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META-ANALYSIS

Prevalence of polymyxin-induced nephrotoxicity and its predictors in critically ill adult patients: A meta-analysis

Jiang-Lin Wang, Bi-Xiao Xiang, Xiao-Li Song, Rui-Man Que, Xiao-Cong Zuo, Yue-Liang Xie

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Abstract

BACKGROUND

Polymyxin-induced nephrotoxicity is a major safety concern in clinical practice due to long-term adverse outcomes and high mortality.

AIM

To conducted a systematic review and meta-analysis of the prevalence and potential predictors of polymyxin-induced nephrotoxicity in adult intensive care unit (ICU) patients.

METHODS

PubMed, EMBASE, the Cochrane Library and Reference Citation Analysis database were searched for relevant studies from inception through May 30, 2022. The pooled prevalence of polymyxin-induced nephrotoxicity and pooled risk ratios of associated factors were analysed using a random-effects or fixed-effects model by Stata SE ver. 12.1. Additionally, subgroup analyses and meta-regression were conducted to assess heterogeneity.

RESULTS

A total of 89 studies involving 12234 critically ill adult patients were included in the meta-analysis. The overall pooled incidence of polymyxin-induced nephrotoxicity was 34.8%. The pooled prevalence of colistin-induced nephrotoxicity was not higher than that of polymyxin B (PMB)-induced nephrotoxicity. The subgroup analyses showed that nephrotoxicity was significantly associated with dosing interval, nephrotoxicity criteria, age, publication year, study quality and sample size, which were confirmed in the univariable meta-regression analysis. Nephrotoxicity was significantly increased when the total daily dose was divided into 2 doses but not 3 or 4 doses. Furthermore, older age, the presence of sepsis or septic

shock, hypoalbuminemia, and concomitant vancomycin or vasopressor use were independent risk factors for polymyxin-induced nephrotoxicity, while an elevated baseline glomerular filtration rate was a protective factor against colistin-induced nephrotoxicity.

CONCLUSION

Our findings indicated that the incidence of polymyxin-induced nephrotoxicity among ICU patients was high. It emphasizes the importance of additional efforts to manage ICU patients receiving polymyxins to decrease the risk of adverse outcomes.

Key Words: Polymyxins; Nephrotoxicity; Critically ill adult patients; Risk factors; Meta-analysis

Core Tip: Polymyxins have recently been reintroduced as a last-line option in chemotherapy for infections caused by multidrug-resistant gram-negative bacteria. However, these agents can cause nephrotoxicity. Notably, the prevalence of and risk factors for polymyxin-associated nephrotoxicity in adult intensive care unit (ICU) patients remain unclear. This is the first systematic review and meta-analysis to estimate the prevalence of and risk factors for polymyxin-induced nephrotoxicity in adult ICU patients. Based on the data collected and analysed, we conclude that the high incidence of polymyxin-induced nephrotoxicity is a primary safety concern and challenge in clinical practice. The avoidance of modifiable risk factors (such as nephrotoxic drugs and dosage regimens containing polymyxins) in adult ICU patients can likely reduce the risk of polymyxin-induced nephrotoxicity.

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INTRODUCTION

Acute kidney injury (AKI), a vastly complex heterogeneous syndrome, is associated with long-term adverse outcomes and high mortality[1]. Nearly 22% of hospitalized patients develop AKI, and the incidence of AKI in patients in intensive care units (ICUs) can reach 50%-70%[2-4]. Nephrotoxic drugs are considered the third most common aetiology for AKI following sepsis and hypovolemia and account for approximately 14% of cases in ICUs[4]. Drug-related risk hypervigilance and nephrotoxic drug stewardship are important strategies for the prevention of AKI in ICU patients[3,5].

Polymyxins (such as colistin and polymyxin B), were introduced into clinical practice in the 1950s but abandoned soon after due to broad toxicity, especially nephrotoxicity. Recently, polymyxins have been reintroduced as a final option in for the treatment of infections caused by carbapenem-resistant gram-negative bacteria in critically ill patients[6,7], though polymyxin-associated nephrotoxicity is still the primary safety concern and obstacle to their widespread clinical application[7,8]. A recent study suggested that among antibiotics, colistin had the highest AKI reporting odds ratios based on real-world data, including 2042801 reports from the Food and Drug Administration (FDA) Adverse Event Reporting System[9]. Hence, there is an urgent need to analyse the prevalence and potential risk factors for polymyxin-induced nephrotoxicity in critically ill patients.

Several systematic reviews and meta-analyses on polymyxin-induced nephrotoxicity and its predictors have been conducted[10-13]. The nephrotoxicity prevalence varies widely, ranging from 26.7% to 45%[10,12,13]. A meta-analysis of 237 studies that enrolled 35569 hospitalized patients treated with systemic or inhaled polymyxins was conducted. Patients receiving inhaled polymyxins showed a significantly lower nephrotoxicity rate than patients receiving systemic polymyxins (13.8% *vs* 29.5%; $P < 0.001$)[13]. Another recent meta-analysis of 48 studies involving 6,199 adult patients with at least 48 h of intravenous polymyxin exposure showed that older age, a high daily dose, accompanying diabetes, and concomitant nephrotoxic drugs uses were independent predictors of nephrotoxicity[12]. However, the incidence of nephrotoxicity was significantly higher in ICU patients than in non-ICU patients [odds ratio (OR) = 1.55; 95% confidence interval (CI), 1.02-2.37; $P = 0.042$][13]. In addition, the severity of patient illness was also reported to be a risk factor for colistin-related nephrotoxicity[14]. In general, previous meta-analyses pooled nephrotoxicity events and assessed risk factors for AKI in hospital patients receiving polymyxins; these data were insufficient to evaluate the prevalence and risk factors for polymyxin-associated nephrotoxicity in adult ICU patients, who account for the majority of the

population using polymyxins in clinical practice.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted and reported in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, respectively.

Literature search

We searched PubMed, EMBASE and the Cochrane Library from inception through May 30, 2022, and limited the search to English-language studies involving humans. When revising the manuscript, we searched the Reference Citation Analysis (RCA) database in order to supplement and improve the highlights of the latest frontier research results, but we did not find any potential articles to be included. Reference lists of the retrieved studies, systematic reviews, and meta-analyses pertaining to our study were also reviewed. The search strategy is provided in Supplementary Table 1.

Study selection and data extraction

Observational studies and randomized clinical trials (RCTs) were eligible for meta-analysis if they met the following criteria: (1) The incidence of nephrotoxicity induced by polymyxin B (PMB) or colistin in adult (age > 18 years) ICU patients was reported; (2) patients received at least 48 h of intravenous polymyxin exposure; and (3) risk factors associated with nephrotoxicity induced by either type of polymyxin were reported as ORs, relative risks (RRs) or hazard ratio (HRs) with 95%CIs. Studies were excluded if they met the following exclusion criteria: (1) Review, abstracts from conference proceedings, comments, or case reports; (2) missing full text or an inability to retrieve data required for analysis; or (3) a sample size of less than 10 patients.

Duplicates were detected and removed first. Then, two authors (Bi-Xiao Xiang and Yue-Liang Xie) independently screened the titles, abstracts and full texts based on the inclusion criteria and exclusion criteria. Two investigators (Jiang-Lin Wang and Bi-Xiao Xiang) independently extracted the data based on the predetermined selection criteria. Data extraction details are presented in the supplementary Method. All disagreements were resolved by consensus and, if not possible, by discussion with the remaining authors.

Risk of bias

Two reviewers (Yue-Liang Xie and Jiang-Lin Wang) independently evaluated the risk of bias of the included studies using the Cochrane Collaboration risk of bias tool and the Newcastle–Ottawa Scale for RCTs and for observational studies (cohort and case–control studies), respectively. Discrepancies were resolved by a third investigator (Xiao-Cong Zuo). The scores on the Newcastle–Ottawa Scale range from 0 to 9. The included studies were classified into one of three categories based on the scores for each study: Low quality (score of less than 4), moderate quality (score of 5-7) and high quality (score of 8-9). The overall risk of bias for each included RCT was classified as low if the risk of bias was low in all domains, unclear if the risk of bias was unclear in one or more domains and with no judgement of high risk of bias, and high if the risk of bias was high in one or more domains[15].

Statistical analysis

Raw data including numbers of nephrotoxic events and total sample size were statistically pooled using a random effects model to calculate the overall event rate and 95%CI. The pooled ORs with 95%CIs of associated factors were calculated using a random-effects or fixed-effects model (I^2 < 50%). In addition, the RRs of colistin *vs* PMB as well as polymyxin treatment regimens *vs* nonpolymyxin-based treatment regimens were computed considering parallel design studies. Studies were weighted using the inverse variance method. We calculated the inconsistency index (I^2) to measure heterogeneity. According to prespecified cut-off values, low heterogeneity was defined as an I^2 < 50%, and high heterogeneity was defined as an I^2 ≥ 50%. For each outcome, sensitivity analysis was performed by sequentially omitting each study from the pool; all studies were removed one at a time to analyse their influence on the pooled estimate and heterogeneity.

To account for potential sources of heterogeneity in the pooled incidence of polymyxin-induced nephrotoxicity, we performed several subgroup analyses detailed in the Supplementary Material. To further investigate potential sources of heterogeneity for the incidence of polymyxin-induced nephrotoxicity, we conducted several meta-regressions. In the first step, we performed univariable meta-regression analyses according to the mean age in each study, sex, study design, sample size, publication year, geographical location, definition of AKI and risk of bias. A multivariable meta-regression analysis was then conducted with the factors significantly associated with polymyxin-induced nephrotoxicity incidence in the univariable meta-regression analyses.

Publication bias was examined visually with the use of funnel plots and filled funnel plots and assessed with Egger's test. When both indicators showed a significant result, it was assumed that publication bias was present. All statistical analyses were performed using Stata SE ver. 12.1 (StataCorp., College Station, TX, United States). Statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Search results

A total of 1437 results were retrieved from the search. After the removal of duplicates and title and abstract screening, 176 full texts were assessed for eligibility, and 89 studies were included for quantitative synthesis (Supplementary Table 1)[16-104]. The detailed study selection process is depicted in Figure 1.

Characteristics of the included studies

The characteristics of the included studies are shown in Supplementary Table 2. This systematic review and meta-analysis included 12234 adult critically ill patients receiving polymyxins, of whom 11211 were included in the colistin-treated groups and 903 were included in the PMB-treatment groups. All studies were published from 2003 to 2022. Among the included studies, 9 were RCTs[16,18,23,34,35,54,57,81,87], 5 were case–control studies[31,47,51,74,86] and 75 were cohort studies[17,19-22,24-30,32,33,36-46,48-50,52,53,55,56,58-73,75-80,82-85,88-104]. The sample sizes per study ranged from 11 to 4910 critically ill patients. This systematic review and meta-analysis included 3 parallel cohort studies that reported outcome measures associated with colistin and PMB use[62,76,80], 2 studies with colistin and PMB use [17,68], 75 studies with colistin use alone[16,18-40,42-57,59-61,64-67,70-75,78,81,83-99,101-102,104] and 9 studies with PMB use alone[41,58,63,69,77,79,82,100,103]. Regarding the geographical distribution, 35 studies were conducted in Europe, 31 in Asia, 6 in North America, 6 in South America and 4 in Africa. Regarding the definitions of AKI, 38, 10, and 8 studies relied on the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE), Kidney Disease Improving Global Outcomes (KDIGO), and Acute Kidney Injury Network (AKIN) classification systems, respectively. The rest adopted self-reported definition of AKI. Only two studies reported median Acute Physiology and Chronic Health Evaluation (APACHE) II scores[44,100], whereas 53 studies reported mean APACHE II scores ranging from 11.8 (± 4.3)[58] to 30.4 (± 9.5)[91]. Nineteen studies and 62 studies described age as the median and the mean, respectively, with ages ranging from 40 to 73.8 years. Among the observational studies, there were 51 studies with a moderate risk of bias, 18 with a high risk of bias and 11 with a low risk of bias (Supplementary Table 3). Among the 9 RCTs, 1 was determined to have a high risk of bias[23], 7 had an unclear risk of bias[16,18,35,54,57,81,87], and 1 had a low risk of bias[34] (Supplementary Table 3).

Incidence of polymyxin-induced nephrotoxicity

Across all studies, 4027 nephrotoxic events in 12234 critically ill adult patients receiving polymyxins were analysed. The pooled incidence of overall polymyxin-induced nephrotoxicity reached 34.8% (95%CI, 30.8%-38.9%, $I^2 = 95.90\%$) (Figure 2). In addition, we did not observe a significant influence of any study on the pooled estimates or heterogeneity (Supplementary Figure 1) in the sensitivity analyses. We classified nephrotoxicity into mild and severe (defined as a RIFLE grade of 'failure' or above, AKIN grade of 3 or KDIGO grade of 3 or required renal replacement therapy [RRT]) groups, and the incidence rates of mild and severe nephrotoxicity were 25.8% (95%CI, 21.6%-29.9%; $I^2 = 96.80\%$) and 12.7% (95%CI, 10.3%-15.0%; $I^2 = 89.60\%$), respectively (Table 1). In addition, ranking of the criteria used to obtain the AKI incidence indicated that the KDIGO criteria were the highest-ranked (46.5%; 95%CI, 35.9%-57.1%; $I^2 = 93.80\%$), followed by the RIFLE (39.6%; 95%CI, 33.9%-45.4%; $I^2 = 93.80\%$), AKIN (37.3%; 95%CI, 27.4%-47.3%; $I^2 = 87.40\%$) and finally other criteria (21.4%; 95%CI, 15.9%-26.9%; $I^2 = 94.20\%$). Since most studies used the standardized RIFLE criteria, we subsequently performed subgroup analyses, and the pooled incidence rates of polymyxin-induced nephrotoxicity classified as 'risk', 'injury' and 'failure' based on RIFLE criteria were 12.7% (95%CI, 9.6%-15.8%), 12.6% (95%CI, 10.0%-15.2%), and 14.9% (95%CI, 11.1%-18.6%), respectively (Supplementary Table 5).

Moreover, to explore potential sources of heterogeneity, we performed several subgroup analyses (Table 1). Regarding specific medications, the pooled incidence of PMB-induced nephrotoxicity was 26.8% lower than that of colistin-induced nephrotoxicity (35.5%; 95%CI, 31.1%-39.8%; $I^2 = 96.1\%$) without significant difference. Furthermore, pairwise meta-analysis showed that adult patients treated with colistin (42.7%) had a higher incidence of AKI than those treated with PMB (21.3%), but this difference was not statistically significant (OR = 2.37; 95%CI, 0.62-9.07; $P = 0.206$) (Supplementary Figure 2). The nephrotoxicity incidence was higher, but not significantly, in critically ill adult patients who received a loading dose (39.1%; 95%CI, 32.1%-46.1%; $I^2 = 95.0\%$) than in those who did not (30.9%; 95%CI, 26.0%-35.7%; $I^2 = 95.2\%$). Subgroup analysis based on dose indicated that the high-dose group (39.5%; 95%CI, 30.2%-48.7%, $I^2 = 52.0\%$) had a higher incidence of nephrotoxicity than the low-dose group (32.4%, 95%CI, 27.8%-37.1%; $I^2 = 96.0\%$). However, no statistical significance was observed.

Table 1 Subgroup analysis of polymyxin-induced nephrotoxicity

Category	Subgroups	No. of studies	No. of nephrotoxicity patients	No. of patients	Events rate (95%CI)	Model	Heterogeneity (I^2)	*P* value
Overall		83	4027	12234	0.348 (0.308-0.389)	Random	95.90	NA
Severity	Severe nephrotoxicity[a]	47	648	5163	0.127 (0.103-0.150)	Random	89.60	NA
	Mild nephro-toxicity	49	1378	5163	0.258 (0.216-0.299)	Random	96.80	
Continent	Africa	4	53	209	0.215 (0.087-0.343)	Random	82.10	0.394
	Asia	31	1230	3099	0.340 (0.264-0.416)	Random	96.30	
	Europe	35	1192	2904	0.364 (0.283-0.446)	Random	97.00	
	South America	6	249	628	0.399 (0.295-0.503)	Random	84.60	
	North America	6	1283	5213	0.329 (0.200-0.459)	Random	92.40	
Polymyxins	Colistin	72	3623	11211	0.355 (0.311-0.398)	Random	96.10	0.151
	Polymyxin B	11	262	903	0.268 (0.171-0.364)	Random	92.20	
Loading dose	Loading dose	32	1305	3233	0.391 (0.321-0.461)	Random	95.00	0.051
	No loading dose	48	2333	8340	0.309 (0.260-0.357)	Random	95.20	
Maintenance dose[b]	Higher dose	5	109	281	0.395 (0.302-0.487)	Random	52.00	0.363
	Normal dose	62	2867	9588	0.324 (0.278-0.371)	Random	96.00	
Dosing interval	Q12H or BID	32	1494	3200	0.421 (0.356-0.485)	Random	93.40	0.001[1]
	Q8-6H or TID	21	380	1322	0.251 (0.172-0.330)	Random	93.90	
Nephrotoxicity Criteria	RIFLE	38	1667	3985	0.396 (0.339-0.454)	Random	93.80	0.000[1]
	KDIGO	10	627	1369	0.465 (0.359-0.571)	Random	93.80	
	AKIN	8	284	761	0.373 (0.274-0.473)	Random	87.40	
	Others	26	1473	6298	0.214 (0.159-0.269)	Random	94.20	
Age (yr)[c]	< 65 yr	59	2450	8980	0.307 (0.263-0.351)	Random	95.10	0.003[1]
	≥ 65 yr	19	1123	2328	0.451 (0.382-0.520)	Random	91.40	
Sex proportion	Males > 50%	60	3064	99908	0.344 (0.297-0.391)	Random	96.10	0.417
	Males ≤ 50%	8	332	757	0.406 (0.243-0.569)	Random	94.50	
APACH II score	< 20	23	653	1690	0.305 (0.209-0.401)	Random	95.80	0.115
	≥ 20	29	1053	2601	0.384 (0.307-0.461)	Random	95.00	

Publication yr	< 2010	10	42	333	0.138 (0.085-0.192)	Random	44.10	0.000[1]
	2010-2015	25	612	2099	0.270 (0.205-0.334)	Random	93.10	
	2015-2022	48	3386	9875	0.421 (0.365-0.476)	Random	96.70	
Study design	Cohort study	72	3685	11491	0.340 (0.296-0.384)	Random	96.50	0.785
	Case-control study	5	185	457	0.410 (0.164-0.656)	Random	96.70	
	RCT	8	158	407	0.341 (0.224 - 0.459)	Random	82.70	
Study quality[d]	Low	11	1402	5715	0.215 (0.130-0.299)	Random	97.30	0.003[1]
	Fair	50	1912	4925	0.363 (0.314-0.411)	Random	93.70	
	High	17	599	1324	0.412 (0.329-0.494)	Random	90.10	
Sample size	≤ 50	30	284	1026	0.261 (0.199-0.323)	Random	87.00	0.000[1]
	50-100	27	657	1965	0.341 (0.260-0.423)	Random	95.40	
	> 100	28	3130	9480	0.436 (0.370-0.501)	Random	97.30	

[1]Significant at P value < 0.05.

[a]Severe nephrotoxicity defined as RIFLE grade of 'failure' or above, AKIN grade of 3 or KDIGO grade of 3 or required renal replacement therapy.

[b]Maintenance dose varied among studies, higher dose as identified as > 9 MIU/d or > 2.5-5.0 mg CBA/kg/d for colistin, or > 2.5-3 mg/kg/d for polymyxin B in this study.

[c]Age cut-off value based on the mean or median age of patients included.

[d]Quality assessment was applied using Newcastle Ottawa Scale assessment for cohort studies and case control studies. Articles that scored less than 4 were classified as low methodological quality, articles with score between 5 and 7 were classified as fair quality, and those with score more than 8 were classified as high quality.

AKIN: Acute Kidney Injury Network; APACHE II: Acute Physiology and Chronic Health Evaluation II; BID: twice daily; CI: Confidence Interval; KIDGO: Kidney Disease Improving Global Outcomes; RCT: Randomized Controlled Trials; RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; TID: Three times daily; NA: Not available.

In addition, the meta-analysis showed that the incidence of nephrotoxicity was higher in patients who received twice-daily polymyxin therapy (42.1%; 95%CI, 35.6%-48.5%; I^2 = 93.4%) than in patients who received multiple daily polymyxin therapy (25.1%; 95%CI, 17.2%-33.0%; I^2 = 93.9%) (Table 1).

Regarding geographical distribution, the highest pooled incidence of polymyxin-induced nephrotoxicity was 39.9% in South America, followed by 36.4% in Europe, 32.9% in North America, 34.0% in Asia and 21.5% in Africa (Figure 3 and Table 1). In the subgroup analysis of age, the overall pooled polymyxin-induced nephrotoxicity incidence was significantly lower in younger patients (aged < 65 years) than in older patients (aged ≥ 65 years). In the univariable meta-regression, we found a significant age trend associated with the incidence of AKI in adults (regression coefficient (Q) = -0.1427, P = 0.003) (Table 2 and Supplementary Figure 3). Furthermore, we did not observe a difference in the nephrotoxicity incidence between males > 50% (34.4%; 95%CI, 29.7%-39.1%; I^2 = 96.1%) and males ≤ 50% (40.6%; 95%CI, 24.3%-56.9%; I^2 = 94.5%) or between a mean or median APACHE II score ≥ 20 group (38.4%; 95%CI, 30.7%-46.1%; I^2 = 95.0%) and a score < 20 group (30.5%; 95%CI, 20.9%-40.1%; I^2 = 95.8%) .

Subgroup analysis based on publication year showed that the incidence of nephrotoxicity caused by polymyxins was highest between 2015 and 2022 (42.1%; 95%CI, 36.5%-47.6%; I^2 = 96.7%), followed by 2010 to 2015 (27.0%; 95%CI, 20.5%-33.4%; I^2 = 93.1%) and before 2010 (13.8%; 95%CI, 8.5%-19.2%; I^2 = 44.1%). A significant time trend of nephrotoxicity incidence with year of study publication was observed in the univariable meta-regression analysis (regression coefficient (Q) = 0.1337, P < 0.001) (Table 2 and Supplementary Figure 4). In addition, the nephrotoxicity incidence varied by sample sizes of the studies (P < 0.001 for subgroup analysis). Smaller studies (< 50 participants) showed the lowest incidence of nephrotoxicity compared to medium (50-100 participants) and large (≥ 100 participants) studies (Table 1). We excluded the study with the largest sample size[53] and performed a univariable meta-regression analysis according to the sample size of the studies. The results showed an association between the sample size of the studies and the incidence of nephrotoxicity caused by polymyxins (regression coefficient (Q) = 0.0873, P < 0.001) (Table 2 and Supplementary Figure 5). In addition, we

Table 2 Meta-regression analysis for polymyxin-induced nephrotoxicity incidence

Variable	Coefficient	Standard error	Lower 95%CI	Upper 95%CI	*P* value	R^2, %
Univariable analysis						
Continent	0.0148	0.0222	-0.0294	0.0590	0.508	-0.64
Polymyxins	-0.0865	0.0597	-0.2052	0.0322	0.151	1.41
Loading dose	-0.0814	0.0412	-0.1634	0.0005	0.051	3.62
Maintenance dose[a]	-0.0845	0.0928	-0.2703	0.1004	0.363	-0.41
Dosing interval	-0.1704	0.0476	-0.2659	-0.0749	0.001[1]	20.58
Nephrotoxicity criteria	-0.0577	0.0141	-0.0858	-0.0295	0.000[1]	18.55
Age[b]	-0.1427	0.0470	-0.2362	-0.0492	0.003[1]	11.08
Gender	0.0627	0.0768	-0.0907	0.2162	0.417	-0.20
APACH II score	0.0812	0.0505	-0.0204	0.1827	0.115	3.52
Publication yr	0.1377	0.0261	0.0857	0.1896	0.000[1]	26.95
Study design	0.0096	0.0351	-0.0601	0.0794	0.785	-1.15
Study quality[c]	0.0966	0.0313	0.0343	0.1590	0.003[1]	10.66
Sample size	0.0873	0.0220	0.0435	0.1311	0.000[1]	17.08
Multivariable analysis						
Nephrotoxicity criteria	-0.0344	0.0141	-0.0625	-0.0064	0.017	40.00
Publication yr	0.0940	0.0278	0.0386	0.1495	0.001	
Sample size	0.0357	0.0203	-0.047	0.0760	0.082	
Study quality[c]	0.0387	0.0267	-0.0144	0.0919	0.151	

[1]Significant at *P* value < 0.05.

[a]Maintenance dose varied among studies, higher dose as identified as > 9 MIU/d or > 2.5-5.0 mg CBA/kg/d for colistin, or > 2.5-3 mg/kg/d for polymyxin B in this study.

[b]Age was mean or median age of patients included.

[c]Quality assessment was applied using Newcastle-Ottawa Scale assessment for cohort studies and case-control studies. Articles that scored less than 4 were classified as low methodological quality, articles with score between 5 and 7 were classified as fair quality, and those with score more than 8 were classified as high quality.

found that the type of study did not impact the incidence of polymyxin-associated nephrotoxicity (Table 1). However, the pooled incidence rates of nephrotoxicity differed significantly among quality subgroups (P = 0.001). The highest pooled incidence of nephrotoxicity was 41.2% in high-quality studies, followed by 36.3% in moderate-quality studies and 21.5% in low-quality studies (Table 1). Univariable meta-regression indicated that studies with a higher risk of bias reported significantly lower rates of polymyxin-induced nephrotoxicity (regression coefficient (Q) = 0.0966, P = 0.003) (Table 2 and Supplementary Figure 6). Although we performed subgroup analyse, the heterogeneity of each group remained high. The final multivariable meta-regression model, which included the sample sizes of studies, publication year, study quality and definitions of AKI, was able to explain a significant proportion of the heterogeneity reported (R^2 = 40.00%; P = 0.001) (Table 2).

Visual inspection of the funnel plots revealed potential asymmetry for the incidence of nephrotoxicity caused by polymyxins (Supplementary Figure 7A), with a significant Egger's test result (P = 0.001). The trim-and-fill method also showed significant publication bias for the incidence of polymyxin-induced nephrotoxicity (Supplementary Figure 7B).

Polymyxin exposure and risk of nephrotoxicity

Twelve studies compared nephrotoxicity rates in critically ill adult patients with and without polymyxin use. Meta-analysis showed that polymyxin therapy was associated with a higher prevalence of nephrotoxicity than nonpolymyxin therapies (OR = 2.145; 95%CI, 0.997-4.614, I^2 = 74.8%) (Figure 4), but the difference was not statistically significant. We performed sensitivity analysis and found that the exclusion of Rocco *et al*[66], Gounden *et al*[39] or Garnacho-Montero *et al*[37] changed the magnitude of the summary effect (Supplementary Figure 8). The funnel plots (Supplementary Figure 9) and Egger's regression asymmetry tests (P = 0.686) suggested that there was no significant publication bias in this meta-analysis.

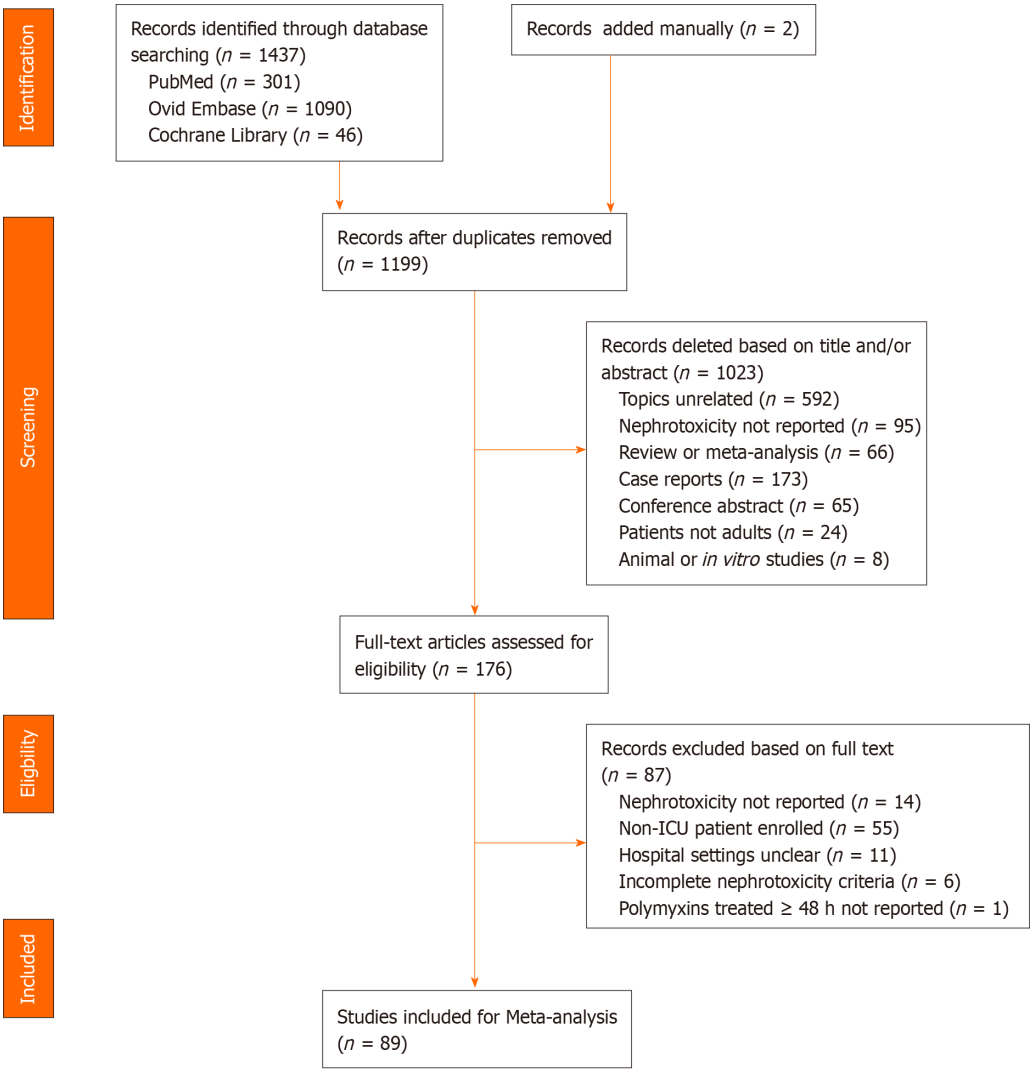

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Figure 1 PRISMA flow diagram of study selection. ICU: Intensive care unit.

Risk factors for polymyxin-induced nephrotoxicity

Given the potential predictors of polymyxin-induced nephrotoxicity (Table 3 and Supplementary Table 4), older age, the presence of sepsis or septic shock, hypoalbuminemia, and concomitant use of vancomycin or vasopressors were independent risk factors for polymyxin-induced nephrotoxicity according to the pooled OR, RR and HR based on the univariate analyse. In contrast, patients with a high baseline glomerular filtration rate were 0.883 times less likely to experience nephrotoxicity associated with polymyxins than those with a low glomerular filtration rate (OR = 0.883; 95%CI, 0.820-0.952). However, sex, the APACHE II score, diabetes mellitus, concomitant diuretics, the daily dose of polymyxins and the duration of polymyxin therapy did not influence the risk of polymyxin-induced nephrotoxicity. Furthermore, older age (OR = 1.035; 95%CI, 1.021-1.050), APACHE II score (OR = 1.031; 95%CI, 1.017-1.045), the use of concomitant vasopressor (OR = 3.099; 95%CI, 1.169-8.219) and the use of concomitant diuretics (OR = 2.979; 95%CI, 1.290-6.882) were independent risk factors for polymyxin-induced nephrotoxicity according to the pooled OR, RR and HR based on the multivariate analysis (Table 3 and Supplementary Table 4).

DISCUSSION

Nephrotoxicity due to polymyxin use is a major safety concern in clinical practice. In contrast to other meta-analyses[10,13], our study did not find that polymyxin therapy was associated with a higher risk of nephrotoxicity than other therapies (OR = 2.145; 95%CI, 0.997-4.614) in adult critically ill patients (Figure 4). Antimicrobial drugs, which are used in at least 70% of critically ill patients[105], include a wide range of medications that can cause nephrotoxicity, *e.g.*, vancomycin, aminoglycosides, polymyxins, *etc.*[106]. I has been shown that earlier administration of appropriate antimicrobials for

Table 3 Pooled odds ratio estimates for potential predictors of polymyxin-induced nephrotoxicity

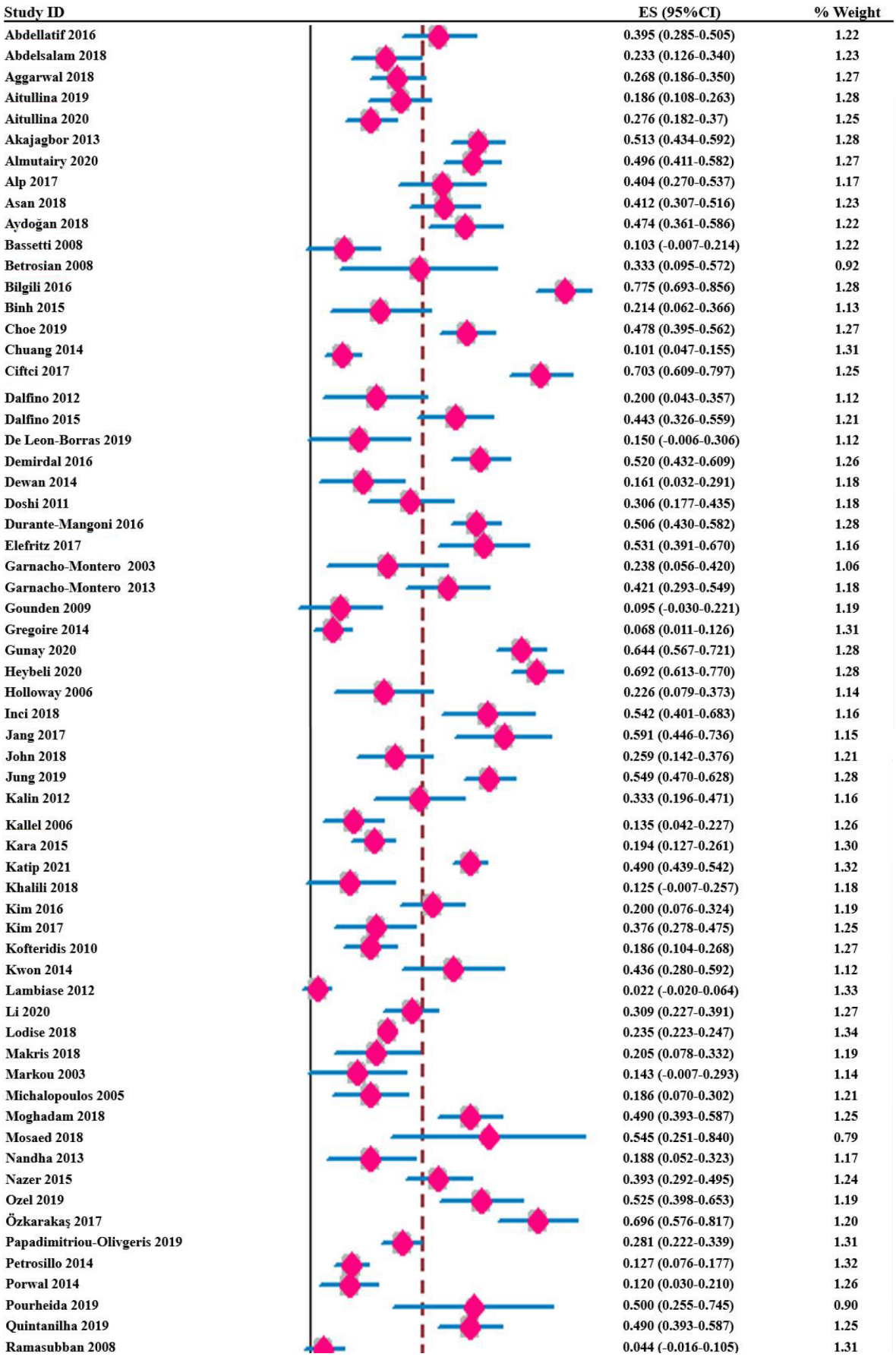
Variables	Effect size				Heterogeneity	
	OR (95%CI)	Model	Z	*P* value	I^2 (%)	*P* value
Pooled OR, RR, HR based on univariate analysis						
Male gender	1.570 (0.930-2.660)	Fixed	1.67	0.095	0	0.964
Female gender	0.773 (0.418-1.427)	Random	0.82	0.410	65.6	0.033
Age (yr)	1.025 (1.012-1.039)	Random	3.65	0.000[1]	51.9	0.052
Age (> 61 yr)	2.072 (1.092-3.933)	Fixed	2.23	0.026[1]	0	0.576
APACHE II score	1.036 (1.002-1.071)	Fixed	2.06	0.039[1]	14.7	0.319
Sepsis[a]	2.114 (1.412-3.164)	Fixed	3.64	< 0.001[1]	45.3	0.139
Baseline eGFR (mL/min/1.73 m^2)	0.883 (0.820-0.952)	Fixed	3.26	0.001[1]	0	0.696
Albumin (hypoalbuminemia)[b]	2.795 (1.620-4.825)	Fixed	3.69	< 0.001[1]	0	0.565
Diabetes mellitus	1.229 (0.624-2.421)	Fixed	0.60	0.550	0	0.542
Concomitant diuretics	0.853 (0.252-2.890)	Random	0.26	0.799	77.2	0.004
Concomitant vancomycin	2.110 (1.190-3.730)	Fixed	2.55	0.011[1]	0	0.667
Concomitant vasopressor	1.496 (1.007-2.222)	Random	2.00	0.046[1]	72.0	0.013
Daily dose (mg/kg/d)	0.996 (0.991-1.000)	Fixed	1.77	0.077	0	0.523
Duration of therapy (d)	1.019 (0.979-1.061)	Fixed	0.92	0.359	34.5	0.191
Pooled OR, RR, HR based on multivariate analysis						
Age (yr)	1.035 (1.021-1.050)	Fixed	4.95	< 0.001[1]	0	0.863
APACHE II score	1.031 (1.017-1.045)	Fixed	4.36	0.000	26.1	0.255
Concomitant vasopressor	3.099 (1.169-8.219)	Random	2.27	0.023[1]	80.4	0.002
Concomitant diuretics	2.979 (1.290-6.882)	Fixed	2.56	0.011[1]	2.6	0.358

[1]Significant at *P* value < 0.05.
[a]Sepsis or septic shock were pooled.
[b]Hypoalbuminemia and serum albumin levels < 2 g/dL were pooled.
APACHE II: Acute Physiology and Chronic Health Evaluation II; CI: Confidence interval; eGFR: Estimated glomerular filtration rate; HR: Hazard ratio; OR: Odds ratio; RR: Relative risk.

sepsis or septic shock can decrease mortality[107], and early use of PMB-based combination therapy is associated with a significant decrease in mortality compared with delayed administration[108]. Therefore, polymyxin-based combination therapy regimens for carbapenem-resistant gram-negative bacterial infections should be administered early despite the concern about nephrotoxicity in adult critically ill patients[109-111].

The overall prevalence of polymyxin-induced nephrotoxicity was 34.8% (95%CI, 30.8%-38.9%, I^2 = 95.9%) in our study, which was slightly lower than that in other meta-analyses[12,13]. This result was consistent with other analyses showing that the nephrotoxicity rate was associated with the definition of nephrotoxicity[11,13]. The pooled prevalence of nephrotoxicity using standardized international criteria, such as the AKIN, KDIGO and RIFLE criteria, was similar, ranging from 37.3% to 46.5% (Table 1), which was similar to that in a previous meta-analysis[10,13] and may be the true prevalence of polymyxin-induced nephrotoxicity. Furthermore, we also evaluated the degree of nephrotoxicity using the RIFLE criteria, which were used by most of the studies in this meta-analysis. The prevalence of polymyxin-associated nephrotoxicity classified as failure (F) was 14.9%, higher than the 10% reported in the previous literature[12] (Supplementary Table 5). This finding indicated that 15 of 100 patients experienced acute renal failure during polymyxin treatment and developed AKI, resulting in 67% mortality and a higher risk of death than that in non-AKI patients[112]. Thus, nephrotoxicity caused by polymyxins and early identification of potential risk factors should be of great concern among ICU patients.

Among the potential predictors of polymyxin-induced nephrotoxicity, older age, the presence of sepsis or septic shock, hypoalbuminemia and concomitant vancomycin or vasopressor use were independent potential risk factors for polymyxin-associated AKI among ICU patients. Studies in sepsis patients showed a 2-fold higher risk of nephrotoxicity (OR = 2.114; 95%CI, 1.412-3.164), and patients


Study ID
ES (95%CI)
% Weight
Abdellatif 2016 0.395 (0.285-0.505) 1.22
Abdelsalam 2018 0.233 (0.126-0.340) 1.23
Aggarwal 2018 0.268 (0.186-0.350) 1.27
Aitullina 2019 0.186 (0.108-0.263) 1.28
Aitullina 2020 0.276 (0.182-0.37) 1.25
Akajagbor 2013 0.513 (0.434-0.592) 1.28
Almutairy 2020 0.496 (0.411-0.582) 1.27
Alp 2017 0.404 (0.270-0.537) 1.17
Asan 2018 0.412 (0.307-0.516) 1.23
Aydoğan 2018 0.474 (0.361-0.586) 1.22
Bassetti 2008 0.103 (-0.007-0.214) 1.22
Betrosian 2008 0.333 (0.095-0.572) 0.92
Bilgili 2016 0.775 (0.693-0.856) 1.28
Binh 2015 0.214 (0.062-0.366) 1.13
Choe 2019 0.478 (0.395-0.562) 1.27
Chuang 2014 0.101 (0.047-0.155) 1.31
Ciftci 2017 0.703 (0.609-0.797) 1.25
Dalfino 2012 0.200 (0.043-0.357) 1.12
Dalfino 2015 0.443 (0.326-0.559) 1.21
De Leon-Borras 2019 0.150 (-0.006-0.306) 1.12
Demirdal 2016 0.520 (0.432-0.609) 1.26
Dewan 2014 0.161 (0.032-0.291) 1.18
Doshi 2011 0.306 (0.177-0.435) 1.18
Durante-Mangoni 2016 0.506 (0.430-0.582) 1.28
Elefritz 2017 0.531 (0.391-0.670) 1.16
Garnacho-Montero 2003 0.238 (0.056-0.420) 1.06
Garnacho-Montero 2013 0.421 (0.293-0.549) 1.18
Gounden 2009 0.095 (-0.030-0.221) 1.19
Gregoire 2014 0.068 (0.011-0.126) 1.31
Gunay 2020 0.644 (0.567-0.721) 1.28
Heybeli 2020 0.692 (0.613-0.770) 1.28
Holloway 2006 0.226 (0.079-0.373) 1.14
Inci 2018 0.542 (0.401-0.683) 1.16
Jang 2017 0.591 (0.446-0.736) 1.15
John 2018 0.259 (0.142-0.376) 1.21
Jung 2019 0.549 (0.470-0.628) 1.28
Kalin 2012 0.333 (0.196-0.471) 1.16
Kallel 2006 0.135 (0.042-0.227) 1.26
Kara 2015 0.194 (0.127-0.261) 1.30
Katip 2021 0.490 (0.439-0.542) 1.32
Khalili 2018 0.125 (-0.007-0.257) 1.18
Kim 2016 0.200 (0.076-0.324) 1.19
Kim 2017 0.376 (0.278-0.475) 1.25
Kofteridis 2010 0.186 (0.104-0.268) 1.27
Kwon 2014 0.436 (0.280-0.592) 1.12
Lambiase 2012 0.022 (-0.020-0.064) 1.33
Li 2020 0.309 (0.227-0.391) 1.27
Lodise 2018 0.235 (0.223-0.247) 1.34
Makris 2018 0.205 (0.078-0.332) 1.19
Markou 2003 0.143 (-0.007-0.293) 1.14
Michalopoulos 2005 0.186 (0.070-0.302) 1.21
Moghadam 2018 0.490 (0.393-0.587) 1.25
Mosaed 2018 0.545 (0.251-0.840) 0.79
Nandha 2013 0.188 (0.052-0.323) 1.17
Nazer 2015 0.393 (0.292-0.495) 1.24
Ozel 2019 0.525 (0.398-0.653) 1.19
Özkarakaş 2017 0.696 (0.576-0.817) 1.20
Papadimitriou-Olivgeris 2019 0.281 (0.222-0.339) 1.31
Petrosillo 2014 0.127 (0.076-0.177) 1.32
Porwal 2014 0.120 (0.030-0.210) 1.26
Pourheida 2019 0.500 (0.255-0.745) 0.90
Quintanilha 2019 0.490 (0.393-0.587) 1.25
Ramasubban 2008 0.044 (-0.016-0.105) 1.31

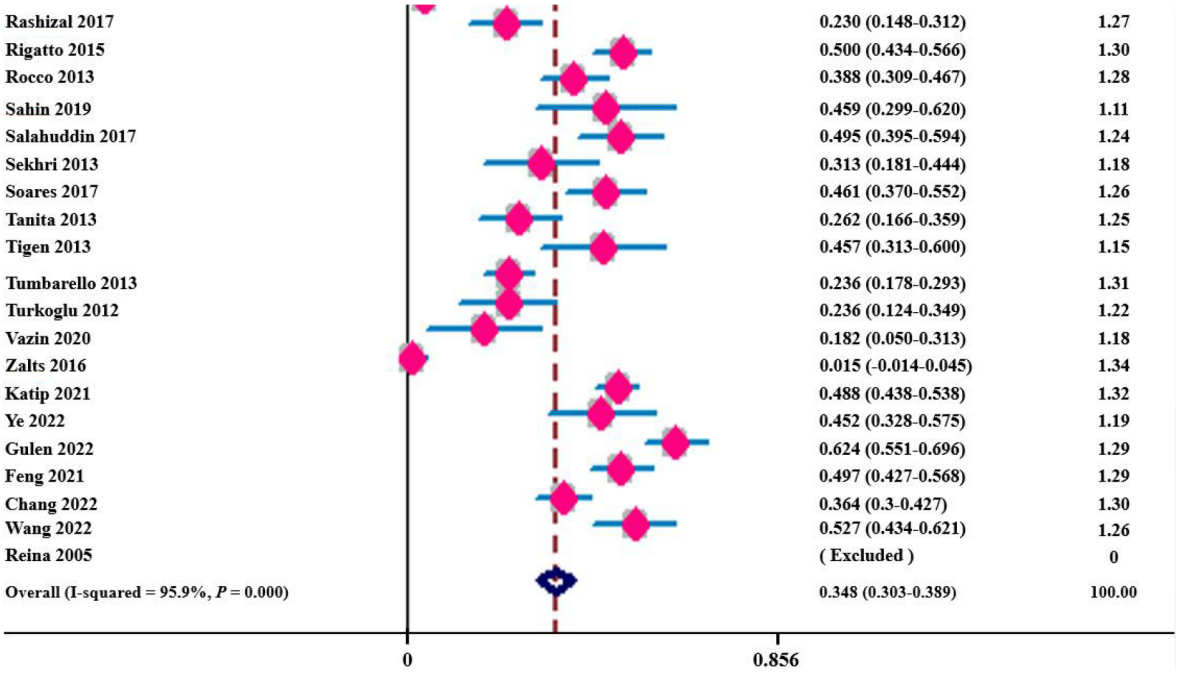


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Figure 2 Forest plot portraying pooled incidence of polymyxin-induced nephrotoxicity.

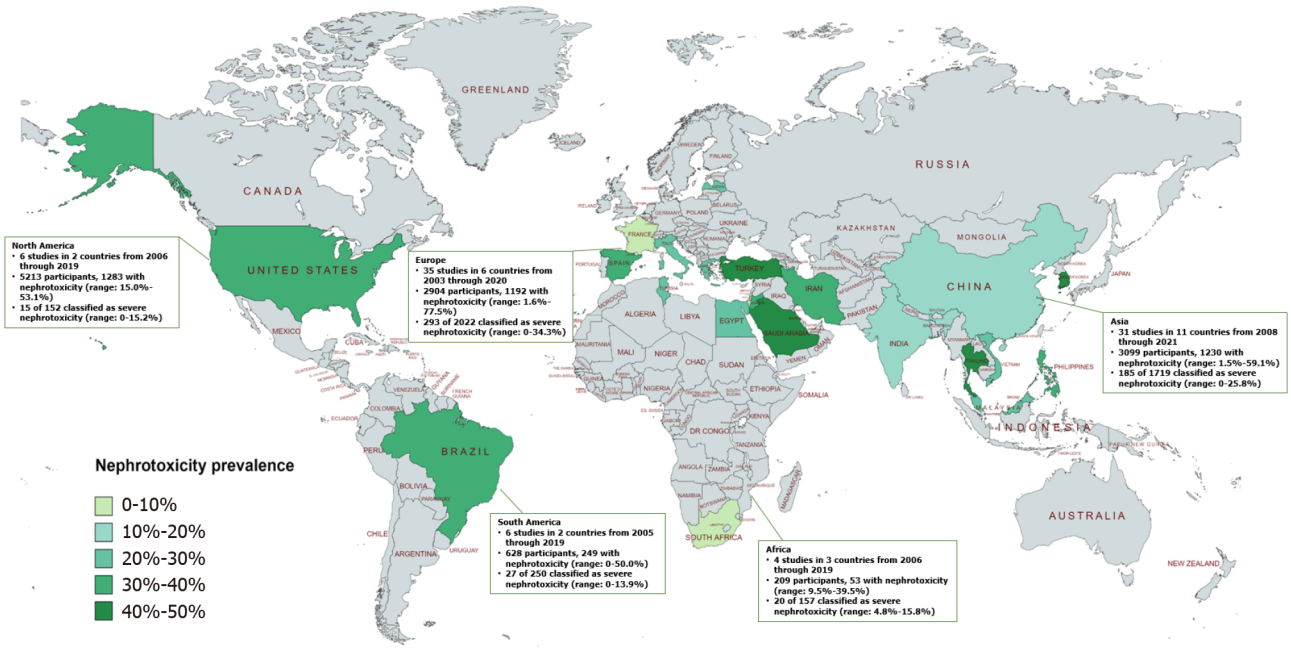

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Figure 3 World map of nephrotoxicity prevalence.

with concomitant vasopressor use showed a 3-fold higher risk of nephrotoxicity than that in patients without sepsis (OR = 3.099; 95%CI, 1.169-8.219), which indicates that prompt treatment of sepsis and timely withdrawal of vasoactive drugs may be potential protective factors against polymyxin-induced nephrotoxicity. Sepsis is the most common aetiology of AKI in critically ill patients[113,114]. Multiple pathophysiological pathways of sepsis-associated AKI have been shown to be involved in the complex mechanism of polymyxin-induced damage in renal tubular cells[113-115].

Moreover, interactions between polymyxins and the cell membrane are also responsible for nephrotoxicity due to the amphipathic nature and accumulation of polymyxins in renal proximal tubular cells [116,117]. Therefore, nephrotoxicity caused by polymyxins has been reported to vary with pharmacokinetics and renal disposal mechanisms. Colistin methane sulfonate is a prodrug with approximately

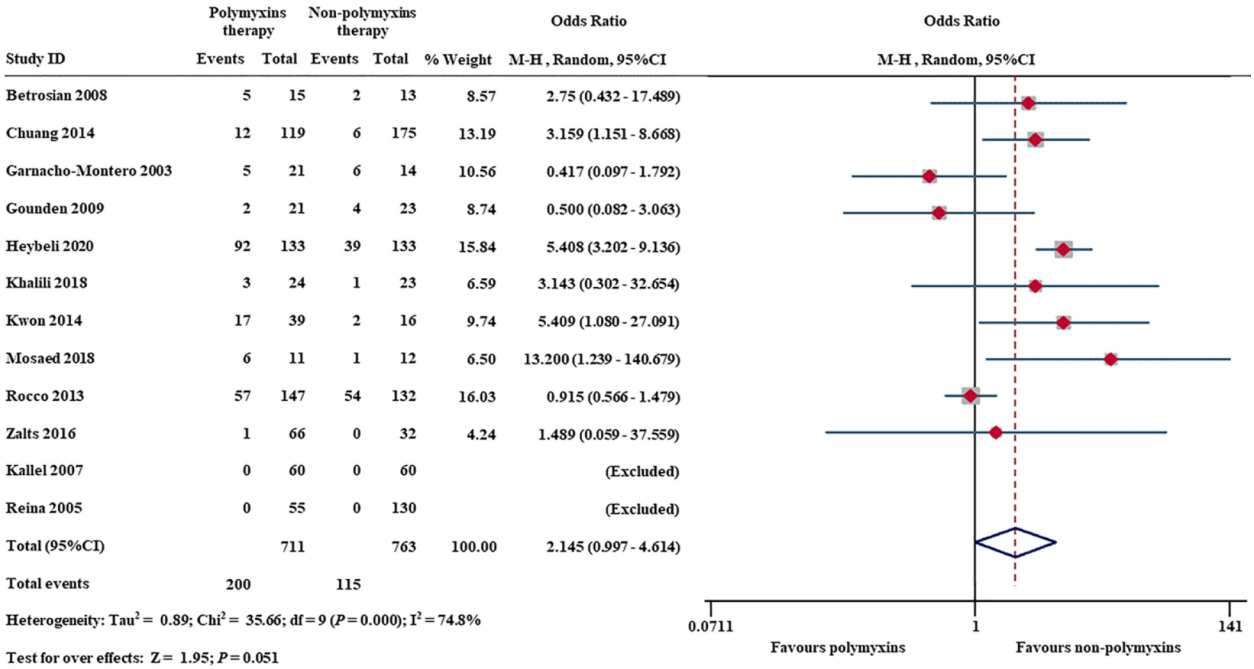

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Figure 4 Forest plot of nephrotoxicity rates in patients receiving polymyxins compared to patients receiving other regimens.

40%-70% of the dose excreted in urine and ongoing conversion to colistin in the kidneys and bladder [118]. PMB is eliminated mainly by the nonrenal pathway with very low urinary recovery (approximately 4%)[7]. In our study, the prevalence of colistin-induced nephrotoxicity (35.5%; 95%CI, 31.1%-39.8%) was slightly higher than that of PMB-induced nephrotoxicity (26.8%; 95%CI, 17.1%-36.4%) without statistical significance (P = 0.151), similar to previous results[11-13]. Conversely, we found that nephrotoxicity was significantly increased when the total daily dose was divided into 2 doses but not 3 or 4 doses. Manchandani *et al*[119] emphasized that the steady-state trough concentration ($C_{ss\ trough}$) and average plasma concentration ($C_{ss\ avg}$) were higher in those receiving a dosing regimen of Q12H than in those receiving a dosing regimen of Q8H, which were confirmed as independent risk factors for nephrotoxicity[120], and it was demonstrated that a higher baseline estimated glomerular filtration rate was associated with a reduced risk of AKI (Table 3). This partly explains why hypoalbuminemia was also a risk factor for polymyxin-induced nephrotoxicity in our and previous meta-analyses[12]. Zavascki *et al* [121] indicated that plasma protein binding of PMB was higher in critically ill patients (ranging from 78.5% to 92.4%) than in healthy participants (approximately 50%). Hence, unbound plasma concentrations of PMB increased, and extensive accumulation of PMB inside tubular epithelial cells may, at least in part, explain the potential nephrotoxicity in critically ill individuals. Accordingly, albumin infusion was described to play a potential nephroprotective role in critically ill patients[122].

In addition, megalin, a crucial endocytic receptor highly expressed in the apical membranes of proximal renal epithelial cells, has been implicated in contributing to the nephrotoxicity of polymyxins [123]. Megalin plays a dual role in AKI, initially mediating nephrotoxins (*e.g.*, polymyxin, vancomycin, aminoglycosides, *etc.*) in proximal renal epithelial cells, which induce the development or progression of AKI and mediate a variety of endogenous substances (*e.g.*, vitamins and proteins, *etc.*) involved in AKI recovery[124]. Therefore, we speculated that megalin would be saturated by a variety of nephrotoxic drugs, such as aminoglycosides, vancomycin, and other nephrotoxins, leading to insufficient uptake of endogenous nephroprotective substances and increased nephrotoxicity. This is supported by a previous study in which polymyxin nephrotoxicity increased with the number of concomitant nephrotoxins[13]. In the present meta-analysis, vancomycin exposure significantly increased the odds of nephrotoxicity (OR = 2.110; 95%CI, 1.190-3.730; P = 0.011).

Some limitations should be considered in the interpretation of the findings of the current meta-analysis. First, although we established strict inclusion and exclusion criteria for the literature, our meta-analysis revealed high heterogeneity, which is a common concern in epidemiological meta-analyses[125] and is consistent with a previous systematic review that estimated the prevalence of polymyxin-induced nephrotoxicity in the general population[10-13]. The high between-study variability was associated with a single cohort in most studies and influenced to a greater extent by other factors, such as the numbers of enrolled patients, study quality and heterogeneous nephrotoxicity criteria. Then, we performed subgroup analyses and a meta-regression analysis to identify potential heterogeneity factors, and the multivariable meta-regression analysis explained almost 40% of the observed heterogeneity (Table 3). Moreover, to weaken the effects of diagnostic criteria on outcomes, we explored the incidence and

severity of polymyxin-induced nephrotoxicity using only the RIFLE criteria, but high heterogeneity remained, in accordance with a previous study[12]. AKI in critically ill patients is a complicated heterogeneous syndrome[113]; hence, inconsistency among patient populations was also a potential source of heterogeneity.

Second, to comprehensively evaluate the incidence of polymyxin-associated nephrotoxicity, we made an effort to include all relevant studies, including not only studies in ICU patients but also those including subgroups of ICU patients[76,79,80,89,96,103] in this analysis. Nevertheless, it is possible that some potentially eligible studies were not captured by our search strategy. Third, during the pooled prevalence meta-analysis, zero-event studies were automatically excluded. Although this strategy is widely accepted, there is no consensus concerning whether it is the most reliable methodology, and the effect on pooled estimates is unclear. In addition, considering the limited data, other potential risk factors for polymyxin-induced nephrotoxicity that we could not capture may exist. For the above reasons, our findings should be interpreted with caution, and further studies are required to strengthen our results.

CONCLUSION

In conclusion, the present meta-analysis showed that the prevalence of nephrotoxicity during polymyxin treatment in the ICU was 34.8%, similar to that in the non-ICU setting, but the incidence of severe renal injury was higher in ICU patients. Older age (particularly > 65 years), the presence of sepsis or septic shock, hypoalbuminemia and concomitant vancomycin or vasopressor use were potential independent predictors of nephrotoxicity. Furthermore, a dosage regimen of 3 or 4 doses per day and dosage adjustment of colistin based on the renal baseline estimated glomerular filtration rate were associated with lower nephrotoxicity rates. Therefore, it is beneficial to adjust colistin doses in critically ill adult patients with renal impairment.

ARTICLE HIGHLIGHTS

Research background

The prevalence of and risk factors for polymyxin-associated nephrotoxicity in intensive care unit (ICU) adult patients remain unclear.

Research motivation

The incidence of nephrotoxicity among polymyxin-treated patients is common and is one of the reasons why the use of polymyxins has been restricted. Nevertheless, the prevalence of and potential risk factors for polymyxin-induced nephrotoxicity in adult ICU patients are controversial. Therefore, a meta-analysis was carried out to assess the prevalence of and potential risk factors for polymyxin-induced nephrotoxicity.

Research objectives

This study aimed to meta-analyse reports evaluating the prevalence and potential predictors of polymyxin-induced nephrotoxicity in adult ICU patients.

Research methods

We performed a systematic literature search in PubMed, EMBASE, the Cochrane Library and RCA database from inception to May 30, 2022 and included eligible randomized clinical trials and observational studies in a meta-analysis evaluating the prevalence and potential predictors of polymyxin-induced nephrotoxicity in adult ICU patients.

Research results

The overall pooled incidence of polymyxin-induced nephrotoxicity was 34.8%. Older age (particularly > 65 years), the presence of sepsis or septic shock, hypoalbuminemia and concomitant vancomycin or vasopressor use were risk factors for polymyxin-induced nephrotoxicity. In addition, our findings showed that a dosage regimen of 3 or 4 doses per day and dosage adjustment of colistin based on the renal baseline estimated glomerular filtration rate were associated with a lower nephrotoxicity rate.

Research conclusions

The incidence of polymyxin-induced nephrotoxicity was high in ICU adult patients. Patients with older age, the presence of sepsis or septic shock, and a decreased baseline glomerular filtration rate had a potentially higher risk of polymyxin-induced nephrotoxicity. A polymyxin dosage regimen of 3 or 4 doses per day, dosage adjustment of colistin based on the renal baseline estimated glomerular filtration

rate, and avoidance of other nephrotoxic drugs (vancomycin or vasopressors) were helpful in decreasing the risk of polymyxin-induced nephrotoxicity.

Research perspectives

Exploring alternative treatments in patients with clinical or microbiologic carbapenem-resistant gram-negative bacterial infection treatment failures is required in the future to increase treatment efficacy and reduce adverse outcomes.

FOOTNOTES

Author contributions: Wang JL acquisition of data, analysis and interpretation of data, drafting the article, final approval; Xiang BX acquisition of data, final approval; Song XL acquisition of data, final approval; Que RM acquisition of data, final approval; Zuo XC critical revision, final approval; Xie YL conception and design of the study, critical revision, final approval.

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P-Editor: Liu JH

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