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Effect of N-acetylcysteine on antimicrobials induced nephrotoxicity: a meta-analysis

Xianming Qiu[1†], Shenao Yang[2†], Yuke Zhang[1], Quanzhen Wang[1], Li Kong[3*] and Lei Zhou[3*]

Abstract

Objective N-acetylcysteine (NAC) has antioxidant effects in reducing acute kidney injury. This study systematically reviewed and assessed the efficacy of NAC in preventing antimicrobials induced nephrotoxicity.

Methods Pubmed, Embase, Web of Science, and the Cochrane Library were searched extensively for relevant studies that evaluating NAC on antimicrobials induced nephrotoxicity until June 1, 2024. Eligible records were screened according to the inclusion and exclusion criteria. The odds ratio (OR) was selected to evaluate the effect of NAC on nephrotoxicity. We pooled the extracted data using a random effects model.

Results Three randomized controlled trials were included in the analysis. The pooled results showed that NAC could reduce the incidence of antimicrobials induced nephrotoxicity (OR = 0.487, 95% CI = 0.258, 0.918, $P = 0.03$, $I^2 = 0\%$). Serum creatine (Scr) on Day 2 was significantly decreased in the NAC group compared to the placebo group (SMD, − 0.298; 95%CI, − 0.585 to − 0.010; $I^2 = 23\%$; $P = 0.04$). No difference was observed in blood urea nitrogen (BUN), and creatinine clearance (CrCl).

Conclusion In this meta-analysis, NAC was associated with a benefit in the prevention of antimicrobials induced nephrotoxicity. However, large-scaled and well-designed RCTs are required in the future.

Keywords N-acetylcysteine, Antimicrobials, Nephrotoxicity, Meta-analysis

Introduction

Antimicrobials are commonly used in clinical practice to treat various infectious diseases. In accordance with the Surviving Sepsis Campaign guidelines, clinicians are encouraged to administer early, broad-spectrum anti-infective regimens to patients diagnosed with sepsis [1]. The guidelines posit that prompt diagnosis (within one hour) and prompt application of effective antimicrobials can increase patient survival by 7.6% [2, 3]. Nevertheless, the administration of antimicrobials is accompanied by the potential for adverse effects, including nephrotoxicity, which is defined as kidney injury resulting from the administration of pharmaceutical agents or toxic substances. Antimicrobials induced nephrotoxicity has the potential to result in acute kidney injury [4] (AKI), prolonged hospitalization, and elevated healthcare costs [5, 6].

It has been established that several classes of antibiotics have the potential to cause nephrotoxicity. These include aminoglycosides, vancomycin, fluoroquinolones, and beta-lactams [7]. Aminoglycosides are known to have nephrotoxicity, particularly in patients with pre-existing renal impairment or those receiving prolonged courses

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of treatment [8]. Vancomycin induced nephrotoxicity has been linked to the development of interstitial nephritis and acute tubular necrosis [8]. Fluoroquinolones have been associated with an elevated risk of nephrotoxicity, particularly in older adults and those with preexisting kidney disease [8]. Beta-lactams, including penicillins and cephalosporins, have been demonstrated to induce nephrotoxicity through a range of mechanisms, including interstitial nephritis, acute tubular necrosis, and crystal nephropathy [8]. Despite the implementation of various strategies to prevent nephrotoxicity, the occurrence of antimicrobials induced AKI remains a common phenomenon.

N-acetylcysteine (NAC) is a frequently prescribed antioxidant agent that has demonstrated favorable renoprotective outcomes in numerous researches [9, 10]. NAC has been reported to attenuate oxidative stress and inflammation, improve renal function, and protect against nephrotoxic injuries in both experimental animal models [11] and clinical setting [12, 13].

Although NAC may reduce the incidence of AKI in patients with cardiac surgery [14] and contrast administration [12], the absence of randomized clinical trials present a significant challenge in evaluating its efficacy in patients recieving antimicrobials. Therefore, we conducted a systematic review and meta-analysis to assess the impact of NAC administration on clinical outcomes in patients with antimicrobials compared with placebo.

Methods

The systematic review and protocol were registered with the PROSPERO registry (CRD 42024534827) in accordance with the relevant guidelines. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline [15].

Search strategy and Study selection

A comprehensive search of the Pubmed, Embase, Web of Science, and Cochrane library databases was conducted for randomized clinical trials (RCTs) published from the inception of the databases until June 1 2024. In order to be included in the review, studies had to be conducted in adults, published in English, and have compared NAC with placebo or a control for the prevention of nephrotoxicity in the setting of antimicrobial administration.

The following combination of terms are provided: "N-acetylcysteine," or "NAC"; and "nephrotoxicity," "acute kidney injury," "acute kidney failure," "acute renal failure," "acute renal injury," "acute kidney insufficiency," "acute renal insufficiency," "acute renal dysfunction," "acute kidney dysfunction," or "AKI."

Two independent reviewers (XMQ and SAY) conducted a preliminary screening of titles and abstracts to determine their eligibility. Subsequently, the reviewers conducted a second screening of the full-text articles to confirm their eligibility. Any discrepancies were resolved through discussion and consensus.

Studies were included if they align with the following criteria: (1) studies evaluating the effects of NAC treatment on nephrotoxicity; (2) nephrotoxicity incidence reported in each group in the included studies; (3) studies on nephrotoxicity from antimicrobials; The exclusion criteria were as follows: (1) Studies lacking sufficient data; (2) Case reports, reviews, newspaper articles, editorials/commentaries, theses, or congress abstracts; (3) In vitro studies and studies on animal models; (4) Studies on nephrotoxicity from non-antimmicrobials. To ensure the reliability of the results, two independent researchers conducted the search and identification processes.

Data extraction

A data extraction protocol was developed by an independent reviewer and subsequently modified based on feedback from the other investigators. The following information was extracted from all included studies: study characteristics, setting of antimicrobial administration, definition of nephrotoxicity, sample size, characteristics of the study population, dose and route of NAC, incidence of nephrotoxicity, serum creatinine level (SCr), blood urea nitrogen (BUN), and creatinine clearance (CrCl).

Assessment of bias risk of the included studies

The potential for bias in the included randomized controlled trials (RCTs) was evaluated by two independent reviewers. The Cochrane Risk of Bias (RoB) 2.0 tool was used to assess the risk of the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and the overall RoB for each study [16].

Jadad scale was used to assess the risk of bias [17]. The first term is related to the randomization of samples with the appropriate method (the score range is 0–2). The second term is related to the two-way blinding of the study (score range 2–0). The third term is related to the mention of the number and reasons for the drop in samples (score range 0–1). The overall score of the scale is 5 points according to all these statements. A Jadad score of less than 3 indicates poor study quality and a score greater than or equal to 3 indicates good study quality [18].

Statistical analysis

Outcomes were treated as dichotomous or continuous variables. The association between NAC and nephrotoxicity was assessed using odds ratios (OR) with 95% confidence intervals (CI), while standard mean differences (SMD) with 95% CI were used to evaluate the impact of NAC on Scr, BUN, and CrCl. The presence of significant statistical heterogeneity was determined by evaluating the I^2 statistic, with values exceeding 50% indicating substantial heterogeneity. The association size was calculated and presented using a random effects model, as described by DerSimonian and Laird. Sensitivity analyses were conducted to test the robustness of the overall pooled effect. The presence of publication bias was evaluated using a funnel plot. All comparisons were two-sided, and a $P<0.05$ was considered statistically significant. All analysis was conducted with R software [19].

Results

Search results and study characteristics

An electronic database search yielded 1189 citations, of which 402 were duplicates. Consequently, the total number of abstracts and titles subjected to screening was 787. This resulted in the exclusion of 770 records and the screening of 17 full texts for eligibility. Following this process, 14 trials were excluded from the 17 studies identified. Two articles [20, 21] were produced by the same research team during the same time period. However, one of the articles from the limited sample was excluded due to its methodological deficiencies. Consequently, three studies [20, 22, 23] were included for analysis (Fig. 1). All studies in the data synthesis were RCTs with two arms (NAC and control groups), comprising a total of 315 patients: 154 in the NAC group and 161 in the control group. Details are available in Table 1.

Risk of bias assessment and publication bias of the included studies

A summary of the risk of bias in the included studies is presented in Fig. 2. There is no significant publication bias of mortality (Fig. 3, $P=0.117$ for the Begg's test, $P=0.225$ for the Egger's test).

The incidence of antimicrobials induced nephrotoxicity

Three studies [20, 22, 23] reported the incidence rate of nephrotoxicity. The data from the trials showed that there was a significant difference in the incidence of nephrotoxicity between the NAC groups and the controlled groups

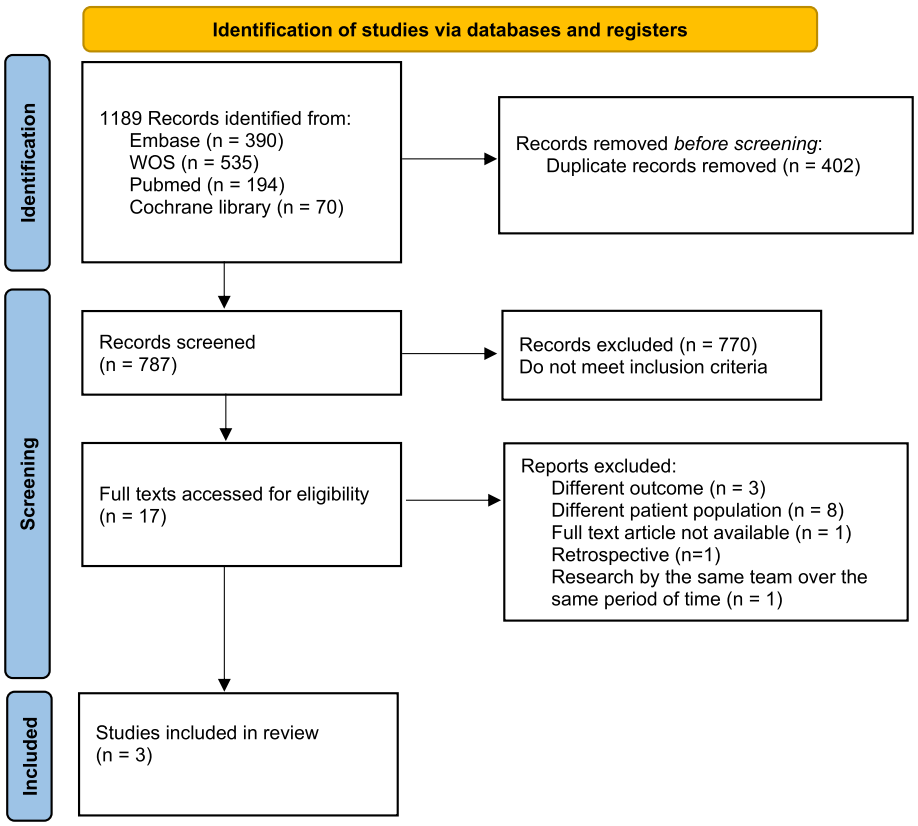

Fig. 1 Study flowchart

Table 1 Summary characteristics of the included studies

Author, year	Number of participant (NAC/Placebo)	Drug	Intervention (NAC)	Nephrotoxicity assessment	Nephrotoxicity incidence (NAC/Placebo, %)	Jadad score
Karimzadeh et al, 2015 [20]	27/27	amphotericin B	600 mg oral twice daily during the treatment course	Decline in estimated ClCr (≥ 50% calculated by the Cockcroft-Gault formula) or increases in Scr (doubling from the baseline)	34.78/65.22	4
Badri et al, 2020 [22]	84/95	vancomycin	600 mg oral every 12 h for 10 days	≥ 0.5 mg/dL or at least 50% increase in Scr from baseline	4.76/12.63	5
Mosayebi et al., 2021 [23]	43/39	colistin	600 mg twice daily simultaneously with colistin for 10 days	KDIGO definition and classification	18.6/28.2	5

NAC N-acetylcysteine, *ClCr* creatinine clearance, *Scr* serum creatinine, *KDIGO* Kidney Disease Improving Global Outcomes

KDIGO definition and classification of AKI were used as follows: stage 1, an increase in SCr equal to 0.3 mg/dl or more within 48 h or an increase in SCr ≥ 1.5–2 times the baseline (initial) value within 7 days; Stage 2, an increase in SCr ≥ 2–3 times the baseline value within 7 days; and Stage 3, an increase in SCr ≥ 3 times the baseline value within 7 days [24]

(OR = 0.487, 95%CI = 0.258, 0.918, $P = 0.03$, $I^2 = 0\%$) as shown in Fig. 3A.

As the antimicrobials included in the study were not identical, a sensitivity analysis was conducted using a case-by-case exclusion method. The sensitivity analysis revealed that the meta-analysis model was not stable (Fig. 4B).

Effect of NAC on Scr, BUN, and CrCl

Two studies [22, 23] reported serum biomarkers among all included patients. NAC treatment was associated with decreased Scr on Day 2 (SMD, − 0.298; 95%CI, − 0.585 to − 0.010; I2 = 23%; $p = 0.04$) (Fig. 4A). No significant difference was found for BUN and CrCl between the NAC and the controlled groups as depicted in Fig. 5.

Discussion

This systematic review and meta-analysis evaluated the effect of NAC in three RCTs. They found that NAC treatment significantly reduced incidence of antimicrobials induced nephrotoxicity (including colistin, vancomycin, and amphotericin B). Meanwhile, NAC treatment reduced Scr levels on Day 2.

Medication-induced nephrotoxicity accounts for about one-fourth of all acute kidney injury (AKI) cases among hospitalized patients [25, 26]. It is well established that antibiotics and other antimicrobials are among the most commonly implicated medications in the development of AKI [8]. These agents have been identified as significant contributors to structural and functional renal impairment. A multiplicity of mechanisms has been delineated, though the most prevalent are acute interstitial nephritis [27], acute tubular necrosis [28], intratubular crystal deposition, and proximal/distal tubulopathy with electrolyte wasting abnormalities [7]. Therefore, the utilization of specific anti-inflammatory and antioxidant pharmaceutical agents to avert antibiotic-associated nephrotoxicity represents a crucial strategy [29].

Acute tubular necrosis (ATN) is recognized for the mechanism of antimicrobials associated with nephrotoxicity [25]. ATN refers to cellular deterioration and sloughing of the proximal and distal basement membranes. Damaged mitochondria lead to cytotoxicity in the tubules, a disrupted tubular transport mechanism and an increase in oxidative stress caused by the production of free radicals [25]. NAC exhibits its antioxidant property in several ways, including interaction with the electrophilic groups of reactive oxygen species (ROSs) and acting as a precursor to glutathione (GSH) [30]. The deleterious effects of oxidative stress and the beneficial impact of NAC have been substantiated in sepsis [31], reperfusion-ischemia [32], and drug-induced nephrotoxicity [33].The biological functions of NAC are strongly associated with the pathogenesis of antimicrobials-induced nephrotoxicity. Given the inconsistency of results observed across multiple clinical trials investigating the efficacy of NAC in reducing nephrotoxicity [20, 34], we conducted a systematic review and meta-analysis to gain further insight into this area of research.

The pooled data of RCTs revealed that NAC co-administration significantly affected the incidence of nephrotoxicity when compared with the control group. Of note, the credibility of study may be compromised by small sample sizes and the different antimicrobials

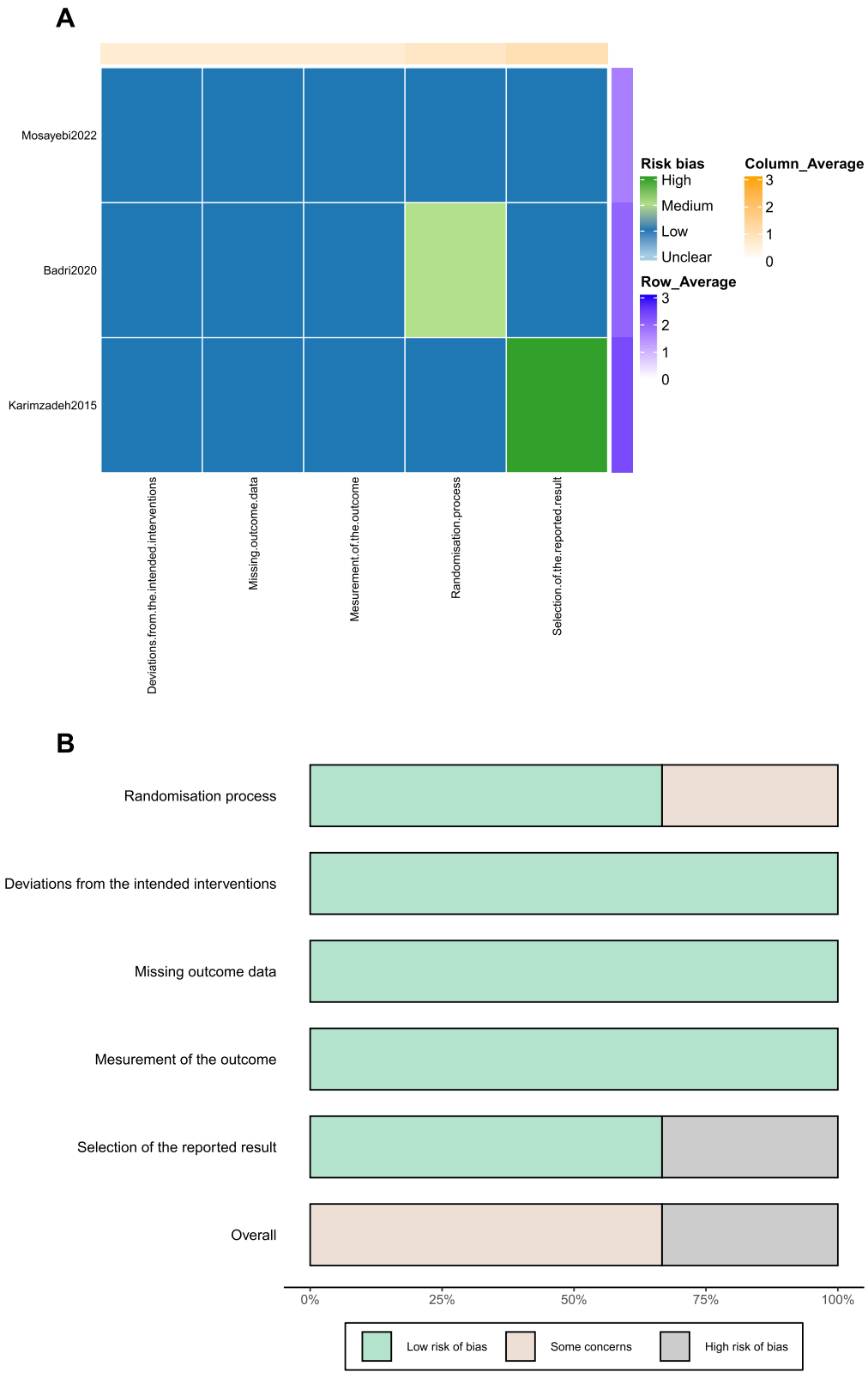

Fig. 2 Risk of bias assessment

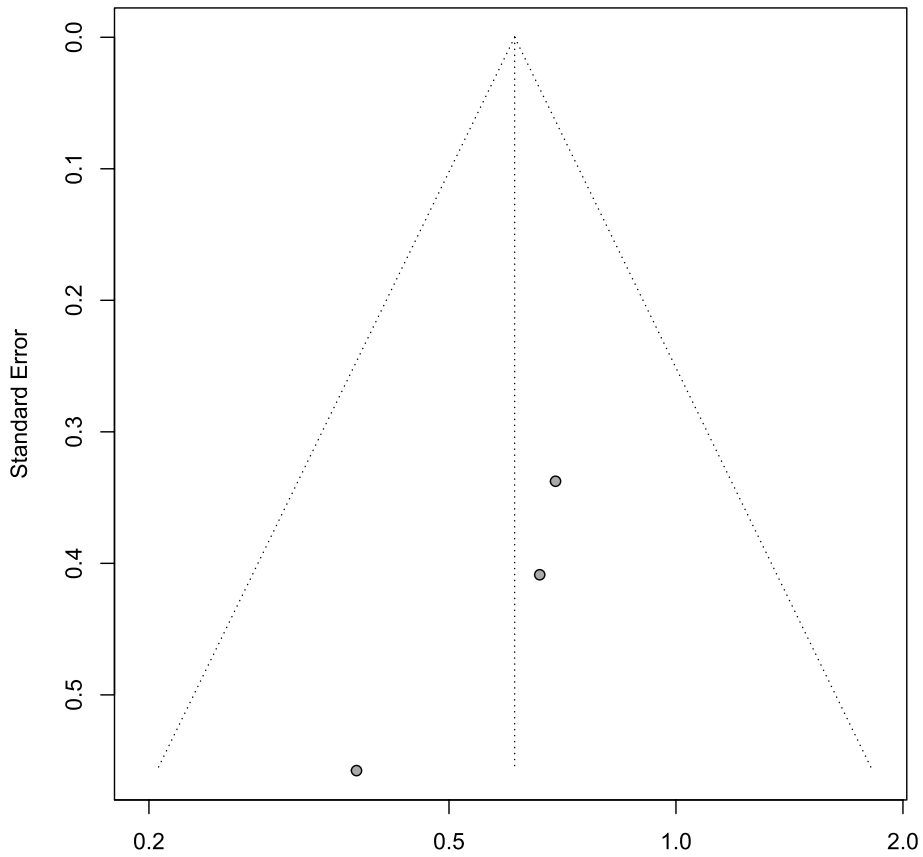

Fig. 3 Funnel plot

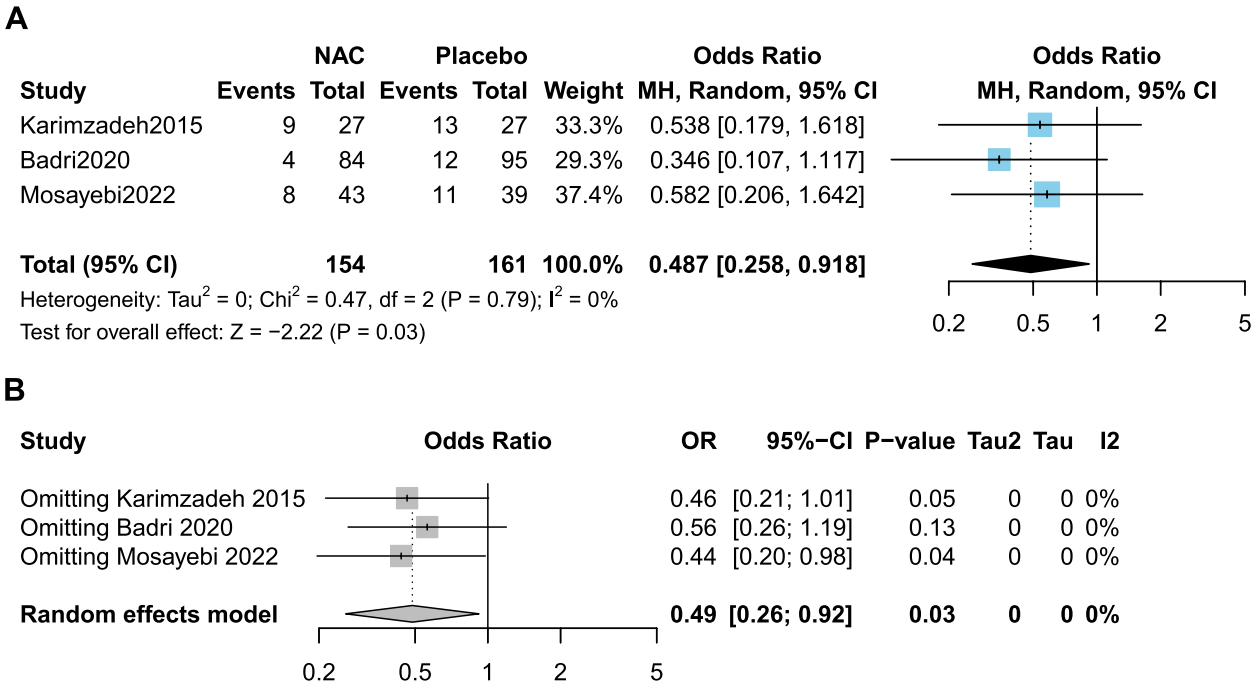

Fig. 4 The effects of NAC on the incidence of nephrotoxicity. **A** Forest plot of the incidence of nephrotoxicity between NAC and controlled groups. **B** Sensitivity analysis

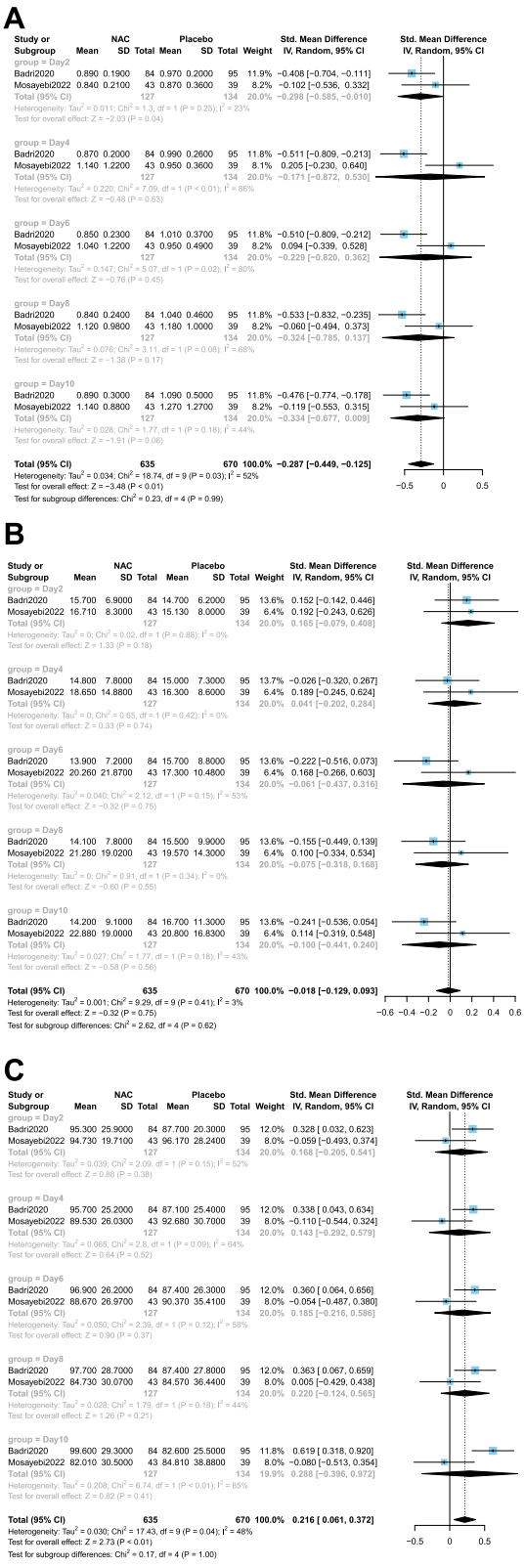

Fig. 5 Forest plot of the effects of NAC on the serum biomarkers. **A** Forest plot of Scr. **B** Forest plot of BUN. **C** Forest plot of CrCl

drugs. Concomitantly, with limited information, there were no meaningful alterations in serum biomarkers including Scr and BUN.

A large amount of evidence suggest that NAC plays an important role in improving renal function [12, 31, 32]. Most NAC studies have focused on protection against contrast-induced renal damage, but previous reports show inconsistent findings [12, 14]. A previous study has revealed that NAC supplement could alleviates the progression in chronic kidney disease [35]. In animal studies, NAC, as an effective antioxidant, dramatically reduced the production of ROS, and decreased oxidative stress in kidney [36, 37]. Ceylan et al. found that the rats treated with 300,000 IU/ kg/day colistimethate sodium for 10 days exhibited notable increases in Cr and urine N-acetyl-β-D-glucosaminidase (NAG) levels, while no significant changes were detected in serum Cr in the NAC group [38]. It is noteworthy that NAC was able to reverse the adverse effects of colistin, as evidenced by an increase in the apoptosis index and renal histological damage score, as well as a reduction in renal expression levels of eNOS, SOD2, and matrix metalloproteinase (MMP) [38]. Further basic research is needed to understand precisely how NAC preserves renal function in the setting of antibiotic-associated nephrotoxicity.

NAC has been proved safety in clinical therapy. However, Karimzadeh et al. reported the adverse reaction (new onset unpleasant taste and nausea/vomiting) incidence was significantly higher than those received placebo (51.85 vs 3.7%, respectively; $p < 0.001$) [20]. The adverse effects associated with the use of NAC are somewhat dependent on the route of administration [39].

It is important to note the limitations of the present study. Firstly, the number of included studies and sample size were insufficient for us to perform further subgroup analysis. Fortunately, one RCT of NAC on colistin nephrotoxicity is recruiting patients in Iran (IRCT20200328046886N5). Secondly, it is important to note that data for different drugs were combined in the current study. This raises the question of whether all drugs cause kidney damage in the same way. Further evidence is needed to verify these issues. Thirdly, for the limited information of some potential methodological and clinical confounding factors, such as underlying disease, and drug use, we were unable to take all factors into account. Finally, the definitions of nephrotoxicity varied across the included studies. All of these factors may influence the results of our study. More well-designed studies are required to evaluate these factors.

Conclusions

Limited evidence suggests that NAC has been shown to reduce antimicrobial related nephrotoxicity, making it a valuable tool for clinicians to consider for use. Further research is required in the form of large-scale RCT to confirm these promising findings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04037-y.

Additional file 1.

Acknowledgements
It was registered with the PROSPERO registry (CRD 42024534827) .

Authors' contributions
Xianming Qiu and Lei Zhou initiated the study and participated in its design. Xianming Qiu, Yuke Zhang, Quanzhen Wang and Shenao Yang were responsible for the study selection, data extraction and analysis. Xianming Qiu and Lei Zhou wrote the manuscript. Li Kong oversawed all aspects of the study. All of the authors contributed to the article and provided their approval for the submitted version.

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Data availability
The study contains original contributions that are included in the article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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