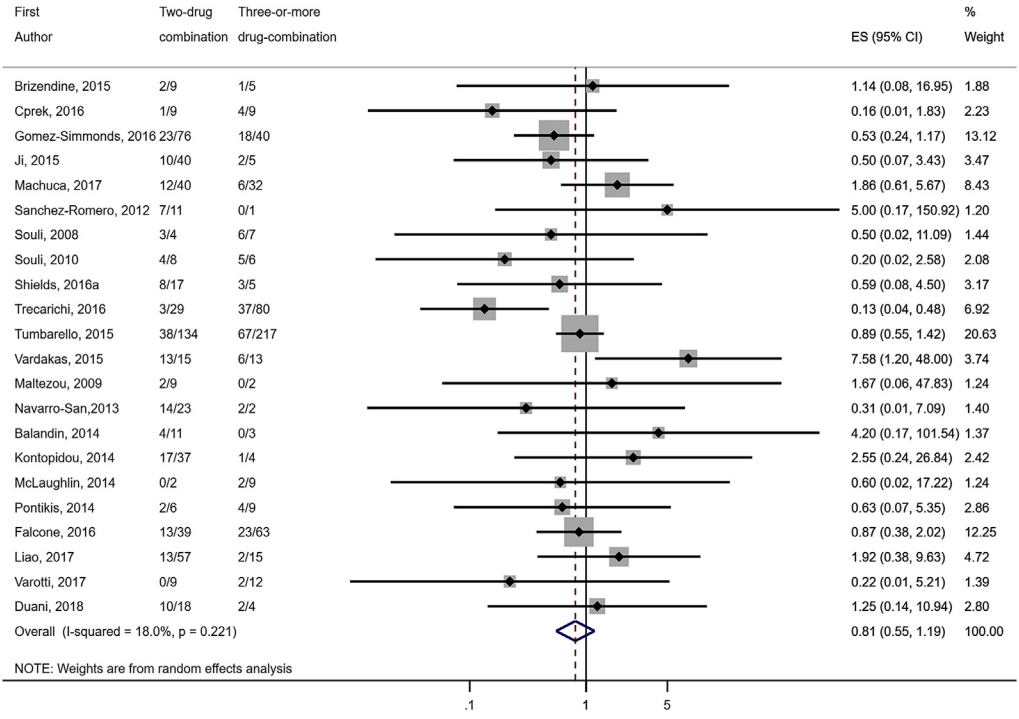


**Fig. 5.** Comparison of mortality between CRKP-infected patients treated with ≥3-drug and those on 2-drug combination therapies.

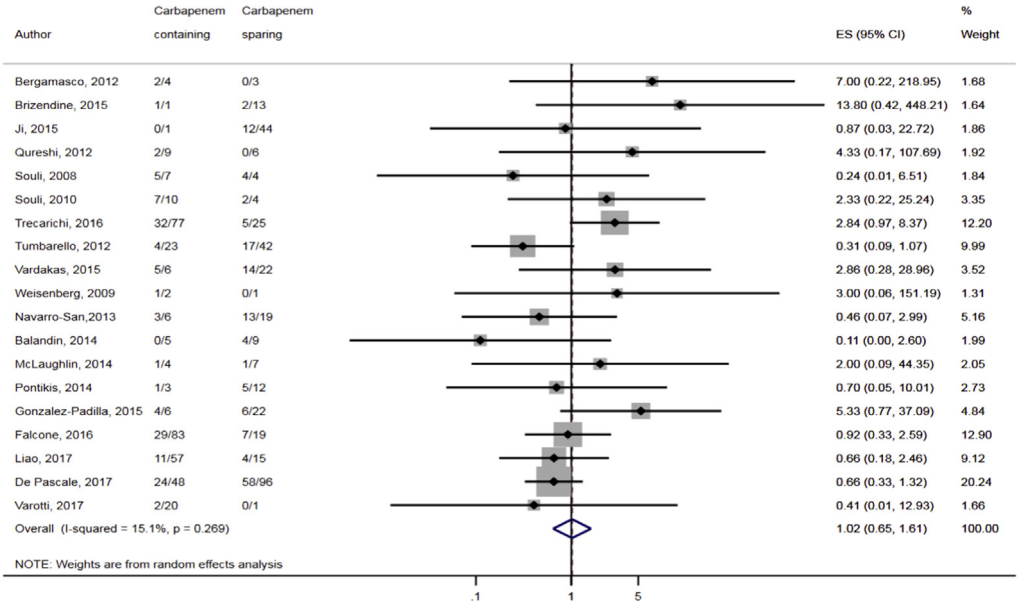


**Fig. 6.** Comparison of mortality between CRKP-infected patients treated with carbapenem-containing and carbapenem-sparing combination therapies.

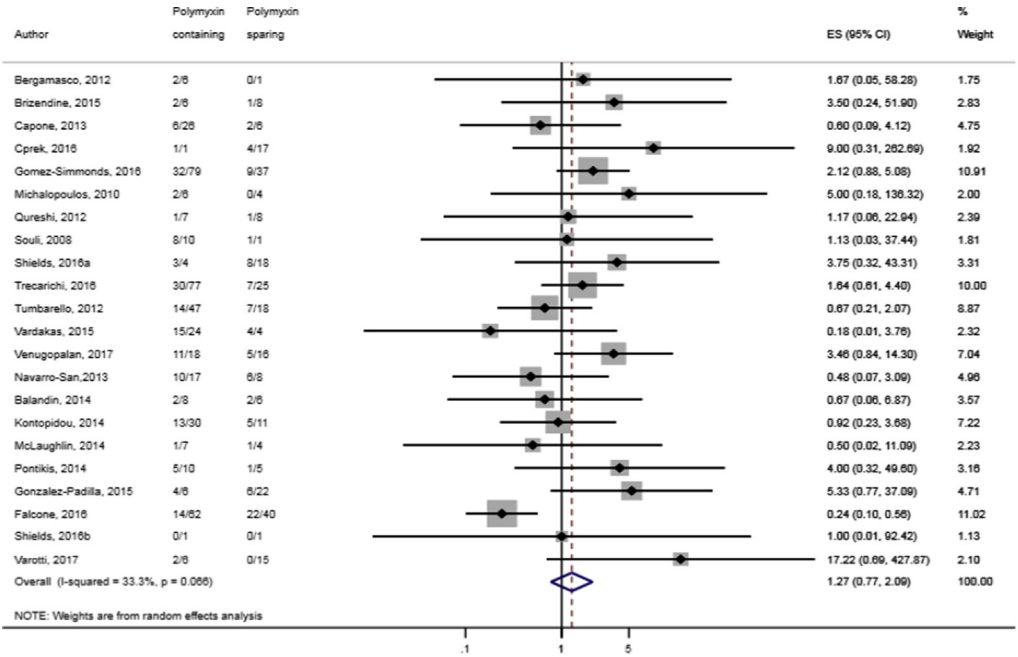


**Fig. 7.** Comparison of mortality between CRKP-infected patients treated with polymyxin-containing and polymyxin-sparing combination therapies.

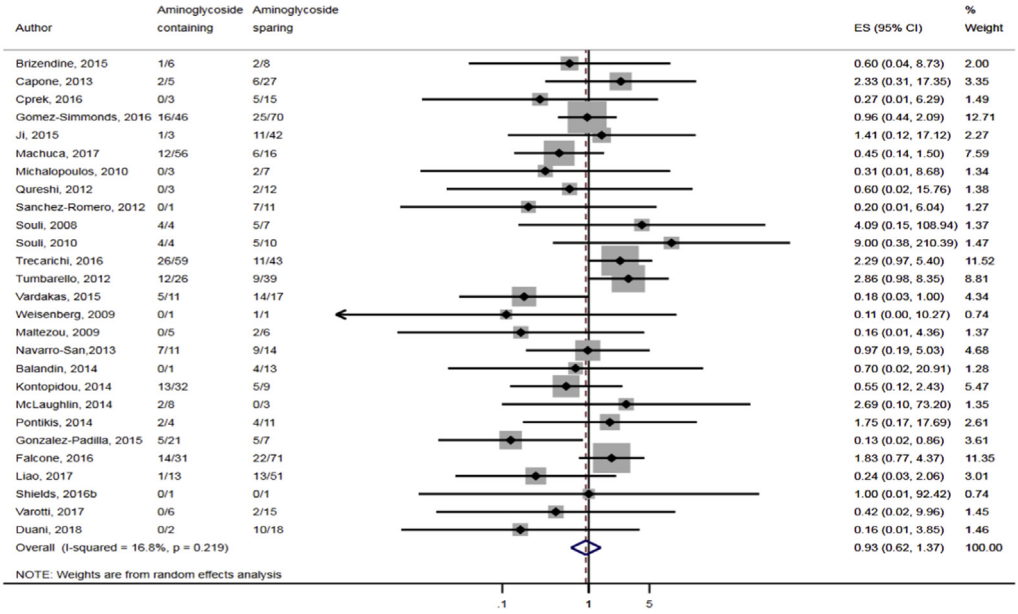


**Fig. 8.** Comparison of mortality between CRKP-infected patients treated with aminoglycoside-containing and aminoglycoside-sparing combination therapies.

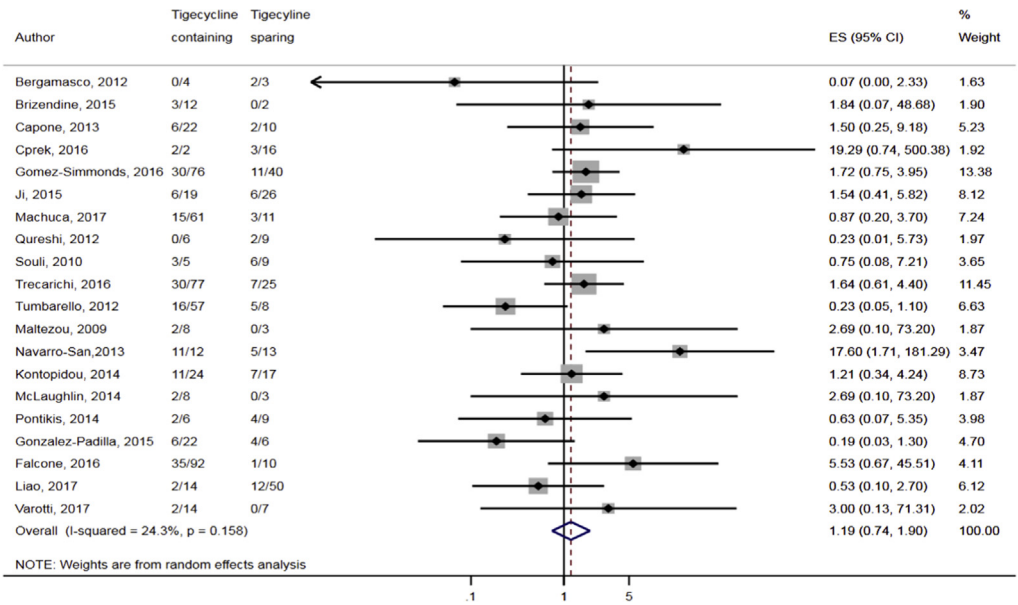


**Fig. 9.** Comparison of mortality between CRKP-infected patients treated with tigecycline-containing and tigecycline-sparing combination therapies.

**Table 2**
Comparison of mortality, microbiological and clinical response rate according to various antibiotic monotherapies.

| Outcome | No. of studies pooled | No. of patients | Odds Ratio (OR) (95% CI) | Heterogeneity of included studies |
|---|---|---|---|---|
| Mortality | | | | |
| Carbapenem vs polymyxin | 7 | 98 | 0.83 (0.29–2.40) | 18.3%, p = 0.290 |
| Carbapenem vs aminoglycoside | 10 | 110 | 1.83 (0.67–4.97) | 11.3%, p = 0.339 |
| Carbapenem vs tigecycline | 8 | 103 | 1.43 (0.56–3.69) | 0.0%, 0.540 |
| Polymyxin vs aminoglycoside | 11 | 377 | 1.10 (0.70–1.71) | 0.0%, p = 0.557 |
| Polymyxin vs tigecycline | 11 | 422 | 0.84 (0.56–1.25) | 0.0%, p = 0.788 |
| Aminoglycoside vs tigecycline | 11 | 188 | 0.53 (0.27–1.04) | 0.0%, p = 0.980 |
| Clinical response | | | | |
| Carbapenem vs polymyxin | No pooled data (1 datapoint) | – | – | – |
| Carbapenem vs aminoglycoside | 3 | 19 | 0.75 (0.08–7.08) | 0.0%, p = 0.592 |
| Carbapenem vs tigecycline | 3 | 27 | 0.92 (0.14–5.91) | 0.0%, p-0.554 |
| Polymyxin vs aminoglycoside | 2 | 50 | 1.10 (0.13–9.61) | 28.7%, p = 0.236 |
| Polymyxin vs tigecycline | 4 | 69 | 2.27 (0.46–11.27) | 0.0%, p = 0.564 |
| Aminoglycoside vs tigecycline | 3 | 56 | 2.58 (0.79–8.41) | 0.0%, p = 0.997 |
| Microbiological response | | | | |
| Carbapenem vs polymyxin | No pooled data (0 datapoint) | – | – | – |
| Carbapenem vs aminoglycoside | No pooled data (1 datapoint) | – | – | – |
| Carbapenem vs tigecycline | No pooled data (1 datapoint) | – | – | – |
| Polymyxin vs aminoglycoside | No pooled data (1 datapoint) | – | – | – |
| Polymyxin vs tigecycline | 2 | 50 | 2.76 (0.87–8.68) | 0.0%, p = 0.344 |
| Aminoglycoside vs tigecycline | 2 | 65 | 3.00 (0.60–15.1) | 0.0%, p = 0.580 |

**Table 3**
Sub-group analyses of 14-day and 30-day mortality following specific antibiotic therapies among CRKP-infected patients.

| Mortality | No. of studies pooled | No. of patients | Odds Ratio (OR) (95% CI) | Heterogeneity of included studies |
|---|---|---|---|---|
| By 14-day | | | | |
| Monotherapy vs combination | 8 | 935 | **1.42 (1.06–1.90); p = 0.020** | $I^2 = 0.0\%$; p = 0.907 |
| 2-drug vs ≥ 3-drug combination | 8 | 490 | 0.91 (0.59–1.41); p = 0.674 | $I^2 = 0.0\%$; p = 0.844 |
| Carbapenem-containing vs carbapenem-sparing | 4 | 65 | 1.39 (0.31–6.16); p = 0.664 | $I^2 = 0.0\%$; p = 0.700 |
| Polymyxin-containing vs polymyxin-sparing | 5 | 114 | 1.45 (0.50–4.16); p = 0.491 | $I^2 = 0.0\%$; p = 0.531 |
| Aminoglycoside-containing vs aminoglycoside-sparing | 6 | 117 | 0.46 (0.17–1.24); p = 0.125 | $I^2 = 0.0\%$; p = 0.504 |
| Tigecycline-containing vs tigecycline-sparing | 5 | 106 | 1.70 (0.60–4.78); p = 0.315 | $I^2 = 0.0\%$; p = 0.890 |
| By 28-day or 30-day | | | | |
| Monotherapy vs combination | 14 | 763 | **1.54 (1.09–2.17); p = 0.015** | $I^2 = 1.2\%$; p = 0.436 |
| 2-drug vs ≥ 3-drug combination | 13 | 555 | 0.91 (0.59–1.42); p = 0.684 | $I^2 = 9.2\%$; p = 0.353 |
| Carbapenem-containing vs carbapenem-sparing | 11 | 470 | 0.65 (0.37–1.12); p = 0.123 | $I^2 = 14.2\%$; p = 0.309 |
| Polymyxin-containing vs polymyxin-sparing | 12 | 457 | 1.33 (0.64–2.75); p = 0.446 | $I^2 = 53.8\%$; p = 0.014 |
| Aminoglycoside-containing vs aminoglycoside-sparing | 13 | 545 | 0.99 (0.58–1.67); p = 0.956 | $I^2 = 27.0\%$; p = 0.172 |
| Tigecycline-containing vs tigecycline-sparing | 11 | 507 | 1.09 (0.48–2.45); p = 0.844 | $I^2 = 56.1\%$; p = 0.012 |

The bold values represent the significant results.

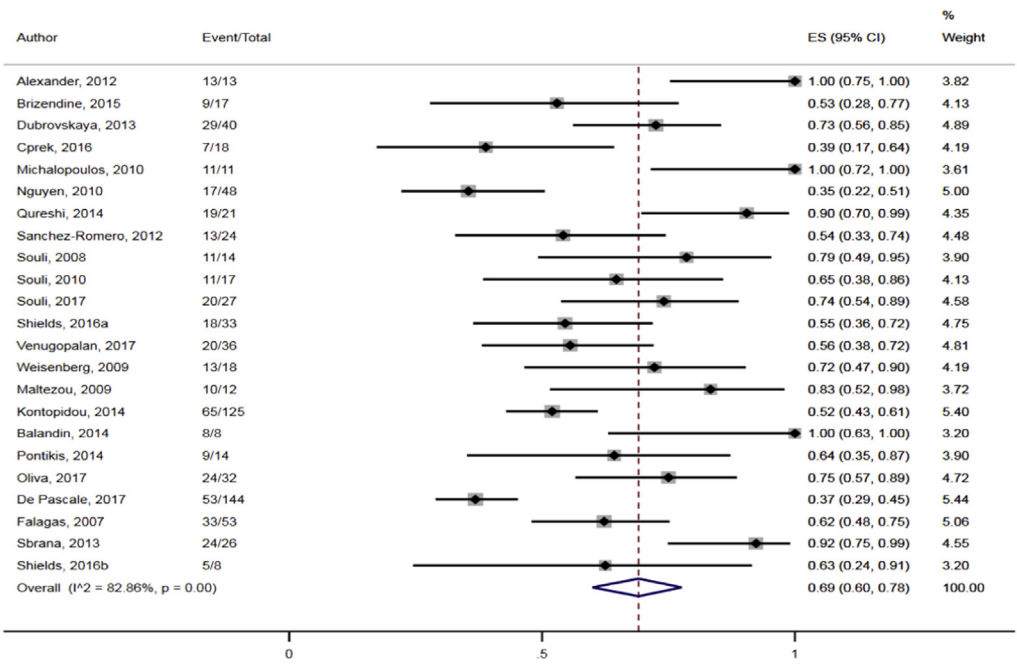


**Fig. 10.** Pooled clinical response rates following antibiotic treatment among CRKP-infected patients in the included studies.

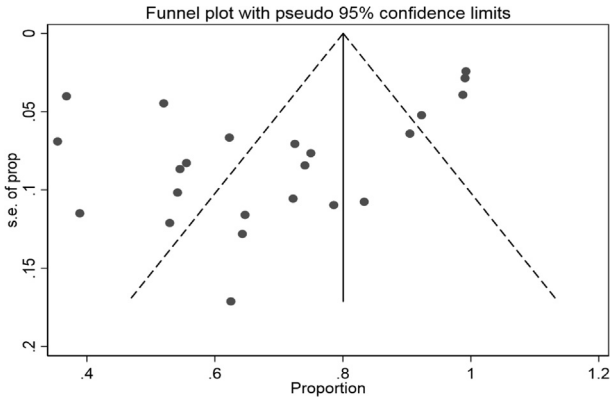


**Fig. 11.** Funnel plot depicting reported clinical response rates following antibiotic therapy across included studies.

patients were included if the treatment outcomes of the infected patients could be separately extracted. Studies were excluded if they were based upon case reports or case series of <10 patients, focused on children or were *in vitro* or animal studies. Conference abstracts and meeting reports were also excluded.

### *3.2. Data extraction*

A pre-designed data extraction form was used to collect relevant data. The extracted information included study details (first author, publication year, sample size, period, design, and country),

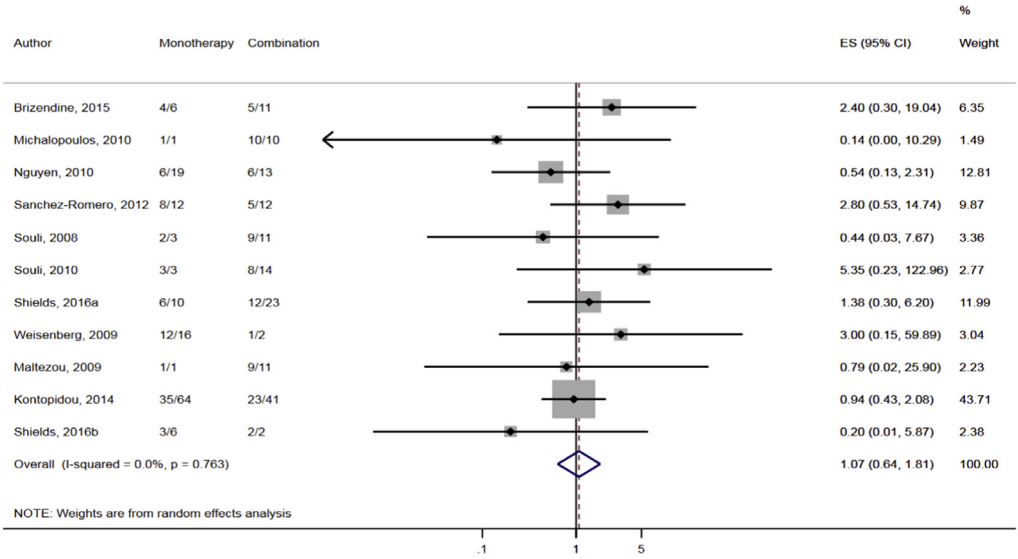


**Fig. 12.** Comparison of clinical response between CRKP-infected patients treated with monotherapy and combination therapies.

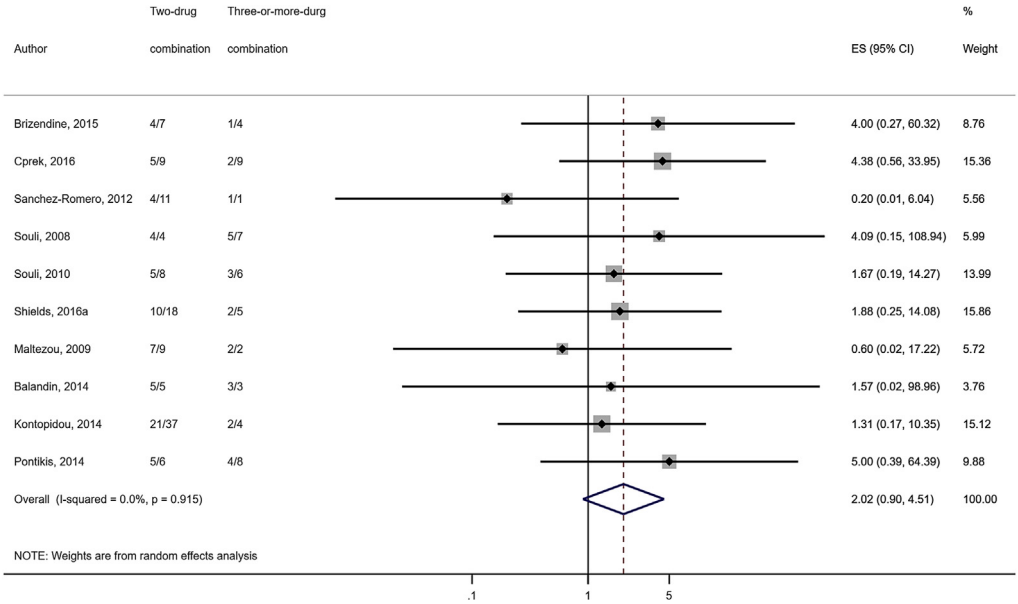


**Fig. 13.** Comparison of clinical response between CRKP-infected patients treated with ≥3-drug and those on 2-drug combination therapies.

population characteristics (gender distribution, mean age, site of infection etc.), antibiotic susceptibility testing (AST), details of antibiotic regimen, treatment outcomes (mortality, clinical response, and microbiological response) and any reported adverse events. All-cause mortality evaluated at end of patient follow-up was the primary outcome measurement. We additionally extracted data specifically

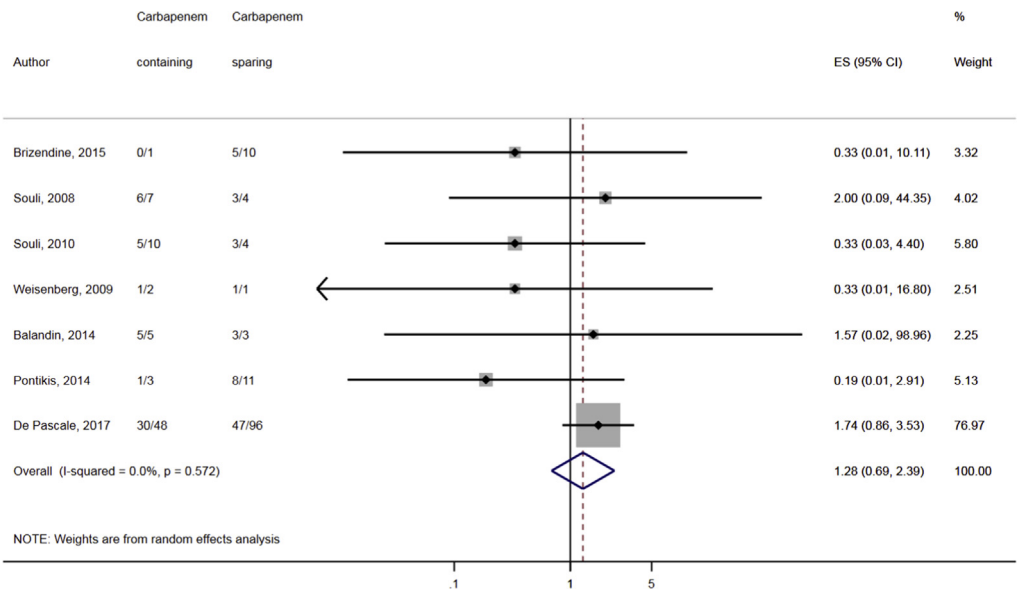


**Fig. 14.** Comparison of clinical response between CRKP-infected patients treated with carbapenem-containing and carbapenem-sparing combination therapies.

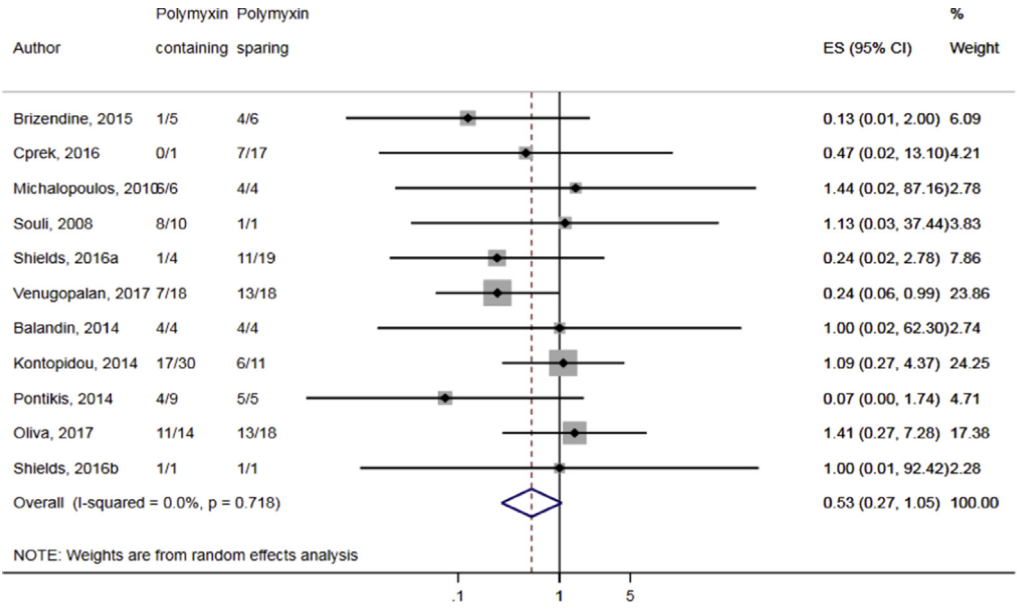


**Fig. 15.** Comparison of clinical response between CRKP-infected patients treated with polymyxin-containing and polymyxin-sparing combination therapies.

for 14-day and 30-day mortality. The secondary outcomes were clinical response, microbiological response and adverse events. Due to the lack of standard and uniform criteria for the assessment and reporting of clinical response and microbiological response we adopted the definitions as employed in

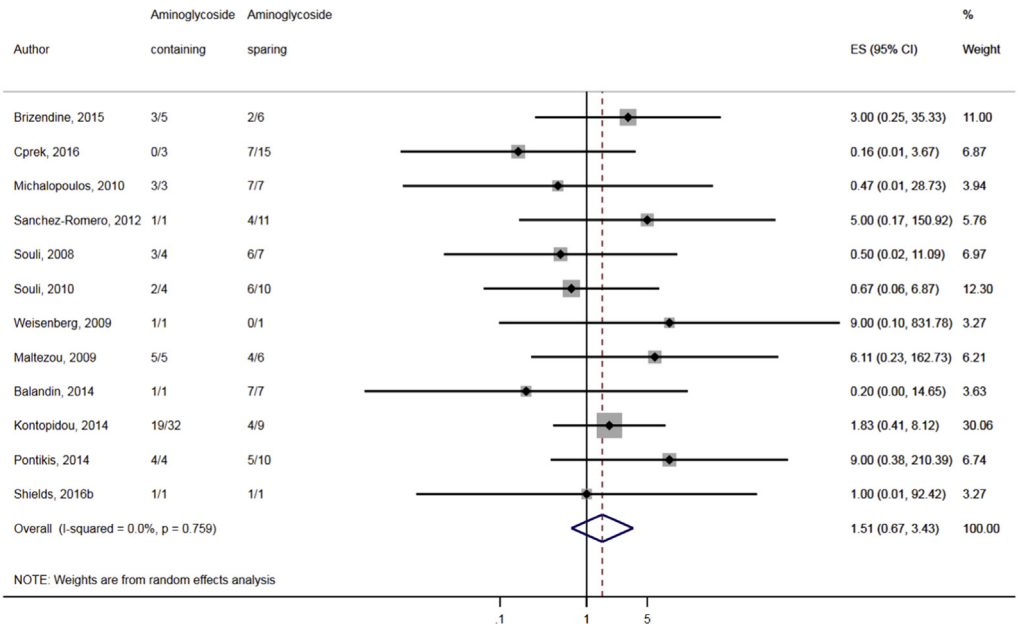


**Fig. 16.** Comparison of clinical response between CRKP-infected patients treated with aminoglycoside-containing and aminoglycoside-sparing combination therapies.

individual studies. The articles' screening and selection process was conducted according to the PRISMA Guidelines [57].

### 3.3. Data analysis

The overall all-cause mortality, clinical response and microbiological response rates were determined via meta-analysis proportion. The meta-analysis was performed using the Freeman-Tukey

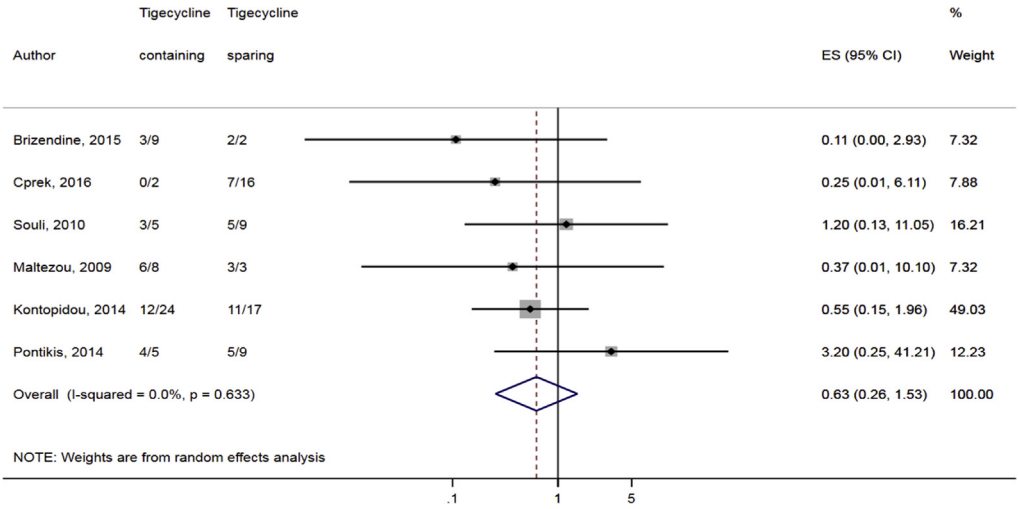


**Fig. 17.** Comparison of clinical response between CRKP-infected patients treated with tigecycline-containing and tigecycline-sparing combination therapies.

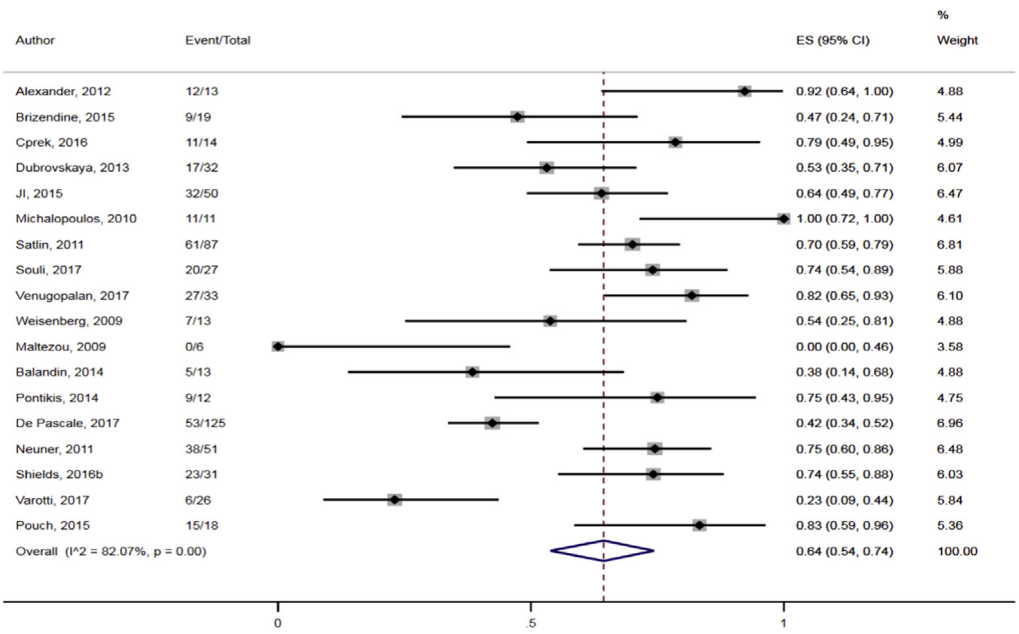


**Fig. 18.** Pooled microbiological response rates following antibiotic treatment among CRKP-infected patients in the included studies.

double arcsine transformed proportions to stabilize the variance [58]. A random-effects (DerSimonian and Laird) model was used in the meta-analysis due to the anticipated heterogeneity across studies. For the comparative assessment of treatment outcomes following specific antibiotic therapies, the effect measure was expressed as odds ratios (ORs). Cochran's Q test and the $I^2$ statistic were used to quantify the presence of statistical heterogeneity [59]. $I^2$ values of 25%, 50%, and 75% were considered to be low, moderate, and high degrees of heterogeneity, respectively. To examine the potential sources of heterogeneity in the pooled mortality, clinical and microbiological response rates, we performed subgroup analyses based on the following characteristics: geographic region (North America *vs.* other), publication years (≤2012 *vs.* 2013–2018) and study design (prospective *vs.* retrospective). The presence of

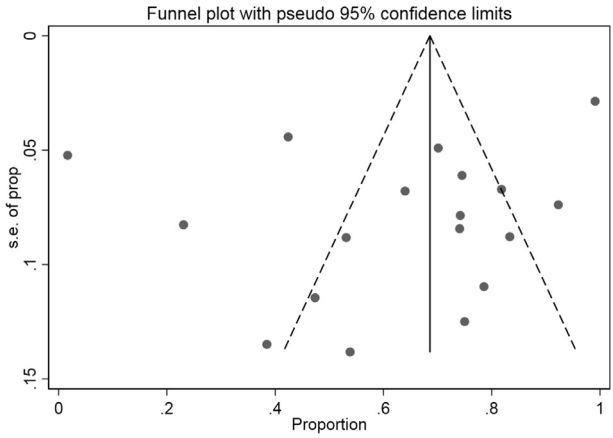


**Fig. 19.** Funnel plot depicting reported microbiological response rates following antibiotic therapy across included studies.

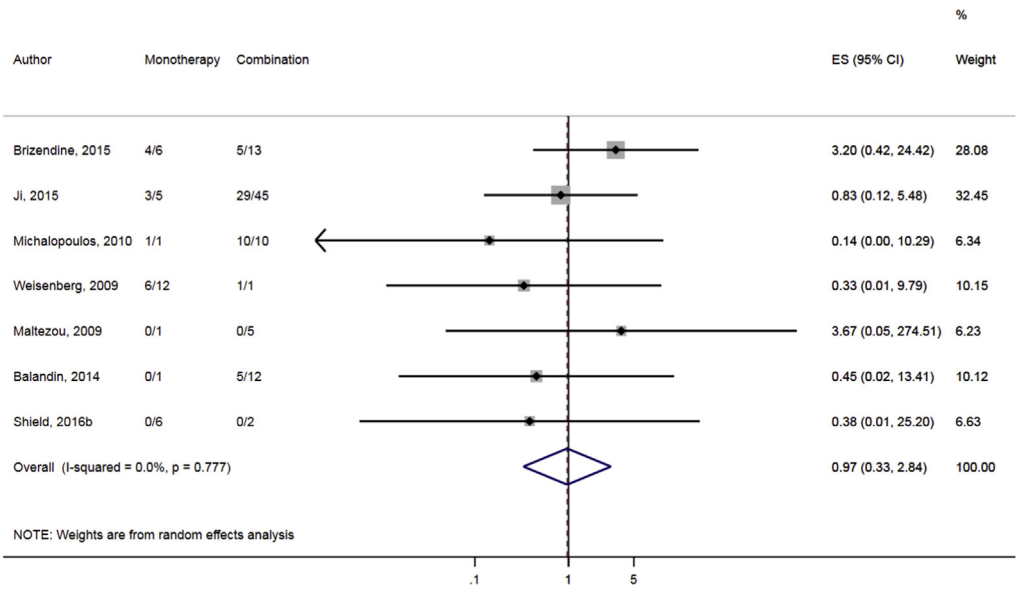


**Fig. 20.** Comparison of microbiological response between CRKP-infected patients treated with monotherapy and combination therapies.

publication bias was assessed by direct observation of funnel plots and quantified with Egger's regression test [60]. To examine the robustness of our pooled estimates, leave-one-out sensitivity analyses were performed. A study was considered influential if the pooled estimate without it was outside the 95% CIs of the overall pooled estimate. All analyses were performed using Stata 15/IC (StataCorp LP, College Station, Texas, USA). P-value <0.05 was considered as statistically significant.

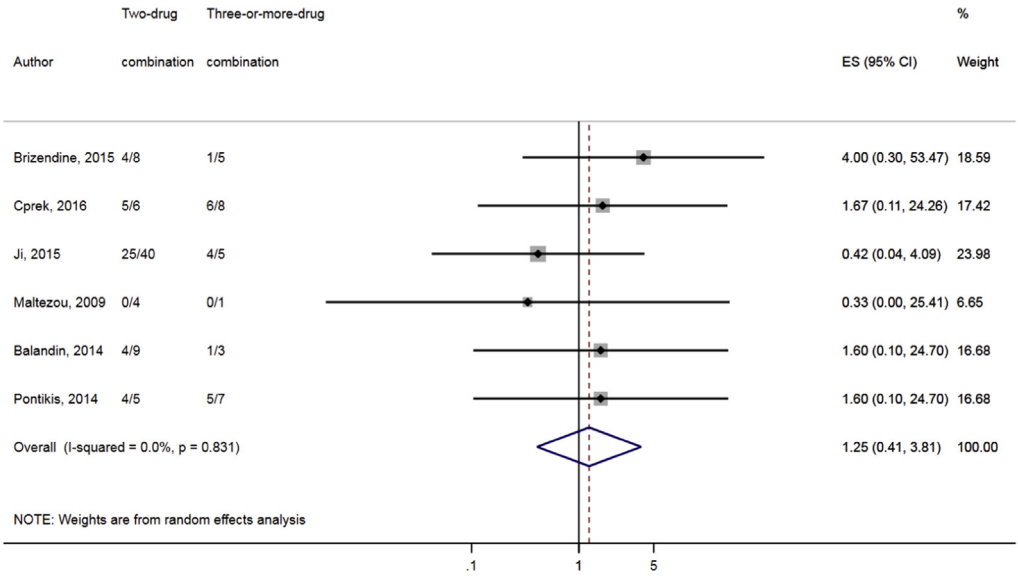


**Fig. 21.** Comparison of microbiological response between CRKP-infected patients treated with ≥3-drug and those on 2-drug combination therapies.

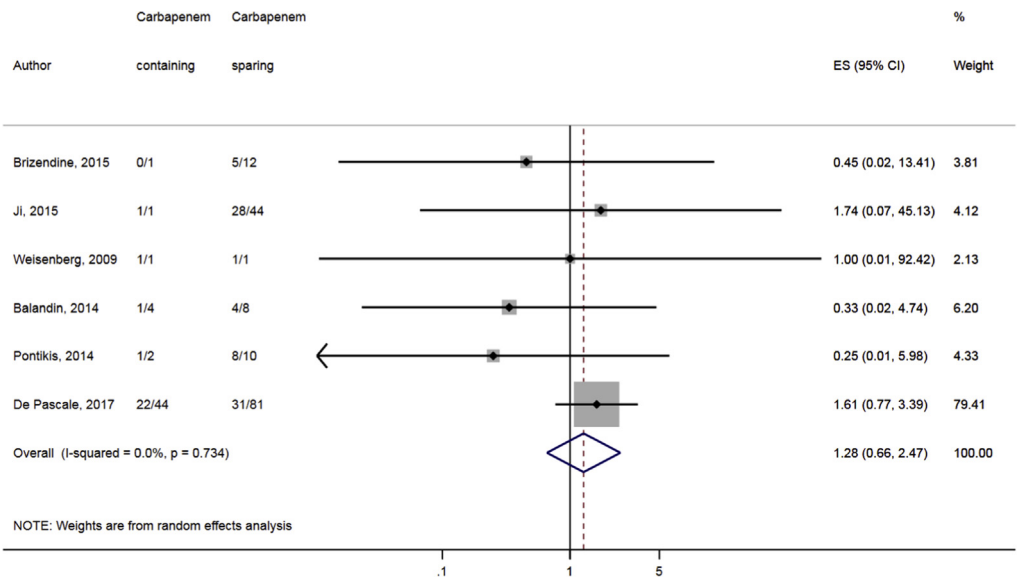


**Fig. 22.** Comparison of microbiological response between CRKP-infected patients treated with carbapenem-containing and carbapenem-sparing combination therapies.

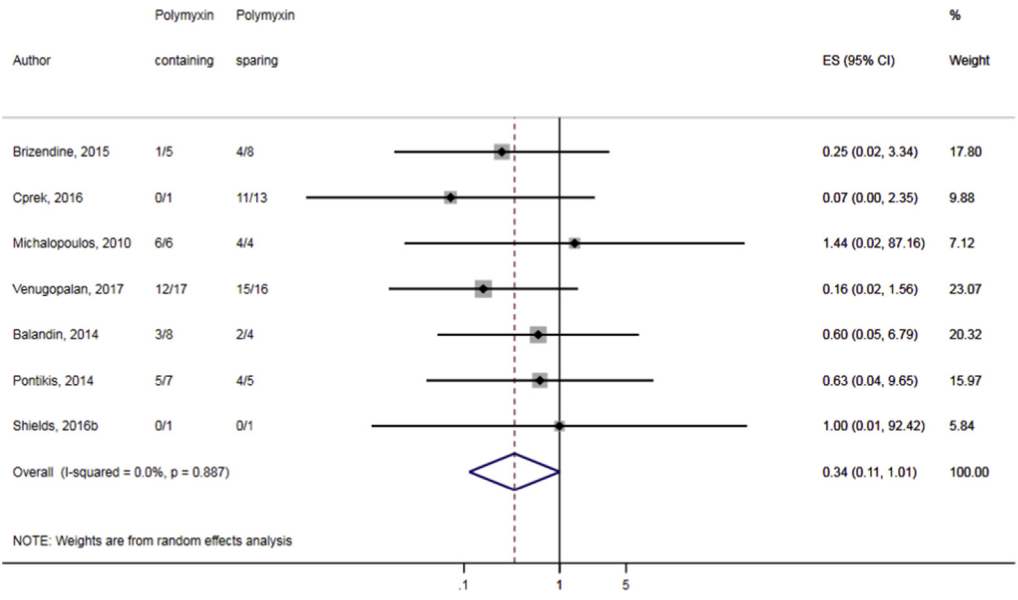


**Fig. 23.** Comparison of microbiological response between CRKP-infected patients treated with polymyxin-containing and polymyxin-sparing combination therapies.

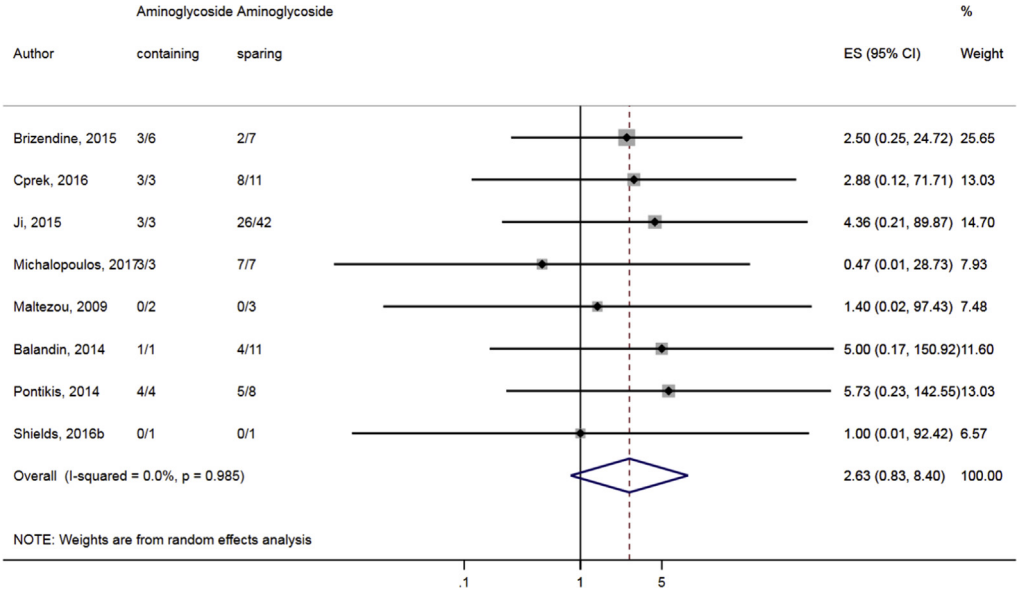


**Fig. 24.** Comparison of microbiological response between CRKP-infected patients treated with aminoglycoside-containing and aminoglycoside-sparing combination therapies.

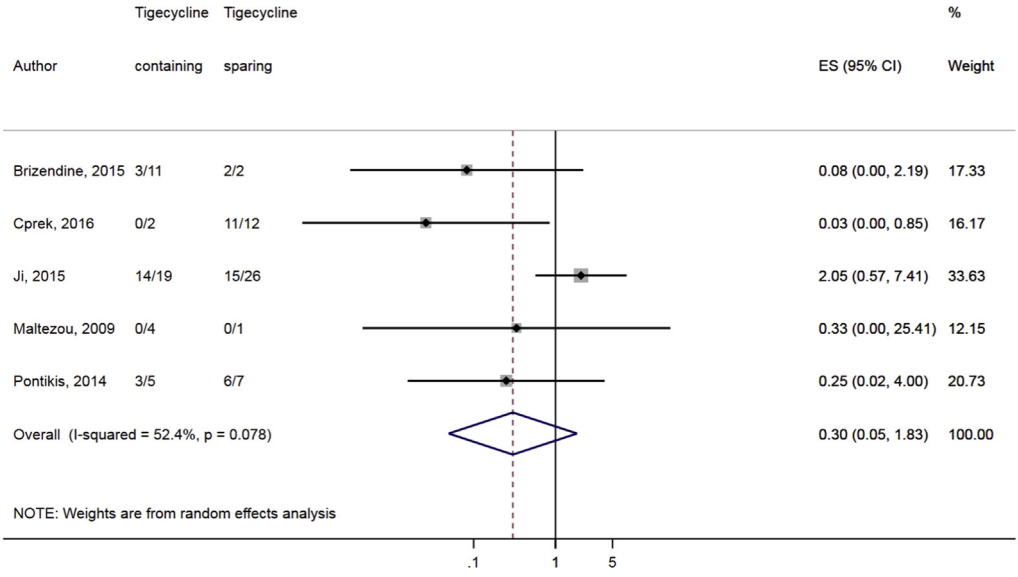


**Fig. 25.** Comparison of microbiological response between CRKP-infected patients treated with tigecycline-containing and tigecycline-sparing combination therapies.

**Table 4**
Search strategy for Ovid Medline which was adapted for other databases.

| | |
|---|---|
| 1 | (Klebsiella adj2 pneumoniae).mp |
| 2 | *Klebsiella pneumoniae*.mp. or exp *Klebsiella pneumoniae*/ |
| 3 | exp Enterobacteriaceae/or Enterobacteriaceae.mp. |
| 4 | or/1-3 |
| 5 | (antibiotic adj2 therap*).mp. |
| 6 | (antibiot* adj2 treatment).mp. |
| 7 | (antibacterial adj2 agent*).mp. |
| 8 | (antibacterial adj2 therap*).mp. |
| 9 | antibacterial agent.mp. |
| 10 | (antibacterial* adj2 activit*).mp. |
| 11 | or/5-10 |
| 12 | (carbapenem adj2 resist*).mp. |
| 13 | (carbapenemase adj2 producing).mp. |
| 14 | carbapenem resistance.mp. |
| 15 | KPC.mp |
| 16 | (Metallo adj2 Lactamase).mp. |
| 17 | Metallo beta lactamase.mp. |
| 18 | VIM-producing.mp. |
| 19 | (VIM adj2 produc*).mp. |
| 20 | IMP-producing.mp. |
| 21 | (IMP adj2 produc*).mp. |
| 22 | NDM-producing.mp. |
| 23 | (NDM adj2 produc*).mp. |
| 24 | OXA.mp. |
| 25 | CRE.mp. |
| 26 | Carbapenem-resistant.mp. |
| 27 | or/12-26 |
| 28 | 4 and 11 and 27 |
| 29 | limit 28 to English language |

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## Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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