Iranian Journal of Microbiology
Volume 16 Number 6 (December 2024) 722-731

REVIEW ARTICLE

Systematic review and meta-analysis of colistin plus meropenem therapy for the treatment of nosocomial pneumonia

Hazhir Moradi[1], Zahra Sadat Sajadi-Javan[1], Sarah Mousavi[2], Soodabeh Rostami[1*], Bita Moradi Khaniabadi[1]

[1]Nosocomial Infection Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

Received: March 2024**, Accepted:** August 2024

ABSTRACT

Background and Objectives: Nosocomial pneumonia caused by multidrug-resistant gram-negative bacteria presents a significant challenge for healthcare systems, as there are limited effective treatments available. This systematic review and meta-analysis aim to investigate the outcomes of colistin plus meropenem combination therapy on nosocomial pneumonia.
Materials and Methods: An exhaustive search of PubMed, Scopus, Web of Science (WOS), and Embase databases was conducted, resulting in the extraction of 5 studies for qualitative assessment and meta-analysis. The study sample included 991 patients admitted with nosocomial pneumonia. The outcomes evaluated were clinical improvement, microbiological response, mortality, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE II) score, Charlson Comorbidity Index (CCI), Clinical Pulmonary Infection Score (CPIS), C-reactive protein (CRP) levels, procalcitonin (PCT) levels, and intensive care unit (ICU) duration.
Results: The results demonstrated that colistin plus meropenem combination therapy significantly improved clinical outcomes (OR = 1.37, 95% CI = 1.04-1.81, p = 0.027), reduced SOFA scores (OR = -0.28, 95% CI = -0.44 to -0.11, p = 0.001), and increased CCI scores (OR = 0.16, 95% CI = 0.02-0.29, p = 0.021) compared to other medications. However, other evaluated parameters did not show significant differences.
Conclusion: This meta-analysis indicates that colistin-meropenem combination therapy is superior to other colistin-based treatments for nosocomial pneumonia in terms of clinical improvement, SOFA score reduction, and CCI score increase. Nevertheless, other variables assessed did not exhibit remarkable differences between the treatment regimens.

Keywords: Meropenem; Colistin; Multiple drug-resistance; Nosocomial infection; Pneumonia

INTRODUCTION

Nosocomial pneumonia, which includes hospital-acquired (HAP) and ventilator-associated pneumonia (VAP), accounts for more than 20% of all hospital-acquired infections and significantly affects both morbidity and mortality rates (1). This condition places a heavy burden on the healthcare system and necessitates extensive use of antibacterial agents, often leading to overuse and subsequent resistance (2, 3).

The US Centers for Disease Control and Prevention (CDC) define multidrug resistance (MDR) as non-susceptibility to at least one agent in three or more antimicrobial categories; extensively drug-resistant

*Corresponding author: Soodabeh Rostami, Ph.D, Nosocomial Infection Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98-9131011846 Fax: +98-3137925308 Email: Srostami1876@gmail.com

(XDR) as susceptibility limited to two or fewer categories; and pan drug resistance (PDR) as nonsusceptibility to all agents in all antimicrobial categories (4). Increasing evidence indicates a steady rise in XDR *Acinetobacter baumannii*, XDR *Pseudomonas aeruginosa*, and carbapenem-resistant *Enterobacterales* (CRE), resulting in severe outcomes (5, 6). The severity of nosocomial pneumonia caused by these pathogens is so pronounced that the World Health Organization (WHO) has prioritized the search for new antimicrobial agents against them. Additionally, the CDC has identified these pathogens as urgent threats to human health, underscoring the need for immediate action (7, 8).

Despite notable drawbacks, including less efficacy compared to beta-lactams, nephrotoxicity with high dosing, and the development of resistance during therapy, polymyxins (colistin and polymyxin B) have remained the primary treatment for multidrug-resistant gram-negative bacteria (MDRGN bacteria) for several decades. To enhance outcomes, physicians often use colistin in combination with other antibiotics to potentially prevent resistance, achieve higher success rates, and allow for lower doses or shorter treatment durations (9-11).

Combining colistin with carbapenems has been proposed as a potentially effective approach, with promising results observed in both *in vitro* and in vivo studies (12-14). However, research on human subjects remains limited. This systematic review and meta-analysis aim to evaluate the outcomes of colistin plus meropenem combination therapy in treating nosocomial pneumonia caused by carbapenem-resistant gram-negative bacteria (CRGNB).

MATERIALS AND METHODS

Research strategy. This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15). We conducted a comprehensive search using PubMed, Web of Science (WOS), Scopus, Embase, Science Direct, and Cochrane databases from January 1, 2012, to December 31, 2022. This search yielded 348 articles, with 45 from PubMed, 30 from WOS, 257 from Scopus, 6 from Embase, 10 from Science Direct, and none from Cochrane.

The search strategy was formulated based on keywords derived from MeSH. [(Healthcare Associated Pneumonia) OR (Healthcare-Associated Pneumonias) OR (Pneumonia, Healthcare-Associated) OR (Nosocomial Pneumonia) OR (Nosocomial Pneumonias) OR (Pneumonia, Nosocomial) OR (Hospital Acquired Pneumonia) OR (Hospital Acquired Pneumonias) OR (Pneumonia, Hospital Acquired) OR (Ventilator-Associated Pneumonia) OR (Pneumonia, Ventilator-Associated)] AND [(Colistin) OR (Polymyxin E) OR (Colimycin) OR (Colisticin) OR Totazina) OR (Colistin Sulfate) OR (Sulfate, Colistin) OR) Coly-Mycin)] AND [(Meropenem) OR (3-(5-Dimethylcarbamoylpyrrolidin-3-ylthio)-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo(3.2.0)hept-2-ene-2-carboxylic acid) OR Merrem) OR Ronem) OR Penem) OR SM 7338) OR SM-7338) OR SM7338)] AND [(Treatment Outcome) OR (Outcome, Treatment) OR (Patient-Relevant Outcome) OR (Outcome, Patient-Relevant) OR (Outcomes, Patient-Relevant) OR (Patient Relevant Outcome) OR (Patient-Relevant Outcomes) OR (Clinical Effectiveness) OR (Effectiveness, Clinical) OR (Treatment Effectiveness) OR (Effectiveness, Treatment) OR (Rehabilitation Outcome) OR (Outcome, Rehabilitation) OR (Treatment Efficacy) OR (Efficacy, Treatment) OR (Clinical Efficacy) OR (Efficacy, Clinical)].

Inclusion and exclusion criteria. We included clinical trials that assessed the outcomes of colistin plus meropenem treatment for healthcare-associated pneumonia (HAP and VAP) within the specified period (2012-2022). Studies not designed as clinical trials, those assessing other antimicrobial regimens, or reporting *in vitro* or *in vivo* results were excluded.

Study selection. Two authors independently reviewed the databases and selected studies, resolving any disagreements with a third author. Duplicated articles were removed, and the remaining articles were screened for eligibility. Articles meeting the criteria were included in the qualitative analysis.

Data extraction. Data extraction was performed independently by the authors, capturing information such as the first author's name, year of publication, population studied, administered regimens (including dosing and treatment duration), and study objectives.

Statistical procedure. A meta-analysis was conducted to compare the effectiveness of colistin plus meropenem therapy against other antibiotics or therapies for multidrug-resistant bacterial infections. Com-

prehensive Meta-Analysis (CMA) Software Version 3.3.070 (Biostat, Englewood, NJ) was used for statistical analysis. For categorical outcomes, differences were expressed as odds ratios (ORs) using the Mantel-Haenszel (M-H) model, while Hedge's g effect size was utilized for continuous outcomes. The Z test determined the significance of pooled ratios, with a p-value less than 0.05 considered statistically significant.

Heterogeneity among studies was assessed using Cochran's Q test, and the I-squared statistic categorized heterogeneity as low (<25%), moderate (25-50%), or high (>50%) (24). A random-effects model was used for high heterogeneity and a fixed-effects model for low to moderate heterogeneity.

This study evaluated various outcomes including clinical improvement, microbiological response, mortality, Charlson Comorbidity Index (CCI), Clinical Pulmonary Infection Score (CPIS), C-reactive protein (CRP), procalcitonin (PCT), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II), and ICU length of stay. Each outcome was analyzed individually.

The analysis was divided into three parts:

1. Forest Plot: Displayed the point estimates of each study and the pooled point estimate, where each square represented a study's point estimate and the diamond represented the pooled estimate.

2. Funnel Plot Analysis: Assessed publication bias by detecting asymmetry in the distribution of studies.

3. Publication Bias Tests: Included the Classic Fail-safe N test, Begg and Mazumdar rank correlation test, and Duval and Tweedie's trim and fill method.

RESULTS

Characteristics of studies included. The database search yielded 348 articles (PubMed=45, WOS=30, Scopus=257, Embase=6, Science Direct=10, and Cochrane=0). After applying the eligibility and exclusion criteria, only 5 studies comprising 991 patients were included in the meta-analysis. The detailed study selection process is illustrated in Fig. 1 and Table 1 summarized the key characteristics of the included trials. These studies were conducted across various regions, including the U.S., European countries (Israel, Greece, Italy, and Bulgaria), Asian countries (Iran, Thailand, and Taiwan), and an African country (Egypt). All were randomized clinical trials involving adult participants, with an average age of 61 years (standard deviation of 5.7 years).

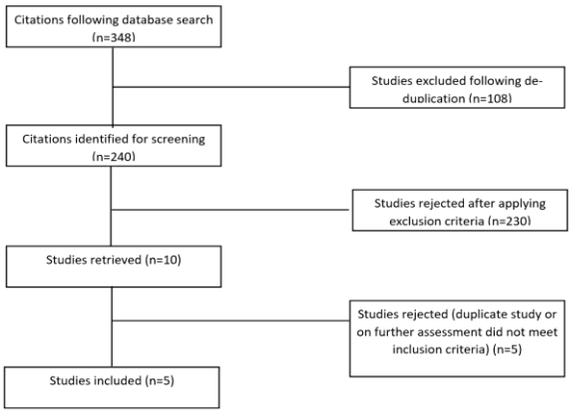

Fig. 1. Flow chart illustrating summary of literature search results

The studies varied in their geographical locations, ensuring a diverse representation of populations and healthcare settings. The randomized design of these clinical trials enhances the reliability of the results, while the relatively consistent average age of participants allows for a more standardized comparison of outcomes across studies.

Clinical improvement. The meta-analysis included data from all five studies (5, 15-18) on clinical improvement, encompassing a total of 991 patients. Among these, 501 patients received colistin plus meropenem combination therapy, while 490 patients were treated with other antibiotics and therapies. The fixed effects model demonstrated a significant association between the treatment and clinical improvement (OR = 1.38, 95% CI = 1.05-1.82, p-value = 0.021), as shown in Fig. 2A. This indicates that patients who received the colistin plus meropenem combination therapy were 38% more likely to experience clinical improvement compared to those who received other antibiotics and therapies.

The funnel plot analysis, presented in Fig. 3A, further illustrates the assessment of publication bias in this meta-analysis.

Overall, these findings suggest that the colistin plus meropenem combination therapy is significantly associated with clinical improvement in patients with nosocomial pneumonia caused by carbapenem-resistant gram-negative bacteria (CRGNB), despite some indications of publication bias.

Microbiological response. Three studies reported on microbiological response (5, 15, 18). The fixed effects model indicated no significant difference between colistin plus meropenem combination therapy (447

Table 1. Overview of the set of articles incorporated in this meta-analysis.

Fist author /Year of pub	Region/ study period	Study design	Groups of study	Sample size	Age (years)	Gender / n (%)	SOFA (baseline)	SOFA (second)	CCIS	CPIS score	CRP	PCT	APACHE II score	Length of ICU stay (days)	Mortality	Clinical improvement	Microbiological response
Paul /2018	Israel, Greece, & Italy / Oct 2013-Dec 2016	Investigator-initiated, multicenter, open-label, parallel group, and RCT	Col plus Meropenem	208	Mean=66, SD=18	F / 133 (63%)	Median=5, IQR=(4-8)	At day 14 Median=4, IQR=(2-7)	Median=2, IQR=(0-4)	NR	NR	NR	NR	Median=22, IQR=(13-28)	Up to 28 days 94 (45%)	At day 14 56 (27%)	135 (65%)
			Col monotherapy	198	Mean=66, SD=16	F / 122 (62%)	Median=6, IQR=(3-8)	At day 14 Median=5, IQR=(3-7)	Median=2, IQR=(0-3)	NR	NR	NR	NR	Median=17, IQR=(8-28)	Up to 28 days 86 (43%)	At day 14 42 (21%)	136 (69%)
Khalili / 2018	Iran / Oct 2015-Oct 2017	Open-label, RCT	Col plus Meropenem	24	Mean=61, SD=13	M / 16 (67%)	NR	AETC Median=5.5, R=(0-12)	Median=4, R=(0-9)	Median=8.5, R=(6-11)	Mean=72.4, SD=38.0	Median=1.2.0, R=(0.1-44.7)	NR	Median=10, R=(2-51)	Up to 28 days 10 (42%)	18 (75%)	21 (88%)
			Meropenem Plus ampicillin-sulbactam	23	Mean=56, SD=12	M / 16 (67%)	NR	AETC Median=6.5, R=(0-19)	Median=3, R=(0-10)	Median=8, R=(5-11)	Mean=90.5, SD=44.0	Median=0.8, R=(0.1-90.8)	NR	Median=8, R=(2-27)	Up to 28 days 9 (39%)	16 (70%)	21 (92%)
Abdelsalam / 2018	Egypt / May 2016 – Oct 2016	Prospective, comparative, single-blind, randomized	High dose of Col plus Meropenem	30	Mean=56, SD=16	M / 12 (40%)	Mean=11.7, SD=2.7	AETC Mean=1.7, SD=0.8	NR	NR	AETC Mean=54.7, SD=39.1	ATEC Mean=0.2, SD=0.02	Mean=18.9, SD=5.5	Mean=14, SD=2.5	[illegible]	25 (83%)	NR
			High dose of Col	30	Mean=56, SD=18	M / 16 (53)%	Mean=12.4, SD=3.1	AETC Mean=1.9, SD=0.9	NR	NR	AETC Mean=47.3, SD=39.0	ATEC Mean=0.2, SD=0.02	Mean=18.1, SD=4.0	Mean=18, SD=2.4	13 (43%)	17 (57%)	NR
Momenzadeh / 2022	Iran / Sep 2020 – Feb 2021	Randomized controlled clinical trial	Col plus Meropenem	29	Mean=56, SD=20	M / 17 (59%)	Mean=7.4, SD=2.7	AETC Mean=7.5, SD=2.7	NR	AETC Mean=4.4, SD=2.4	AETC Mean=79.9, SD=38.2	AETC Mean=1.8, SD=3.2	AETC Mean=17.8, SD=7.6	NR	AETC 4 (14%)	12 (41%)	ATEC 12 (48%)
			Col plus Levofloxacin	26	Mean=56, SD=21	M / 19 (73)%	Mean=7.6, SD=2.7	AETC Mean=8, SD=3.8	NR	AETC Mean=3.8, SD=4.6	AETC Mean=74.8, SD=30.7	ATEC Mean=2.6, SD=8.3	AETC Mean=16.7, SD=10.2	NR	AETC 6 (23%)	16 (62%)	ATEC 14 (70%)
Kaye / 2022	US, Thailand, Taiwan, Israel, Greece, Italy, & Bulgaria / Oct 2012-Aug 2020	Randomized, double blind, placebo-controlled trial	Col plus Meropenem	210	Mean=69, SD=16	F / 75 (36%)	NR	NR	Baseline Median=5, IQR=(4-7)	NR	NR	NR	Baseline Median=21, IQR=(17-26)	NR	Up to 28 days 77 (37%)	80 (38%)	ATEC 103 (49%)
			Col plus Placebo	213	Mean=68, SD=17	F / 83 (39%)	NR	NR	Baseline Median=5, IQR=(4-7)	NR	NR	NR	Baseline Median=22, IQR=(17-26)	NR	Up to 28 days 92 (43%)	65 (31%)	ATEC 106 (50%)

AETC: at the end of treatment course; APACHE II: acute physiology and chronic health evaluation; CCI: Charlson comorbidity index score; CI: clinical improvement; CPIS: clinical pulmonary infection assessment; CRP: C-reaction protein; F: female; ICU: intensive care unit; Mean: the average value; M: male; SD: standard deviation; IQR: interquartile range (= 3rd quartile – 1st quartile); NR: not reported; PCT: procalcitonin; R: range (= minimum – maximum); RCT: randomized clinical trial.

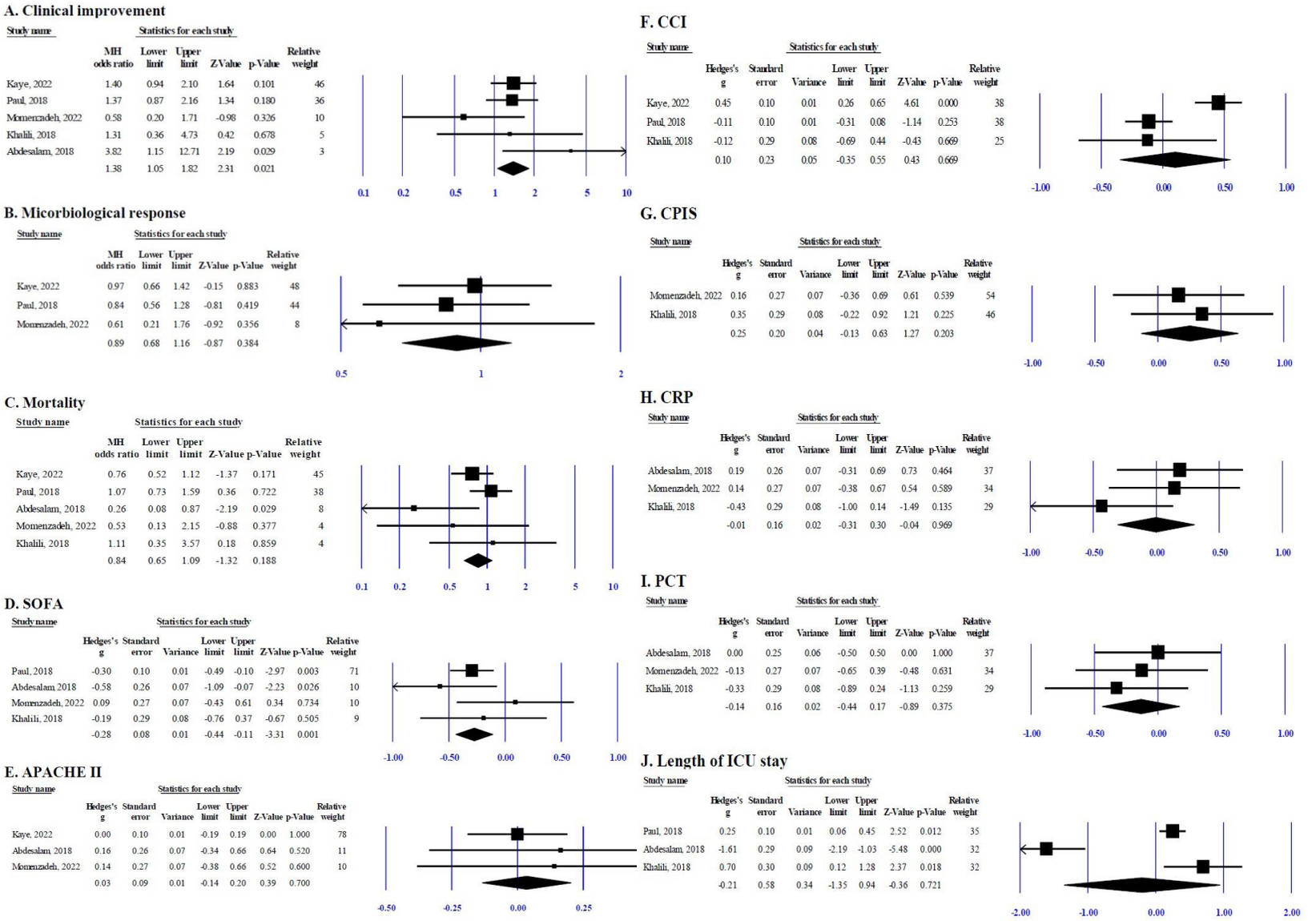

Fig. 2. The forest plot and point estimate of outcomes

IRAN. J. MICROBIOL. Volume 16 Number 6 (December 2024) 722-731

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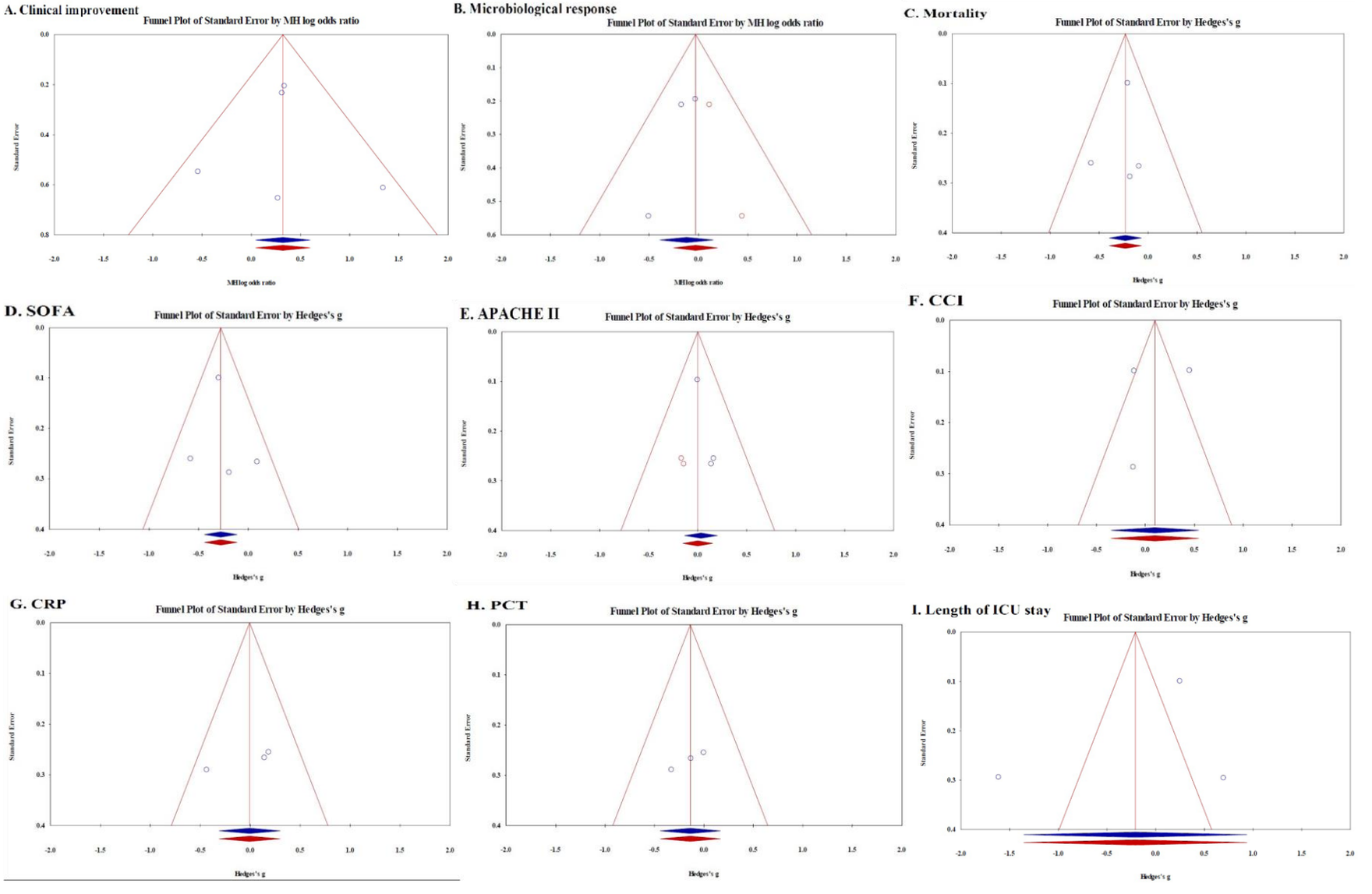

Fig. 3. Funnel plot analysis on the detection of publication bias in the meta-analysis. (owing to the limited number of studies on the CPIS scores outcome (fewer than three studies), the procedures for detecting publication bias were not executed. Consequently, the funnel plot for this outcome in not available.)

patients) and other antibiotics/therapies (437 patients) regarding microbiological response (OR = 0.89, 95% CI = 0.68-1.16, p-value = 0.384), as shown in Figure 2-B. None of the three publication bias analyses revealed any evidence of bias for microbiological response (Table 2). The funnel plot for microbiological response is displayed in Fig. 3B.

Mortality. All five studies, involving 991 patients (501 receiving colistin plus meropenem combination therapy and 490 receiving other antibiotics/therapies), reported on mortality (5, 15-18). Fig. 2C shows no statistically significant difference in mortality between the two groups (OR = 0.84, 95% CI = 0.65-1.09, p-value = 0.188). Additionally, none of the three methods indicated publication bias for mortality (Table 2 and Fig. 3C).

SOFA score. Four studies reported SOFA scores (15-18). The fixed-effects model estimated the SOFA score effect at -0.28 (95% CI, -0.44 to -0.11, p-value = 0.001), indicating significantly lower SOFA scores for the combination therapy group compared to other therapies (Fig. 2D). The classic fail-safe N test suggested one missing study (Table 2). Duval and Tweedie's trim and fill method, after trimming one study to the left side of the mean, showed an adjusted OR of -0.32 (95% CI, -0.48 to -0.16), with negligible changes in OR. The funnel plot for the SOFA score is displayed in Fig. 3D.

APACHE II score. Three studies measured the APACHE II score (5, 15, 16), assessing illness severity and risk of death in ICU patients. The fixed-effects model showed an overall effect size of 0.03, indicating no significant difference between colistin plus meropenem combination therapy and other therapies (95% CI, -0.14 to 0.20, p-value = 0.700) (Fig. 2E).

Table 2. The results of heterogeneity and publication bias tests in the meta-analysis.

Outcome	Model	Heterogeneity				Tau-squared	Classic fail-safe N				Begg and Mazumdar rank correlation			Duval and Tweedie's trim and fill			
														Left side of the mean		Right side of the mean	
		Q-value	df	p-value	I^2 (%)	$\tau^2 \pm SE$	Z-value	*N*	N'	p-value	τ †	Z-value	p-value	Studies trimmed	Adjusted point estimation (95% CI)	Studies trimmed	Adjusted point estimation (95% CI)
Clinical improvement	Fixed	5.24	4	0.263	24	0.04 ± 0.12	2.06	5	1	0.040	-0.10	0.24	0.807	0	1.38 (1.04 , 1.82)	0	1.38 (1.04 , 1.82)
Microbiological response	Fixed	0.77	2	0.680	0	<0.0001 ± 0.07	-1.08	3	0	0.278	-0.67	1.04	0.296	0	0.89 (0.68 , 1.16)	2	0.97 (0.78 , 1.21)
Mortality	Fixed	6.00	4	0.199	33	0.06 ± 0.13	-1.75	5	0	0.081	-0.10	0.24	0.807	0	0.85 (0.65 , 1.10)	1	0.90 (0.70 , 1.15)
SOFA	Fixed	3.38	3	0.337	11	1. ± 0.04	-2.76	4	1	0.006	0.16	0.34	0.734	1	-0.32 (-0.48 , -0.16)	0	-0.28 (-0.44 , -0.11)
APACHE II	Fixed	0.54	2	0.763	0	<0.0001 ± 0.04	0.67	3	0	0.500	0.00	0.00	>0.999	2	0.00 (-0.15 , 0.15)	0	0.03 (-0.13 , -0.20)
CCI	Random	17.49	2	<0.001	89	0.13 ± 0.17	1.75	3	0	0.079	0.00	0.00	>0.999	0	0.10 (-0.35 , 0.55)	0	0.10 (-0.35 , 0.55)
CPIS	Fixed	0.23	1	0.635	0	<0.0001 ± 0.11	-	-	-	-	-	-	-	-	-		-
CRP	Fixed	3.06	2	0.217	35	0.04 ± 0.11	-0.13	3	0	0.899	-0.67	1.04	0.296	0	-0.01 (-0.31 , 0.30)	0	-0.01 (-0.31 , 0.30)
PCT	Fixed	0.72	2	0.698	0	<0.0001 ± 0.07	-0.93	3	0	0.353	-0.67	1.04	0.296	0	-0.14 (-0.44 , 0.17)	0	-0.14 (-0.44 , 0.17)
Length of ICU stay	Random	40.18	2	<0.001	95	0.97 ± 1.09	-0.34	3	0	0.734	0.00	0.00	>0.999	0	-0.21 (-1.35 , 0.94)	0	-0.21 (-1.35 , 0.94)

APACHE II: acute physiology and chronic health evaluation; CCI: Charlson comorbidity index score; CPIS: clinical pulmonary infection assessment; CRP: C-reaction protein; ICU: intensive care unit; PCT: procalcitonin; SOFA: sequential organ failure assessment. df: degrees of freedom; SE: standard error; N: number of observed studies; †: Kendall's τ : with continuity correction; N': number of missing studies that would bring p-value > 0.05; 95% CI: 95% confidence interval.

CCI score. Three studies examined the CCI score, measuring the severity of chronic diseases and risk of death in patients with multiple comorbidities (5, 17, 18). Combining data from baseline and end-of-treatment course, the random-effects model showed an effect size of 0.10, not statistically significant (95% CI, -0.35 to 0.55, p-value = 0.669) (Fig. 2F). No tests indicated publication bias for the CCI score (Table 2), and the funnel plot is shown in Fig. 3F.

CPIS score. Two studies evaluated the CPIS score, assessing clinical signs of pulmonary infection in mechanically ventilated patients (15, 17). The fixed-effects model at the end of the treatment course showed an effect size of 0.25 (95% CI, -0.13 to 0.63, p-value = 0.203), indicating no significant difference between the two groups (Fig. 2G). Due to the small number of studies, publication bias analysis for CPIS was not performed.

Inflammation and sepsis indicators (CRP and PCT). CRP: Three studies measured CRP levels (15-17). The fixed-effects model showed a near-zero effect size (-0.01), with no significant difference between the two groups (95% CI, -0.31 to 0.30, p-value = 0.969) (Figure 2-H). No publication bias was indicated for CRP (Table 2), and the funnel plot is displayed in Fig. 3G.

PCT. Three studies reported PCT levels (15-17). The fixed-effects model showed an effect size of -0.14 (95% CI, -0.44 to 0.17, p-value = 0.375), indicating no significant difference between the combination therapy and other therapies (Fig. 2I). No publication bias was indicated for PCT (Table 2), and the funnel plot is displayed in Fig. 3H.

Length of ICU stay. Three studies reported on the length of ICU stay (16-18). The random-effects model showed an effect size of -0.21 (95% CI, -1.35 to 0.94, p-value = 0.721), indicating no significant difference between the two groups regarding ICU stay length (Fig. 2J). No publication bias was indicated for ICU stay length (Table 2), and the funnel plot is displayed in Fig. 3I.

DISCUSSION

Extensive drug resistance poses a significant challenge for healthcare systems globally, with even combination antibiotic therapies for CRGNB often resulting in poor outcomes. As a result, there has been a growing interest in using colistin and its combination with carbapenems, such as meropenem, which have shown promising results in both *in vitro* and *in vivo* studies.

Summary of meta-analysis findings. In this meta-analysis, we evaluated clinical trials that assessed the outcomes of colistin plus meropenem on healthcare-associated pneumonia (HCAP), including ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) infections positive for CRGNB. The key outcomes assessed included clinical improvement, microbiological response, mortality, SOFA and APACHE II scores, CCI and CPIS, laboratory biomarkers (CRP and PCT), and length of hospital stay.

Clinical Improvement. Clinical improvement was a primary outcome in the included studies, with our analysis indicating a 37% increased rate of clinical improvement among patients treated with colistin plus meropenem compared to other therapeutic strategies. Despite this overall improvement, definitions of clinical improvement varied across studies. Abdelsalam et al. reported significant improvement with colistin plus meropenem, including a decrease in SOFA scores and discharge from the ICU (16). Momenzadeh et al. found comparable outcomes with colistin combined with either meropenem or levofloxacin, but neither regimen was superior (17). Other studies also reported no significant differences when comparing colistin plus meropenem to colistin plus ampicillin-sulbactam (18) or colistin alone (6, 19, 20).

Microbiological response. The combination of colistin and meropenem did not significantly impact microbiological response, defined as the eradication of CRGNB in sputum cultures. Kaye et al. reported similar eradication rates for colistin plus meropenem and colistin alone (6). Momenzadeh et al. also found no significant difference between colistin-meropenem and colistin-levofloxacin (17). Other studies confirmed these findings, with lower eradication rates reported for colistin alone (19).

Mortality. Mortality rates, particularly 28-day mortality, showed no significant difference between colistin-meropenem and other therapies. While Abdelsalam et al. reported lower mortality with colis-

tin-meropenem (16.7% vs. 43.3% with colistin alone) (16), other studies found no significant differences across treatment regimens (6, 17-21).

SOFA and APACHE II scores. SOFA scores indicated better outcomes with colistin-meropenem compared to other regimens, while APACHE II scores showed no meaningful difference. These findings are consistent with mortality assessments, as both SOFA and APACHE II scores predict mortality risk (22, 23). Abdelsalam et al. reported significant decreases in SOFA scores with colistin alone or in combination with meropenem (16).

CCI and CPIS. The CCI score, measuring chronic disease severity, showed positive effects of colistin-meropenem, while the CPIS score, assessing pneumonia severity, did not show significant differences between regimens. Momenzadeh et al. found significant improvement in CPIS scores for both colistin-meropenem and colistin-levofloxacin groups, but no statistical difference between the groups (17). Other studies confirmed these findings (6, 18, 19).

CRP and PCT. CRP and PCT levels, indicators of inflammation and sepsis, showed no significant differences between the evaluated regimens. Abdelsalam et al. highlighted the superiority of PCT over CRP for assessing disease progression, although they did not compare regimens (16).

Length of ICU stay. Colistin-based regimens did not significantly affect ICU stay length. This was consistent with findings from two trials (18, 19), but Abdelsalam et al. reported shorter ICU stays with colistin-meropenem (13 days vs. 17 days for colistin alone) (16).

Strengths and limitations. This meta-analysis has several strengths:
- Inclusion of only randomized clinical trials (RCTs), enhancing reliability and minimizing bias.
- Comprehensive coverage of various factors, offering a broad perspective on the outcomes of colistin-meropenem therapy.
- Focus on HCAP, providing specific insights into this nosocomial infection type.
However, there are notable limitations:
- Heterogeneity in study subjects, disease severity, and settings, leading to a heterogeneous study population.
- Limited number of included RCTs and study subjects, with evaluated colistin-based combination therapies restricted to a few antibiotics.
- Lack of evaluation of antibiotic interactions and adverse effects, which are crucial for critically ill patients.
- General assessment of CRGNB without subgroup analysis for specific pathogens like *A. baumannii*.

Future large-scale studies exploring various colistin-based combination regimens are warranted to address these limitations and provide more definitive conclusions.

CONCLUSION

In general, the findings of the current meta-analysis, which analyzed five RCTs, demonstrate a statistically significant superiority of colistin-meropenem combination therapy over other medications in terms of clinical improvement and a shorter length of ICU stay. However, other assessed variables did not show remarkable differences when comparing colistin-meropenem with other colistin-based therapies against CRGNB infections. Further investigations are strongly recommended to explore these findings in greater detail.

Ethics approval and consent to participate: This research was conducted ethically in accordance with the Isfahan University of Medical Sciences. The ethics review committee of the Isfahan University of Medical Sciences approved this study on Number IR.ARI.MUI.REC.1401.204.

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