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Efficacy and safety of clarithromycin for patients with sepsis or septic shock: a systematic review and meta-analysis

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Abstract

Background: Clarithromycin exerts an immunomodulatory role in several human diseases. However, whether this effect improves the prognosis in patients with sepsis remains controversial, and higher levels of clinical evidence are urgently needed. To the best of our knowledge, no meta-analysis to date has reported the clinical efficacy and safety of clarithromycin in sepsis.

Methods: A comprehensive literature search of PubMed, EMBASE, and the Cochrane Library was conducted up to December 31, 2022. Only randomized controlled trials comparing the clinical efficacy and safety of clarithromycin with controls among patients with sepsis or septic shock were included. Data were pooled by applying a fixed-effects model and a relative risk (RR) estimate with 95% confidence intervals (CIs) using Review Manager (version 5.3; Cochrane Collaboration, Copenhagen, Denmark).

Results: Three randomized controlled trials involving a total of 910 patients were included. The pooled results confirmed that clarithromycin had no beneficial effect on progression to multiple organ dysfunction syndrome (RR: 1.51; 95% CI: 1.02–2.25; $P = 0.04$; $I^2 = 0\%$), 28-day mortality (RR: 1.09; 95% CI: 0.87–1.36; $P = 0.46$; $I^2 = 0\%$), and 90-day mortality (RR: 0.86; 95% CI: 0.71–1.03; $P = 0.10$; $I^2 = 81\%$) in patients with sepsis or septic shock. Moreover, there was no difference in other serious adverse events between patients who received clarithromycin and those in the control group (RR: 1.02; 95% CI: 0.87–1.19; $P = 0.83$; $I^2 = 18\%$).

Conclusion: Our meta-analysis did not reveal an improvement to short-term outcomes in patients with sepsis treated with clarithromycin. However, administration of clarithromycin did not increase the risk of adverse events.

Keywords: Clarithromycin, Meta-analysis, Outcomes, Sepsis, Septic shock

Introduction

The latest definition of sepsis is a dysregulated host response to infection that leads to life-threatening organ dysfunction.[1] According to the Global Burden of Disease Study,[2] there were approximately 11 million sepsis-related deaths in 2017. Although there were decades of attempts to develop effective treatments for sepsis, no encouraging results have been reported.[3] As of now, the treatment of sepsis is limited and includes source control, fluid resuscitation, and monitoring of organ dysfunction.[4] Therefore, a deeper understanding of the pathogenesis and pathophysiology of sepsis may be essential to improving the treatment and prevention of sepsis.

Effective antibiotic therapy is a decisive factor in improving the high mortality rate of sepsis and septic shock. Although the exact timing of early antibiotic initiation in patients with sepsis remains controversial internationally, early therapy seems to be one of the accepted guidelines for sepsis treatment.[5] Respiratory infections have become an increasingly significant source of sepsis and are attributable to a variety of factors, including an aging population, increased susceptibility due to immune compromise, pathogen evolution, and rising antibiotic resistance rates.[6] As potent bacteriostatic agents that hinder protein synthesis, macrolide antibiotics exhibit a robust inhibitory effect against *Streptococcus pneumoniae* and play a pivotal role in the management of respiratory infections, particularly community-acquired pneumonia (CAP).[7] Although 2 meta-analyses showed a survival benefit of macrolides in CAP, the intervention groups in these studies received more than 1 macrolide.[8,9] Studies investigating the role of clarithromycin in human diseases have rarely been reported.

Clarithromycin, also known as 6-O-methylerythromycin, TE-031, A-56268, or Biaxin, is a second-generation macrolide antibiotic. It is an erythromycin derivative with a 14-member cyclic semisynthetic

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All data generated or analyzed during this study are included in this published article and its supplementary information files.

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structure. Compared with the first-generation erythromycin, it exhibits advantages such as gastric acid stability, longer half-life, and minimal gastrointestinal adverse reactions. The antibacterial mechanism involves actions on the bacterial 50S ribosomal subunit and inhibition of bacterial protein synthesis by blocking transpeptidation and mRNA displacement.[10] Previous studies have illustrated that clarithromycin, a macrolide antibiotic, not only plays an antibacterial role in *Helicobacter pylori* and *Bordetella pertussis* infections[11,12] but also exerts immune-modulating effects on several human diseases such as coronavirus disease 2019, CAP, and sepsis.[13,14] Kyriazopoulou et al.[15] conducted a retrospective study and found that a combination of clarithromycin and β-lactam significantly improved the 28-day mortality of patients with sepsis compared with those treated with β-lactam monotherapy, which initially demonstrated the potential of clarithromycin to improve sepsis outcomes. However, a recently published multicenter randomized clinical trial (INCLASS study) confirmed that clarithromycin did not reduce the 28-day mortality in patients with sepsis, although it was associated with lower sepsis recurrence.[16] To address the controversial role of clarithromycin in sepsis, higher-level clinical evidence is urgently required. To the best of our knowledge, no meta-analysis has reported the clinical efficacy of clarithromycin in the treatment of sepsis. We performed the current study to investigate the clinical efficacy and safety of clarithromycin in patients with sepsis and septic shock.

Methods

Protocol and registration

Throughout this meta-analysis, we strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses. The PROSPERO registration ID for this study is CRD42022341535.[17]

Retrieval strategy

Systematic retrieval of PubMed, EMBASE, and the Cochrane Library was performed independently by 2 authors (Zhao P and Yao R) for literature on clarithromycin and sepsis up to December 31, 2022.[18] The individual keyword terms were as follows: "sepsis," "Pyemia," "Pyaemia," "Septicemia," "Blood Poisoning," "Severe Sepsis," "Shock, Septic," "Septic Shock," "Shock, Toxic," "Toxic Shock," "Toxic Shock Syndrome," "Shock, Endotoxic," "Endotoxic Shock," "Clarithromycin," "6-*O*-methylerythromycin," "TE-031," "A-56268," and "Biaxin." We also identified and added potential studies by screening the reference lists of similar systematic reviews. The detailed search strategies are shown in Supplemental Table 1, http://links.lww.com/ECCM/A77.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) population: patients with sepsis or septic shock were included in the study using contemporaneous diagnostic criteria, such as Sepsis 2.0[19] and the post-2016 Sepsis 3.0[1]; (2) intervention: clarithromycin was administered via any route or dosage; (3) comparison: placebo or normal saline was used as a comparison; (4) outcomes: survival and adverse effects were measured, whereas other indicators were not limited; and (5) study design: only randomized controlled trials (RCTs) were considered.

The exclusion criteria were as follows: (1) unwillingness to provide informed consent, pregnancy or breastfeeding, presence of malignant tumors, or macrolide allergies; (2) interventions involving drugs other than clarithromycin; (3) insufficient baseline data for patients with sepsis, including sex, age, group status, survival information, and adverse reactions; (4) inadequate elucidation of clinical trial protocols, such as random generation method, blind method setting, and control selection; (5) single-arm uncontrolled studies; and (6) ongoing clinical trials.

Outcomes and quality assessment

The primary outcome was 28-day mortality, and secondary outcomes included 90-day mortality and serious adverse events (SAEs). We used the Jadad scale to evaluate the study quality, and a Jadad score between 3 and 5 points was considered high quality. Furthermore, we applied the Cochrane Collaboration tool to evaluate the risk of bias in the eligible studies.[20]

Data extraction

The reviewers (Zhao P and Yang J) utilized a standardized and predesigned table to independently extract data from all eligible studies. The recorded characteristics of these studies included the first author, publication year, study type, total number of enrolled patients, intervention and comparison methods, and primary outcomes. Inconsistencies in the extracted data were resolved through discussion or consultation with another reviewer (Du X) until consensus was reached.

Statistical analyses

Meta-analyses were conducted using Review Manager (version 5.3; Cochrane Collaboration, Copenhagen, Denmark). The I^2 statistic was calculated to evaluate the heterogeneity of each outcome; an I^2 value greater than 50% indicated significant heterogeneity, and a random-effects model was applied accordingly. Conversely, if the I^2 value was <50%, a fixed-effects model was used. In addition, sensitivity analyses were performed by excluding 1 study at a time to assess the stability of the conclusions. Moreover, we constructed a funnel plot and performed the Egger test to assess publication bias.

Results

Literature search and characteristics of included studies

The database search initially presented 275 pertinent articles (PubMed: 97 articles; EMBASE: 172 articles; Cochrane Library: 6 articles). First, 260 records were eliminated because of case reports, duplicate records, reviews, non-English language, basic experiments, inappropriate interventions, and no comparisons. Second, the remaining 15 clinical studies were analyzed for suitability by perusing the entire text, and 12 were excluded because of inapplicable outcomes, inaccurate intervention, and duplication. Finally, 3 multicenter RCTs with 910 patients were included (Fig. 1).

Table 1 presents detailed characteristics of the included studies.[16,21,22] Notably, the experimental groups in these qualified studies were administered 1 g of clarithromycin daily for 3 or 4 consecutive days. In addition, all eligible studies used 28-day mortality as the primary outcome, whereas the secondary endpoints included progression to multiple organ dysfunction syndrome, time until resolution of ventilator-associated pneumonia, sepsis recurrence, and SAEs.

Primary and secondary outcomes

As presented in Fig. 2, pooled results from RCTs confirmed that clarithromycin had no beneficial effect on 28-day mortality (relative risk [RR]: 1.09; 95% confidence interval [CI]: 0.87–1.36; $P = 0.46$; $I^2 = 0\%$). Moreover, clarithromycin did not show promising results in improving progression to multiple organ dysfunction syndrome (RR: 1.51; 95% CI: 1.02–2.25; $P = 0.04$; $I^2 = 0\%$) and 90-day mortality of patients with sepsis or septic shock (RR: 0.86; 95% CI: 0.71–1.03; $P = 0.10$; $I^2 = 81\%$). We confirmed the stability of our

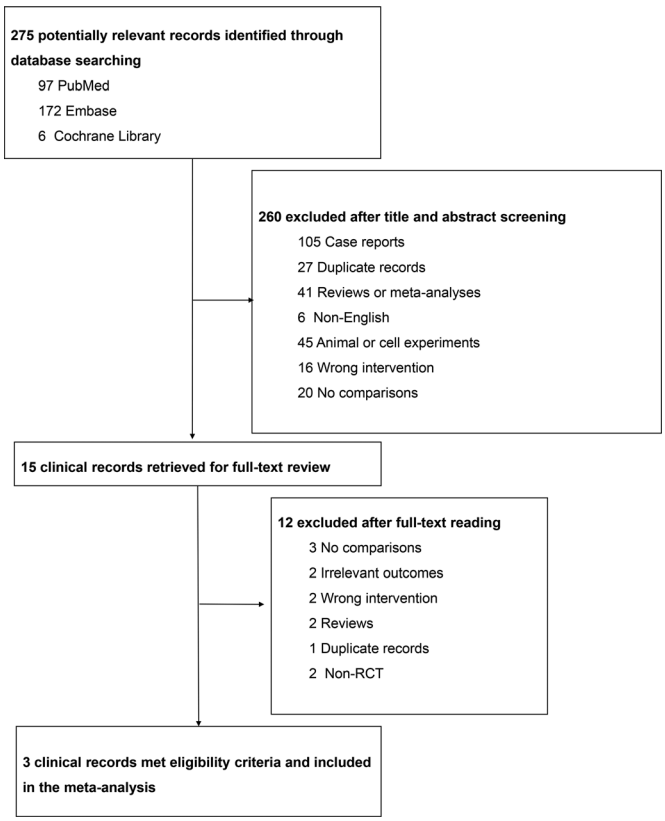

Figure 1. Flowchart for selection process. RCT, randomized controlled trial.

conclusions by conducting a sensitivity analysis that excluded each study individually.

In addition to assessing the clinical efficacy, safety evaluation is an essential component in determining the potential use of a drug for human diseases. Serious adverse events were defined as any unexpected occurrence resulting in death, life-threatening situations, prolonged hospitalization, permanent or significant disability, or grade IV laboratory abnormalities. Sepsis-related organ failure and death were not considered as SAEs. For detailed information on the SAEs from the 3 included studies, refer to Table 2. As presented in Fig. 2D, no difference was noted regarding additional SAE between patients who received clarithromycin and those in the control group (RR: 1.02; 95% CI: 0.87–1.19; $P = 0.83$; $I^2 = 18\%$). Correspondingly, this conclusion is consistent with that of the sensitivity analysis.

Quality evaluation and publication bias

Regarding the quality of the included studies, 2 exhibited a high risk of detection bias because of inadequate blinding in the outcome assessment during the experimental process. The results of the bias assessment are presented in Fig. 3. Furthermore, all the studies included in this meta-analysis scored between 3 and 5 points on the Jadad scale, indicating high quality (Table 3). In addition, a funnel plot was constructed to evaluate potential publication bias for the primary outcomes (Fig. 4), which revealed no evidence of publication bias upon visual inspection (Egger test: $P = 0.73$).

Discussion

Macrolide antibiotics, which are broad-spectrum antibiotics produced by *Streptomyces* and characterized by a basic lactone ring structure, exhibit efficacy against both gram-positive and gram-negative bacteria, particularly *Mycoplasma*, *Chlamydia*, *Legionella*, *Spirochetes*, and *Rickettsia*.[23] Because of their ability to effectively combat various pathogens, macrolides are widely used in the clinical treatment of respiratory tract, gastrointestinal, and maternal infections.[24]

Table 1

Characteristics of Included Clinical Studies

Study	Types of Studies	No. Patients	Patient Types	Intervention		Primary Endpoint	Second Endpoints
				Treatment	Comparison		
Giamarellos-Bourboulis et al.,[21] 2008	Double-blind, multicenter, RCT	200	Clarithromycin group: Male/female = 74/26; sepsis/severe septic/septic shock = 25/33/42 Placebo group: Male/female = 73/27; sepsis/severe septic/septic shock = 26/31/43	Clarithromycin (1 g daily for 3 consecutive days)	Placebo (normal saline)	28-d all-cause mortality	Progression to MODS; time until progression to MODS; time until resolution of VAP; serious adverse events
Giamarellos-Bourboulis et al.,[22] 2014	Double-blind, multicenter, RCT	600	Clarithromycin group: Male/female = 149/153; sepsis/severe septic/septic shock = 177/79/46 Placebo group: Male/female = 121/177; sepsis/severe septic/septic shock = 189/65/44	Clarithromycin (1 g intravenously once daily for 4 consecutive days)	Placebo (equal volume of normal saline)	28-d mortality	Time to resolution of the infection; time to progression to MODS; serious and nonserious adverse events
Karakike et al.,[16] 2022	Double-blind, multicenter, RCT	110	Clarithromycin group: Male/female = 39/16; sepsis/septic shock = 25/30 Placebo group: Male/female = 33/22; sepsis/septic shock = 16/39	Clarithromycin (1 g intravenously once daily for 4 consecutive days)	Placebo (equal volume of normal saline)	28-d all-cause mortality	90-d mortality; sepsis response; sepsis recurrence; serious treatment-emergent adverse events

MODS, multiple organ dysfunction syndrome; RCT, randomized controlled trials; VAP, ventilator-associated pneumonia.

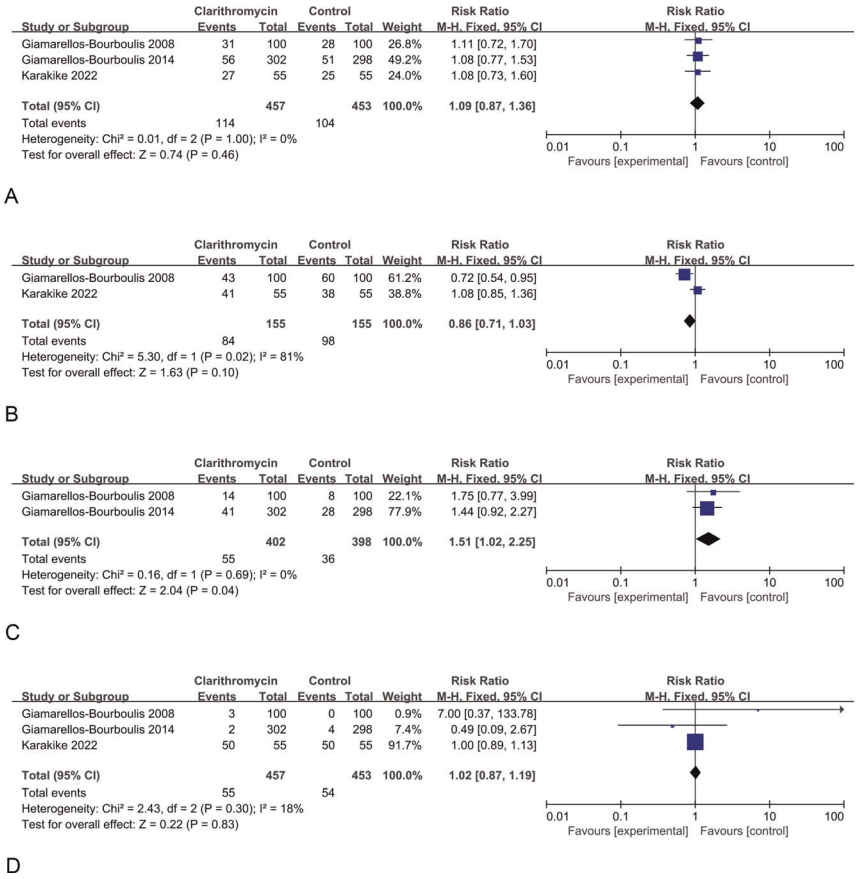

Figure 2. Forest plots for the primary and secondary outcomes. (A) Twenty-eight-day mortality (24.9% vs. 23.0%; RR: 1.09; 95% CI: 0.87–1.36; $P = 0.46$; $I^2 = 0\%$). (B) Ninety-day mortality (54.2% vs. 63.2%: RR: 0.86; 95% CI: 0.71–1.03; $P = 0.10$; $I^2 = 81\%$). (C) Progression to MODS (13.7% vs. 9.0%; RR: 1.51; 95% CI: 1.02–2.25; $P = 0.04$; $I^2 = 0\%$). (D) SAEs (12.0% vs. 11.9%; RR: 1.02; 95% CI: 0.87–1.19; $P = 0.83$; $I^2 = 18\%$). CI, confidence interval; M-H, Mantel-Haenszel; MODS, multiple organ dysfunction syndrome; RR, risk ratio; SAE, serious adverse event.

Table 2

Serious Adverse Events of Included Clinical Studies

Study	No. Adverse Events		Details of Adverse Events*		*P*
	Clarithromycin	Placebo	Clarithromycin	Placebo	
Giamarellos-Bourboulis et al.,[21] 2008	3/100	0/100	Bronchospasm (1) Increase in liver aminotransferase levels (2)	None	0.250
Giamarellos-Bourboulis et al.,[22] 2014	2/302	4/298	Acute myocardial infarction (1) Thrombocytopenia (1)	Acute pancreatitis (1) Acute stroke (1) Atrial fibrillation (1) Increase of ALT/AST > 10 × ULN (1)	0.502
Karakike et al.,[16] 2022	50/55	50/55	Infections and infestations (31) Acute kidney injury (7) Arterial ischemia (7) Cardiac disorders (7) Vascular disorders (8) Hemorrhagic complications (3) Metabolic and nutrition disorders (2) Thoracic, pulmonary, or mediastinal disorders (3) Neurological disorders (1) Surgery complications (4)	Infections and infestations (31) Acute kidney injury (1) Arterial ischemia (5) Cardiac disorders (5) Vascular disorders (6) Thoracic, pulmonary, or mediastinal disorders (2) Neurological disorders (3) Surgery complications (1)	>0.99

ALT, alanine aminotransferase; AST, asparagine aminotransferase; ULN, upper limit of normal.

*Percentages may not add up to 100% because some patients have experienced more than 1 serious adverse event.

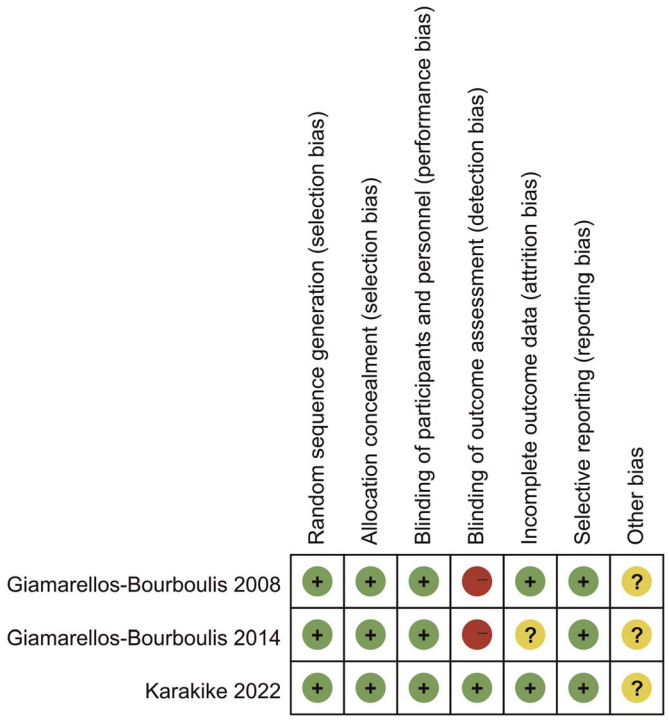

Figure 3. Risk of bias of included studies.

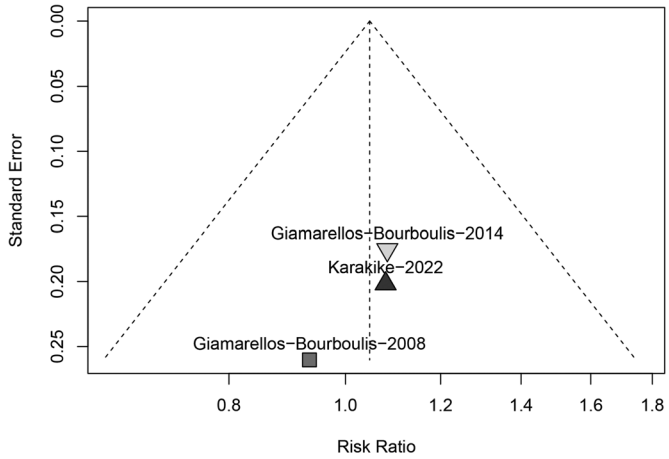

Figure 4. Funnel plot of all eligible studies.

A recent multicenter prospective clinical study demonstrated that a single oral dose of azithromycin can reduce the risk of maternal sepsis or death in women planning a vaginal birth.[25]

Notably, the latest definition of sepsis highlights the role of immune dysregulation, indicating a new direction for research on immunomodulation in sepsis. Interestingly, as research on macrolides deepens, it has been discovered that, in addition to their antibiotic properties, they also exhibit immunomodulatory effects, particularly clarithromycin and azithromycin. Studies have clarified that this can be attributed to various mechanisms, including reducing the release of anti-inflammatory cytokines, alleviating the overactivation of reactive oxygen species, and inhibiting the production of neutrophil chemoattractant and leukocyte adhesion molecules.[26] In addition, during clinical treatment, some patients still experience clinical improvement despite resistance of the infection to macrolides. This suggests that the efficacy of treatment does not rely solely on the bactericidal effects of antibacterial drugs. It is possible that for pathogenic microorganisms directly invaded by virulence factors, the immunomodulatory effect may not be effective. However, for pathogenic microorganisms acting on the body through immune injury, drugs with dual bacteriostatic and immunomodulatory effects have greater clinical application.

Previous studies have conducted systematic reviews and meta-analyses on the safety and efficacy of macrolides in various diseases, such as preterm rupture of membranes, feeding intolerance in preterm low-birth-weight infants, and CAP.[27–29] Despite limitations, such as small sample sizes and the absence of RCTs, the final results demonstrate the clinical benefits of macrolides. In 2011, a systematic review investigated the immunomodulatory effects of macrolides in CAP.[30] Corrales-Medina and Musher[30] identified 6 cohort studies, 4 of which showed that patients with pneumococcal pneumonia treated with β-lactams alone had a 3-fold higher mortality rate than those who received both macrolides and β-lactams, whereas 2 reported no significant difference between the 2 regimens. Finally, the authors recommended the combined use of macrolides and β-lactam antibiotics for the treatment of CAP and suggested that it is necessary to validate the efficacy of macrolides as immunomodulators in CAP. To the best of our knowledge, this is the first meta-analysis on the clinical efficacy and safety of clarithromycin in sepsis. Our study did not reveal clarithromycin as superior in ameliorating short-term outcomes in patients with sepsis. However, early results from a retrospective study indicated that a combination of clarithromycin and β-lactam significantly improved the 28-day mortality of patients with sepsis compared with those treated with β-lactam monotherapy.[15] Notably, the potential harm of clarithromycin is also a significant issue that cannot be neglected, as it may prolong QT, pose a risk of cholestasis, and cause ototoxicity.

Spyridaki et al.[31] explored the mechanism of action of clarithromycin in ventilator-associated pneumonia and sepsis caused by gram-negative bacteria. By measuring the circulating levels of inflammatory markers in the enrolled patients, they found that the circulating monocytes from the clarithromycin group released more tumor necrosis factor α, interleukin 6, and the receptor expressed on myeloid cells-1 than those in the placebo group. These studies further highlight the role of clarithromycin in the treatment of sepsis. To further explore the effect of clarithromycin on the host immune response in patients with sepsis, Karakike et al.[16] found a significant increase in nonclassic monocytes and human leukocyte antigen DR in an experimental

Table 3

Jadad Scale of Randomized Controlled Trials Included in the Meta-analysis

Study	Random Sequence Generation	Appropriate Randomization	Blinding of Participant or Personnel	Binding of Outcome Assessor	Withdrawals and Dropouts	Total Jadad Score
Giamarellos-Bourboulis et al.,[21] 2008	Yes	Yes	Yes	No	Yes	4
Giamarellos-Bourboulis et al.,[22] 2014	No	Yes	Yes	No	Yes	3
Karakike et al.,[16] 2022	Yes	Yes	Yes	Yes	Yes	5

group after 10 days of clarithromycin treatment, which adds to our understanding of macrolide-mediated immunomodulation.

Interpreting our findings necessitated the consideration of several inevitable limitations. First, the number of included studies was relatively small, which somewhat compromised the reliability of the conclusions. This was due to our strict inclusion criteria; however, despite the limited number of studies included, these RCTs provided high levels of clinical evidence that bolstered our confidence in the results. Second, various outcomes exhibited significant heterogeneity, which weakened the robustness of the conclusions. To mitigate this issue among the included studies, we conducted sensitivity analyses to confirm the conclusion stability by excluding 1 study at a time. Third, all selected studies originated from 1 country, which may limit generalizability; nevertheless, it also highlights that clarithromycin remains an extensive and unexplored area in sepsis. The global burden of sepsis, as an acute and critical disease, necessitates a pressing need for innovative advancements in basic and clinical research. This calls for collaborative efforts by researchers worldwide to generate comprehensive data, ultimately enhancing the prognosis of patients with sepsis. Furthermore, it is important to acknowledge that variations in diagnostic criteria over time may have contributed to heterogeneity in disease severity among the included studies. As our understanding of the condition improves and the clinical diagnostic criteria evolve, it may be more reasonable to consider starting the analysis with the latest diagnostic criteria. However, this approach resulted in fewer studies being included in the analysis. Nonetheless, we will continue to prioritize this crucial clinical issue in future investigations.

Conclusion

To the best of our knowledge, this is the first meta-analysis assessing the clinical efficacy and safety of clarithromycin in sepsis. Our study did not provide evidence that clarithromycin improves short-term patient outcomes in sepsis. Moreover, clarithromycin administration did not increase the risk of adverse events. However, given the limited number of included studies, further high-quality clinical studies are warranted to confirm the safety and efficacy of clarithromycin in the treatment of sepsis.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Zhao P and Yao R conceived the study. Yang J extracted all dada. Zhao P, Yao R, and Yang J undertook and refined the searches. Zhao P wrote the paper. Yao R and Yang J undertook the statistical analyses. Wen W, Yao Y, and Du X helped to revise the intellectual content. All authors read and approved the final manuscript.

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Ethical approval of studies and informed consent

All studies included in this study followed the principles of the Declaration of Helsinki as revised in 2013.

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None.

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