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Comparison of different colistin regimens for the treatment of pneumonia caused by multidrug-resistant microorganisms: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Multidrug-resistant pneumonia is a common cause of hospital-related morbidity and mortality across the world. The high prevalence of multidrug-resistant pneumonia due to resistant gram-negative pathogens has led to a re-introduction of colistin. The adverse events associated with intravenous colistin can be alleviated by administering the drug nasally (i.e., inhalation) or in a combination including both inhalation and intravenous presentations of the drug. A review study compared the impact of these administration methods on clinical, morbidity, and mortality-related outcomes in patients with multiple-drug resistant pneumonia. However, the publication of newer cohort trials, warrants an update of the state of the evidence.

To compare the clinical, morbidity, and mortality outcomes in patients with multidrug-resistant pneumonia receiving either intravenous colistin or combined drug presentations (ie, inhaled and intravenous).

MATERIALS AND METHODS: A systematic search of the academic literature was performed according to the PRISMA guidelines across five databases (Web of Science, EMBASE, CENTRAL, Scopus, and MEDLINE). We conducted a random-effect meta-analysis to compare outcomes such as rate of clinical cure, microbiological eradication, nephrotoxicity, and overall mortality in patients with multidrug-resistant pneumonia receiving either intravenous colistin, inhaled colistin, or a combination of those administration routes.

RESULTS: From 963 studies, we found 16 eligible studies with 1651 patients (61.6 ± 7.7 years) with multidrug-resistant pneumonia who had received either intravenous, inhaled colistin or a combined inhaled/intravenous administration. Our meta-analysis revealed higher rates of clinical cure (OR, 1.61) and microbiological eradication (1.37) in patients receiving combined intravenous/inhaled colistin than in those receiving intravenous colistin alone. Additional analyses revealed higher rates of nephrotoxicity (1.30) and mortality (1.44) in patients receiving intravenous colistin than in those receiving combined intravenous/inhaled colistin.

CONCLUSIONS: We provide evidence showing improved clinical, morbidity, and mortality outcomes in patients with multidrug-resistant pneumonia receiving inhaled colistin or combined inhaled/intravenous colistin than those receiving intravenous colistin alone. These findings should help clinicians stratify the risks associated with different colistin administration routes to manage multidrug-resistant pneumonia.

Key Words:
Drug resistance, Pneumonia, Colistin, Intravenous, Aerosol, Mortality.

Introduction

Acute respiratory drug-resistant pneumococcal infections are considered a leading cause of mortality in hospital settings worldwide[1-3]. According to the World Health Organization, the onset of pneumonia in a medical facility is facilitated by the presence of multidrug-resistant pathogens including *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*[4]. Epidemiological studies[5,6] have reported a high incidence of multidrug-resistant pneumonia in hospital settings, 15% to 24%; and, a recent Global Burden of Disease study found that almost 2.3

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million patients worldwide perish annually due to multidrug-resistant pneumonia[7,8].

The prevalence of multidrug-resistant pneumococcal infections has been increasing[9] due to the ineffectiveness of conventional antibiotics against drug-resistant pathogens. Therefore, older polymyxin antibiotics like colistin have garnered attention for the management of multidrug-resistant pneumonia[10-12]. Studies[13,14] have suggested that the cationic colistin molecule acts by binding electrostatically to the negatively charged lipid-A of the gram-negative bacteria, thereby damaging the cell membrane's structure of the bacteria by displacing its divalent calcium and magnesium cations. This ionic change destabilizes the phospholipid bilayer of the gram-negative bacteria ultimately resulting in a leakage of its cellular contents and its destruction[15-17]. Doshi et al. (2013)[18]suggested that the efficacy of colistin is dependent upon its administration route. These authors suggested that while conventional intravenous colistin may not permeate to the lung parenchyma, the aerosol route could allow larger and quicker deposition of the drug at the infection site. Many animal studies have confirmed the beneficial impact of aerosol/combination (inhalation + intravenous) routes of colistin administration as compared to intravenous administration alone[19-21]; however, a consensus of the evidence in humans is lacking.

Many cohort studies[22-24] have compared clinical, morbidity, and mortality-related outcomes in patients with multidrug-resistant pneumonia receiving colistin via different routes. However, a consensus on the overall mortality according to these administration routes has not been reached. We found studies[18,22,24-26] reporting higher mortalities in patients receiving intravenous colistin than in those receiving other regimens and we found other studies routes[27-30] reporting higher mortalities for patients receiving colistin via inhalation/combination routes. Similarly, the clinical cure rates of the different regimens also remain unclear; while some studies reported higher clinical cure rates in patients receiving colistin via combined/inhaled route[25-27,31-33], others reported the opposite effect[28,30,34].

To the best of our knowledge, one review study[35] has compared clinical, morbidity, and mortality-related outcomes of the different colistin administration routes in patients with multidrug-resistant pneumonia. However, since the publication of that review, several high-quality cohort studies[22-24, 27-29], have been published and warrant an updated analysis. Thus, we designed this systematic review and meta-analysis to synthesize the evidence on the available literature.

We compared the outcomes (clinical cure rate, microbiological eradication rate, nephrotoxicity, and overall mortality) of these colistin regimens in patients with multidrug-resistant pneumonia. Our findings should provide clinicians with a clearer view of the morbidity and mortality-related risks associated with different routes of colistin administration in patients with multidrug-resistant pneumonia.

Materials and Methods

We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[36] while conducting this meta-analysis.

Data Search Strategy

We performed the literature search in five scientific databases (Web of Science, MEDLINE, CENTRAL, EMBASE, and Scopus) from inception till March 2021. We used a combination of MeSH keywords including "Colistin", "inhalation", "intravenous", "IV colistin", "pneumonia", "drug resistance", "morbidity", and "mortality". Additionally, we manually searched the bibliography section of the included studies to identify further relevant studies. The inclusion criteria were the following:

- Studies comparing clinical cure, microbiological eradication, and nephrotoxicity rates in patients with multidrug-resistant pneumonia receiving either intravenous colistin or combination regimens with inhaled colistin.
- Studies comparing the overall mortality outcomes in patients with multidrug-resistant pneumonia receiving either intravenous colistin or combination regimens with inhaled colistin.
- Studies with human participants.
- Case-control studies, prospective cohort trials, or retrospective cohort trials.
- Studies published in peer-reviewed scientific journals.
- Studies published in English.

Two reviewers independently screened the studies. Cases of disagreements were resolved by discussion with a third independent reviewer.

Quality Assessment

We conducted the risk of bias assessment of the included studies using the Newcastle Ottawa

scale[37]. This tool evaluates the outcomes for selective reporting, confounding bias, measurement of outcomes, and incomplete data availability as threats that can compromise the validity of the analysis results. Two reviewers independently were in charge of the methodological quality assessment; and again, disagreements were solved by arbitration with a third reviewer.

Data Analysis

We conducted a within-group meta-analysis using the Comprehensive Meta-analysis version 2.0 software[38] based on the random-effects model[39]. We calculated the odds ratio to evaluate the odds of clinical cure, microbiological eradication, nephrotoxicity, and mortality in patients receiving either intravenous colistin or combined/inhaled colistin regimens. We assessed the heterogeneity among the studies by computing I^2 statistics; we considered values between 0 and 25% as indicating negligible heterogeneity, between 25% and 75% as indicating moderate heterogeneity, and ≥75% as indicating substantial heterogeneity[40]. We used the method listed by Hozo, Djulbegovic, and Hozo[41] to convert medians and ranges into means and standard deviations. Furthermore, we evaluated publication bias using Duval and Tweedy's trim and fill procedure (Duval & Tweedie, 2000), which is characterized by imputation of studies from either side of a plotted graph to identify unbiased effects. The significance level for this study was determined at 5%.

Results

Our search across the five academic databases provided 950 studies. We identified an additional 13 during the screening of the reference sections of the included studies. After application of our inclusion criteria, we were left with 16 studies (Figure 1). From all the included studies 13 were retrospective cohort studies[18,22-24,26,28-30,32,33,42,43], two were retrospective case control studies[25,44], and two prospective cohort studies[27,31]. We used tables to organize the extracted data (Table I).

Participant Information

We obtained data from 1651 (476F, 1002M) patients in the 16 studies included. A total of 883 patients (256F, 539M) received either inhalation/intravenous or inhalation colistin, and 768 (220F, 463M) received intravenous colistin only. Two studies did not define the gender distribution of their sample[26,27].

The average age of the participants was as 61.6 ± 7.7 years with the average age of patients recei-

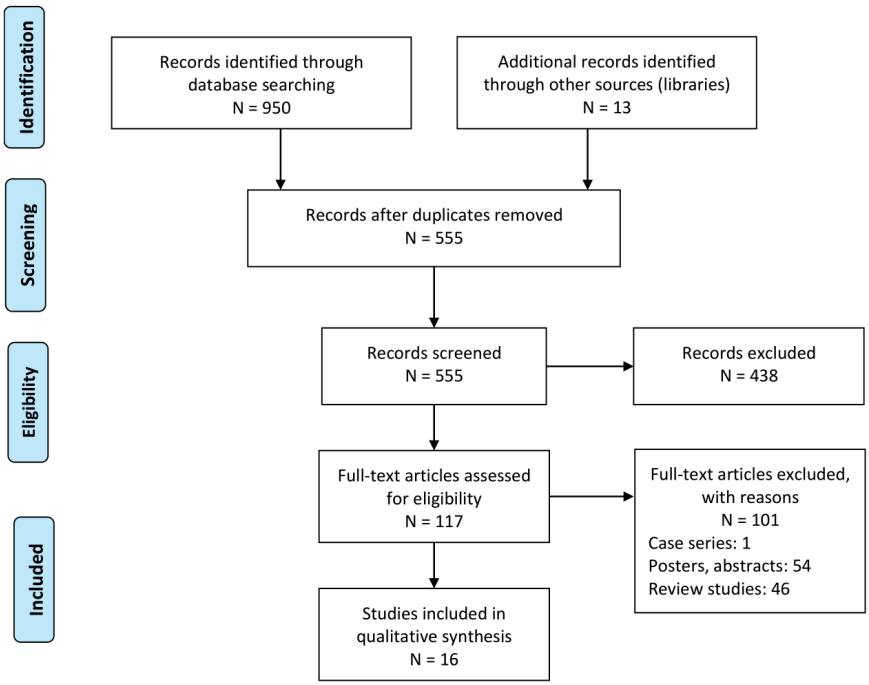

Figure 1. PRISMA flowchart.

Table I. Details of the studies included.

Study	Country	Type of study	Sample descriptive	Age (M ± SD years)	Pathogen	Clinical cure	Microbiological eradication	Nephrotoxicity	Mortality
Zheng et al. (2020)	Taiwan	Retrospective cohort study	INH: 128 (45F, 83M) IV: 18 (8F, 10M)	INH: 77.5 ± 14.3 IV: 73.4 ± **17.1**	*A. calcoaceticus, A. baumannii*	INH: 102 IV: 9	INH: 95 IV: 9	-	INH: 17 IV: 5
Choe et al. (2019)	South Korea	Retrospective cohort study	INH: 35 (4F, 31M) IV: 86 (18F, 64M)	INH: 67 IV: 63	*A. baumannii, P. aeruginosa, K. pneumoniae*	INH: 17 IV: 36	INH: 21 IV: 27	INH: 16 IV: 23	INH: 8 IV: 42
Moradi Moghaddam et al. (2019)	Iran	Retrospective cohort study	INH+IV: 57 (17F, 40M) IV: 57 (17F, 40M)	INH+IV: 49.1 ± 21.6 IV: 47.3 ± **18.3**	-	-	-	-	INH+IV: 8 IV: 9
Jang et al. (2017)	South Korea	Retrospective cohort study	INH: 51 (15F, 36M) IV: 44 (9F, 35M)	INH: 67.5 ± 12.6 IV: 60 ± 15.2	*A. baumannii*	INH: 5 IV: 4	INH: 33 IV: 26	INH: 8 IV: 26	INH: 10 IV: 6
Kim et al. (2017)	South Korea	Retrospective cohort study	INH: 126 (50F, 76M) IV: 93 (30F, 63M)	INH: 70 IV: 65	*A. baumannii*	-	-	-	INH: 51 IV: 55
Demirdal et al. (2016)	Turkey	Retrospective cohort study	INH+IV: 43 (10F, 33M) IV: 80 (30F, 50M)	INH+IV: 66.6 ± 15.4 IV: 62.8 ± **18.8**	*A. baumannii*	INH+IV: 16 IV: 30	INH+IV: 20 IV: 40	INH+IV: 21 IV: 43	INH+IV: 23 IV: 38
Abdellatif et al. (2016)	Tunisia	Prospective cohort study	INH: 73 IV: 76	INH: 50 ± 16 IV: 53 ± **17**	*S. maltophilia, P. aeruginosa, enterobacteria, A. baumannii*	INH : 61 IV: 44	-	INH : 13 IV : 30	INH: 20 IV: 18
Zah BogoviĆ et al. (2014)	Croatia	Retrospective cohort study	INH+IV: 8 (3F, 5M) IV: 23 (9F, 14M)	INH+IV: 72.4 ± 11.8 IV: 72.5 ± **12.9**	*A. baumannii, P. aeruginosa, K. pneumoniae*	-	INH+IV: 5 IV: 3	INH+IV: 1 IV: 4	INH+IV: 6 IV: 17
Doshi et al. (2013)	USA	Retrospective cohort study	INH+IV: 44 (22F, 22M) IV: 51 (18F, 33M)	INH+IV: 60.9 ± 15.3 IV: 57.3 ± **15.6**	*Acinetobacter* spp, *Pseudomonas* spp, vancomycin- resistant *Enterococcus*, methicillin- resistant *S. aureus*, extended spectrum beta lactamase	INH+IV : 24 IV : 20	INH+IV: 8 IV : 11	-	INH+IV: 6 IV : 19
Tumbarello et al. (2013)	Italy	Retrospective case-control study	INH+IV: 104 (30F, 74M) IV: 104 (46F, 58M)	INH+IV: 64 IV: 66	*A. baumannii, P. aeruginosa, K. pneumoniae*	INH+IV: 72 IV: 57	INH+IV: 53 IV: 42	INH+IV: 26 IV: 23	INH+IV: 45 IV:48
Amin et al. (2013)	Egypt	Prospective cohort study	INH+IV: 28 (13F, 15M) IV: 12 (5F, 7M)	INH+IV: 55.6 ± 21.9 IV: 60.5 ± 4.5	*A. baumannii, P. aeruginosa, K. pneumoniae*	INH+IV: 22 IV: 7	-	-	INH+IV: 8 IV:5
Kalin et al. (2012)	Turkey	Retrospective cohort study	INH+IV: 29 (10F, 19M) IV: 15 (2F, 13M)	INH+IV: 51.1 ± 19.7 IV: 48.1 ± 22.2	*A. baumannii*	INH+IV: 4 IV: 6	INH+IV: 22 IV: 11	INH+IV: 12 IV: 3	INH+IV: 16 IV: 7

Table continued

Table I. ***(Continued).*** Details of the studies included.

Study	Country	Type of study	Sample descriptive	Age (M ± SD years)	Pathogen	Clinical cure	Microbiological eradication	Nephrotoxicity	Mortality
Naesens et al. (2011)	Belgium	Retrospective cohort study	INH+IV: 9 INH: 6 IV: 5	INH+IV: 67.9 INH: 62.5 IV: 64.8	*P. aeruginosa*	INH+IV: 7 INH: 6 IV: 2	-	-	INH+IV: 3 INH: 3 IV: 5
Pérez-Pedrero et al. (2011)	Spain	Retrospective cohort study	INH+IV: 21 (5F, 16M) IV: 18 (3F, 15M)	INH+IV: 55.5 ± 19.8 IV: 60.1 ± 17.4	*A. baumannii*	INH+IV: 18 IV: 12	INH+IV: 8 IV: 15	INH+IV: 1 IV: 2	INH+IV: 4 IV: 5
Kofteridis et al. (2010)	Greece	Retrospective case-control study	INH+IV: 43 (15F, 28M) IV: 43 (13F, 30M)	INH+IV: 62 ± 15.1 IV: 62.3 ± 14.9	*A. baumannii, P. aeruginosa, K. pneumoniae*	INH+IV: 23 IV: 14	INH+IV: 19 IV: 17	INH+IV: 8 IV: 8	INH+IV: 10 IV: 18
Korbila et al. (2010)	Greece	Retrospective cohort study	INH+IV: 78 (17F, 61M) IV: 43 (12F, 31M)	INH+IV: 60.9 ± 15.7 IV: 59.2 ± 19.2	*A. baumannii, P. aeruginosa, K. pneumoniae*	INH+IV: 62 IV: 26	-	-	INH+IV: 31 IV: 19

Legends: M: Mean: SD: Standard deviation, F: Female, M: Male; INH+IV: Inhalation and intravenous, IV: Intravenous, INH: Inhalation

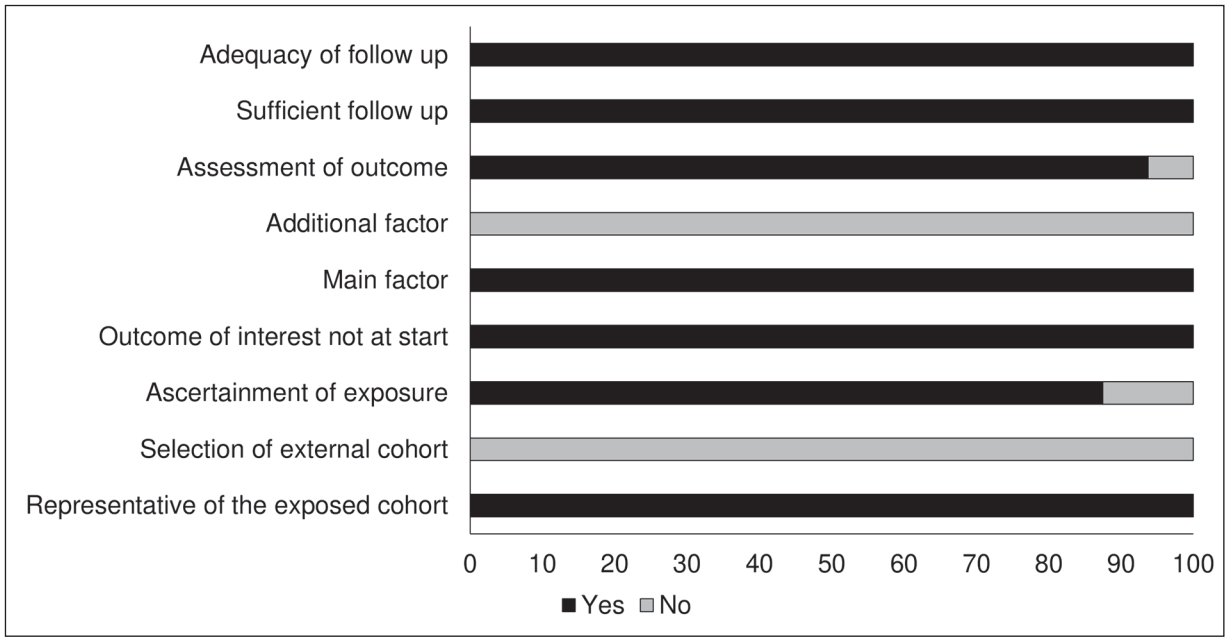

Figure 2. Risk of bias according to the Newcastle Ottawa scale for cohort studies.

ving a combination regimen colistin or inhalation colistin at 62.3 ± 8.3 years and the average age of patients receiving only intravenous colistin at 60.9 ± 7.2 years.

Quality Assessment for Cohort Studies

We analyzed the risk of bias in the methodology of the cohort studies using the Newcastle Ottawa scale. Table II shows the results of this analysis. We found an overall low risk for the included studies. Figure 2 depicts the overall risk on a graph.

Publication Bias

We used Duval and Tweedy's trim and fill method to identify missing studies on either side of the mean effect of the funnel plot according to the random effect model. Our findings indicated that two studies were missing on the left side of the mean effect. We applied overall random effect models to determine the point estimate (1.44) and the 95% confidence interval (1.08 to 1.93) for all the combined studies; after applying the trim and fill model the imputed point estimates were 1.39 and (1.02 to 1.89). Figure 3 shows the publication bias analysis results.

Meta-Analysis Report

Clinical Cure Rate

The odds ratios are presented as black boxes and 95% confidence intervals as whiskers. A reduced odds ratio represents the higher clinical cure rate for the group receiving intravenous colistin, a high odds ratio reflects the higher clinical cure rate for the group receiving combined/inhaled colistin (INH+IV, inhaled plus intravenous; INH, inhaled only).

We found 12 studies reporting the odds of clinical cure in patients receiving intravenous colistin or combined/inhaled colistin. We observed increased odds of clinical cure rate in patients receiving combined/inhaled colistin than in patients receiving intravenous colistin (Figure 4) (Odds ratio, 1.72; 95% CI, 1.26 to 2.36; p=0.001) with negligible heterogeneity (I^2, 9.7%).

We conducted an additional sub-group analysis to evaluate differential effects between studies comparing the efficacy of colistin when delivered via inhalation, intravenously, or in a combined regimen. We found nine studies reporting the odds of clinical cure in patients receiving intravenous colistin or a combined colistin regimen. We observed increased odds of clinical cure rate in patients receiving the combined regimen than in those receiving intravenous colistin alone (Figure 5) (Odds ratio, 1.72; 95% CI, 1.15 to 2.59; p=0.008) with negligible heterogeneity (I^2, 12.4%).

The odds ratios are presented as black boxes and the 95% confidence intervals as whiskers. A reduced odds ratio represents the higher clinical cure rate for the group receiving intravenous colistin; a higher odds ratio represents the higher cli-

Table II. Risk of bias for individual studies based on the Newcastle Ottawa scale.

Study	Selection			Comparability		Outcome			Total
	Representative of the exposed cohort	Selection of external cohort	Ascertainment of exposure	Outcome of interest not present at start	Main factor	Additional factors	Assessment of outcome	Sufficient follow-up	Adequacy of follow-up	(9/9)
Zheng et al. (2020)	+	0	+	+	+	0	+	+	+	6
Moradi Moghaddam et al. (2019)	+	0	0	+	+	0	0	+	+	5
Choe et al. (2019)	+	0	+	+	+	0	+	+	+	7
Jang et al. (2017)	+	0	+	+	+	0	+	+	+	7
Kim et al. (2017)	+	0	+	+	+	0	+	+	+	6
Demirdal et al. (2016)	+	0	+	+	+	0	+	+	+	7
Abdellatif et al. (2016)	+	0	+	+	+	0	+	+	+	7
Zah BogoviĆ et al. (2014)	+	0	+	+	+	0	+	+	+	7
Doshi et al. (2013)	+	0	+	+	+	0	+	+	+	7
Tumbarello et al. (2013)	+	0	+	+	+	0	+	+	+	7
Amin et al. (2013)	+	0	+	+	+	0	+	+	+	6
Kalin et al. (2012)	+	0	+	+	+	0	+	+	+	7
Naesens et al. (2011)	+	0	0	+	+	0	+	+	+	5
Pérez-Pedrero et al. (2011)	+	0	+	+	+	0	+	+	+	7
Kofteridis et al. (2010)	+	0	+	+	+	0	+	+	+	7
Korbila et al. (2010)	+	0	+	+	+	0	+	+	+	7

nical cure rate for the group receiving inhalation colistin (INH+IV, inhaled plus intravenous; INH, inhaled only).

Moreover, the odds of clinical cure in patients receiving intravenous colistin or inhaled colistin were reported by four studies. We observed increased odds of clinical cure rate in patients receiving inhaled colistin than in those receiving intravenous colistin (Figure 6) (Odds ratio, 1.73; 95% CI, 0.97 to 3.09; p=0.06) with negligible heterogeneity (I^2, 9.5%).

Microbiological Eradication

The odds ratios are presented as black boxes and the 95% confidence intervals as whiskers. A reduced odds ratio represents the higher microbiological eradication rate for the group receiving intravenous colistin, a higher odds ratio represents the higher microbiological eradication rate for the group receiving combined/inhaled colistin (INH+IV, inhalation plus intravenous; INH, inhalation only).

The odds of microbiological eradication in patients receiving intravenous colistin or combined/inhaled colistin were reported by 12 studies. We observed increased odds of microbiological eradication rate in patients receiving combined/inhaled colistin than in those receiving intravenous colistin (Figure 7) (Odds ratio, 1.37; 95% CI, 0.80 to 2.32; p=0.24) with moderate heterogeneity (I^2, 26.7%).

The odds ratios are presented as black boxes and the 95% confidence intervals as whiskers. A reduced odds ratio represents the higher microbiological eradication rate for the group receiving intravenous colistin, a higher odds ratio represents the higher microbiological eradication rate for the group receiving the combined colistin regimen (INH+IV, inhalation plus intravenous, INH, inhalation only).

We conducted an additional sub-group analysis to evaluate differential effects between studies comparing the efficacy of colistin delivered via inhalation, intravenously, or a combined regimen.

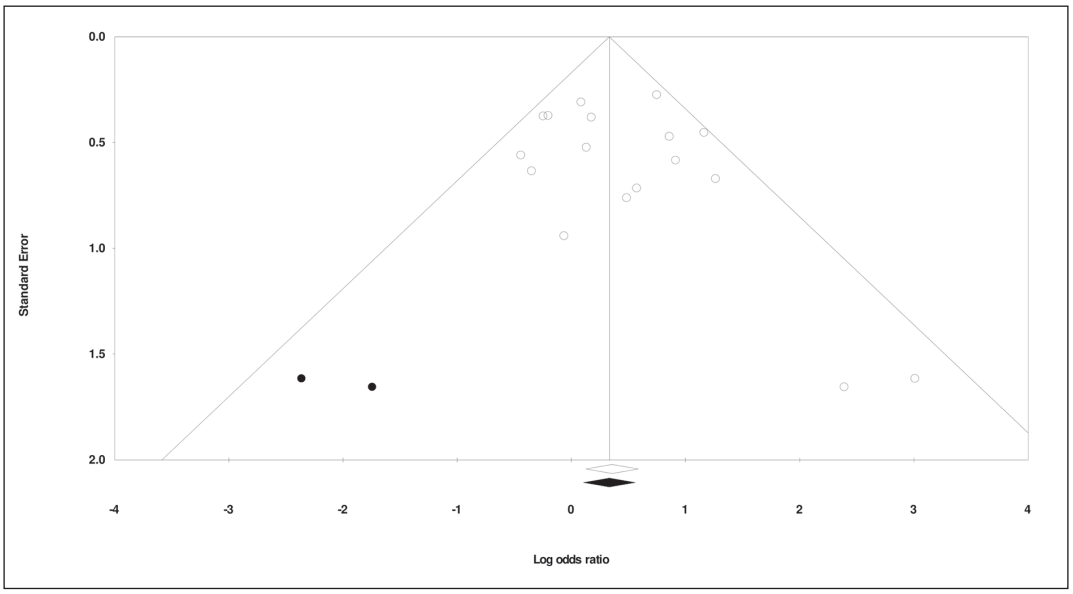

Figure 3. Publication bias by Duval and Tweedy's trim and fill method.

We found seven studies reporting the odds of clinical cure in patients receiving intravenous colistin or a combined colistin regimen. We observed increased odds of clinical cure rate in patients receiving a combined colistin regimen than in those receiving intravenous colistin (Figure 8) (Odds ratio, 1.07; 95% CI, 0.55 to 2.10; p=0.83) with moderate heterogeneity (I^2: 32.39%).

Moreover, the odds of clinical cure in patients receiving intravenous colistin or inhalation colistin were reported by three studies. We observed increased odds of clinical cure rate in patients re-

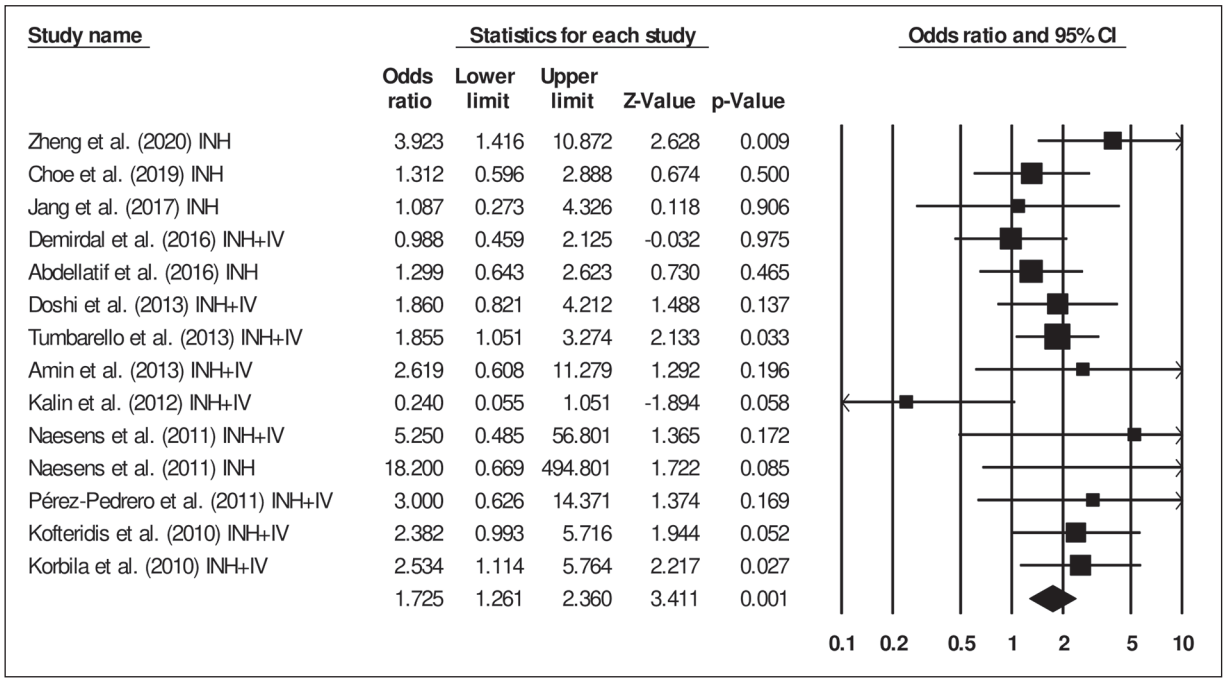

Figure 4. Forest plot for studies evaluating the rate of clinical cure in patients receiving intravenous colistin or combined/inhaled colistin.

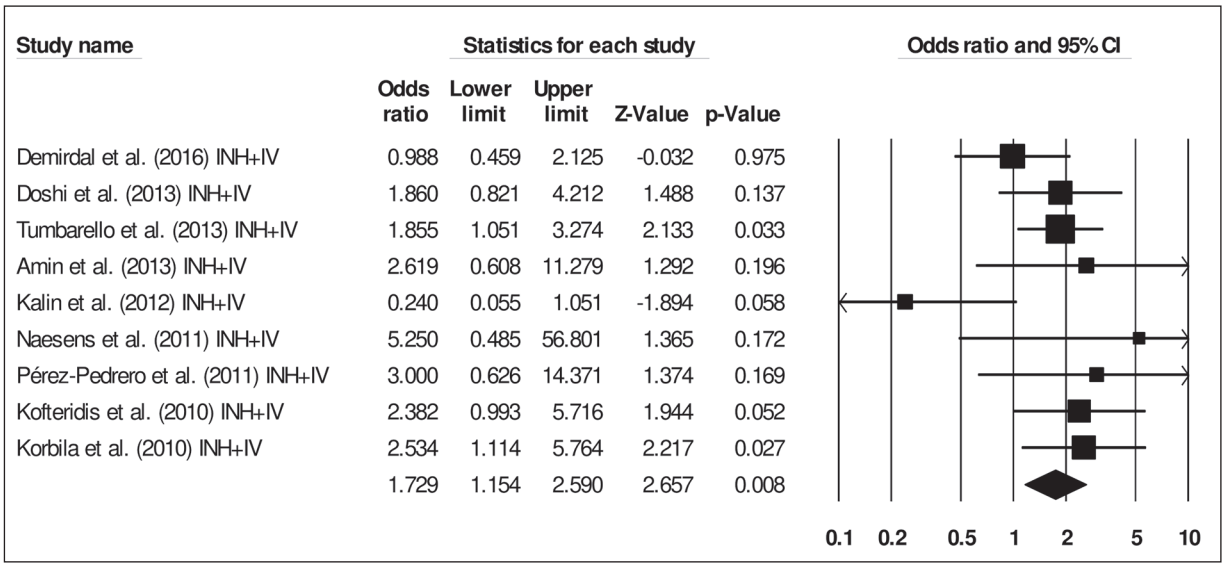

Figure 5. Forest plot for studies evaluating the rate of clinical cure in patients receiving intravenous colistin or combined regimen. The odds ratios are presented as black boxes and the 95% confidence intervals as whiskers. A reduced odds ratio represents the higher clinical cure rate for the group receiving intravenous colistin, a high odds ratio represents the higher clinical cure rate for the group receiving a combined colistin regimen (INH+IV, inhaled plus intravenous; INH, inhaled only).

ceiving inhalation colistin than in those receiving intravenous colistin (Figure 9) (Odds ratio, 2.18; 95% CI, 1.30 to 3.66; p=0.003) with moderate heterogeneity (I^2, 53.2%).

Nephrotoxicity

The odds ratios are presented as black boxes and the 95% confidence intervals as whiskers. A reduced odds ratio represents the higher odds of nephrotoxicity for the group receiving combined/inhaled colistin, a higher odds ratio represents the higher odds of nephrotoxicity for the group receiving intravenous colistin (INH+IV, inhalation plus intravenous; INH, inhalation only).

The odds of nephrotoxicity in patients receiving intravenous colistin or combined/inhaled colistin were reported by 9 studies. We observed increased odds of nephrotoxicity in patients receiving intravenous colistin than in those receiving combined/inhaled colistin (Figure 10) (Odds ratio, 1.30; 95% CI, 0.67 to 2.54; p=0.43) without heterogeneity (I^2, 0%).

The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A reduced odds ratio represents a higher nephrotoxicity rate for the group receiving intravenous colistin, a higher odds ratio represents a higher nephrotoxicity rate for the group receiving a combined colistin regimen (INH+IV, inhalation plus intravenous, INH, inhalation only).

Additional sub-group analysis was conducted to evaluate differential effects between studies comparing the efficacy of colistin delivered via inhalation as compared to colistin delivered intravenously, and colistin delivered in combination (i.e., intravenous and inhalation together) as compared to colistin delivered intravenously. Here, the odds of clinical cure in patients receiving intravenous colistin or a combined colistin regimen were reported by six studies. We observed increased odds of clinical cure rate in patients receiving a combined colistin regimen than in those receiving intravenous colistin (Figure 11) (Odds ratio, 1.06; 95% CI, 0.70 to 1.62; p=0.75) without heterogeneity (I^2, 0%).

Moreover, the odds of clinical cure in patients receiving intravenous colistin or inhalation colistin were reported by three studies. We observed increased odds of clinical cure rate in patients receiving inhalation colistin than in those receiving intravenous colistin (Figure 12) (Odds ratio, 2.13; 95% CI, 0.43 to 10.4; p=0.35) with negligible heterogeneity (I^2: 10.31%).

Mortality

The odds of overall mortality in patients receiving intravenous colistin or combined/inhaled colistin were reported by 17 studies. We observed increased odds of mortality in patients receiving intravenous colistin than in those receiving com-

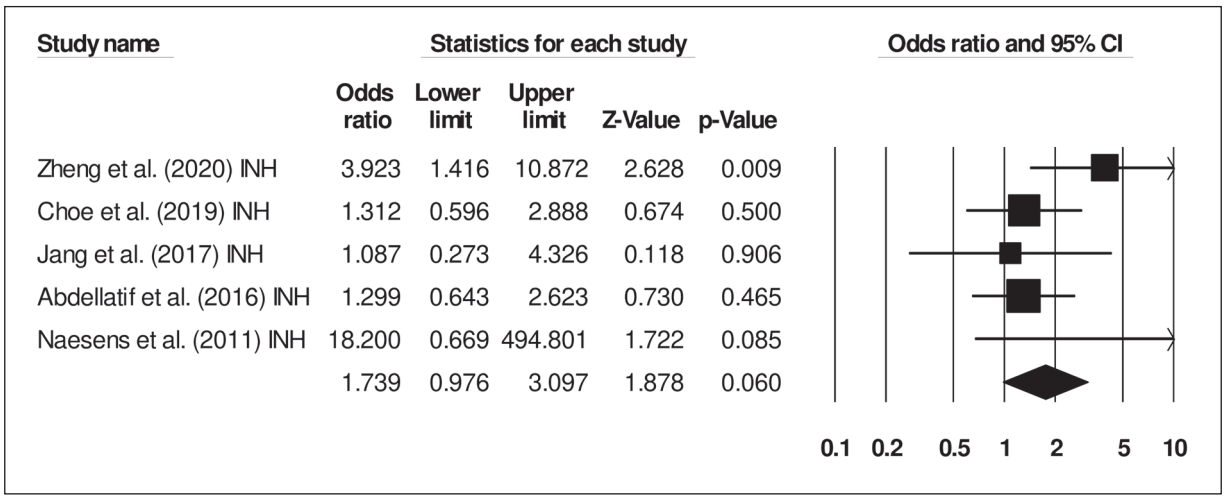

Figure 6. Forest plot for studies evaluating the rate of clinical cure in patients receiving intravenous colistin or inhalation colistin.

bined/inhaled colistin (Figure 13) (Odds ratio, 1.44; 95% CI, 1.08 to 1.93; p=0.01) with moderate heterogeneity (I^2, 1.23%).

We also conducted a sub-group analysis to evaluate differential effects between studies comparing the efficacy of colistin delivered via inhalation, intravenously, and in a combination regimen. We found eleven studies reporting the odds of clinical cure in patients receiving intravenous colistin or a combined colistin regimen. We observed increased odds of clinical cure rate in patients receiving a combined colistin regimen than in those receiving intravenous colistin (Figure 14) (Odds ratio, 1.26; 95% CI, 0.93 to 1.72; p=0.12) with negligible heterogeneity (I^2: 0.2%).

The odds of clinical cure in patients receiving intravenous colistin or inhaled colistin were reported by six studies. We observed increased odds of clinical cure rate in patients receiving inhaled colistin than in those receiving intravenous colistin (Figure 15) (Odds ratio, 1.67; 95% CI, 0.93 to 2.99; p=0.08) with negligible heterogeneity (I^2: 6.49%).

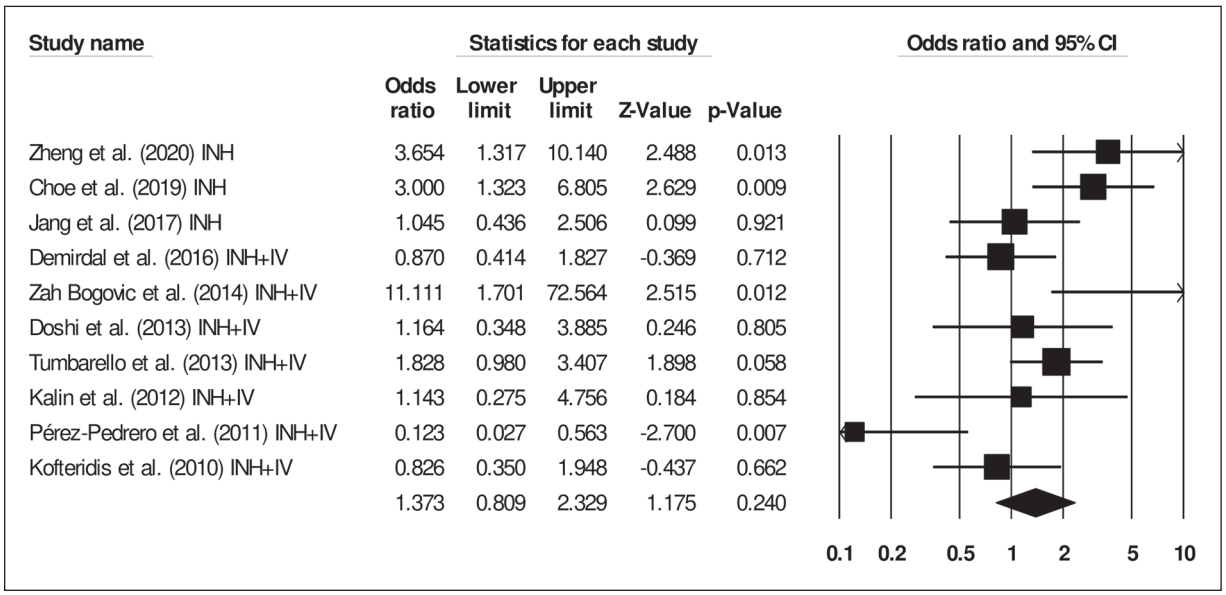

Figure 7. Forest plot for studies evaluating the risk of microbiological eradication in patients receiving intravenous colistin or combined/inhaled colistin.

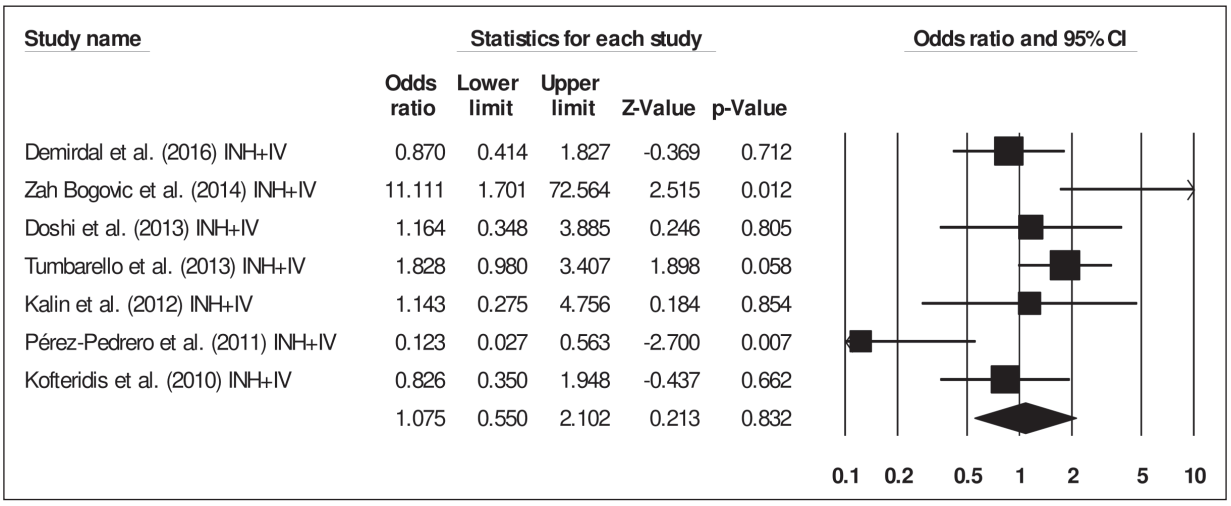

Figure 8. Forest plot for studies evaluating the risk of microbiological eradication in patients receiving intravenous colistin or combined colistin regimen.

Discussion

This systematic review and meta-analysis provides a comprehensive comparison of the clinical, morbidity, and mortality-related outcomes in patients with multidrug-resistant pneumonia receiving either intravenous colistin or combined/inhaled colistin regimens. We found improved rates of clinical cure and microbiological eradication in patients receiving colistin via inhalation or combined routes as compared to those receiving intravenous colistin. We also provide evidence showing higher nephrotoxicity and mortality outcomes for the patients receiving intravenous colistin than for those receiving colistin via inhalation/combination routes.

The management of multidrug-resistant pneumonia is challenging for clinicians because of its poor prognosis and heterogeneous manifestations[45-47]. Patients with multidrug-resistant pneumonia exhibit poor morbidity and mortality-related outcomes due to lack of treatment options[2,8]. Administration of the old polymyxin antibiotic "colistin" has been widely recommended to improve these outcomes[10,48]. Studies have suggested that colistin can improve the mortality outcomes, the patient's lung capacity, and the overall quality of life[49]. However, the evidence on the admi-

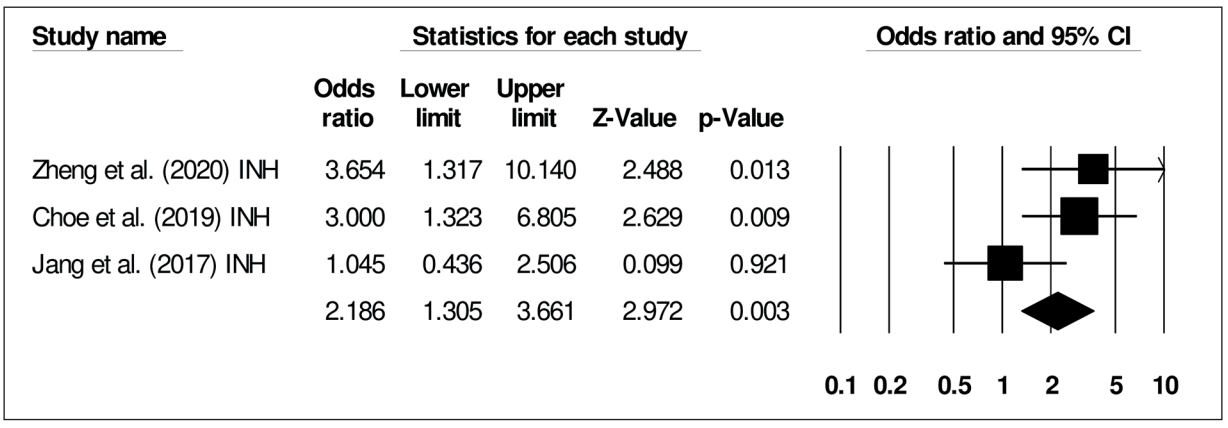

Figure 9. Forest plot for studies evaluating the risk of microbiological eradication in patients receiving intravenous colistin or inhalation colistin. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A reduced odds ratio represents a higher microbiological eradication rate for the group receiving intravenous colistin, a higher odds ratio represents a higher microbiological eradication rate for the group receiving inhalation colistin (INH+IV, inhalation plus intravenous, INH, inhalation only)

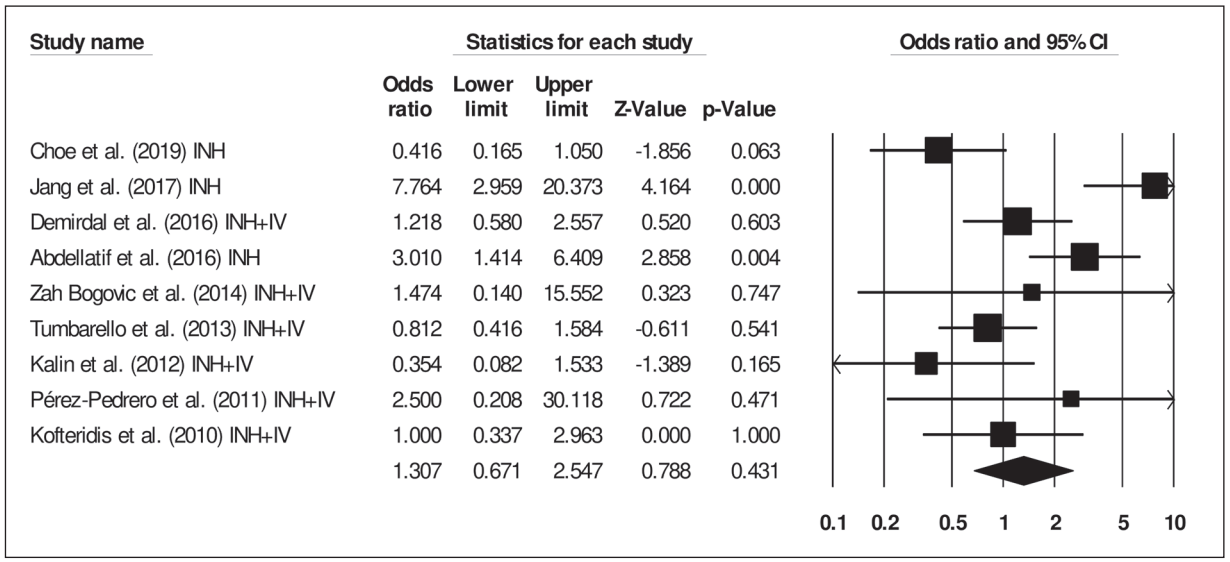

Figure 10. Forest plot for studies evaluating the risk of nephrotoxicity in patients receiving intravenous colistin or combined/inhaled colistin.

nistration route with the best prognostic outcome for patients with multidrug-resistant pneumonia remains unclear.

In this systematic review, we observed that all the included studies had reported improved clinical cure and microbiological eradication rates in patients receiving colistin via inhalation/combination routes than those receiving intravenous colistin. Zheng et al[24], in a cohort representative of the Taiwanese population, reported higher levels of microbiological eradication in the inhalation group (78.5%) than in the intravenous group (50%). The authors further associated this increase in microbiological eradication with improvements in other clinical outcomes including the clinical failure rate (20.3% in the inhaled colistin group, 50% in the intravenous colistin group) and the treatment length (12.4 ± 4.9 days in the inhaled colistin group, and 16.2 ± 7.6 days in the intravenous colistin group). The authors also attributed this improved efficacy to the high and fast colistin deposition in the lung epithelial lining fluid of the inhaled colistin group. Similarly, Naesens, Vlieghe, Verbrugghe, Jorens, and Ieven (2011)[26] reported higher clinical cure rates in the group receiving colistin via the inhalation (100%), and combined routes (77%) than those receiving intravenous colistin (40%), attributing these results

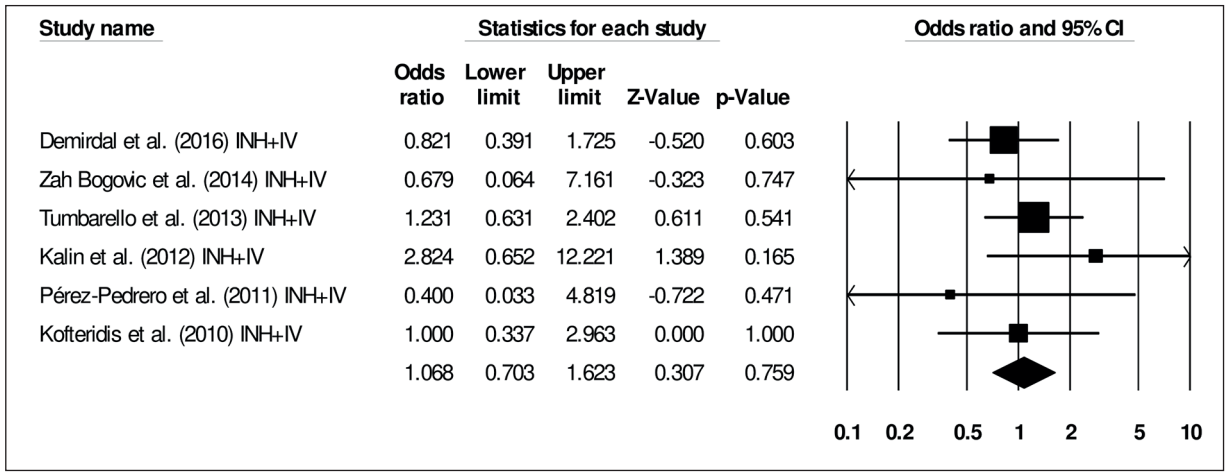

Figure 11. Forest plot for studies evaluating the risk of nephrotoxicity in patients receiving intravenous colistin or a combined colistin regimen.

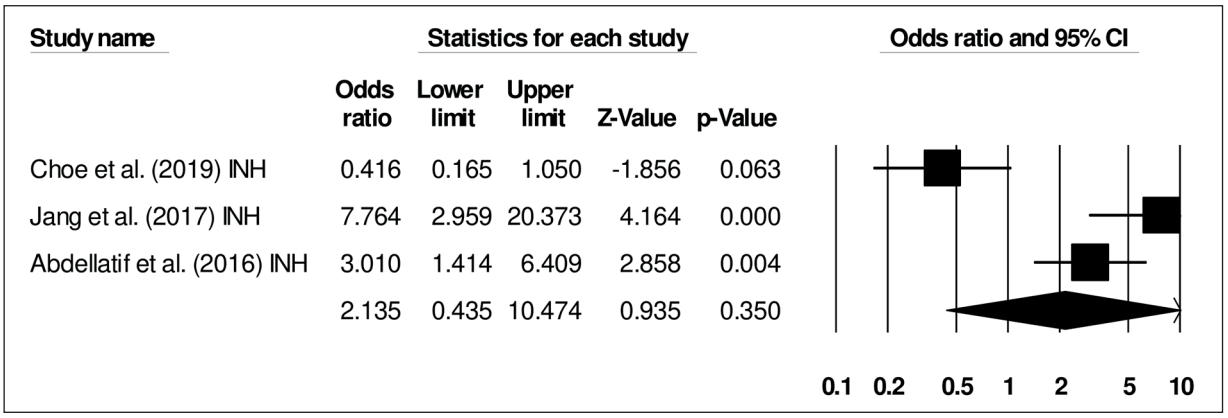

Figure 12. Forest plot for studies evaluating the risk of nephrotoxicity in patients receiving intravenous colistin or inhalation colistin. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A reduced odds ratio represents a higher nephrotoxicity rate for the group receiving intravenous colistin, a higher odds ratio represents a higher nephrotoxicity rate for the group receiving inhalation colistin (INH+IV, inhalation plus intravenous, INH, inhalation only).

to the better pharmacokinetic profile of the inhalation route when compared to that of the intravenous route. Likewise, Tumbarello et al. (2013)[44] reported improved clinical cure and microbiological eradication rates in the combined colistin regimen group, suggesting that the influence of colistin's route of administration was limited to the clinical outcomes, and that the mortality and

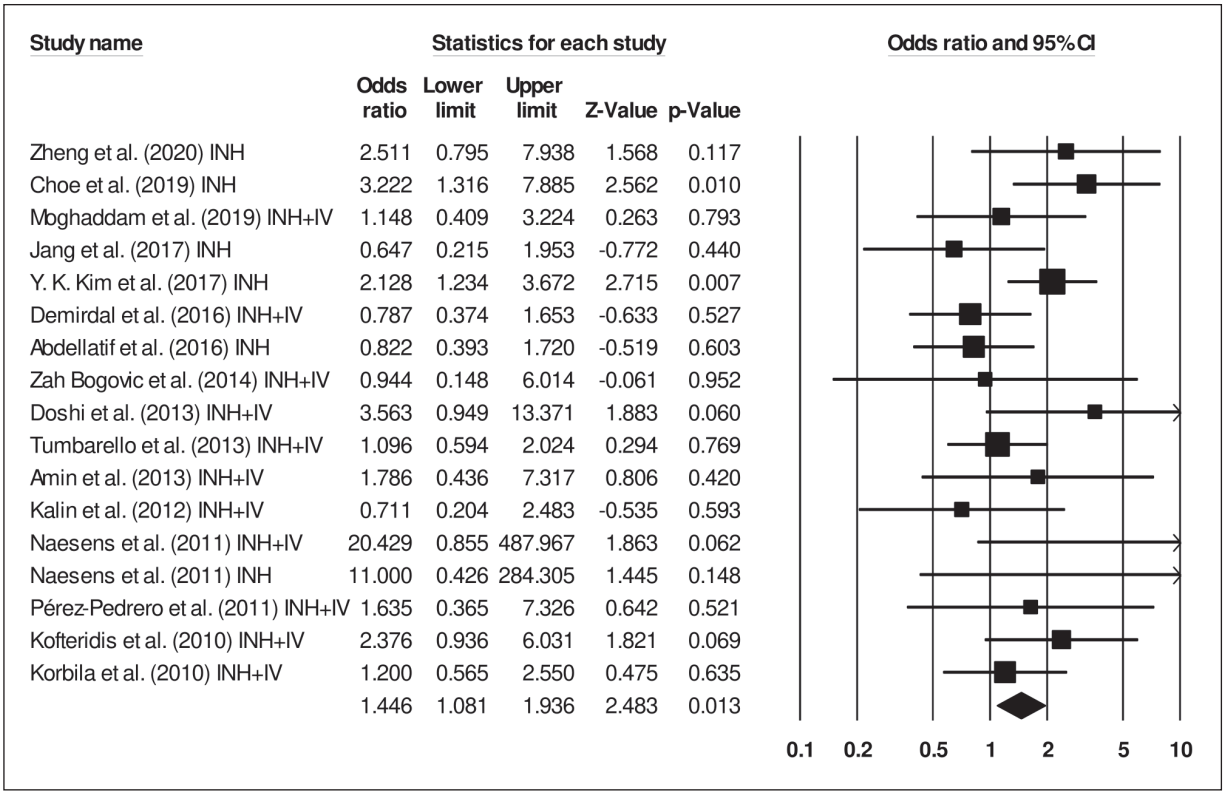

Figure 13. Forest plot for studies evaluating the risk of overall mortality in patients receiving intravenous colistin or combined/inhaled colistin. The odds ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A reduced odds ratio represents higher odds of mortality for the group receiving combined/inhaled colistin, a higher odds ratio represents higher odds of mortality for the group receiving intravenous colistin (INH, inhalation only; INH+IV, inhalation plus intravenous).

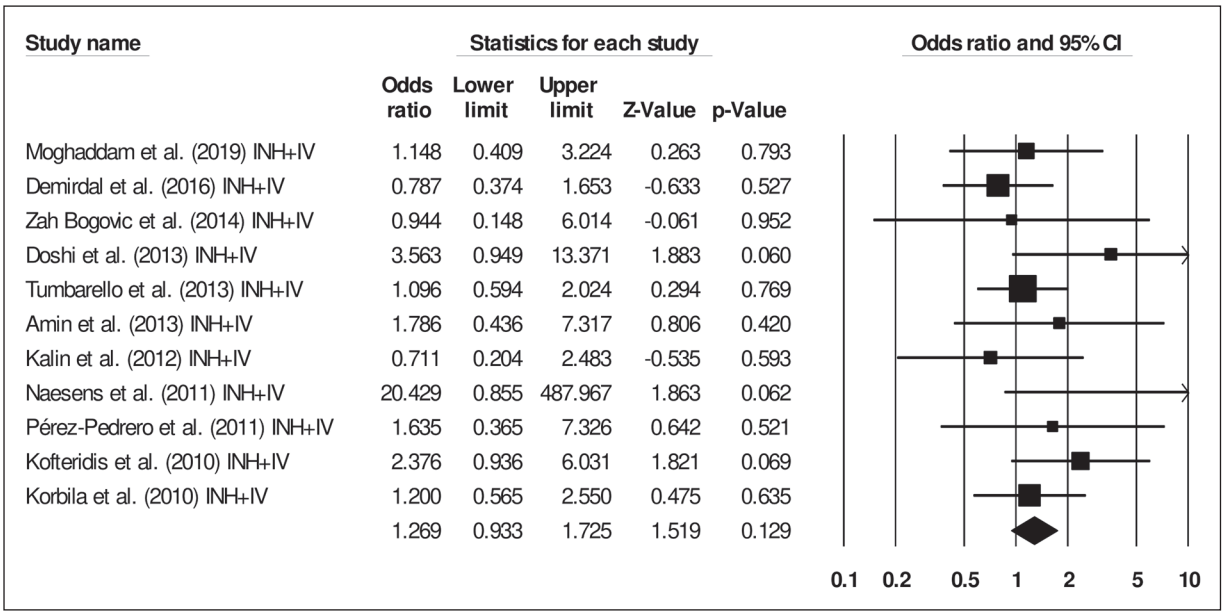

Figure 14. Forest plot for studies evaluating the risk of mortality in patients receiving intravenous colistin or a combined colistin regimen. The odds ratios are presented as black boxes and the 95% confidence intervals as whiskers. A reduced odds ratio represents the higher mortality rate for the group receiving intravenous colistin, a higher odds ratio represents the higher mortality rate for the group receiving a combined colistin regimen (INH+IV, inhalation plus intravenous, INH, inhalation only).

morbidity outcomes were all similar in all the administration route groups. In our meta-analysis, we observed that both the clinical cure (OR, 1.61) and the microbiological eradication (OR, 1.37) rates were better in patients receiving inhaled/combined colistin than in those receiving intravenous colistin.

We also assessed the impact of different routes of colistin administration on morbidity and mortality-related outcomes in patients with multidrug-resistant pneumonia. We observed a lack of consensus regarding the impact of different routes of administration on nephrotoxicity events. Jang et al. (2017)[29], in a

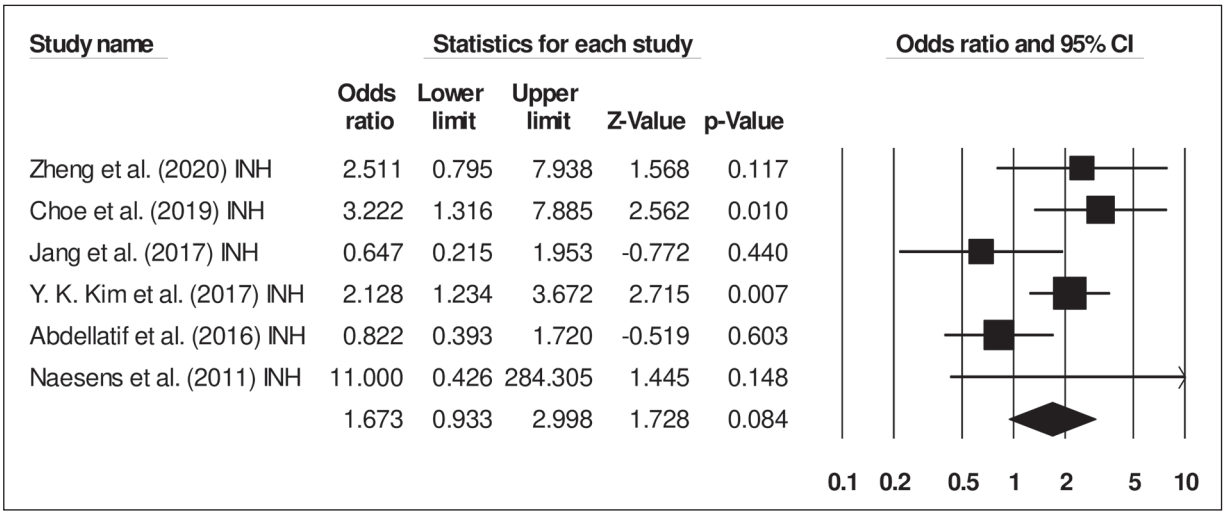

Figure 15. Forest plot for studies evaluating the risk of mortality in patients receiving intravenous colistin or inhalation colistin. The odds ratios are presented as black boxes and the 95% confidence intervals as whiskers. A reduced odds ratio represents the higher mortality rate for the group receiving intravenous colistin, a higher odds ratio represents the higher mortality rate for the group receiving inhalation colistin (INH+IV, inhalation plus intravenous, INH, inhalation only).

retrospective cohort study among 95 patients with ventilator-associated *Acinetobacter baumannii* pneumonia, found that the nephrotoxicity events rate to be higher in patients receiving colistin via the intravenous route (60.5%) than in those receiving inhalation colistin (15.7%) and they attributed this result to the high dosage of colistin delivered via the intravenous route. However, Kalin et al[30] found more nephrotoxicity events in the inhalation group (41%) than in the intravenous group (18%) and they suggested this was due to the severe disease of their patients at the time of admission. In our meta-analysis, we found higher levels of nephrotoxicity in patients receiving colistin intravenously than in those of the inhalation/combination route groups (OR, 1.30). We also observed a lack of consensus in terms of mortality and the different routes of administration. Doshi et al (2013)[18] reported higher mortality in patients receiving colistin intravenously (70.4%) than in those receiving combination regimens (40%), and their subgroup analysis using high-quality respiratory cultures found a higher mortality in the intravenous group (66.7%) than in the combination group (35.7%). However, Demirdal, Sari, and Nemli (2016)[28] reported a higher mortality in the patients receiving colistin via the combination route (53.5%) than in those receiving intravenous colistin (47.5%). We found higher overall mortality in patients receiving colistin intravenously (OR, 1.44) than in those receiving inhaled/combined regimens.

We are aware of the limitations in our systematic review and meta-analysis. First, this study was not pre-registered in a systematic review repository such as PROSPERO York or Joanna Briggs Institute. We understand that the lack of prior registration may raise concerns on the validity of our findings[50]. However, we assure our readers that we made several attempts to register this review, but the registration times at the repositories have been extended by more than one year due to the COVID-19 pandemic crisis. Second, we presume that the small sample size in a couple of our included studies –(26) (n=14), (43) (n=31)– could have biased our interpretation of the overall clinical, and mortality outcomes. For instance, for the mortality, we computed extremely high odds of 20.42 from the data provided by Naesens et al. (2011)[26]. Similarly, during our analysis of the microbiological eradication, we observed odds of 11.1 from the data reported by Zah Bogović et al (2014)[43]. Although we did not observe substantial heterogeneity in any of these analyses, we recommend a careful interpretation of these findings as we cannot rule out a type II error[51]. Future studies with large sample sizes are needed to confirm our results about the mortality of patients under different colistin regimens.

Conclusions

We found increased risks of mortality and nephrotoxicity in patients receiving intravenous colistin than in those receiving inhalation/combined regimens. We found improved clinical outcomes such as clinical cure and microbiological eradication rates for the patients receiving colistin via inhalation/combination regimens than for those receiving intravenous colistin. Our findings suggest that the inhalation/combined colistin regimens should be preferred for managing patients with multidrug-resistant pneumonia.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that they have no competing interests.

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None.

Authors' Contributions

HC designed the project; XL and YL were involved in data collection and data analysis; HC prepared the manuscript; YS edited the manuscript; all authors read and approved the final manuscript.

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