Heliyon 9 (2023) e15774

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Efficacy and safety of intravenous combined with aerosolised polymyxin versus intravenous polymyxin alone in the treatment of multidrug-resistant gram-negative bacterial pneumonia: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Polymyxin
Intravenous
Aerosolised
MDR
Pneumonia

ABSTRACT

Background: Previous studies have questioned the efficacy and safety of intravenous combined with aerosolised (IV + AS) polymyxin versus intravenous (IV) polymyxin alone in the treatment of patients with multidrug-resistant gram-negative bacterial (MDR-GNB) pneumonia. Therefore, we conducted a meta-analysis to evaluate the efficacy and safety of IV + AS polymyxin in the treatment of MDR-GNB pneumonia.

Methods: We identified all relevant studies by searching the PubMed, EMBASE and Cochrane library databases from their inception to May 31, 2022. All included studies were evaluated using the Newcastle Ottawa scale (NOS) checklist. The summary relative risk (RR) and 95% confidence interval (CI) were used to determine the outcome differences between the IV + AS and the IV groups. Subgroup analysis was performed based on population, polymyxin dose and kinds of polymyxin.

Results: A total of 16 studies were included in the meta-analysis. The IV + AS group had lower mortality (RR = 0.86, 95% CI: 0.77–0.97, P = 0.01) than the IV group. Subgroup analysis revealed that IV + AS polymyxin could reduce mortality only when used in low doses. Simultaneously, the IV + AS group outperformed the IV group in terms of clinical response rate, clinical cure rate, microbiological eradication and duration of mechanical ventilation. The duration of hospitalisation and the incidence of nephrotoxicity did not differ significantly between the two groups.

Conclusions: IV + AS polymyxin is beneficial in the treatment of MDR-GNB pneumonia. It could lower patient mortality and improve clinical and microbial outcomes without increasing the risk of nephrotoxicity. However, retrospective analysis in the majority of studies and heterogeneity between studies implies that our findings must be interpreted carefully.

1. Introduction

Multi-drug resistant (MDR) bacterial pneumonia has a high incidence in the intensive care unit (ICU), with MDR Gram-negative

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https://doi.org/10.1016/j.heliyon.2023.e15774
Received 5 February 2023; Received in revised form 18 April 2023; Accepted 21 April 2023
Available online 25 April 2023

bacterial (GNB) pneumonia accounting for the vast majority [1]. *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are the most common pathogens of MDR-GNB pneumonia, including hospital-acquired pneumonia (HAP) and ventilator-related pneumonia (VAP) in China and other countries [2–5].

Treatment of MDR-GNB pneumonia is a difficult clinical problem, particularly after the emergence of Carbapenem-resistant organisms (CRO). The antibiotics currently available include polymyxin, tegacyclin, fosfomycin, ceftazidime/avibatan and some new drugs such as imipenem/cilastatin/relebactam [6]. Polymyxin is a bactericide that can kill bacteria by destroying the bacterial cell membrane and causing cell lysis [7]. The US Food and Drug Administration (FDA) approved the drug for clinical use in the 1950s, but it was quickly withdrawn due to its nephro- and neurotoxicity [8]. Polymyxin has been used again in the last 20 years due to the development of antimicrobial resistance, and it has become an important choice for treating MDR-GNB [7].

Although the incidence of neurotoxicity is not as high as previously thought, intravenous (IV) polymyxin has a relatively high nephrotoxicity incidence [9]. Therefore, clinicians have tried different routes of administration to reduce the adverse reactions of polymyxin, particularly aerosolised (AS) polymyxin [10,11]. The guideline recommended that for VAP patients caused by polymyxin-sensitive GNB, aerosolised combined with intravenous (IV + AS) antibiotics be considered instead of IV antibiotics alone, despite low-quality evidence [12]. However, aerosolised polymyxin can cause bronchospasm. The European position paper does not recommend aerosolised antibiotics [13].

Therefore, we are unsure whether aerosolised polymyxin has better efficacy and safety as adjuvant therapy. Some previous studies have shown that IV + AS polymyxin can improve the microbial outcome of patients with MDR-GNB pneumonia but not reduce mortality [14]. However, an earlier meta-analysis revealed that adjunctive aerosolised polymyxin had lower mortality [15]. Similarly, two recent studies suggest that aerosolised polymyxin as an adjuvant therapy has completely different outcomes in reducing mortality [16,17]. Therefore, we included the relevant studies for meta-analysis to evaluate the efficacy and safety of IV + AS polymyxin in treating MDR-GNB pneumonia, expecting it to be helpful in clinical practice.

2. Methods

2.1. Literature search strategy

Two researchers independently searched the literature in PubMed, EMBASE and Cochrane Library electronic databases based on the inclusion and exclusion criteria. The retrieval time range from the inception of these databases to May 31, 2022, and the language is not restricted. The following terms were used in the search: "Atomisation inhalation/Aerosol Inhalation/aerosolised/Inhalation/Inhaled", "intravenous injection/Intravenous" "Polymyxin/Polymyxin B/Polymyxin E/Colistin/Colistimethate sodium/Colistin methanesulfonate/CMS", "Multi-drug resistance/MDR", "pneumonia/Ventilator-associated pneumonia/VAP/Hospital-acquired pneumonia/HAP". The disagreements in research are resolved through discussion. When the discussion fails to resolve the differences, the third author participates and makes a decision.

2.2. Eligibility criteria

Eligibility criteria included: (1). The meta-analysis includes observational, non-randomised controlled, and randomised controlled studies (RCTs). (2). These studies evaluate and compare the efficacy and safety of IV + AS polymyxin with IV polymyxin alone in treating MDR-GNB pneumonia. Furthermore, the research subjects are not limited to adults or children of any gender. (3). Any of the following can be used as study outcome indicators: All-cause mortality, clinical response rates, clinical cure rates, microbiological eradication, the incidence of nephrotoxicity, neurotoxicity, duration of hospitalisation and duration of mechanical ventilation. (4). A specific time and location for the studies. (5). The sample size of the IV + AS and IV groups was clear and definite. (6). The IV + AS and IV groups had comparable baseline characteristics. (7). The treatment measures for the IV + AS and the IV groups were clear and definite. (8). The outcome indicators were defined clearly and precisely.

2.3. Exclusion criteria

Animal experimental studies, case reports, reviews, systematic reviews, meta-analyses, letters, studies with inconsistent literature, incomplete original data, and repeated publication were all excluded.

2.4. Definitions

Main interventions and outcome indicators are defined as follows: (1). Dose of Polymyxin: A daily average/median IV polymyxin dose of more than 6 million international units (MIU) is considered a high dose; otherwise, it is regarded as a low-dose, the equivalent dose of polymyxin in different dosage forms can be converted [18]. (2). All-cause mortality: If relevant data were available, 28 or 30-day mortality was analysed. If not, the closest of any other time point was included. (3). Clinical response rates: Clinical response was defined as the remission of symptoms and signs of pneumonia at the end of treatment. (4). Clinical cure rates: It was defined as the disappearance of the symptoms and signs of pneumonia at the end of treatment. (5). Microbiological eradication was defined as the absence of baseline pathogen growth on the culture medium of respiratory specimens after administration. (6). HAP/VAP: HAP was defined as pneumonia occurring 48 h after admission. VAP is defined as pneumonia occurring 48 h after endotracheal intubation or tracheotomy and ventilator-assisted ventilation; pneumonia occurring within 48 h after tracheal intubation extraction is also classified

as VAP [19].

2.5. Methodological quality assessment

The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of all studies. The NOS checklist contains three quality parameters: (1). selected populations, (2). Groups comparability, and (3). assessment of exposure or results of interest in case-control or cohort studies. Each study scored from 0 to 9. Studies with a score $\geq$7 are considered high-quality studies.

2.6. Data extraction

The data included in the studies were extracted independently by two authors. If there were any disagreements, the third author was invited to discuss and reach a consensus. The data were extracted using a self-made data extraction table, and the following information was extracted for each study: (1). Basic study information, including the name of the first author, publication year, country, and research type. (2). Patient baseline characteristics such as sample size and disease type. (3). Intervention measures include the specific treatment measures of the IV + AS and the IV groups, the polymyxin treatment dose and time of use (4). Outcome indicators include all-cause mortality, clinical response rates, clinical cure rates, microbiological eradication, the incidence of nephrotoxicity, duration of hospitalisation and duration of mechanical ventilation.

2.7. Statistics analysis

The Review Manager 5.4 software provided by Cochrane International Cooperation organisation and STATA version 17.0 (StataCorp., College Station, TX) were used for data analysis. The significance level for the 2-sided tests was 0.05, and $P < 0.05$ was considered statistically significant. The effect statistics for metrological data were analysed by mean deviation (MD) and standard deviation (SD), and for counting data by relative risk (RR) and 95% confidence interval (95% CI). Peto Mantel-Haenszel fixed effect model was used if there was no significant heterogeneity ($I^2 < 50\%$, $P > 0.05$). In contrast, the Dersimonian Laird random effect model has used if the heterogeneity test was significant ($I^2 \geq 50\%$, $P < 0.05$). A funnel plot was used to analyse potential publication bias, the Egger's test and Begg's test were used to evaluate asymmetry in the funnel plots. When there was publication bias, potentially missing studies were included using the "trim and fill" method.

3. Results

3.1. Literature retrieval results

A total of 152 research articles were searched, with 65 from PubMed, 52 from EMBASE and 35 from Web of Science. After removing duplicate articles, 82 articles remained. Following a summary review, some articles were excluded, including systematic reviews, case reports and coverage mismatch. There are 19 articles left for a full reading. Three studies were excluded due to the lack of required data for analysis. Finally, 16 studies met the complete inclusion criteria. Fig. 1 depicts the detailed PRISMA flow chart.

3.2. Basic characteristics of the included studies

Table 1 displays the detailed baseline characteristics. A total of 16 studies [20–35] were included. All of the included studies were published between 2009 and 2021. There was 1537 patients total, with 641 in the IV + AS group and 896 in the IV group. Two of the 16 studies included children as research objects [24,25], while the remaining studies had adult research objects [20–23,26–35]. Concurrently, 15 of these studies were retrospectively observational cohort studies [21–35], with only one conducted prospectively [20]. Most of the studies were conducted in Europe [25,26,28–35], four in Asian countries [21–24], one in Africa [20] and one in North America [27]. The majority of studies included VAP patients [24–26,28–30,34,35], four studies included HAP patients [20,21,27,31], one study included HAP and VAP patients [22,32,33], and the remaining three studies included pneumonia caused by MDR bacterial infection [23], regardless of HAP, VAP or Community-acquired pneumonia (CAP). *Acinetobacter baumannii* was the most common pathogen, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [20,22–31,33,34].

3.3. Results of methodological quality evaluation

After carefully evaluating the methodological quality of all 16 included studies, we identified that 12 were classified as high-quality studies [20–25,27–30,32,33], while the remaining four were of low quality [26,31,34,35]. Table 2 represents the specific methodological quality assessment of each study.

3.4. Results of meta-analysis

3.4.1. All-cause mortality

A total of 16 studies were included [20–35], with 641 patients in the IV + AS group and 896 patients in the IV group. Two studies involved children [[24,25]], while the others involved adults [20–23,26–35]. The fixed effect model was used as the forest plot

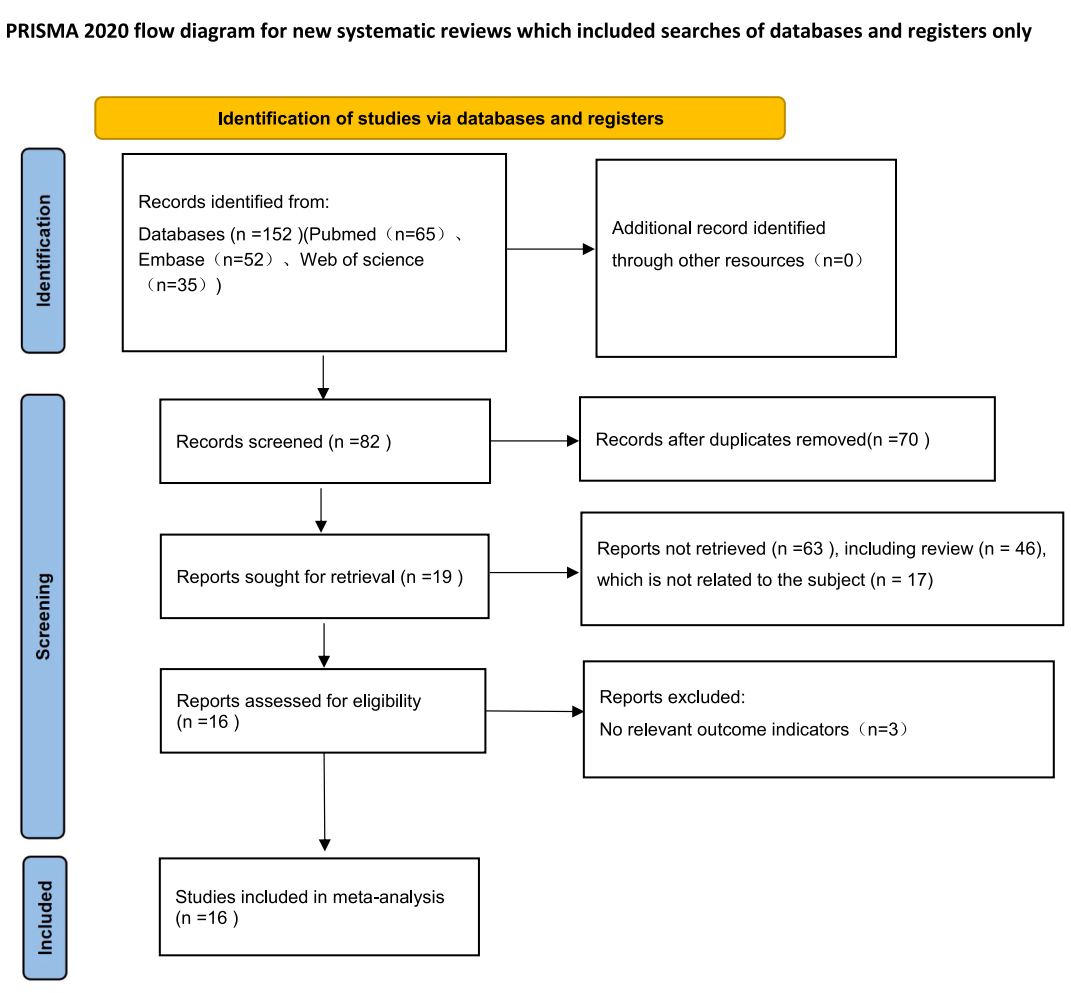

Fig. 1. PRISMA flow diagram of the study selection process.

revealed no statistical heterogeneity among studies ($P = 0.11$, $I^2 = 31\%$). The findings indicated that the IV + AS group had lower mortality than the IV group (RR = 0.86, 95% CI: 0.77–0.97, $P = 0.01$) (Fig. 2). Subgroup analysis demonstrated that the IV + AS group had lower mortality than the IV group in adult patients (RR = 0.86, 95% CI: 0.76–0.97, $P = 0.01$) (Fig. 2). Although the IV + AS group also had lower mortality than the IV group in children, the difference between the two groups was statistically insignificant (RR = 0.91, 95% CI: 0.52–1.60, $P = 0.74$) (Fig. 2). This could be attributed to the small number of studies involving children and the small sample size.

The polymyxin dose used in nine of the 16 included studies was defined as high [21,22,26,28–31,34,35], four studies were defined

Table 1
The detailed characteristics of the included studies.

Trial	Location	Study design	Patient	Kinds	pathogen	Group	No.of patients	Intervention	All-cause mortality	Clinical response rates	Clinical cure rates	Microbiological eradication	Incidences of nephrotoxicity	Duration of hospitalisation	Neurotoxicity	Duration of mechanical ventilation
Amin2013	Egypt	Prospective	HAP	Colistimethate sodium	Acinetobacter baumannii (18/28) *Pseudomonas aeruginosa* (7/28) Klebsiella pneumonia (3/28)	IV + AS	28	IV : 62500iu/kg/d, 12-15 d AS : 2Miu q12 h, 12-15 d	8/28	–	22/28	–	–	–	–	–
					Acinetobacter baumannii (8/12) *Pseudomonas aeruginosa* (3/12) Klebsiella pneumonia (1/12)	IV	12	62500iu/kg/day, 12-15 d	5/12	–	7/12	–	–	–	–	–
Almangour2021	Saudi Arabia	Retrospective	HAP	Colistin	*Pseudomonas aeruginosa* (35/65) Acinetobacter baumannii (21/65) *Klebsiella pneumoniae* (7/65) Other (2/65)	IV + AS	65	IV : 10 M iu/d, adjust based on creatinine levels, ≥48 h; 11.5±6 d AS : 2 M iu qh, ≥48 h; 6.5 ± 2.5 d	28/65	–	42/65	27/65	20/65	115 ± 98 d	0/65	29 ± 21
					Pseudomonas aeruginosa (34/70) Acinetobacter baumannii (26/70) *Klebsiella pneumoniae* (9/70) Other (1/70)	IV	70	10 M iu/d, ≥48 h; 11.0 ±6 d	41/70	–	26/70	12/70	29/70	110 ± 105 d	0/70	31 ± 18
Choe2019	Korea	Retrospective	HAP/VAP	Colistin	Acinetobacter baumannii (34/35) *Pseudomonas aeruginosa* (2/35)	IV (LD)+ AS	35	AS:150 mg q8h, 12 (6–16)d LD : 5 mg/kg or 15000 iu/kg 150 mg q12	8/35	–	17/35	21/35	16/27	20 (10–33) d	–	–

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Table 1 (*continued*)

Trial	Location	Study design	Patient	Kinds	pathogen	Group	No.of patients	Intervention	All-cause mortality	Clinical response rates	Clinical cure rates	Microbiological eradication	Incidences of nephrotoxicity	Duration of hospitalisation	Neurotoxicity	Duration of mechanical ventilation
								h, adjust based on creatinine levels; 14 (12–17)d								
					Acinetobacter baumannii (76/86) *Pseudomonas aeruginosa* (19/86) Klebsiella pneumonia (1/86)	IV (LD)	86	LD : 5 mg/kg or 15000 iu/kg 150 mg q12 h, adjust based on creatinine levels; 14 (9–15)d	42/86	–	36/86	27/81	23/61	12 (8–18) d	–	–
					Acinetobacter baumannii (59/70) *Pseudomonas aeruginosa* (17/70)	IV	70	150 mg q12 h, adjust based on creatinine levels; 14 (10–15)d	32/70	–	32/70	21/67	27/50	13 (8–21) d	–	–
Zheng2019	China, Taiwan	Retrospective	MDR pneumonia	Colistin	Acinetobacter baumannii	IV + AS	37	IV : 2.5–5 mg/kg/day (normal renal function), adjust based on creatinine levels, ≥7 d; AS : 66.8 q8h-133.8 mg q8h, ≥7 d;	13/37	–	–	22/37	–	–	–	–
					Acinetobacter baumannii	IV	18	2.5–5 mg/kg/day (normal renal function), adjust based on creatinine levels, ≥7 d;	5/18	–	–	9/18	–	–	–	–
Hussain2020	Pakistan	Retrospective	VAP	Colistimethate sodium	Acinetobacter baumannii (13/16) *Klebsiella pneumoniae* (2/16) *Pseudomonas*	IV + AS	16	IV : 2.5–5.0 mg/kg/d, ≥3 d AS : 4 mg/kg bid, ≥3 d	4/16	13/16	9/16	11/16	1/16	–	1/16	7.5 (3–10)

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Table 1 (*continued*)

Trial	Location	Study design	Patient	Kinds	pathogen	Group	No.of patients	Intervention	All-cause mortality	Clinical response rates	Clinical cure rates	Microbiological eradication	Incidences of nephrotoxicity	Duration of hospitalisation	Neurotoxicity	Duration of mechanical ventilation
					aeruginosa (3/16)											
					Acinetobacter baumannii (12/16) *Klebsiella pneumoniae* (3/16) *Pseudomonas aeruginosa* (2/16)	IV	16	2.5–5.0 mg/kg/d, ≥3 d	7/16	9/16	5/16	7/11	5/16	–	2/16	11.5 (8–15)
Polat2015	Turkey	Retrospective	VAP	Colistimethate sodium	Acinetobacter baumannii (12/18) *Pseudomonas aeruginosa* (6/18)	IV + AS	18	IV : 2.5–5 mg/kg/d,≥72 h, 14 (5–21)d AS:75 mg q12 h (aged>1 year) 4 mg/kg/q12 h (aged<1 year),≥72 h	8/18	15/18	7/18	15/18	0/18	–	0	19 (6–36)
					Acinetobacter baumannii (25/32) *Pseudomonas aeruginosa* (7/32)	IV	32	2.5–5 mg/kg/d,≥72 h; 16 (10–22)d	12/32	23/32	13/32	23/32	1/32	–	0	22.5 (5–76)
Bovogic2014	Croatia	Retrospective	VAP	Colistin	Acinetobacter baumannii (5/8) *Pseudomonas aeruginosa* (7/8)	IV + AS	8	IV : 9Miu/d, 10.3 ± 5.72 d AS : 4Miu/d	6/8	–	–	5/8	1/8	30.5 ± 11.56 d	–	–
					Acinetobacter baumannii (12/23) *Pseudomonas aeruginosa* (19/23) Klebsiella pneumonia (5/23)	IV	23	9Miu/d, 16.9 ± 15.10 d	17/23	–	–	3/23	4/23	33.8 ± 21.88 d	–	–
Doshi2013	America	Retrospective	HAP	Colistin	Acinetobacter baumannii (36/44) *Pseudomonas*	IV + AS	44	IV : 0.75–5 mg/kg/day (normal renal	15/44	–	20/47	18/44	–	–	–	–

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Table 1 (*continued*)

Trial	Location	Study design	Patient	Kinds	pathogen	Group	No.of patients	Intervention	All-cause mortality	Clinical response rates	Clinical cure rates	Microbiological eradication	Incidences of nephrotoxicity	Duration of hospitalisation	Neurotoxicity	Duration of mechanical ventilation
					aeruginosa (18/44) Klebsiella pneumonia (2/44)			function), adjust based on creatinine levels, 12.2 ± 7.2 d AS : 75–150 mg q12 h, 11.0 (7–16.25)d							
					Acinetobacter baumannii (25/51) *Pseudomonas aeruginosa* (35/51) Klebsiella pneumonia (9/51)	IV	51	0.75–5 mg/kg/day (normal renal function), adjust based on creatinine levels, 11.2 ± 7.7 d	27/51	–	24/51	27/51	–	–	–	–
Kalin2012	Turkey	Retrospective	VAP	Colistin	Acinetobacter baumannii	IV + AS	29	IV : 2.5 mg/kg q12 h, 14 days adjust based on creatinine levels AS:150 mg qd, 14 days	16/29	–	4/29	22/29	12/29	33 ± 34.93 d	–	–
					Acinetobacter baumannii	IV	15	2.5 mg/kg q12 h, 14 days adjust based on creatinine levels	7/15	–	6/15	11/15	3/15	36 ± 37.63 d	–	–
Kofteridis2010	Greece	Retrospective	VAP	Colistin	Acinetobacter baumannii (66/86) Klebsiella pneumonia (12/86) *Pseudomonas aeruginosa* (8/86)	IV + AS	43	IV : 9Miu/d,≥3 d, 13 (5–56)d AS: 2Miu/d, 13 (5–56)d	10/43	–	23/43	19/43	8/43	20.5 (3–93) d	0/43	–
						IV	43	9 M iu/d, ≥3 d, 10 (4–36) d	18/43	–	14/43	17/43	8/43	18 (3–78) d	0/43	–
Korbila2009	Greece	Retrospective	VAP	Colistin	Acinetobacter baumannii (57/78) *Pseudomonas aeruginosa* (17/78) Klebsiella	IV + AS	78	IV : 7.0 ± 2.4 Miu, ≥3 d AS: 2.1 ± 0.9 Miu, ≥3 d	31/78	–	62/78	–	–	–	–	–

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Table 1 (*continued*)

Trial	Location	Study design	Patient	Kinds	pathogen	Group	No.of patients	Intervention	All-cause mortality	Clinical response rates	Clinical cure rates	Microbiological eradication	Incidences of nephrotoxicity	Duration of hospitalisation	Neurotoxicity	Duration of mechanical ventilation
					pneumonia (4/78)											
					Acinetobacter baumannii (35/43) *Pseudomonas aeruginosa* (5/43) Klebsiella pneumonia (3/43)	IV	43	6.4 ± 2.3 Miu, ≥3 d	19/43	–	26/43	–	–	–	–	–
Korkmaz2016	Turkey	Retrospective	HAP	Colistin	Acinetobacter baumannii *Pseudomonas aeruginosa*	IV + AS	69	Media dose:225 mg/d	45/69	–	–	–	–	–	–	–
						IV	210	Media dose:300 mg/d	128/210	–	–	–	–	–	–	–
Naesens2011	Belgium	Retrospective	MDR pneumonia	Colistin	*Pseudomonas aeruginosa*	IV + AS	9	IV : 62500iu/kg/d, adjust based on creatinine levels AS: 2 Miu tid	3/9	7/9	–	–	–	–	–	–
					Pseudomonas aeruginosa	IV	5	62500iu/kg/d, adjust based on creatinine levels	5/5	2/5	–	–	–	61,9 ± 35	–	–
Pérez-Pedrero2011	Spain	Retrospective	MDR pneumonia	Colistin	Acinetobacter baumannii	IV + AS	15	–	2/15	12/15	–	9/15	–	64,1 ± 63	–	–
						IV	18	–	5/18	12/18	–	8/18	–	–	–	–
Tumbarello2013	Italy	Retrospective	VAP	Colistimethate sodium	Acinetobacter baumannii (72/104) *Pseudomonas aeruginosa* (24/104) Klebsiella pneumonia (8/104)	IV + AS	104	IV : 100000iu/kg/d 75000iu/kg/d (creatinine clearance rates < 50 mL/min), 7 (5–14)d AS: 3 Miu/d	45/104	–	72/104	52/104	26/104	–	–	8 (6–14.5)
					Acinetobacter baumannii (56/104) *Pseudomonas aeruginosa*	IV	104	100000iu/kg/d 75000iu/kg/d (creatinine	48/104	–	57/104	42/104	23/104	–	–	12 (8–21)

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Table 1 (*continued*)

Trial	Location	Study design	Patient	Kinds	pathogen	Group	No.of patients	Intervention	All-cause mortality	Clinical response rates	Clinical cure rates	Microbiological eradication	Incidences of nephrotoxicity	Duration of hospitalisation	Neurotoxicity	Duration of mechanical ventilation
					(28/104) Klebsiella pneumonia (20/104)			clearance rates < 50 mL/min), 10 (5.5–15)d								
Tuna Demirdal 2016	Turkey	Retrospective	VAP	Colistin	Acinetobacter baumannii	IV + AS	43	IV : 150 mg q12 h, 11.23 ± 6.023 d AS: 75 mg q12 h	23/43	–	16/43	20/43	21/43	47.91 ± 47.02 d	0/43	–
					Acinetobacter baumannii	IV	80	150 mg q12 h, 11.21 ± 6.714 d	38/80	–	30/80	40/80	43/80	57.68 ± 56.99 d	0/80	–

HAP: Hospital acquired pneumonia, **VAP**: Ventilator related pneumonia, **MDR**: Multi-drug resistant, **IV**: Intravenous, **AS**: Aerosolised, **LD**: Loading dose.

Table 2
Methodological quality assessment of studies included.

Trial	Quality evaluation	Case definition	Representativeness	Selection of Controls	Definition of Controls	Comparability	Ascertainment of exposure	Same method?	Non-Response rate
Amin2013	8	1	1	0	1	2	1	1	1
Almangour2021	7	1	0	1	1	2	1	1	0
Choe2019	7	1	1	1	1	1	1	1	0
Zheng2019	8	1	1	1	1	2	1	1	0
Hussain2020	7	0	1	1	1	2	1	1	0
Polat2015	7	0	1	1	1	2	1	1	0
Bovogic2014	6	0	1	1	1	1	1	1	0
Doshi2013	7	1	0	1	1	1	1	1	1
Kalin2012	8	1	1	1	1	2	1	1	0
Kofteridis2010	7	1	1	1	1	1	1	1	0
Korbila2013	7	1	1	1	1	1	1	1	0
Korkmaz2016	6	1	0	1	1	2	0	1	0
Naesens2011	8	1	1	1	1	2	1	1	0
Pérez-Pedrero2011	7	1	0	1	1	0	1	1	1
Tumbarello2013	6	1	1	1	1	0	1	1	0
Tuna Demirdal2016	6	0	1	1	1	1	1	1	0

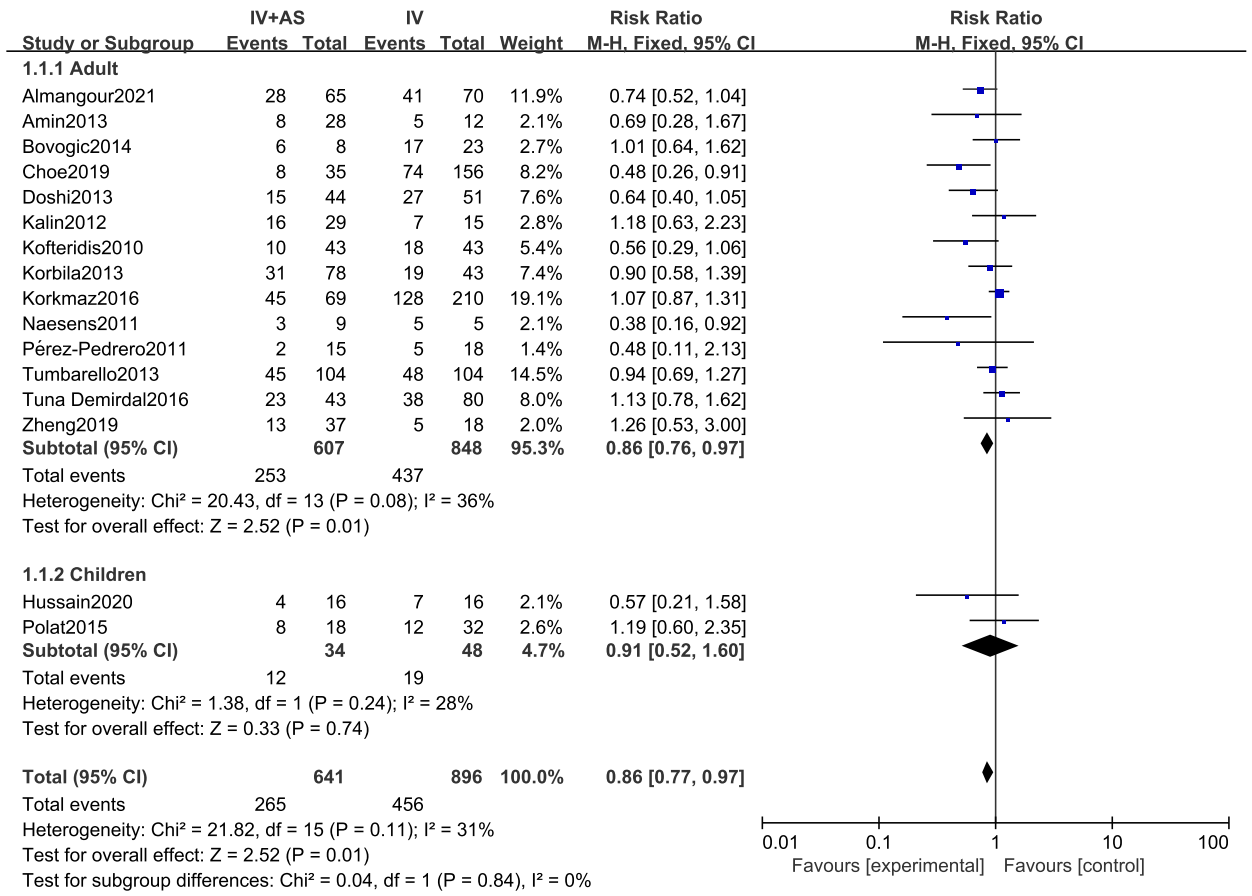

Fig. 2. Forest plot comparing all-cause mortality among the IV + AS and the IV groups.

as low [20,25,27,32], and the specific dose of the remaining three studies was not clear [23,24,33]. Subgroup analysis revealed that at a low dose of IV polymyxin, the IV + AS polymyxin could reduce all-cause mortality compared to IV polymyxin alone (RR = 0.71, 95% CI: 0.51–0.99, $P = 0.04$). However, no significant difference was identified between two groups at high-dose polymyxin (RR = 0.89, 95% CI: 0.79–1.01, $P = 0.08$) (Fig. 3).

Simultaneously, we investigated the effect of different types of polymyxin on mortality. Patients in four studies were treated with colistimentate sodium [20,24,25,34], while the other 12 were treated with colistin [21–23,26–33,35]. In subgroup analysis, when colistin was used for treatment, IV + AS polymyxin had lower mortality than IV polymyxin alone (RR = 0.85, 95% CI: 0.75–0.97, $P = 0.01$). However, there was no significant difference in mortality between the two groups when colistinate sodium was used as treatment (RR = 0.91, 95% CI: 0.70–1.17, $P = 0.45$) (Fig. 4).

3.4.2. Clinical response rates

Four studies were included in the clinical response rate investigation [24,25,32,33], with 58 patients in the IV + AS group and 71 in the IV group. Two studies involved children [24,25], while the other two involved adults [32,33]. The fixed effect model was used because the forest plot revealed no statistical heterogeneity among studies ($P = 0.73$, $I^2 = 0\%$). The findings demonstrated that the clinical response rates of the IV + AS group were higher than those of the IV group (RR = 1.29, 95% CI: 1.03–1.61, $P = 0.03$) (Fig. 5). Subgroup analysis revealed no significant difference between the IV + AS and the IV group, regardless of adult or children. This difference could be due attributed to the small sample size of the study.

3.4.3. Clinical cure rates

A total of 11 studies were included [20–22,24,25,27–30,34,35] with 506 patients in the IV + AS group and 622 patients in the IV group. As previously stated, two studies involved children [24,25], while the remaining nine involved adults [20–22,27–30,34,35]. The forest plot results depicted no statistical heterogeneity between the studies ($P = 0.15$, $I^2 = 31\%$). Therefore, the fixed effect model was used. The results showed that the IV + AS group had a higher clinical cure rate than the IV group (RR = 1.24, 95% CI: 1.1–1.40, $P = 0.0004$). Subgroup analysis revealed a significant difference in clinical cure rate between the IV + AS and the IV groups involving adults (RR = 1.24, 95% CI: 1.10–1.40, $P = 0.0004$), while not significant in the children's group (Fig. 6).

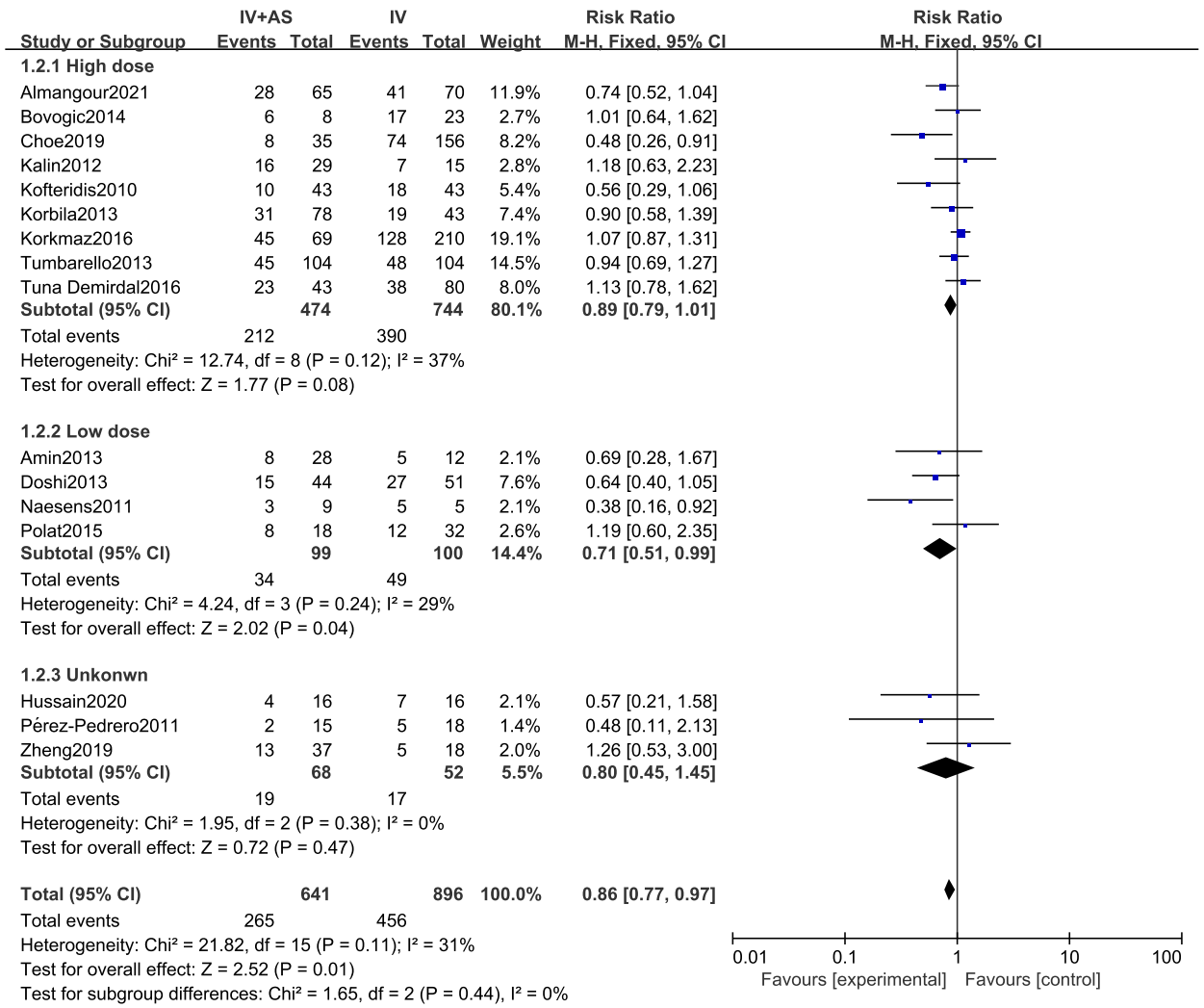

Fig. 3. Subgroup analysis: Effect of different doses of polymyxin on all-cause mortality in the IV + AS and the IV groups.

3.4.4. Microbiological eradication

A total of 12 studies [20–29,34,35] were included for microbiological eradication, with 457 patients in the IV + AS group and 613 patients in the IV group. Two studies involved children [24,25], while the other ten involved adults [20–23,26–29,34,35]. The forest plot results demonstrated the statistical heterogeneity between the studies ($P = 0.02$, $I^2 = 52\%$), implying the random effect model for analysis. The findings revealed that the microbiological eradication of the IV + AS group was greater than that of the IV group (RR = 1.24, 95% CI: 1.03–1.50, $P = 0.02$). Subgroup analysis illustrated higher microbiological eradication of the IV + AS group than the IV group (RR = 1.28, 95% CI: 1.01–1.62, $P = 0.04$), but there was no significant difference in the children's group (Fig. 7).

3.4.5. Incidence of nephrotoxicity

For the incidence of nephrotoxicity, a total of nine studies [21,22,24–26,28,29,34,35] were included, with 353 patients in the IV + AS group and 494 patients in the IV group. Two studies involved children [24,25], while the other seven involved adults [21,22,26,28,29,34,35]. The forest plot results indicated no statistical heterogeneity between the studies ($P = 0.38$, $I^2 = 6\%$). Therefore, a fixed effect model was utilised. The result revealed no significant statistical difference between the two groups (RR = 0.99, 95% CI: 0.81–1.21, $P = 0.90$), implying that aerosolised polymyxin as adjuvant therapy does not increase the risk of nephrotoxicity. Subgroup analysis demonstrated that there was no significant difference in the risk of nephrotoxicity between the IV + AS and the IV groups in either adults or children (Fig. 8).

For the correlation between different polymyxin doses and the incidence of nephrotoxicity, seven studies were defined as high-dose [21,22,24–26,28,29,34,35], one study as low-dose [25], and one study as unclear dose [24]. Subgroup analysis revealed that high-dose polymyxin combined with aerosolised polymyxin did not increase the incidence of nephrotoxicity (RR = 1.03, 95% CI: 0.84–1.25, $P =$ 0.81). However, we cannot further analyse the incidence of nephrotoxicity for low-dose polymyxin due to the availability of only one

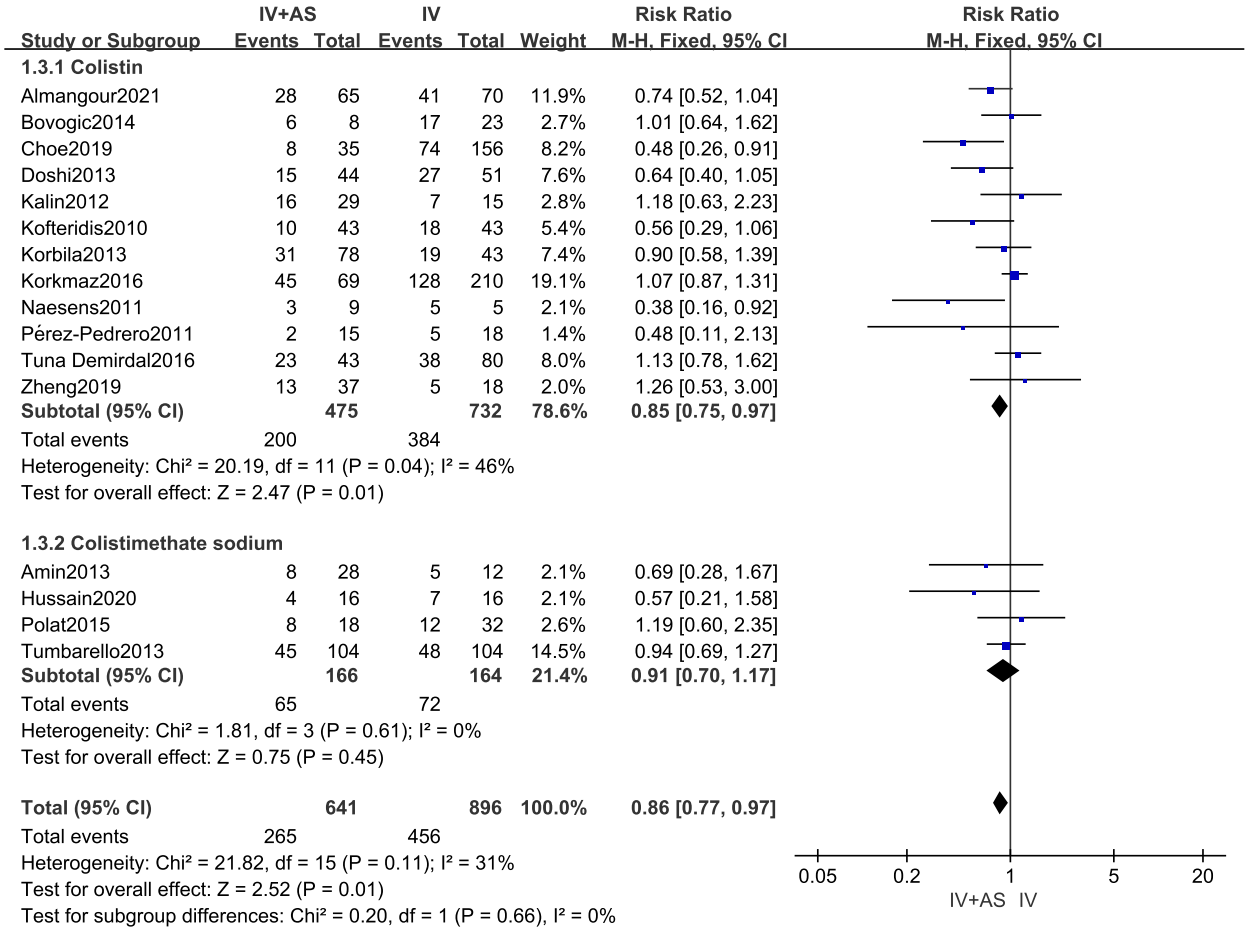

Fig. 4. Subgroup analysis: Effect of different types of polymyxin on all-cause mortality in IV + AS and the IV groups.

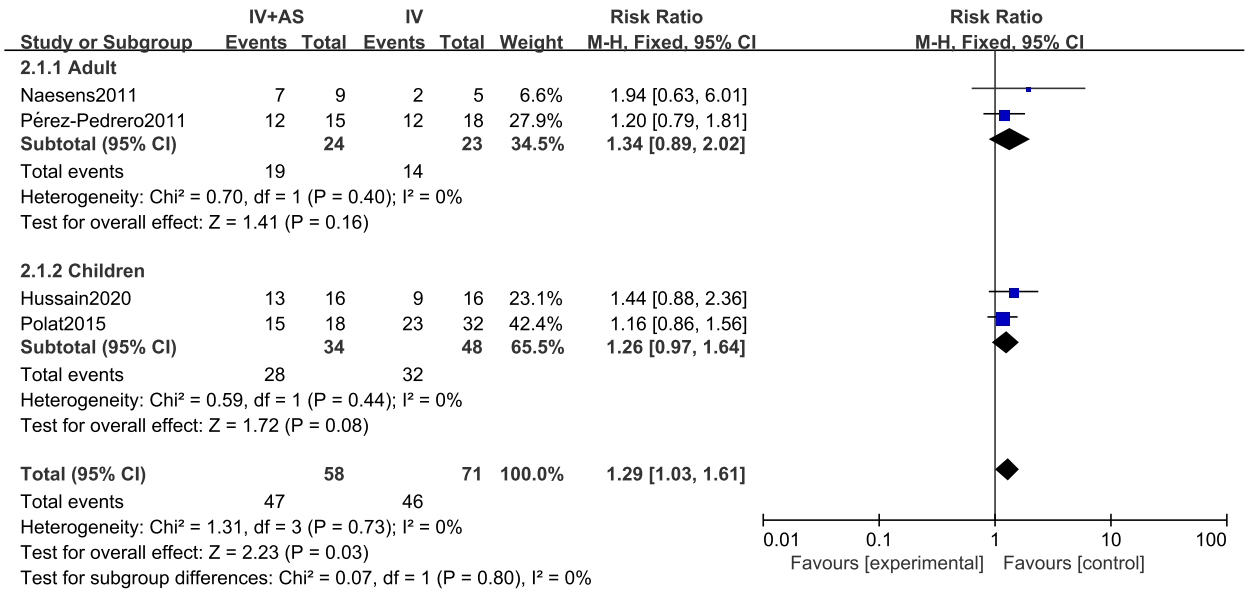

Fig. 5. Forest plot comparing clinical response rates among the IV + AS and the IV groups.

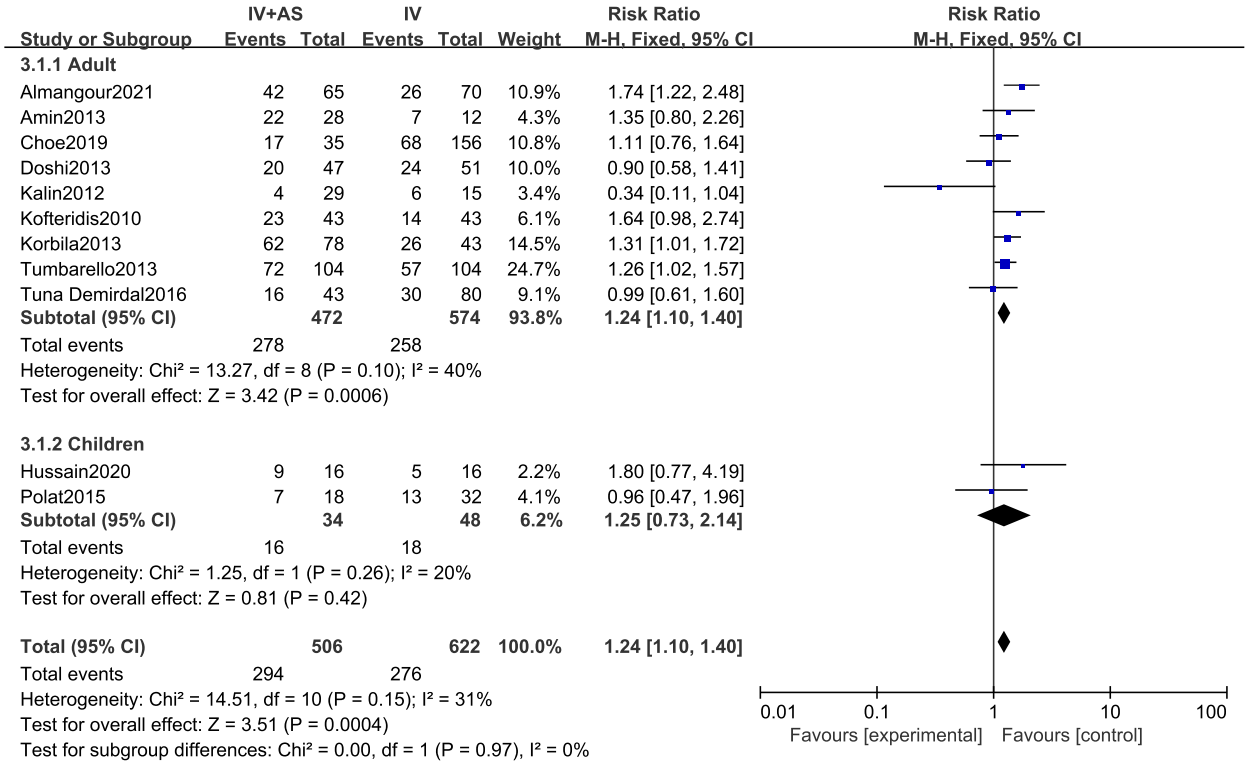

Fig. 6. Forest plot comparing clinical cure rates among the IV + AS and the IV groups.

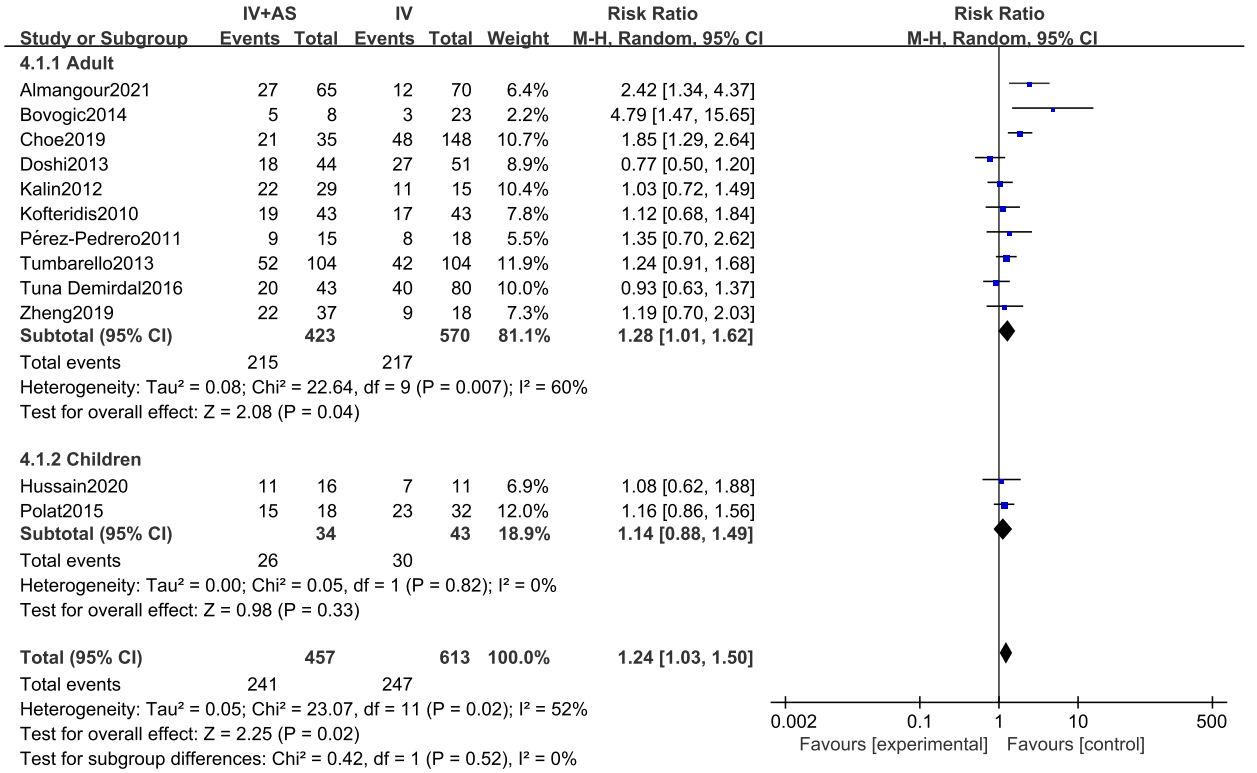

Fig. 7. Forest plot comparing microbiological eradication among the IV + AS and the IV groups.

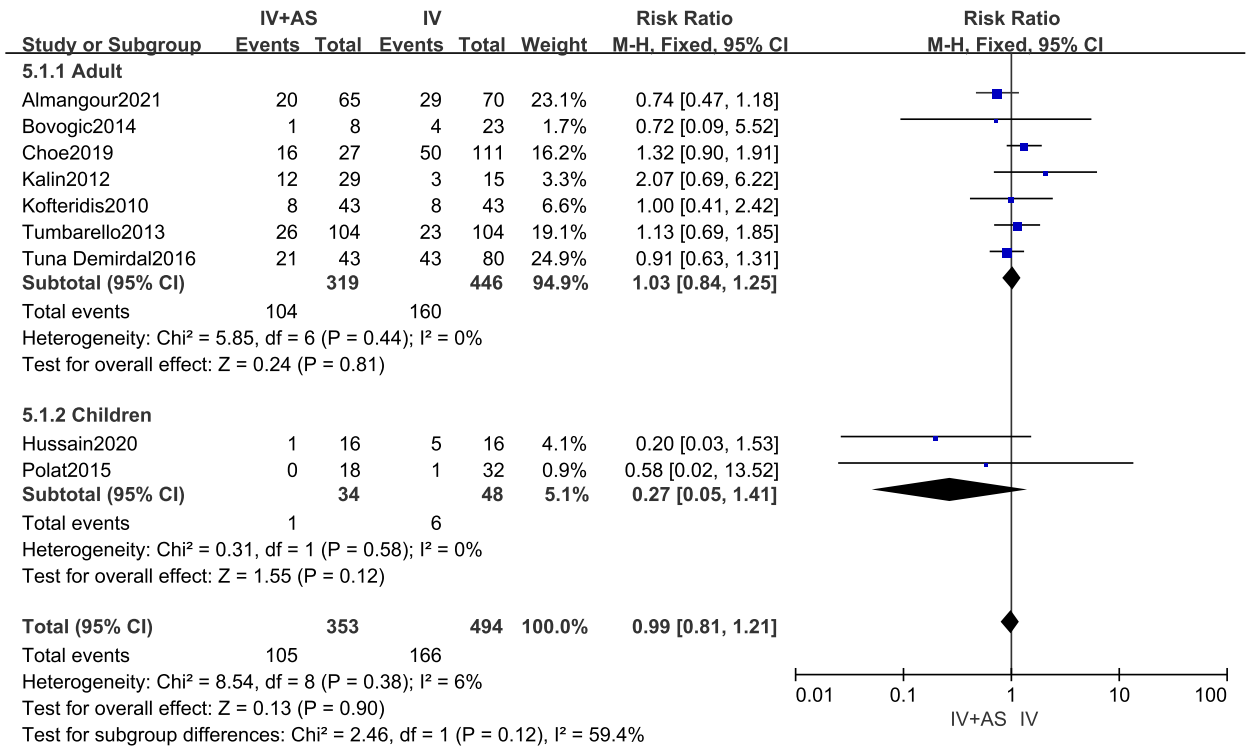

Fig. 8. Forest plot comparing incidences of nephrotoxicity among the IV + AS and the IV groups.

study (Fig. 9). In contrast, using different polymyxin had no significant difference in the incidence of nephrotoxicity (Fig. 10).

3.4.6. Duration of hospitalisation

A total of five studies [21,26,28,29,35] were included, with 188 patients in the IV + AS group and 231 patients in the IV group to investigate the duration of hospitalisation. A fixed effect model was utilised because the forest plot results indicated no statistically significant heterogeneity between the studies ($P = 0.70$, $I^2 = 0\%$). No statistically significant difference was identified among the two groups (MD = 0.09, 95% CI: −5.89–6.06, $P = 0.98$), indicating that aerosolised polymyxin as adjuvant therapy of systemic medication cannot reduce the duration of hospitalisation (Fig. 11).

3.4.7. Duration of mechanical ventilation

For the duration of mechanical ventilation determination, four studies [21,24,25,34] were included, with 203 patients in the IV + AS group and 222 patients in the IV group. Two studies involved children [24,25]. No statistical heterogeneity between the studies ($P = 0.75$, $I^2 = 0\%$) was identified through forest plot, implying the use of a fixed effect model. The findings revealed a statistically significant difference between the two groups (MD = −0.47, 95% CI: −4.61∼-3.53, $P < 0.00001$), indicating that aerosolised polymyxin as adjuvant therapy of systemic medication can reduce the duration of mechanical ventilation. Subgroup analysis demonstrated that whether for adults or children, the IV + AS group had a shorter duration of mechanical ventilation than the IV group (Fig. 12).

3.5. Publication bias analysis

In the present study, the statistical analysis of the impact of all-cause mortality included all 16 studies, and the number of studies was sufficient to assess publication bias. In the funnel chart, we select RR as the abscissa and SE (standard error) as the ordinate because the funnel diagram is visually asymmetric (Fig. 13), and we suspect potential publication bias. Similarly, 11 and 12 studies were included in the meta-analysis of clinical cure rate (Fig. 14) and microbiological eradication (Fig. 15), respectively. The funnel diagram is visually asymmetric, so there is potential publication bias. Other outcome evaluations included less than ten studies, and the publication bias was not assessed. It is unclear whether other outcomes are influenced by publication bias. To quantify potential publication bias, we conducted Egger's test and Begg's test. The results from the Egger's test found a significant publication bias in the outcome of all-cause mortality ($Z = -2.41$, $P = 0.0304$), but the results of Begg's test ($Z = -1.49$, $P = 0.1628$) did not show significant statistical significance. Using the "trim and fill" method, 5 potentially missing studies were included (Fig. 16), and the results showed an adjusted effect size (RR) of 0.953 (95% CI: 0.814–1.116), it was suggested that the current research results were not robust, and more RCT studies with low heterogeneity are needed to confirm our conclusions.

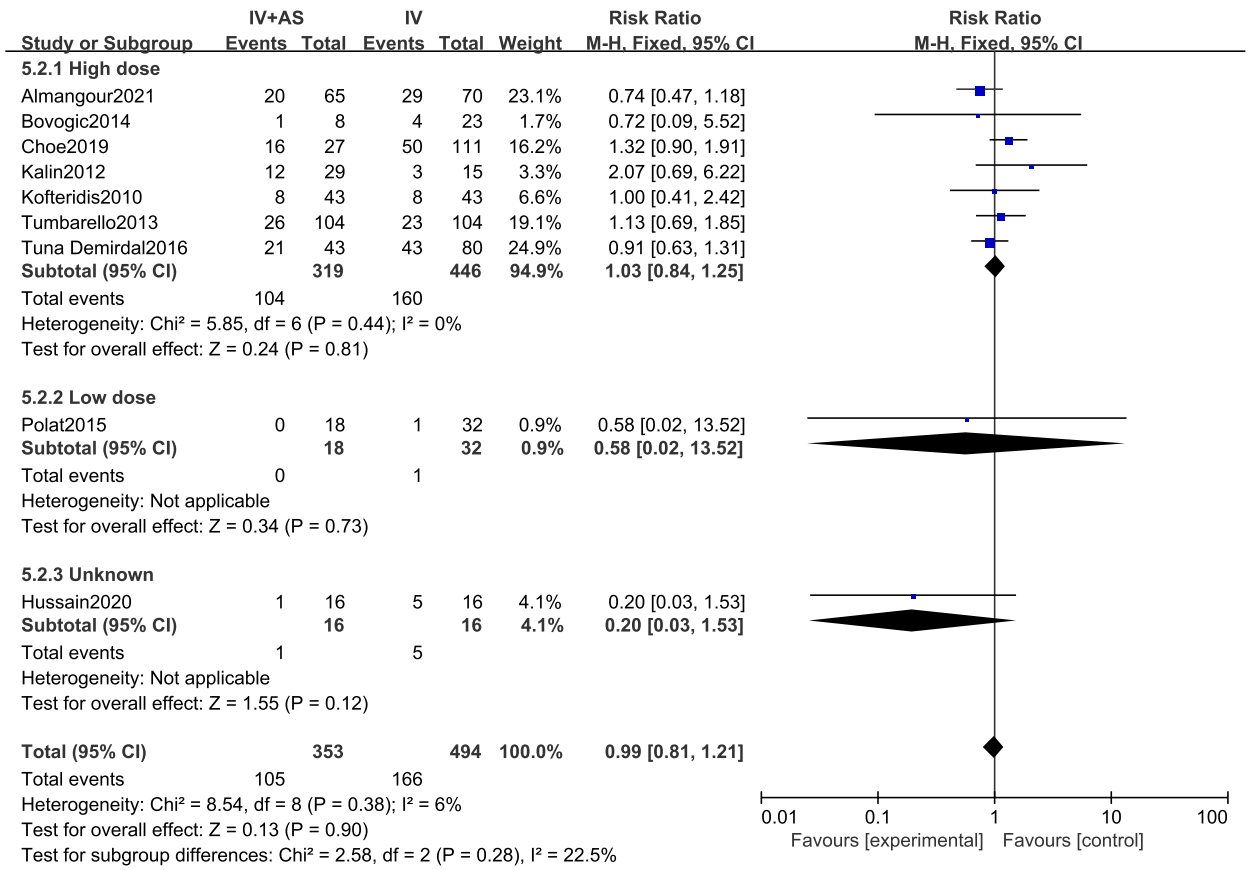

Fig. 9. Subgroup analysis: Effect of different doses of polymyxin on incidence of nephrotoxicity in the IV + AS and the IV groups.

3.6. Sensitivity analysis

We perform a leave-one-out sensitivity analysis to assess the robustness of our meta-analysis and to identify potential sources of heterogeneity. The removal of any study did not affect clinical cure rates, the incidence of nephrotoxicity, duration of hospitalisation and duration of mechanical ventilation, indicating that the conclusions of these studies are robust enough. Fig. 7 illustrates the heterogeneity between the two groups ($P = 0.02$, $I^2 = 52\%$), but we used the leave-one-out sensitivity analysis to identify the potential source of this heterogeneity. We removed Choe 2019, Almangour 2021, Bovogic 2014 and Doshi 2013 one by one, and the I^2 value can be reduced to less than 50%, indicating that these four studies may be the source of heterogeneity. The sample size of these four studies ranges from 31 to 191, and three use high-dose IV polymyxin, which might be the one reason for the potential heterogeneity. We found that the reliability of the results in the meta-analysis of all-cause mortality was significantly low. There was no significant difference between the two groups after the removal of the choe 2019 study. Similarly, when we removed naesens 2011 and Hussain 2020 from the meta-analysis of clinical response rate, there was no significant difference between the two groups. Therefore, it should be interpreted carefully when referring to the effect of IV + AS polymyxin on all-cause mortality, clinical response rates and microbiological eradication.

4. Discussion

This study systematically evaluated the efficacy and safety of IV + AS polymyxin versus IV polymyxin alone in treating MDR-GNB pneumonia. Compared with previous studies, the present analysis included more analysable studies (16 studies, two of which had children as patients) and more patients (1537 total patients, including 641 in the IV + AS group and 896 in the IV group). Our findings revealed that IV + AS polymyxin had a better outcome in treating MDR-GNB pneumonia than IV polymyxin alone, measured by the patient's all-cause mortality, clinical outcome, or microbial outcome. In addition, there was less duration of mechanical ventilation, but there was no significant difference in the duration of hospitalisation between the two groups. Our subgroup analysis demonstrated that using polymyxin in combination could reduce mortality in adult patients, whereas there were few studies in children and no statistically significant difference. We also investigated the relationship between IV polymyxin dose and all-cause mortality. We found that IV low-dose polymyxin (<6 MIU/d) could reduce mortality, whereas high-dose polymyxin (>6 MIU/d) did not affect mortality. Similarly, the safety analysis revealed that IV + AS polymyxin did not increase the incidence of nephrotoxicity. Subgroup analysis

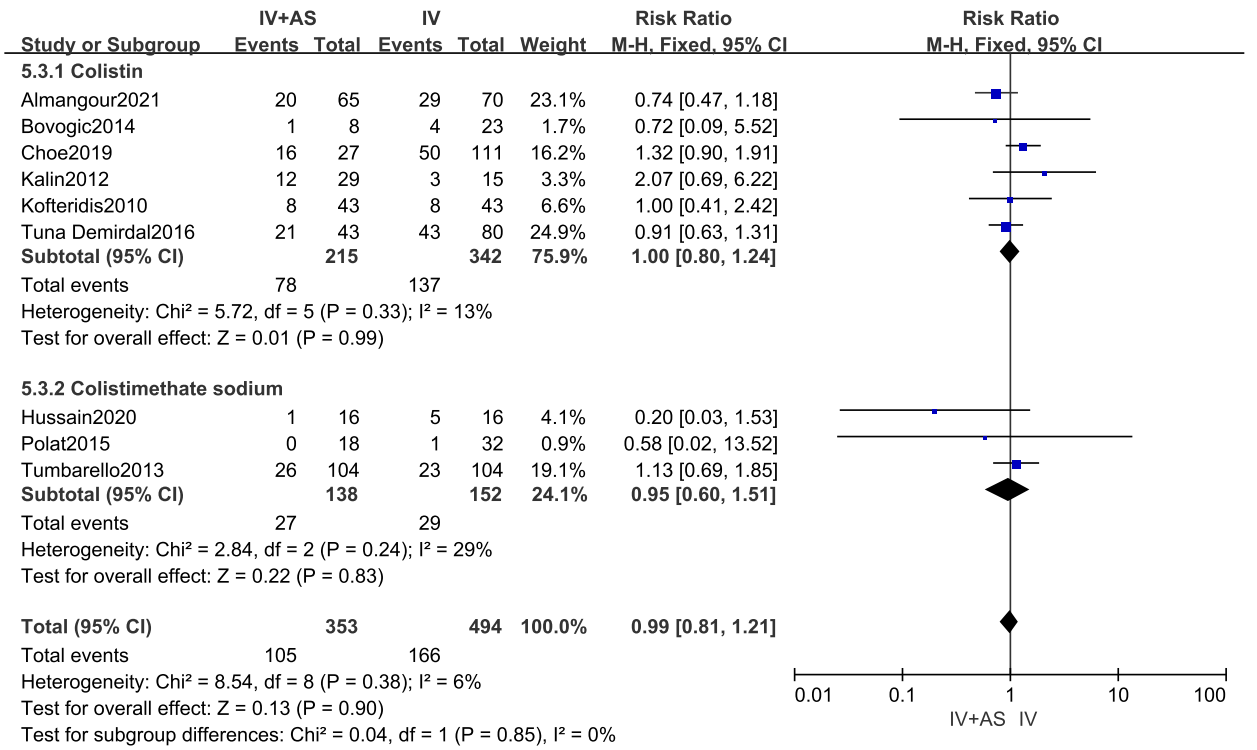

Fig. 10. Subgroup analysis: Effect of different types of polymyxin on incidence of nephrotoxicity in the IV + AS and the IV groups.

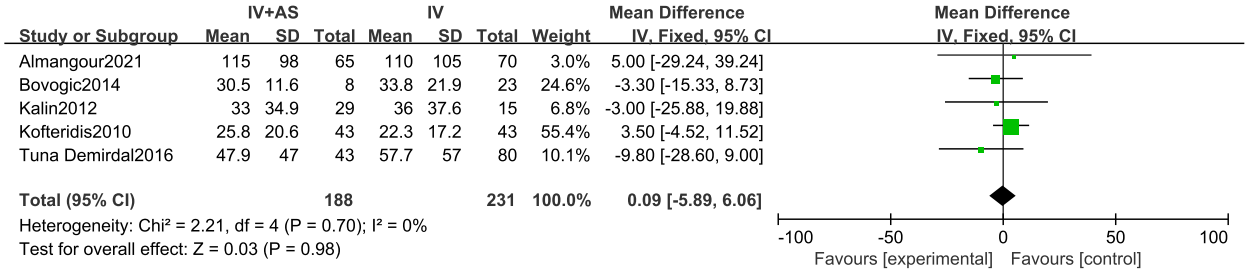

Fig. 11. Forest plot duration of hospitalisation among the IV + AS and the IV groups.

indicated that using either low-dose or high-dose polymyxin did not increase the risk of nephrotoxicity. In conclusion, based on our findings, aerosolised polymyxin as adjuvant therapy for systemic administration has significant benefits in lowering patient mortality and improving clinical and microbiological outcomes without increasing the risk of nephrotoxicity. Colistin outperforms colistine sodium in efficacy against different types of polymyxin, but there is no significant difference in the incidence of nephrotoxicity between the two drugs.

With the increase in antibiotic resistance, MDR-GNB occupies a prominent position among the pathogenic microorganisms of pneumonia, posing a significant challenge to clinical treatment. A retrospective analysis in China found that the incidence of Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and Carbapenems-resistant *Acinetobacter baumanii* (CRAB) in hospitalised patients was 22.62% and 58.05%, respectively [36]. In the United States and Europe, the HAP and VAP caused by GNB were 61.5% and 76.1% in ICU patients, respectively, and antibiotic sensitivity against many pathogens decreased. For example, in the above two regions, the most common GNB, *Pseudomonas aeruginosa,* is only 65.8% and 63.9% sensitive to meropenem and piperacillin/tazobactam respectively, putting significant pressure on the selection of clinical antibiotics [37]. Polymyxin, as one of the few options for treating MDR-GNB [7], plays an important role in the clinical treatment of pneumonia. However, due to the narrow therapeutic window of polymyxin, IV polymyxin often causes adverse reactions such as nephrotoxicity and neurotoxicity [9]. Therefore, other drug delivery routes have been investigated for reducing side effects without compromising the therapeutic effects. Aerosolised polymyxin seems to be an ideal drug delivery method due to its high concentration on the surface of lung epithelium and low concentration throughout the body [38]. The FDA first approved aerosolised polymyxin to treat patients with pulmonary cystic fibrosis complicated by *Pseudomonas aeruginosa* infection [39]. For MDR-GNB pneumonia, previous studies have shown that aerosolised polymyxin alone can improve the

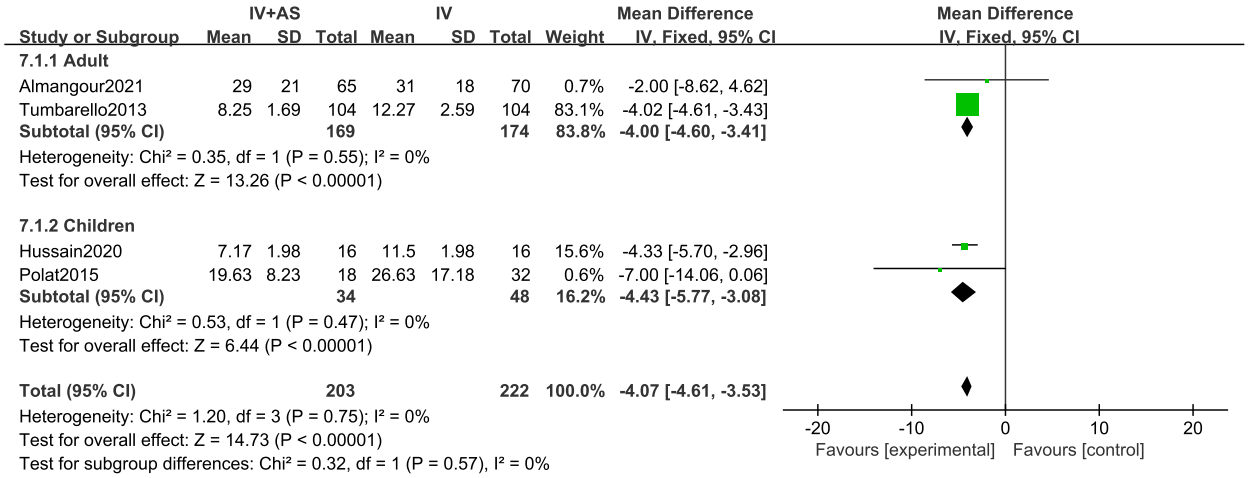

Fig. 12. Forest plot duration of mechanical ventilation among the IV + AS and the IV groups.

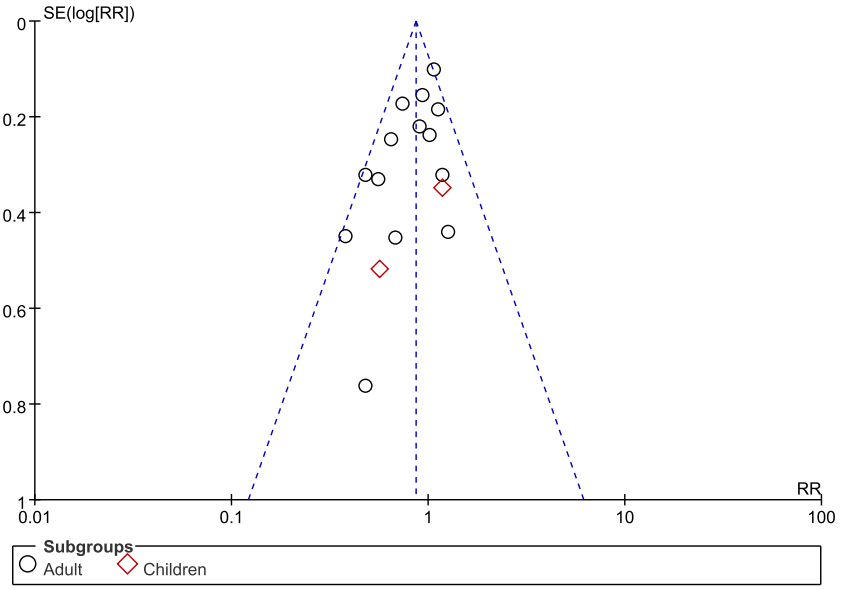

Fig. 13. Funnel chart of publication bias analysis included in all-cause mortality analysis literature.

microbial outcome of VAP patients and reduce ventilator use time. However, there is no significant difference in mortality and clinical cure rate [14,40]. Simultaneously, aerosolised polymyxin may increase the risk of asthma and bronchospasm. Therefore, the current guidelines do not recommend polymyxin atomisation alone to treat pneumonia [13,41].

The use of aerosolised polymyxin as adjuvant therapy is also controversial. Although there are currently several guidelines [13,41] recommending that patients with MDR-GNB HAP/VAP treated with IV polymyxin should receive adjuvant polymyxin aerosol therapy. However, it is a weak recommendation based on low-quality evidence. Previous studies had conflicting results regarding the efficacy and safety of aerosolised polymyxin as adjuvant therapy for systemic administration. An earlier prospective study compared the efficacy of IV + AS polymyxin and IV alone in treating MDR-GNB HAP.

The results indicated that the IV + AS group had lower mortality (8/28, 28%) than the IV group (5/12, 41%) ($P < 0.05$) [20]. Similarly, another retrospective study [22] revealed that adjuvant aerosolised polymyxin was associated with significantly lower mortality in the treatment of carbapenem-resistant GNB pneumonia (OR = 0.338, 95% CI: 0.132–0.864, $P = 0.024$). Although the IV + AS group had lower mortality, many studies revealed no statistically significant difference between the two groups [21,27,29]. Therefore, there seem to be contrary findings about the effect of adjuvant aerosolised polymyxin on improving patient mortality in adult patients. The present meta-analysis demonstrated that adjuvant aerosolised polymyxin could reduce patient mortality.

Further subgroup analysis revealed that IV administration of low-dose polymyxin benefited these patients, whereas IV administration of high-dose polymyxin was not. In general, adjuvant aerosolised therapy improved patient mortality, but the dose selection is

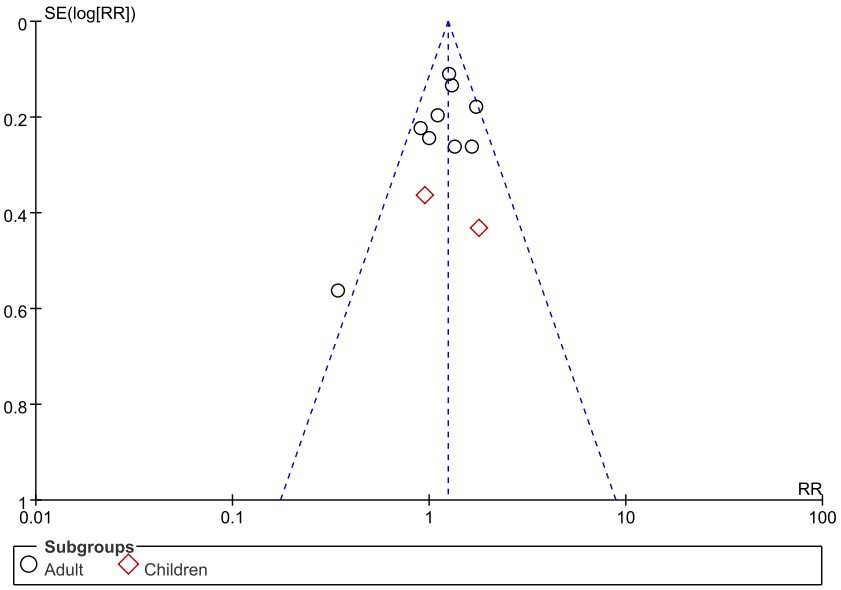

Fig. 14. Funnel chart of publication bias analysis included in clinical cure rate analysis literature.

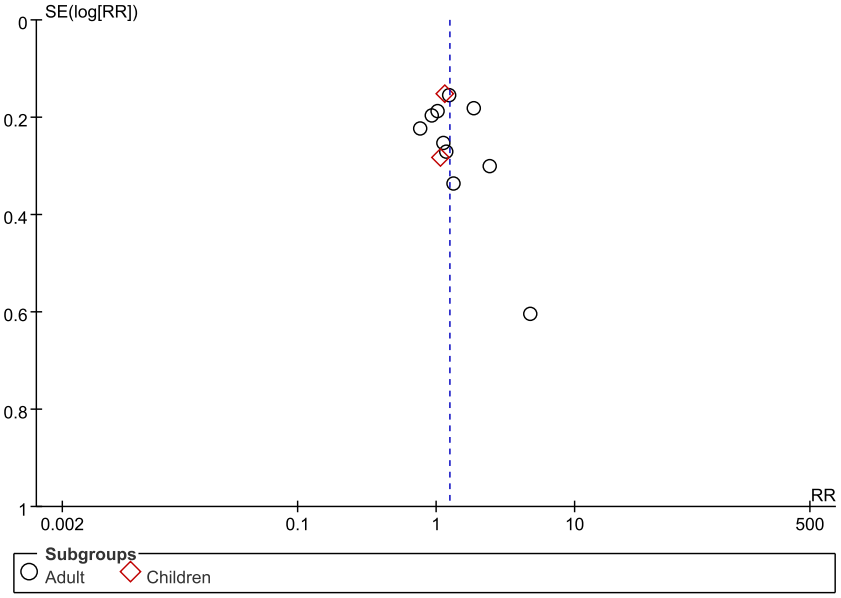

Fig. 15. Funnel chart of publication bias analysis included in microbiological eradication analysis literature.

particularly important, and an excessive polymyxin dose is unfavourable for patients. However, the findings of our sensitivity analysis indicate that the results of all-cause mortality should be interpreted carefully. Concurrently, this conclusion is primarily based on retrospective analysis and requires confirmation through larger-scale prospective RCTs. There have been few studies on children, two studies indicated that IV polymyxin combined with aerosolised polymyxin reduced mortality in VAP children [24,25], but there was no statistically significant difference. Our subgroup analysis also revealed similar results. More studies are required to clarify further the impact of adjuvant aerosolised polymyxin on the mortality of children with MDR-GNB pneumonia due to the small number of included studies and small sample size.

Regarding the effect of different types of polymyxin on mortality, our findings indicated that the patient prognosis is better with colistin use. Why does this happen? We know that IV colistimentate sodium is rapidly cleared by kidneys, and only 20–25% of it is hydrolysed to colistin, which may be attributed to colistin's relatively better effect. Another possible reason could be that only four studies used colistimentate sodium, resulting in a small sample size.

Although there is some disagreement about all-cause mortality, it is encouraging that adjuvant aerosolised polymyxin can improve

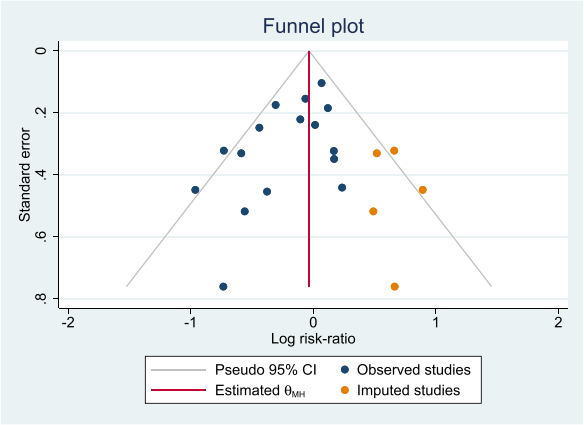

Fig. 16. Funnel chart of publication bias analysis after the "trim and fill" method.

the clinical cure rate of patients. The vast majority of studies [20,21,31,34,35] have also confirmed that the clinical response rate and clinical cure rate of patients improved to varying degrees following the adjuvant aerosolised polymyxin administration. Our sensitivity analysis also advocates that the finding is reliable. The two included studies for children suggest that adjuvant aerosolised polymyxin does not improve clinical outcomes in children. However, due to the small sample size, this conclusion requires further research to support it.

Some studies suggest that adjuvant aerosolised polymyxin has better microbiological eradication [21,22,26,30,31]. However, other studies included did not show statistically significant differences. Simultaneously, neither of the two included studies [24,25] demonstrates a favorable microbiological outcome for children. In general, aerosolised polymyxin as adjuvant therapy for MDR-GNB pneumonia had a higher microbial clearance rate, particularly in adult patients. However, our sensitivity analysis revealed that this conclusion should be interpreted carefully.

In terms of safety, no patients in this study experienced neurotoxic adverse reactions, and there were few included patients, so we did not conduct further analysis. When we analysed the incidence of nephrotoxicity in the two groups, most studies [21,22,26,28,34,35] indicate that the combination of aerosolised polymyxin and IV polymyxin did not increase the risk of nephrotoxicity. The findings of the current meta-analysis also indicated that IV + AS polymyxin did not increase the incidence of nephrotoxicity. Subgroup analysis revealed that IV + AS did not increase the risk of nephrotoxicity in either high-dose or low-dose polymyxin, adult or pediatric patients, or the types of polymyxin. Sensitivity analysis depicted that the findings of the present study were reliable, implying that aerosolised polymyxin was relatively safe as adjuvant therapy.

A meta-analysis [42] of 237 studies involving 35569 patients revealed that the overall incidence of neurotoxicity with polymyxin was 0.030 (95% CI: 0.020–0.043), which was not a high incidence. However, the lack of relevant data in that research makes us unable to perform further appropriate analysis.

Previous studies have shown that aerosol inhalation increases the concentration of polymyxin in the epithelial lining fluid (ELF) [38,43]. Boisson et al. [43] described that the concentration range of polymyxin in ELF after atomisation administration was significantly higher (9.53–1137 mg/L) than that after IV administration (1.48–28.9 mg/L in ELF). Moreover, the concentration of polymyxin in plasma after nebulisation (0.15–0.73 mg/L) was lower than that after IV administration (0.15–4.7 mg/L). This seems to imply that aerosolised polymyxin could be used as adjuvant therapy. However, their use is limited due to a lack of suitable nebulisation agents and specific equipment for antibiotic nebulisation. The optimal droplet size range for airway deposition is 1–5 μm, the pulmonary parenchymal deposition range is < 2 μm, and larger droplets are unlikely to reach the distal airway [44]. Concurrently, the presence of airway secretions and the heterogeneity of lung lesions will affect the drug deposition of drugs that affects the curative effects [45]. In addition, whether the patient is breathing autonomously or by the ventilator, as well as ventilator mode, inspiratory time, inspiratory flow, tidal volume and other factors that will affect drug deposition, must be considered.

On the contrary, other preservatives in atomised preparations will increase the incidence of bronchospasm and asthma [13]. These complex factors raise the technical requirements for using atomised antibiotics, and the standardised atomisation procedure must also be improved. The present research ensures the promising future of aerosolised polymyxin as adjuvant therapy.

Our meta-analysis has the following advantages. First, we systematically assessed the efficacy and safety of IV + AS polymyxin in treating MDR-GNB pneumonia, followed by a sensitivity analysis to evaluate the reliability of the conclusion. Second, we performed several meaningful subgroup analyses to comprehensively assess the efficacy and safety of different doses of polymyxin and the difference in results between adults and children, which may be helpful in guiding clinical practice. However, this meta-analysis has some limitations. First, most of the included studies were retrospective, with only one being prospective. More prospective cohort studies will be required to assess the reliability of research findings. Second, most studies have a small sample size, leading to some bias in the results. Third, there is some heterogeneity among the included studies. Although the sensitivity analysis depicts that the conclusions of the incidence of toxicology, duration of hospitalisation and duration of mechanical utility are significantly reliable, the heterogeneity of the study leads to unreliable findings in terms of all-cause mortality, clinical response rates and microbiological generation. Fourth,

the funnel plot results indicate that we may have potential publication bias, and using the "trim and fill" method, we found that the current research results were not robust enough. Therefore, the findings of the present study must be interpreted carefully.

5. Conclusion

In conclusion, our meta-analysis revealed that IV + AS polymyxin had better efficacy than polymyxin alone in treating MDR-GNB pneumonia, reduced all-cause mortality, and improved clinical and microbiological outcomes without increasing the risk of nephrotoxicity. It could improve the prognosis of patients without increasing the incidence of adverse reactions, primarily when used in low-dose and is considered an excellent clinical treatment option. However, because of the heterogeneity between studies and the fact that most studies are retrospective analyses with a small sample size, the interpretation of the results should be cautious. From a future development perspective, we should pay more attention to the local pharmacokinetics and pharmacokinetics of the lung tissue and increase the local efficacy without increasing the systemic efficacy.

Availability of data and materials

Our data came from other clinical studies, and the data sets used and analysed are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that there is no conflict of interest.

Author contribution statement

Wenchao Mao: Performed the experiments; Analysed and interpreted the data; Wrote the paper.
Difan Liu: Conceived and designed the experiments; Contributed analysis tools and data; Wrote the paper.

Data availability statement

No data was used for the research described in the article.

Additional information

Supplementary content related to this article has been published online at [URL].

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15774.

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