Comparison of mono- and combination antibiotic therapy for the treatment of *Pseudomonas aeruginosa* bacteraemia: A cumulative meta-analysis of cohort studies

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Abstract. It is currently unknown whether antibiotic monotherapy or combination therapy is a more effective treatment for patients with *Pseudomonas aeruginosa* bacteraemia. The present study consists of a systematic review and meta-analysis of cohort studies in associated studies. The treatment options of monotherapy and combination therapy have been compared, to determine which is more effective against *P. aeruginosa* bacteraemia. Several electronic bibliographic databases were systematically searched and clinical studies that compared combination therapy with monotherapy for *P. aeruginosa* bacteraemia were identified. Dersimonian and Laird's random-effects models were used to generate summary estimates of the effects and to assess their association according to different patient characteristics and research quality standards. A total of 17 studies were selected, 3 of which were prospective while the remaining 14 were retrospective. The studies involved a total of 2,504 patients. Significant differences between combination therapy and monotherapy treatment were not found when the data were combined (odds ratio (OR)=0.81, 95% confidence interval (CI)=0.61-1.08; P=0.035). The results demonstrated strength in a number of stratification and sensitivity analyses. The variables used included study type, treatment quality score and survival rate of subgroup analysis. To conduct cumulative meta-analysis, the number of years and samples were calculated. The OR value and 95% CI were stable and demonstrated good change trend. According to the size of the sample order following accumulation, OR values and 95% CI (0.89, 0.76-1.04) exhibited a narrow range. Neither combination therapy or monotherapy exhibited significant effects on the mortality of patients with *P. aeruginosa* bacteraemia. Future research is required and should include large, well-designed prospective cohorts, and grouped clinical studies.

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Introduction

Pseudomonas aeruginosa is a common clinical cause of gram-negative bacterial, nosocomial infections (1), and causes serious infections in neutropenic and immunocompromised patients (2). Within intensive care units, *P. aeruginosa* has become the most common gram-negative bacterial species associated with severe hospital-acquired infections (2,3). At present, the worldwide morbidity and mortality rates of *P. aeruginosa* are 18 and 61% respectively (1-3). The treatment of *P. aeruginosa* infections in a clinical setting remains a notable challenge. The capacity of patients to ingest the appropriate antibiotics in a timely manner positively affects prognosis of severe pseudomonas-infection (4). As such, this variable serves as an important controllable risk factor (4,5). Clinical infection with *P. aeruginosa* may be associated with an increase in 30-day mortality in patients. Treatment with appropriate antibiotics, such as β-lactam and fluoroquinolone, is associated with the prognosis (6). However, the use of appropriate antibiotic treatment does not consistently show satisfactory effects on patients (7,8). It has previously been suggested that the inappropriate use of antibiotics in the treatment of *P. aeruginosa* bacteraemia may be minimised by a combination antibiotic regimen, in which the sensitivity of results is determined following treatment (8). Inappropriate use of empirical antibiotic therapy has been identified as an independent contributor to the high hospital mortality rate of *P. aeruginosa* bacteraemia (8,9). Combination therapy has been shown to yield improved results compared with

single treatment of *P. aeruginosa* bacteraemia (6,9), and combination empirical antimicrobial therapy directed against gram-negative bacteria may be a more appropriate treatment approach than monotherapy (10). Despite the merits of relevant studies on empirical combination therapy, it is still unclear whether the use of combination therapy is more effective than monotherapy in treating *P. aeruginosa* infection (10-18). In the present study a meta-analysis was conducted and the mortality of patients treated with either combination therapy or the appropriate monotherapy for *P. aeruginosa* bacteraemia was compared and evaluated.

Materials and methods

Search terms. Several electronic bibliographic databases were searched including the Chinese Biomedical Literature *Database* (Wanfang, China), China Academic Journals Full-text *database*, Cochrane Library, PubMed and Embase for the identification of relevant studies (as of April 2017). The included search terms were: *Pseudomonas aeruginosa*, bacteremia, monotherapy, combination therapy, antibiotic, mortality and outcome. The databases were searched manually to identify potentially relevant studies. The reference lists of all retrieved articles were also searched to find research that could qualify for the study. Only articles written in Chinese or English were considered; articles written in German, French, Spanish, Italian and Greek were not evaluated. Ultimately, all included papers were written in English. The study inclusion criteria were as follows: i) The study compared the efficacy of monotherapy and combination therapy; ii) retrospective and prospective studies; iii) the treatments discussed in the study included at least one antibiotic agent, which was reported following sustained or initial antibacterial spectrum results (8); and iv) the study results included data on mortality.

Study selection. Two experienced independent reviewers (S-YT and S-WZ) subsequently read through the results and decided which studies were appropriate to be included in the meta-analysis (5,10-25). Any differences in opinion between the two reviewers were resolved by discussion until a consensus was reached. The following data was extracted from each qualified study: Name of first author, type of publication, type of study design, gender and age of patients, sample size, length of hospital stay, type of treatment, type and choice of drugs, mortality, outcomes, number of different populations, and odds ratio (OR) and 95% confidence interval (CI) results. The possible risk estimates were extracted and adjusted using hybrid variables.

Quality assessment. The selected studies were evaluated using a system based on the cohort study using the Newcastle-Ottawa scale (26), which provides a score for studies between 1-9 'stars'. Three aspects were used to assess the quality of studies: i) Choice of learning study, ii) organisational evaluation and iii) evaluation of comparison results. As there is dispute over the number of stars that must be used as an indicator of high-quality studies (27-33), the included studies were compared; studies that received ≥7 stars (7,8,9) were defined as high-quality studies, and those that scored ≤6 were not.

Statistical methods. Statistical analysis was conducted using Stata version 12.0 software (StataCorp LP, College Station, TX, USA). ORs with 95% CIs were extracted from studies to evaluate the outcomes of mortality. Cochrane's X2 Q and I^2 tests were employed to assess the differences in data from different studies. Stochastic models were applied to heterogeneity studies ($P<0.1$ or $I^2>50\%$) (34,35). The Mantel-Haenszel fixed-effect model was used to calculate pools or studies when $P>0.10$ and $I^2\leq 50\%$; otherwise, the Dersimonian and Laird's random-effects model was used to combine results (36). A sensitivity analysis was also conducted to examine the effects of each study on mixed outcomes. To establish the effects of clinical heterogeneity on meta-analysis, a subgroup analysis was conducted based on study characteristics. Egger's precision-weighted linear regression tests and funnel charts were used to assess potential publication bias (37). When a study demonstrated potential publication bias, the nonparametric correction and filling method was applied. The filling method evaluates the possibility of 'missing' studies that may exist and recalculates the pool or merges them (34,35). The results of the meta-analysis were stratified by types of study and treatment. $P<0.05$ was considered to indicate a statistically significant difference, unless otherwise stated.

Results

Search results. Fig. 1 demonstrates the process of study selection and the number of studies excluded at each stage. In the initial search 115 studies were identified, and following a review of the titles, 31 studies were considered for inclusion. The summaries of those 31 studies were reviewed and all studies that were considered eligible were retrieved. Among these studies 14 were excluded for the following reasons: 3 studies did not compare monotherapy and combination therapy; 4 studies did not include mortality rate in the assessment of results; 2 were excluded because patient infection did not cause bacteraemia; and 5 were excluded as data could not be extracted. Therefore, following the screening process 17 studies qualified (5,10-25) and were included in the meta-analysis; they covered a total of 2,504 patients with cases of *P. aeruginosa* bacteraemia.

Study characteristics. Within the qualified studies, 14 were retrospective studies and 3 were prospective studies (Fig. 2). There were 5 studies that reported outcomes of empirical treatment and 12 studies that reported outcomes of definitive treatment (Fig. 3). There were 4 studies conducted in the United States, 7 in Europe, 6 in Asia and 1 was conducted in the United States and Singapore (Table I). According to the Newcastle-Ottawa Scale, 16 of the included studies scored >6 and were rated as good or excellent quality (Table I).

Mortality. There were 8 studies that used survival for 30 days, 1 that used survival for 14 days and 1 that used survival for 10 days as the desired outcome of the study. There were 7 studies that considered overall survival as the desired outcome. In terms of mortality, significant difference was observed between patients who received definitive treatment compared with those who received the appropriate empirical treatment (OR=0.81, 95% CI=0.61-1.08; Fig. 3).

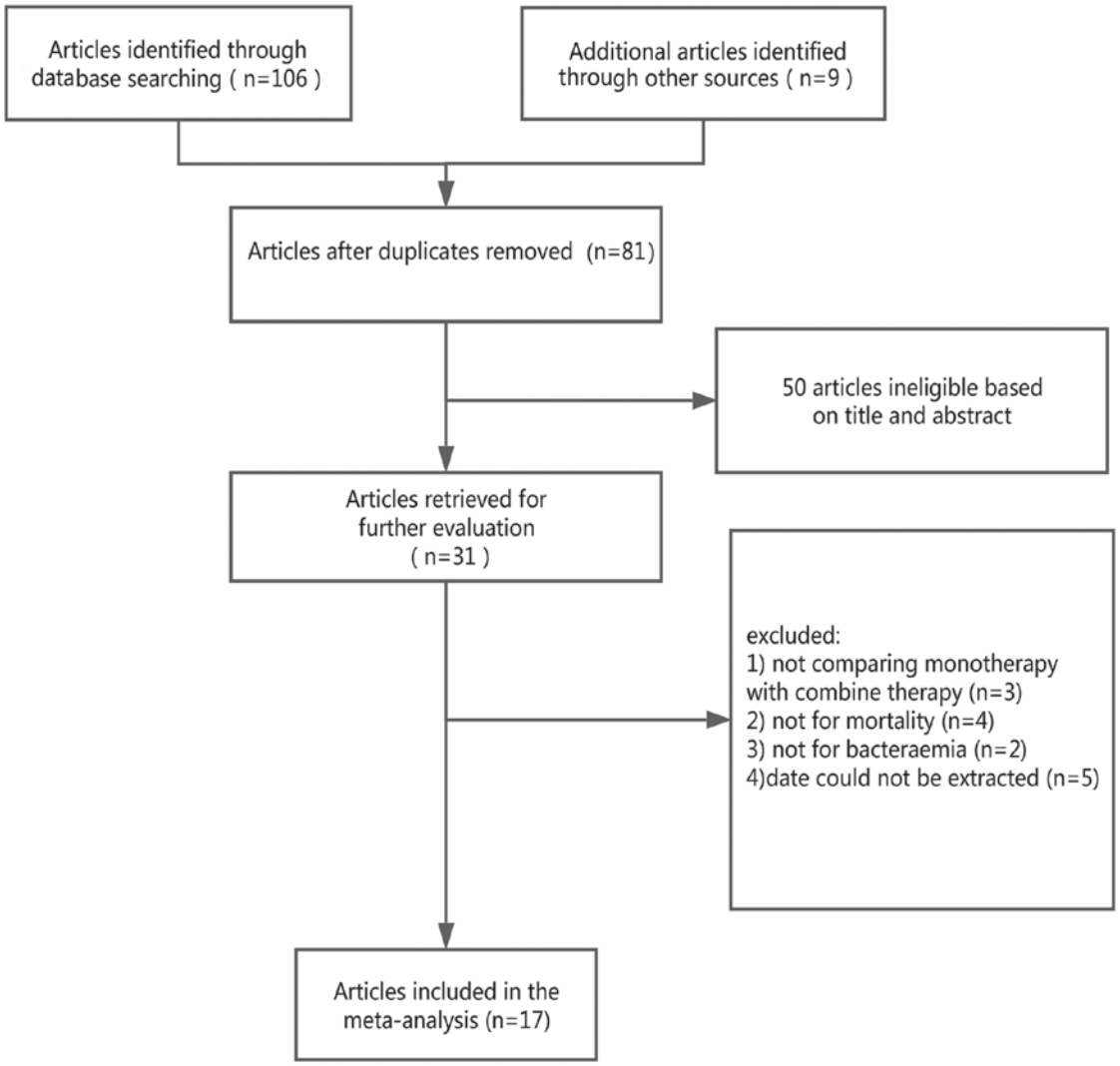

Figure 1. Flow chart of literature study and selection process.

Publication bias. Considering the observed heterogeneity (P=0.035; I^2=42.1%) of the 17 included studies, a random-effects model was used for their analysis (Fig. 2). The following factors were considered: Source of patients, types of study design (OR=0.85, 95% CI=0.60-1.19, P=0.034), types of treatment (OR=0.72, 95% CI=0.42-1.23, P=0.019), study population (OR=0.74, 95% CI=0.41-1.33, P=0.036), literature quality score (OR=0.67, 95% CI=0.45-1.00, P=0.082), and mortality of subgroup stratification analysis (OR=1.17, 95% CI=0.75-1.85, P=0.117; Table II). Retrospective and prospective studies were significantly different in subgroup analysis. Visual inspection of the funnel plots revealed asymmetry among studies (Fig. 4). Consolidation effect was assessed to review the influence results for each study (Fig. 5). Begger's and Egger's tests were conducted to determine publication bias (Figs. 6 and 7) and L'Abbé analysis was performed to assess the heterogeneity of effect sizes, which revealed no marked heterogeneity (Fig. 8). The Z-value and P-value of Begger's test reached 0.21 and 0.805, respectively, and the t-value and P-value of Egger's test totalled -0.24 and 0.815 respectively. Both P-values of Egger's test and Begger's test were >0.05. Therefore, these results indicated that there was no compelling evidence to affirm that results obtained were free from published publication bias.

Subgroup and sensitivity analysis. Table II demonstrates the stratified analysis designed to focus OR of 0.85 (95% CI=0.60-1.19) for 14 retrospective cohorts and the 12 studies with specific definitive therapy OR of 0.88 (95% CI=0.62-1.24). A strong correlation was identified in studies conducted in Asian countries, and study quality and mortality did not significantly affect the results (Figs. 9-11).

The contribution of studies to overall prevalence and 95% CIs was evaluated. In sensitivity analyses, surveyed time strip was omitted and then results were combined with a single dataset on pooled ORs. Corresponding pooled ORs did not change significantly from 0.67 (95% CI=0.45-1.00) to 0.85 (95% CI=0.60-1.19). Therefore, the results obtained were considered statistically strong.

Cumulative meta-analysis. Heterogeneity inspection was conducted initially and the effects, combined effects and their corresponding CI were evaluated to obtain the Q statistic and its corresponding P-value. Heterogeneity=27.63 (degree of freedom=16), P=0.035 and I^2=42.1%. Given

Table I. Characteristics of the eligible studies included in the meta-analysis of monotherapy vs. combination therapy for *Pseudomonas aeruginosa* bacteraemia.

					Drugs			Mortality (mortality cases/total)				
Author, year	Study design	Study period	Country	Therapy type	Combination therapy	Monotherapy	Mortality outcome	Combination therapy	Monotherapy	Study quality[a]	Independent risk factors	(Refs.)
Bowers *et al*, 2013	Retrospective	2002-2011	USA/ Singapore	Appropriate empirical therapy	More than one antipseudomonal agent	An antipseudomonal antimicrobial agent	Mortality	30/82	82/286	9	Diabetes mellitus, liver cirrhosis, respiratory conditions, renal disease	(12)
Park *et al*, 2012	Retrospective	1997-2011	South Korea	Appropriate empirical therapy	A β-Lactam antibiotic and either an aminoglycoside or ciprofloxacin	A β-lactam or ciprofloxacin	28 days	10/33	17/32	9	APACHE II score, liver cirrhosis, immunosuppression, hematologic malignancy	(23)
Bliziotis *et al*, 2011	Retrospective	2001-2007	Greece/ Italy	Definitive treatment	A β-Lactam and an aminoglycoside or a quinolone	β-Lactam antibiotic	Mortality	6/31	8/19	9	AIDS, HIV, solid tumor, respiratory dysfunction, cardiovascular dysfunction	(11)
Micek *et al*, 2005	Retrospective	1997-2002	USA	Definitive treatment	A β-lactam and an aminoglycoside	A β-lactam or ciprofloxacin	Mortality	13/59	16/106	8	APR-DRG score, shock	(5)
Chamot *et al*, 2003	Retrospective	1988-1998	Switzerland	Definitive treatment	A β-lactam and an aminoglycoside or administration of an aminoglycoside together with ciprofloxacin	A β-lactam or aminoglycoside or fluoroquinolones	30 days	10/46	9/33	8	Simple sepsis, severe sepsis, shock	(10)
Siegman-Igra *et al*, 1998	Retrospective	1990-1992	Israel	Definitive treatment	A fluoroquinolone, a third-generation cephalosporin, cilastatin or a ureidopenicillin in combination with an aminoglycoside	A fluoroquinolone, a third-generation cephalosporin or imipenem/cilastatin	Overall mortality	7/15	7/42	7	Malignancy, neutropenia	(15)
Kuikka and Valtonen, 1998	Retrospective	1976-1982, 1992-1996	Finland	Definitive treatment	A β-lactam and either an aminoglycoside or quinolone	β-lactam or ciprofloxacin	30 days	11/41	7/32	7	Leukopenia, cholelithiasis, COPD, alcohol abuse, indwelling urinary catheter	(21)
Mendelson *et al*, 1994	Retrospective	1978-1992	USA	Definitive treatment	Ceftazidime, piperacillin, cefoperazone, aztreonam and an aminoglycoside (gentamicin, tobramycin)	Ceftazidime, piperacillin, cefoperazone, aztreonam or ciprofloxacin	Mortality	4/15	4/9	6	HIV, cryptococcal meningitis, pneumocystis pneumonia	(22)
Leibovici *et al*, 1997	Prospective	1988-1995	Israel	Definitive treatment	A β-lactam and an aminoglycoside	A β-lactam	Mortality	16/77	20/95	7	Septic shock, malignancy, neutropenia, congestive heart failure	(20)
Hilf *et al*, 1989	Prospective	1982-1986	USA	Definitive treatment	An aminoglycoside and an antipseudomonal β-lactam	Antipseudomonal antibiotics including aminoglycoside, β-lactam	10 days	38/143	20/43	7	Malignancy, neutropenia, pneumonia, MODS	(19)

Table I. Continued.

Author, year	Study Design	Study Period	Country	Therapy type	Drugs		Mortality outcome	Mortality (mortality cases/total)		Study quality[a]	Independent risk factors	(Refs.)
					Combination therapy	Monotherapy		Combination therapy	Monotherapy			
Peña *et al*, 2013	Prospective	2010-2011	Spain	Definitive treatment	A β-lactam + aminoglycoside, fluoroquinolones or colistin	A β-lactam or aminoglycoside or fluoroquinolones or colistin	30 days	13/71	70/339	9	Hepatobiliary HIV/AIDS, diabetes mellitus, MODS	(18)
Kim *et al*, 2014	Retrospective	2010-2012	South Korea	Definitive treatment	A β-lactam and aminoglycosides fluoroquinolones, colistin and fluoroquinolones or aminoglycoside	A β-lactam, fluoroquinolones, colistin or aminoglycosides	14 days	6/42	32/141	9	Diabetes mellitus, liver cirrhosis, malignancy, hypertension	(16)
Samonis *et al*, 2014	Retrospective	2004-2010	Greece	Definitive treatment	A β-lactam + aminoglycoside/ fluoroquinolone/ colistin or colistin + other	A β-Lactam or fluoroquinolone, colistin	Mortality	12/37	14/45	8	Chronic lung disease, diabetes mellitus, chronic heart disease, chronic renal disease	(17)
Tan SH *et al*, 2014	Retrospective	2007-2008	Singapore	Definitive treatment	A β-lactam + aminoglycosides or ciprofloxacin	A β-Lactam or aminoglycosides or ciprofloxacin	30 days	2/14	17/77	9	SAPS II score, HIV/AIDS, diabetes mellitus, cardiovascular dysfunction	(25)
Deconinck *et al*, 2017	Retrospective	1994-2014	France	Appropriate empirical therapy	A β-Lactam + an aminoglycoside, aquinolone or colistin	A β-Lactam, aminoglycoside, fluoroquinolone or colistin	30 days	32/85	7/15	9	Shock, SAPS II, multiresistant strains	(13)
Paulsson *et al*, 2017	Retrospective	2005-2010	Sweden	Appropriate empirical therapy	Carbapenem, cefotaxime + tobramycin or piperacillin	Cefotaxime, cefuroxime or piperacillin	30 days	16/79	12/56	7	COPD, neurological paresis, diabetes mellitus, heart disorder, AIDS	(14)
Yoon *et al*, 2017	Retrospective	2012-2015	South Korea	Appropriate empirical therapy	A β-Lactam and an aminoglycoside or a quinolone	A β-lactam or	30 days	25/85	84/179	9	Septic shock, neutropenia, Pitt bacteraemia score	(24)

[a]Study quality was evaluated according to the Newcastle-Ottawa scale (26). AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; SAPS II, simplified acute physiology score; COPD, chronic obstructive pulmonary disease; APR-DRG, all patient refined-diagnosis related group; MODS, multiple organ dysfunction syndrome.

Table II. Stratified analyses of pooled ORs.

Factor	Level	No. of studies	Pooled OR (95% CI)[a]	Heterogeneity test P-value	Heterogeneity test I^2 (%)	(Refs.)
All studies	-	17	0.81 (0.61-1.08)	0.035	42.1	(5,10-18,31-37)
Study population	Asian	6	0.74 (0.41, 1.33)	0.036	58.0	(15,16,32,35-37)
	Non-Asian[a]	11	0.88 (0.65, 1.20)	0.196	26.0	(5,10-14,17,18,31,33,34)
Study design	Prospective cohort[a]	3	0.71 (0.42, 1.18)	0.193	39.2	(18,31,32)
	Retrospective cohort	14	0.85 (0.60, 1.19)	0.034	45.1	(5,10-17,33-37)
Therapy type	Definitive therapy	12	0.88 (0.62, 1.24)	0.173	27.7	(5,10,11,15-18,32-35,37)
	Appropriate empirical therapy	5	0.72 (0.42, 1.23)	0.019	65.9	(12-14,31,36)
Study quality	9 stars	8	0.67 (0.45, 1.00)	0.082	44.5	(11-13,16,18,35-37)
	8 stars	3	1.15 (0.68, 1.95)	0.515	-	(5,10,17)
	7 stars	5	1.03 (0.53, 1.99)	0.029	63.0	(14,15,31-33)
	6 stars[b]	1	0.45 (0.08, 2.60)	-	-	(34)
Outcome	Overall mortality	7	1.17 (0.75, 1.85)	0.117	41.1	(5,11,12,14,15,17,34)
	30-day mortality	8	0.67 (0.49, 0.90)	0.611	0	(10,13,14,18,33,35-37)
	14-day mortality[b]	1	0.57 (0.22, 1.47)	-	-	(16)
	10-day mortality[b]	1	0.42 (0.21, 0.84)	-	-	(31)

[a]The fixed-effect model was used to calculate the pooled OR if P>0.10 and $I^2 \leq 50\%$; otherwise, the random-effect model was used to merge the results. [b]Pooled ORs were not provided when stratified analysis only included one or two studies. CI, confidence interval; OR, odds ratio.

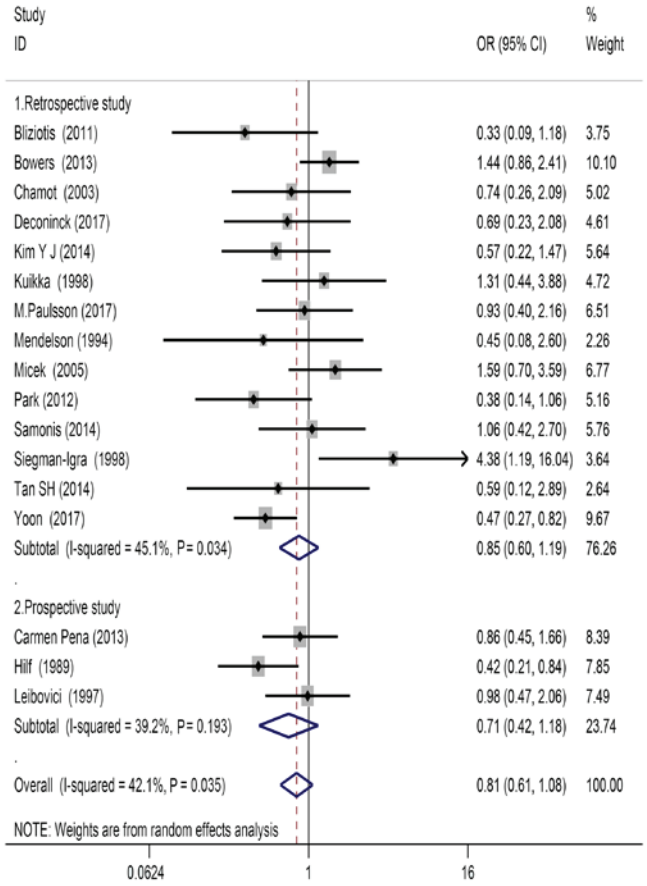

Figure 2. Forest plot of comparison of monotherapy and combination therapy for *Pseudomonas aeruginosa* bacteraemia by study design. OR, odds ratio; CI, confidence interval.

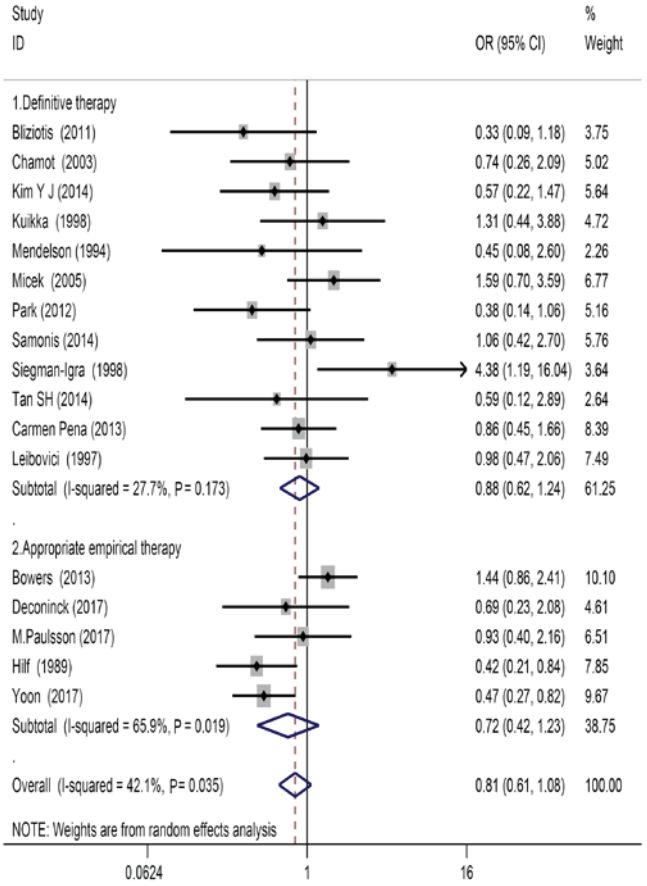

Figure 3. Forest plot of comparison of monotherapy and combination therapy for *Pseudomonas aeruginosa* bacteraemia by type of treatment. OR, odds ratio; CI, confidence interval.

that no clear heterogeneity was observed among studies, cumulative analysis was performed using a random-effects model. Fixed number of years and sample size were considered for cumulative meta-analysis. Organised in chronological order, OR value and 95% CI were stable and demonstrated good change trend, aside from the study by

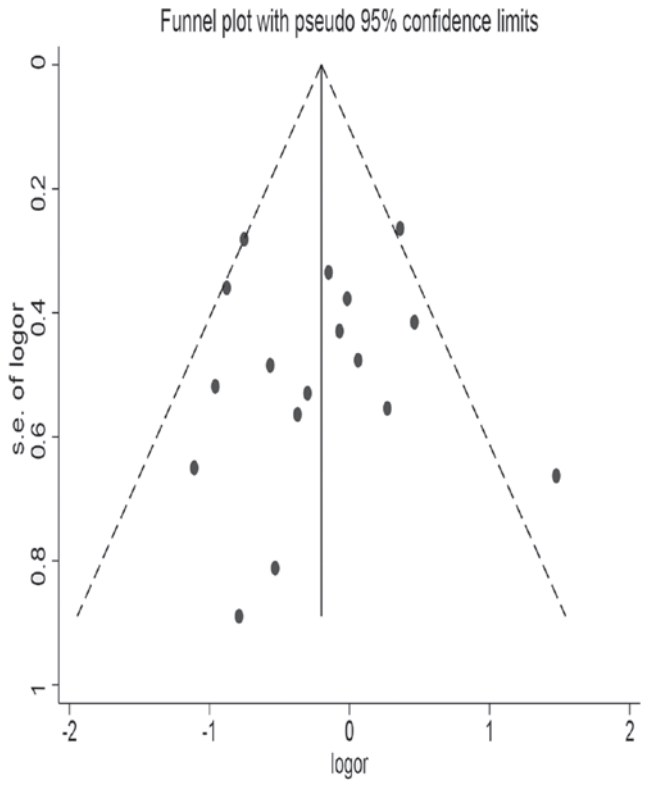

Figure 4. Funnel plot with pseudo 95% confidence limits. s.e., standard error.

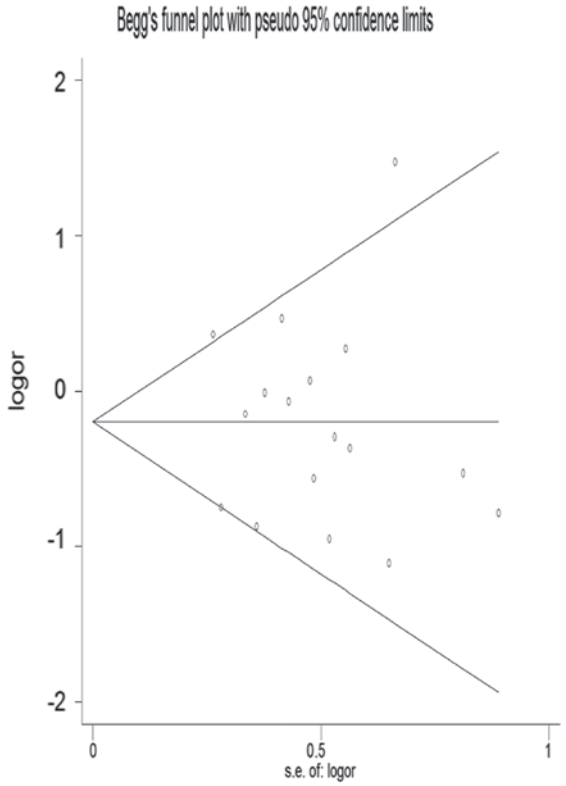

Figure 6. Odds ratio of publication bias plots. s.e., standard error.

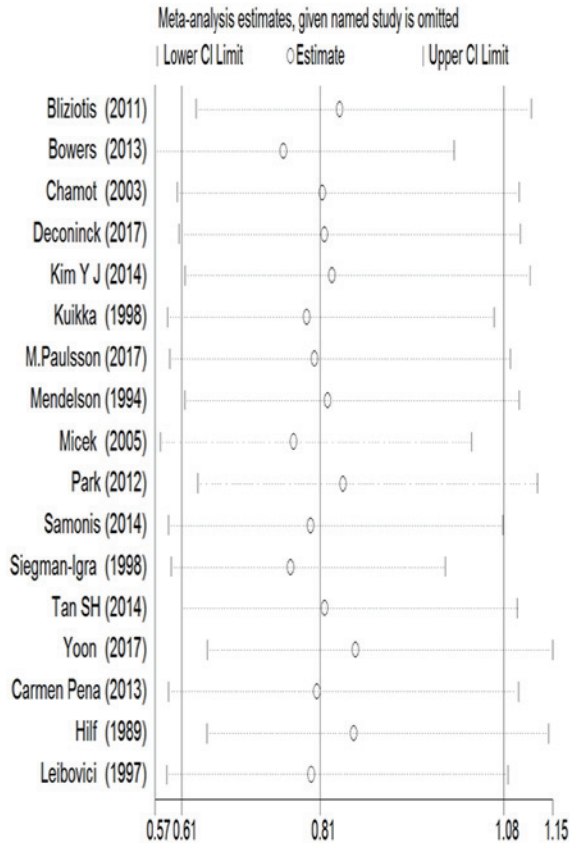

Figure 5. Quantity of studies on combined effects. CI, confidence interval.

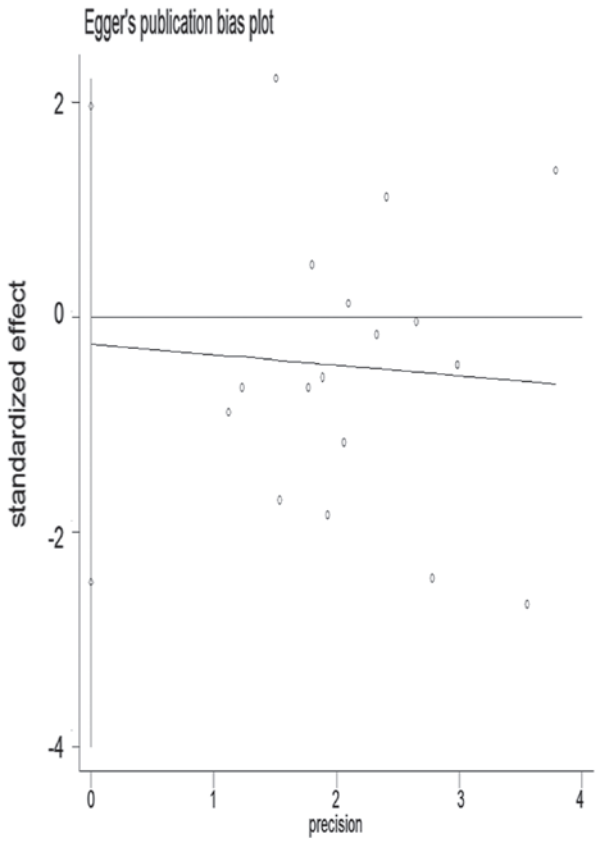

Figure 7. Egger's publication bias plots

Bliziotis *et al* (11) (Fig. 12). Based on sample size order following accumulation, when a large sample was included, the range of OR values and 95% CI (0.89; 0.76-1.04) was decreased (Fig. 13).

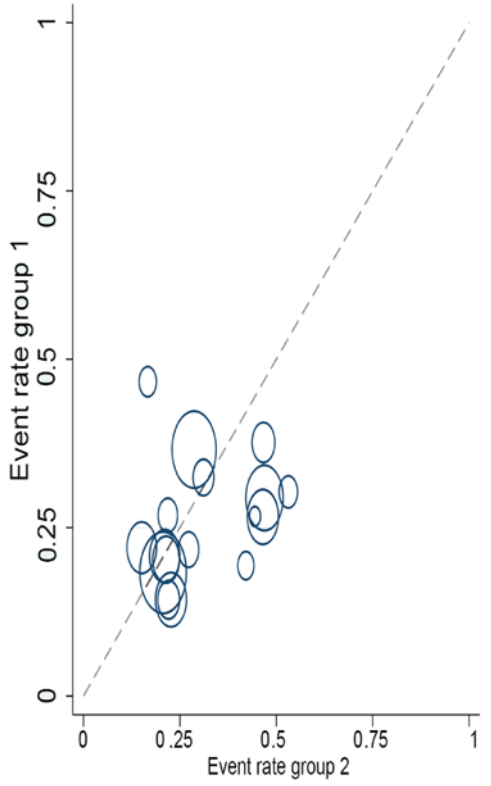

Figure 8. L'Abbé analysis of heterogeneity of effect sizes.

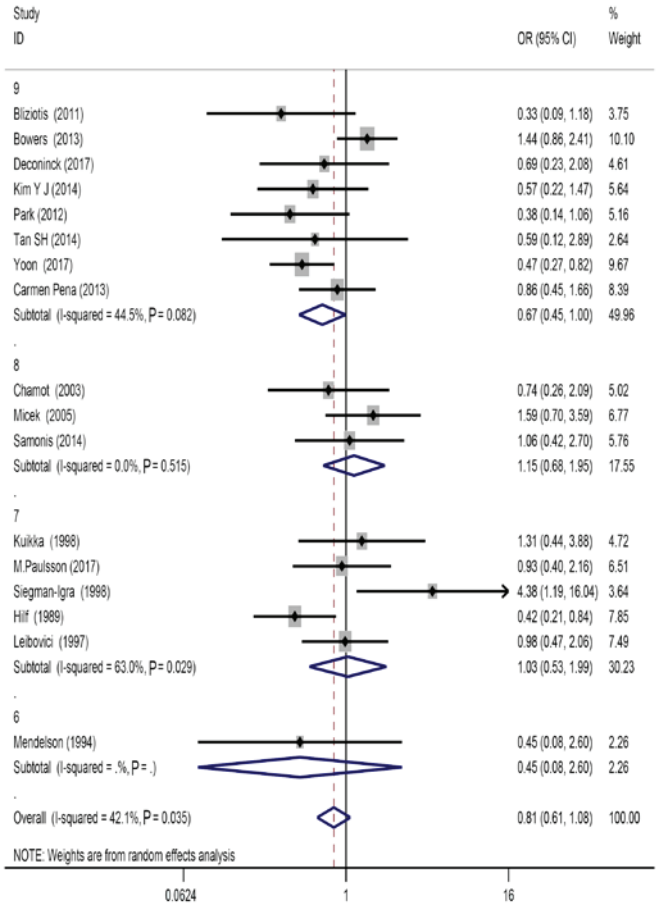

Figure 9. Forest plot of comparison of monotherapy and combination therapy for *P. aeruginosa* bacteraemia by quality evaluation. I^2 and P-values were not provided when stratified analysis only included one or two studies. OR, odds ratio; CI, confidence interval.

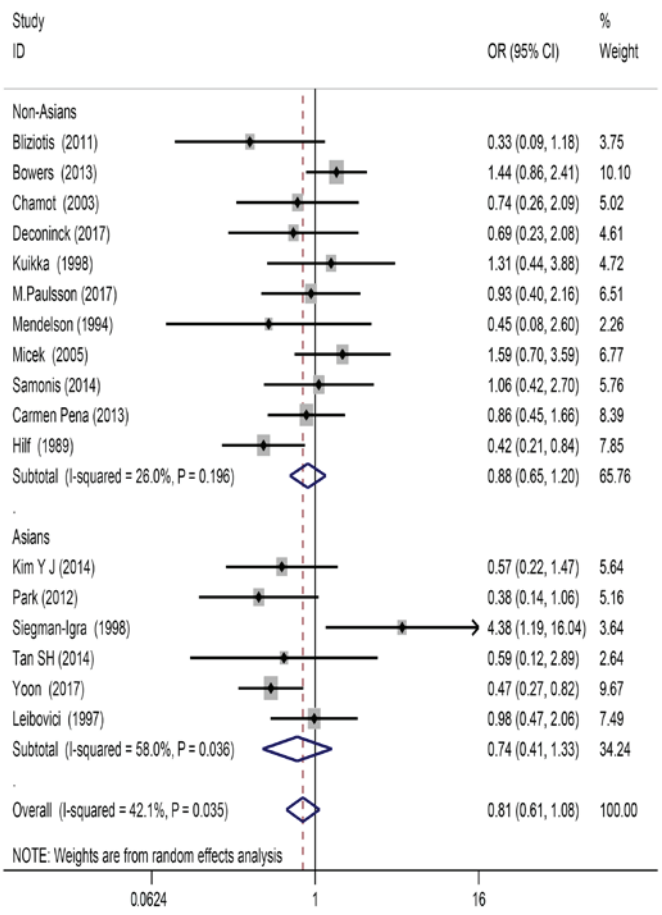

Figure 10. Forest plot of comparison of monotherapy and combination therapy for *P. aeruginosa* bacteraemia by regional distribution. OR, odds ratio; CI, confidence interval.

Discussion

The present study consisted of a meta-analysis that compared the effects of using either a combination of antibiotics or a single antibiotic for the treatment of *P. aeruginosa* bacteraemia. A total of 17 studies were systematically reviewed and compared. The antibiotic and appropriate empirical treatments used were determined by extracting data from the studies, and the patients' all-cause mortality associated with *P. aeruginosa* bacteraemia was analysed. No significant differences were identified between monotherapy and combination therapy in regards to mortality. Therefore, definite combination therapy and appropriate combination of therapies failed to independently provide additional benefits for patient treatment. However, in the subgroup analysis process significant differences were observed in types of study design and types of treatment. In particular, the use of β-lactam and cephalosporin antibiotics as an empirical treatment were able to significantly reduce the mortality rate of patients.

In clinical treatment, patient mortality associated with *P. aeruginosa* bacteraemia remains high (61%) despite the progress of antibiotic therapy; thus, an improved treatment approach is required (38). Bliziotis *et al* (11) reported that combination therapy was superior to monotherapy in treating patients with *P. aeruginosa* bacteraemia; however, 81% of patients (25/31) who received monotherapy only received

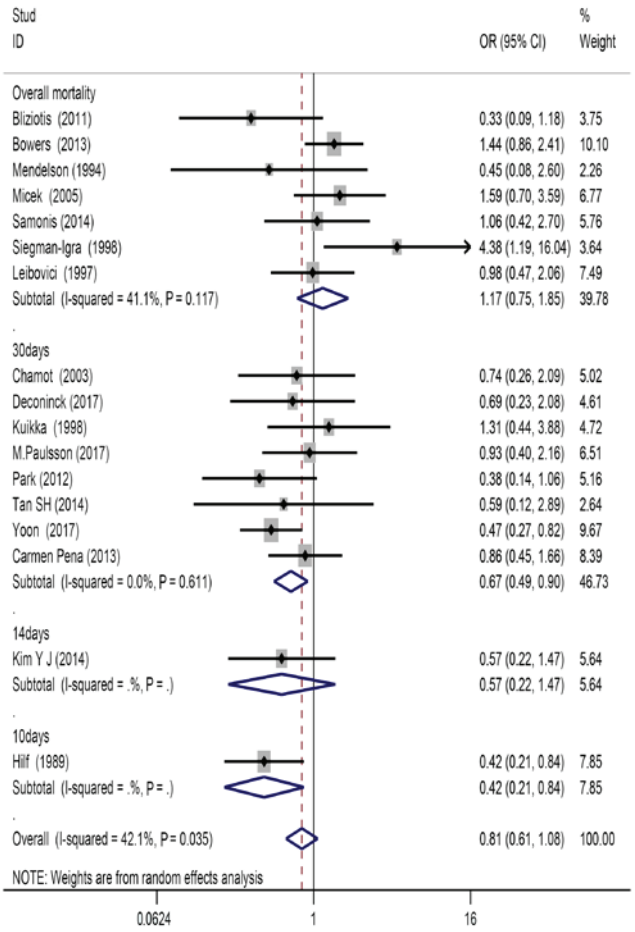

Figure 11. Forest plot of comparison of monotherapy and combination therapy for *P. aeruginosa* bacteraemia by mortality. I^2 and P-values were not provided when stratified analysis only included one or two studies. OR, odds ratio; CI, confidence interval.

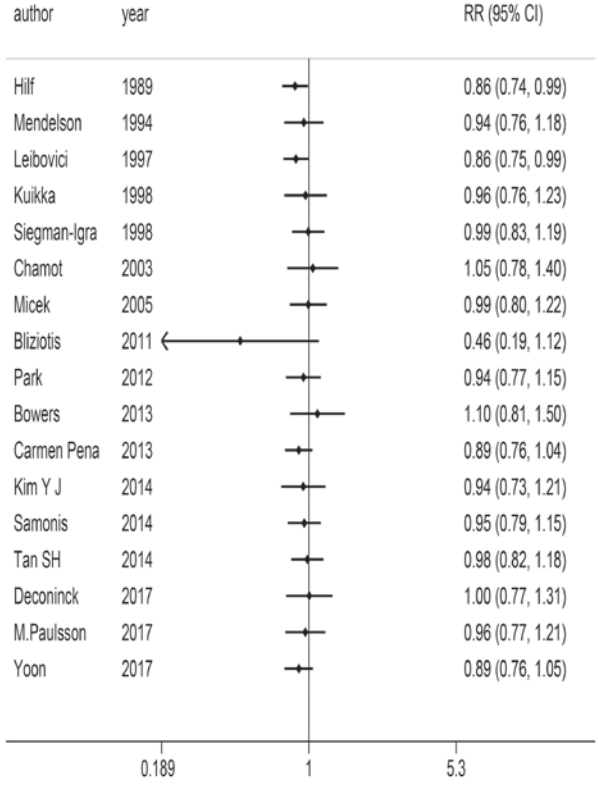

Figure 12. Accumulated studies in chronological order. CI, confidence interval; RR, relative risk.

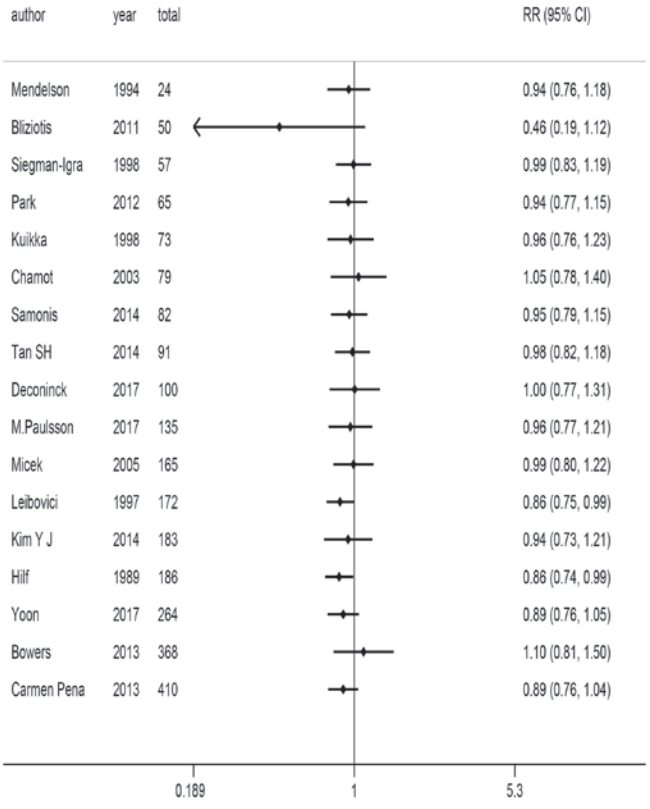

Figure 13. Size of sample order following accumulation. CI, confidence interval; RR, relative risk.

β-lactam, which cannot be considered the optimum monotherapy owing to the increased mortality rate associated with this drug compared with other monotherapies (20,21,39). Micek *et al* (5) observed that compared with single antibiotics, combination therapy yielded improved effects. However, given the open clinical design of the study, patients in a single-treatment group may be more likely to receive additional antibiotics and were therefore considered treatment failures in these studies. The number of patients included in meta-analysed subgroups were assessed in each randomised controlled study. As such, the baseline comparable *P. aeruginosa* bacteraemia infection between monotherapy and combination therapy groups was not established. Confounding factors in the remaining studies may be attributed to lack of randomisation, thus leading to incorrect conclusions (39). Another previous meta-analysis also performed a similar comparison by using β-lactam monotherapy and a combination of β-lactam and aminoglycosides on immunoreactive sepsis patients (6); the results revealed that association of combination therapy with single treatments was not advantageous in all-cause mortality or other treatment failure in patient subgroups with *P. aeruginosa* bacteraemia infection. By contrast, another study focused on analysis of patients with gram-negative bacteraemia. Following subgroup analysis of the results it was identified that combination antibiotic treatment led to a reduction in the mortality rates of *P. aeruginosa* bacteraemia compared with monotherapy, however these results were not

representative of all gram-negative bacteraemia studied (6,40). As previously revealed, inferior quality and heterogeneity of studies considered in these meta-analyses resulted in unreliable clinical data. Differences among patients were also notable and results often differed (39). A recent meta-analysis studied the effects of carbapenem-resistant *P. aeruginosa* bacteraemia on mortality (41). Another meta-analysis study on the benefits of clinical treatment was conducted through the use of an empirical combination therapy using β-lactam combined with an aminoglycoside or fluoroquinolones and β-lactam monotherapy for *P. aeruginosa* infection (42). In a subgroup analysis (5 studies) of *P. aeruginosa* bacteraemia, the results of the clinical treatment demonstrated no significant difference in mortality between patients treated with monotherapy and combination therapy. According to the above variances, a meta-analysis was conducted in the present study; to the best of our knowledge *P. aeruginosa* bacteraemia, although common in patients with bacteraemia, is not very common in clinical settings. Thus, the sample size was limited. The present review also indicated limited clinical reviews and prospective study design. Owing to these limitations, baseline comparison of *P. aeruginosa* bacteraemia infection between monotherapy and combination therapy was not established. Therefore, difficulty arose from completing large randomised prospective clinical trials. Patient complications also differed; multidrug-resistant (MDR) *P. aeruginosa* strains became increasingly common and varied in terms of selection of drug types. Therefore, studies were not analysed according to specific antibiotics, as the present meta-analysis was performed with different antimicrobial therapies. In several studies (13,14,16,18,24), comparisons between selected empirical antibiotic therapy and definitive treatment were retrospectively analysed. Other studies rated the Chronic Health Evaluation score of in-patients (12,16,23,25). Appropriate treatment involves antibiotic isolation therapy for certain *in-vitro*-sensitive agents, especially for aminoglycoside antibiotic-sensitive patients (19,35). The use of monotherapy for treatment of *P. aeruginosa* bacteraemia was considered inappropriate in previous studies comparing single and combination therapies (10,15). Some meta-analyses conducted from the perspective of treatment and mortality compared effectiveness of combination antibiotics and monotherapy in clinical treatment of *P. aeruginosa* (43). The present meta-analysis did not focus on survival rate and quality evaluation. A limitation of the present study was the lack of scope in comparing study type and treatment selection. For patients with MDR bacterial infection and *P. aeruginosa*, providing combination antibiotic therapy may improve results as this method increases possibility of appropriate treatment (42). In addition to the appropriate choice of empirical treatment, the severity of complications is another risk factor that may also affect mortality rate of patients during bacterial infections including *P. aeruginosa* (42). Combination therapy with *P. aeruginosa* also presents potential risks, particularly drug toxicities, including aminoglycoside antibiotics associated with human renal toxicity (6). Likelihood of repeated infection in clinical patients and the increased cost must also be considered in comparing combination therapy with monotherapy.

Limitations of meta-analysis conducted in the present study were recognised. The quality of included studies may be questioned due to incomplete or inaccurate data collection. The research on adjustment of these confusing factors is limited and therefore cannot be studied for potential co-founder influence, including severity of disease and potential for concurrent conditions. The funnel plot and Egger's test indicated a possibility of publication bias, however trim-and-fill analysis revealed that results did not change. Only sensitivity analysis and evaluation, patient source, study types, treatment options and mortality were analysed. Finally, only studies published in English were included. This may introduce language bias, possibly resulting in incomplete study and thus reducing accuracy of analysis of the treatment results.

In conclusion, the results demonstrated no significant difference in mortality between patients administered with combined antibiotic or monotherapy treatment against *P. aeruginosa* bacteraemia. Combination therapy may be associated with clinical treatment of monotherapy, particularly when used in empirical therapy. These results were mainly obtained from retrospective and secondary studies. Thus, no definite conclusions may be drawn regarding combination of effectiveness and single therapy in patients and groups. Relevant evidence obtained was also limited. Therefore, large-scale and well-designed studies must be developed and conducted on credibility of treatment mechanisms to determine whether a causal association exists.

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