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Clinical outcomes of continuous versus intermittent linezolid infusion regimens: a systematic review and meta-analysis

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Objective: We aimed to compare the clinical cure profile of linezolid administered as continuous infusion (CI) vs. intermittent infusion (II), to provide practicable evidence for optimizing linezolid dosing.
Method: A systematic search of major electronic databases (PubMed, Cochrane Library, Web of Science, and Embase) was performed to identify randomized controlled trials (RCTs) that compared continuous versus intermittent infusion linezolid regimens, covering the period from database inception to 2026 April. After literature screening and data abstraction, the methodological quality of the eligible RCTs was appraised using the ROB-2 tool, and meta-analysis along with sensitivity analyses were performed via RevMan 5.4.
Result: Finally, 389 patients from 5 RCTs were finally analyzed. Meta-analysis demonstrated that compared with the II group, the CI group had substantially higher rates of both AUC/MIC > 80 attainment (RR = 1.91, 95% CI: 1.13–3.24, $P = 0.02$) and clinical cure (RR = 1.33, 95% CI: 1.14–1.54, $P < 0.001$). However, no statistically significant differences were observed for mortality (RR = 0.86, 95% CI: 0.60–1.22, $P = 0.39$) or for linezolid-induced thrombocytopenia (RR = 0.71, 95% CI: 0.39–1.28, $P = 0.25$). Sensitivity analyses yielded results consistent with the primary analysis.
Conclusion: Continuous 24-hour infusion of linezolid was associated with higher attainment rate of the pharmacokinetic/pharmacodynamic (PK/PD) target (AUC/MIC > 80) and higher clinical cure rate. However, no significant difference in mortality was observed between continuous and intermittent infusion. Therefore, whether better PK/PD target attainment translated into better patient outcomes remained uncertain. Given these findings, larger-scale, multi-center RCTs focusing on linezolid dosing strategies are urgently warranted to corroborate these observations.

KEYWORDS
clinical cure, continuous infusion, intermittent infusion, linezolid, meta-analysis

1 Introduction

Antibiotic resistance is associated with high morbidity, mortality, and considerable economic costs, which prompting the World Health Organization (WHO) to designate it as one of the top 10 threats to global health (1). According to the 2025 annual report of the China Antimicrobial Surveillance Network (2), *Staphylococcus aureus* was among the three most frequently detected organisms, and the rate of Methicillin-Resistant

Staphylococcus aureus (MRSA) and Methicillin-Resistant *Staphylococcus epidermidis* (MRSE) were 80.8% and 76.5%, respectively. Given this scenario, enhancing the treatment efficacy and preserving the drug susceptibility of Gram-positive pathogens necessitated the refinement of antibiotic administration regimens (3).

For time-dependent antimicrobials such as β-lactams, prolonged (i.e., infusion over > 3 h) or continuous (CI; 24 h constant-rate infusion) administration was reported to improve clinical outcomes (3–5). However, the survival benefit of such prolonged or continuous dosing for time-dependent antibiotics with a long post-antibiotic effect (PAE) remains uncertain.

Linezolid, an oxazolidinone antibiotic (6), was widely used against Gram-positive pathogens (7, 8). As a time-dependent antimicrobial agent with a long PAE (9), its efficacy is best predicted by both the percentage of time that free drug concentrations remain above the MIC (T > MIC) and the AUC/MIC ratio, rather than by peak concentration (C_{max}) (10–12). In this context, after an appropriate loading dose, continuous infusion avoided the peak-to-trough fluctuations associated with intermittent dosing and maintained steady-state plasma concentrations above the MIC, which maximized clinical efficacy (9, 11, 12) Although earlier reports (9, 13, 14) suggested that CI achieved the targeted pharmacokinetic/pharmacodynamic (PK/PD) threshold more effectively and was theoretically preferable to standard intermittent infusion (II) (15). Nevertheless, the clinical value of continuous linezolid infusion remains to be established (9, 13–15).

Accordingly, we undertook this systematic review and meta-analysis to determine whether refining linezolid administration (CI vs. II) could yield a higher clinical cure rate in Gram-positive infections. To this end, we systematically compared the efficacy and safety of the two infusion regimens across all eligible trials.

2 Material and methods

We conducted this systematic review and meta-analysis to assess the clinical cure rates of continuous vs. intermittent linezolid infusion for Gram-positive bacterial infections. The methods followed the PRISMA 2020 guidelines (16), and the study was registered with PROSPERO as CRD420261355214 (PROSPERO, managed by the UK National Institute for Health Research). Our predefined protocol detailed the selection criteria and the analytical approach used throughout the review.

2.1 Literature search and selection criteria (inclusion/exclusion)

A systematic search of PubMed, Embase, Cochrane Library, and Web of Science was undertaken through April 2026 using "linezolid" combined with "continuous infusion" or "intermittent infusion" as the search strategy. The full search strategy was provided in Supplementary Methods.

Inclusion criteria were as follows: (i) patients with documented or suspected Gram-positive infections were enrolled; (ii) linezolid was used as the study drug; (iii) the studies were randomized controlled trials (RCTs); and (iv) at least one of the predefined outcomes was reported: AUC/MIC, clinical cure, mortality, or linezolid-induced thrombocytopenia (LIT).

Exclusion criteria were as follows: (i) studies without full-text publication; (ii) preclinical experiments; (iii) CI protocols without a loading dose.

2.2 Data extraction

Data were independently extracted by two investigators, and any discrepancies were resolved through team discussion to achieve consensus. For each included study, we collected the following information: first author, publication year, sample size, treatment regimens, baseline clinical characteristics (e.g., age, SAPS II), AUC/MIC, clinical cure, mortality, and LIT events. In addition, clinical cure was defined as survival, stable vital signs, and resolution of signs and symptoms of infection. Furthermore, we calculated the probability of target attainment (PTA) for an AUC/MIC threshold of > 80, assuming a MIC of 2 mg/L.

2.3 Primary objectives

We sought to compare the clinical cure rates associated with continuous linezolid infusion versus conventional intermittent infusion.

2.4 Quality assessment

To ensure a rigorous risk-of-bias assessment, we used the Risk of Bias 2 tool (RoB-2 tool) (17) to grade the methodological quality of each included RCT. Two reviewers conducted this evaluation independently; subsequently, any disagreements were adjudicated via discussion within the research team until consensus was reached.

2.5 Statistical methods

All meta-analyses were performed using RevMan 5.4. For dichotomous outcomes, pooled risk ratios (RRs) with 95% confidence intervals (CIs) were estimated; for continuous outcomes, weighted mean difference (WMDs) and their 95% CIs were computed. The I^2 statistic (18) was employed to assess heterogeneity, which represented the proportion of variability attributable to heterogeneity rather than chance. Model selection was based on the I^2 value: random-effects models were used for $I^2 > 50\%$ and fixed-effects models were used for $I^2 \leq 50\%$. Sensitivity analyses were performed by

Abbreviations

RCT, randomized controlled trial; II, intermittent infusion; CI, continuous infusion; PK/PD, pharmacokinetic/pharmacodynamic; MRSA, Methicillin-Resistant *Staphylococcus aureus*; MRSE, Methicillin-Resistant *Staphylococcus epidermidis*; AUC, area under the concentration-time curve; MIC, minimum inhibitory concentration; LIT, linezolid-induced thrombocytopenia; PTA, probability of target attainment; C_{max}, peak plasma concentrations.

altering the statistical model, excluding the study at high risk of bias, and performing a leave-one-out analysis.

3 Results

3.1 Study characteristics and quality assessments

The study selection process for this meta-analysis was depicted in Figure 1 (19). The initial database search retrieved 928 records published up to April 2026. Of these, 42 were excluded as duplicates, and 852 were eliminated after title/abstract screening for various reasons. The remaining 34 full-text articles were assessed for eligibility, of which 5 RCTs comprising 389 patients were ultimately included. Table 1 presented the main baseline and clinical characteristics of the included studies. Tables 2, 3 presented the main dosing regimens and main outcomes in the included RCTs. We appraised the methodological quality of the five RCTs using the RoB-2 tool, and the results were summarized in Figure 2 and Supplementary Figure 1. Among the five included RCTs one was judged to be at high risk of bias. In addition, the GRADE assessment of evidence quality was summarized in Supplementary Figure 2.

3.2 AUC/MIC

A meta-analysis of 3 studies ($n = 70$) provided a pooled WMD of 23.33 (95% CI: 11.39–35.27, $P < 0.001$) for the AUC/MIC ratio (assuming a MIC of 2 mg/L) when comparing CI with II (22–24). Heterogeneity was low ($I^2 = 0\%$, $P = 0.83$) across these trials (Figure 3). The certainty of evidence was high.

3.3 The PTA of AUC/MIC > 80

Three RCTs reported the PTA of AUC/MIC ($n = 70$). The pooled estimate indicated a significant difference favoring continuous infusion (RR = 1.91, 95% CI: 1.13–3.24, $P = 0.02$) for the probability of PTA of AUC/MIC > 80, assuming an MIC of 2 mg/L, when comparing CI with II (22–24). Heterogeneity was negligible ($I^2 = 0\%$, $P = 0.51$) across the included studies (Figure 4). The outcome was supported by high-certainty evidence.

3.4 Clinical cure

Five RCTs comprising 389 patients were included in the analysis of clinical cure. Continuous infusion was associated with a significantly higher clinical cure rate compared with intermittent infusion (RR = 1.33, 95% CI: 1.14–1.54, $P < 0.001$) (20–24). Heterogeneity was negligible ($I^2 = 0\%$, $P = 0.79$) across the included studies (Figure 5). The certainty of evidence was moderate.

However, the timing of clinical cure assessment was not uniform across the included RCTs. Specifically, Ahmed E. (2022) (20) and Ahmed M. (2024) (21) assessed clinical cure

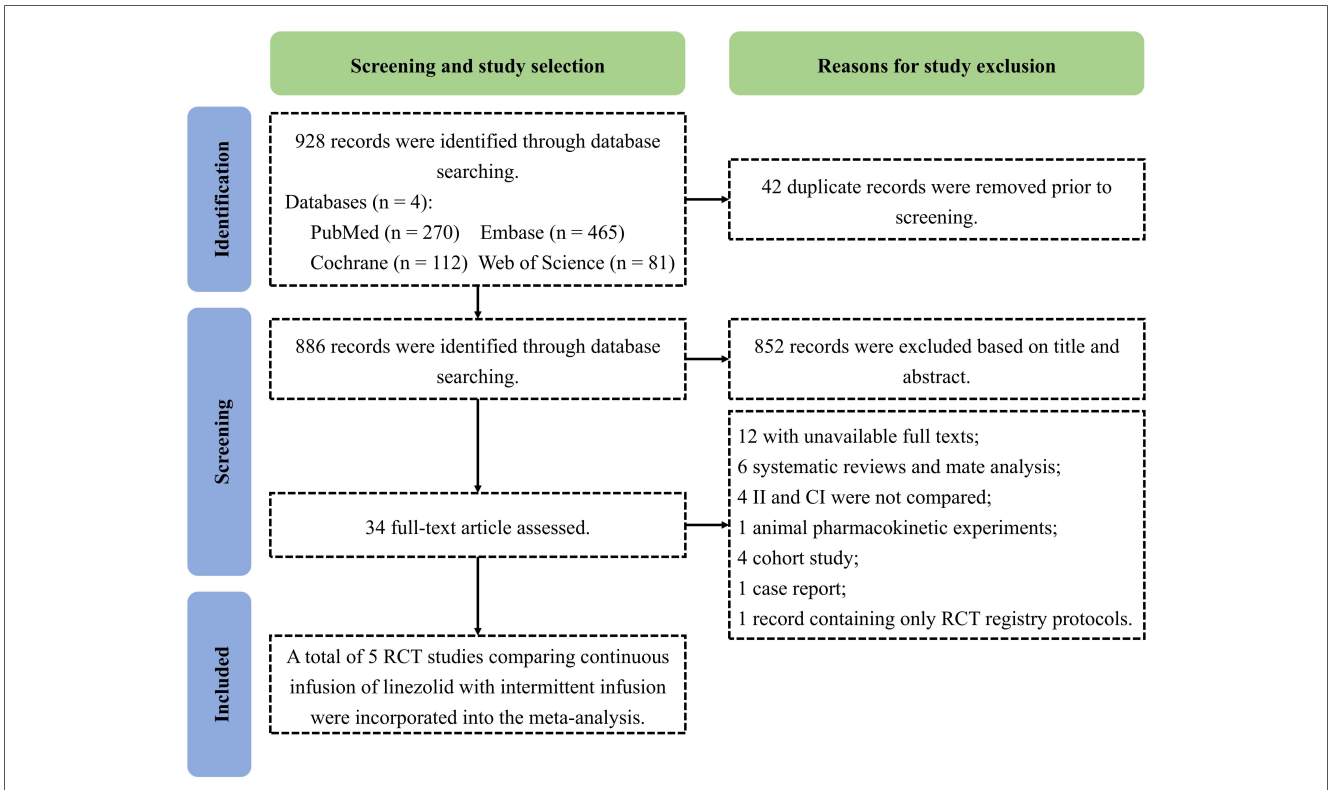

FIGURE 1
Flowchart illustrating the selection process of studies.

TABLE 1 The characteristics of CI and II in individual randomized controlled trials (RCTs).

First author (year)	ICU status	Age[a], years		Number of patients[b]		SAPS II[b]		SOFA		Creatinine clearance, mL/min		Infection type	Mechanical ventilation[b]		Pathogens[d]		MICs, mg/L	
		CI	II	CI	II	CI	II	CI	II	CI	II		CI	II	CI	II	CI	II
Ahmed E. (2022) (20)	ICU	66.55 ± 10.56	66.89 ± 14.93	92	87	43.8 ± 8.61	42.1 ± 8.86	5. (4–7) [c]	5 (3.5–7) [c]	53.05 (28.0–80.0) [c]	28.39 (18.73–64.0) [c] *	VAP ($n = 62$), HAP ($n = 117$)	47	44	*S.* spp.($n = 26$) MRAS ($n = 101$) MSSA ($n = 52$)		/	/
Ahmed M. (2024) (21)	ICU	59.46 ± 12.18	61.1 ± 14.06	70	70	/	/	11 (9–13) [c]	11 (9–13) [c]	/	/	/	/	/	/	/	/	/
Chiara Adembri (2008) (22)	ICU	57 ± 6	64 ± 4	8	8	42.9 ± 15.7	46.5 ± 17.2	5.8 ± 2.0 [c]	7.0 ± 3.3 [b]	100.7 ± 17.7 [a]	89.1 ± 27.6 [a]	/	/	/	*E. spp.* ($n = 4$), MRAS ($n = 4$), MSSA ($n = 1$)	*E. spp.* ($n = 3$), MRAS ($n = 3$), MSSA ($n = 4$)	MIC=1 ($n = 1$) MIC=2 ($n = 7$)	MIC=1 ($n = 1$) MIC=2 ($n = 7$)
Gennaro De (2015) (23)	ICU	64.7 ± 10.4	62.5 ± 10.5	11	11	54.8 ± 12.5	42.7 ± 8.6*	6.4 ± 3.2 [a]	5.6 ± 2.8 [a]	146.1 ± 60 [a]	149.2 ± 61[a]	VAP ($n = 22$)	5	7	/	/	/	/
Rasha M. (2022) (24)	ICU	56 ± 17.63	56.5 ± 12.4	16	16	25.7 ± 21.88	29 ± 28.45	b	/	139.06 ± 153.97[a]	117.58 ± 87.66[a]	VAP ($n = 6$), HAP ($n = 11$)	4	2	*S.* spp. ($n = 6$), RAS ($n = 0$), MSSA ($n = 10$)	*S.* spp. ($n = 1$), MRAS ($n = 2$), MSSA ($n = 13$)	MIC=2 ($n = 9$) MIC=4 ($n = 7$)	MIC=2 ($n = 9$) MIC=4 ($n = 7$)

CI, continuous infusion; II, intermittent infusion; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; VAP, ventilator-associated pneumonia; HAP hospital-acquired pneumonia; *S.* spp., *Streptococcus* spp.; *E.* spp., *Enterococcus* spp.; MRSA, Methicillin-Resistant *Staphylococcus aureus*; MSSA, Methicillin-Susceptible *Staphylococcus aureus*; MICs, minimum inhibitory concentrations; IQR, interquartile range.

[a]Data are reported as Mean ± SD.

[b]Data are reported as absolute number.

[c]Data are reported as Median (IQR).

[d]Multiple pathogens may be detected in the same patient.

*CI vs II, $P < 0.05$.

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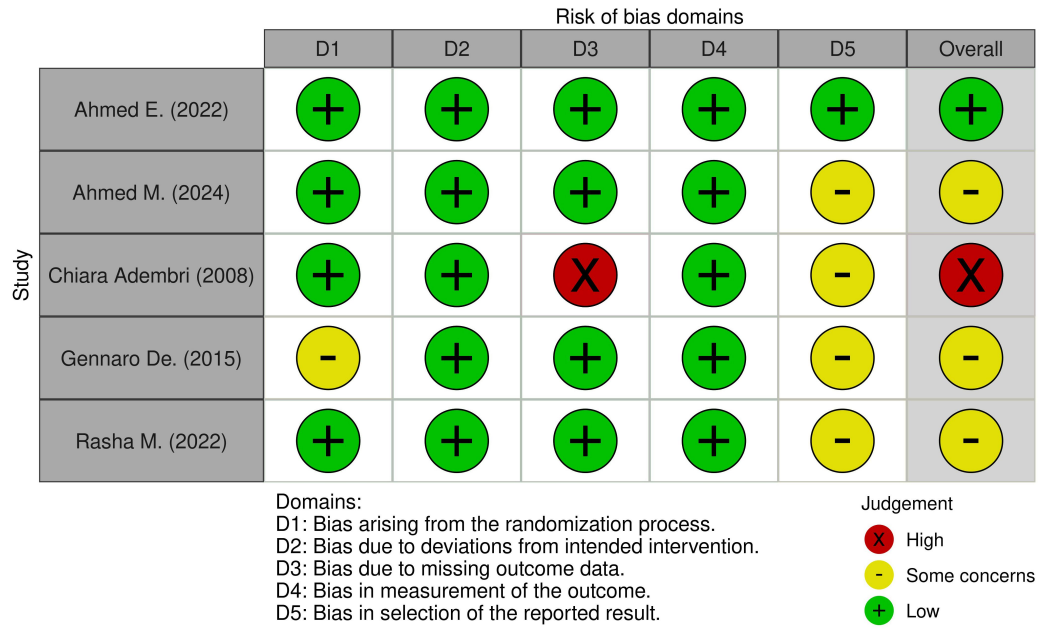

FIGURE 2
Quality assessment of randomized studies through RoB-2 tool ($n = 5$).

TABLE 2 The main dosing regimens of CI and II in individual RCTs.

First author (Year)	Loading dose		Maintenance dose		Infusion duration		Total daily dose	Treatment duration	
	CI	II	CI	II	CI	II		CI	II
Ahmed E. (2022)	600 mg IV	/	50 mg/h	600 mg q12 h	24 h	/	1200 mg	7.0 (7.0–11.0)[a,*]	7.0 (7.0–9.0)[a]
Ahmed M. (2024)	300 mg IV	/	50 mg/h	600 mg q12 h	24 h	1 h	1200 mg	7.39 ± 1.653[b,*]	9.83 ± 2.537[b]
Chiara Adembri (2008)	300 mg PO	/	1200 mg/d	600 mg q12 h	24 h	0.5 h	1200 mg	/	/
Gennaro De (2015)	300 mg IV	/	1200 mg/d	600 mg q12 h	24 h	1 h	1200 mg	/	/
Rasha M. (2022)	300 mg IV	/	1200 mg/d	600 mg q12 h	24 h	0.5 h	1200 mg	/	/

CI, continuous infusion; II, intermittent infusion; IV, intravenous infusion; PO, oral administration.
[a]Data are reported as Median (IQR).
[b]Data are reported as Mean ± SD.
*CI vs II, $P < 0.05$.

after 7 days of linezolid therapy, Gennaro De (2015) (23) after 4 days, whereas, Chiara Adembri (2008) (22) and Rasha M. (2022) (24) evaluated this outcome at the end of the treatment episode. This between-study difference in assessment timing should be taken into account when interpreting the pooled clinical cure estimate.

3.5 Mortality

In contrast to the efficacy outcomes, no statistically significant difference in all-cause mortality was demonstrated between the two groups (RR = 0.86, 95% CI: 0.60–1.22, $P = 0.39$) for mortality when comparing CI with II (20–24). Heterogeneity was low ($I^2 = 36\%$, $P = 0.18$) across the included studies (Figure 6). The certainty of evidence was very low.

3.6 Linezolid-induced thrombocytopenia (LIT)

Thrombocytopenia was assessed in two RCTs ($n = 156$). No statistically significant difference was observed, although the point estimate favored continuous infusion (RR = 0.71, 95% CI: 0.39–1.28, $P = 0.25$) for LIT when comparing CI with II (21, 22). Heterogeneity was negligible ($I^2 = 0\%$, $P = 0.34$) across the included studies (Figure 7). This outcome was supported by low-certainty evidence.

3.7 Sensitivity analysis

We performed sensitivity analyses by altering the statistical model (Supplementary Figure 3), excluding studies at high risk

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TABLE 3 The main outcomes of CI and II in individual RCTs.

First author (Year)	AUC/MIC (mean ± SD)		AUC/MIC >80, %		Mortality, %		Clinical cure, %		LIT, %	
	CI	II	CI	II	CI	II	CI	II	CI	II
Ahmed E. (2022)	/	/	/	/	26	19	56	40	/	/
Ahmed M. (2024)	/	/	/	/	8	17	59	46	13	20
Chiara Adembri (2008)	103.03 ± 39.8	92.2 ± 45.2	7	5	2	2	7	5	1	0
Gennaro De (2015)	101 ± 35.5	76.3 ± 38.1	4	2	1	4	9	8	/	/
Rasha M. (2022)	89.33 ± 21.99	64.93 ± 17.03	10	4	7	8	14	8	/	/

AUC, area under the concentration-time curve, MIC, minimum inhibitory concentration; SD, standard deviation; CI, continuous infusion; II, intermittent infusion; LIT, linezolid-induced thrombocytopenia.

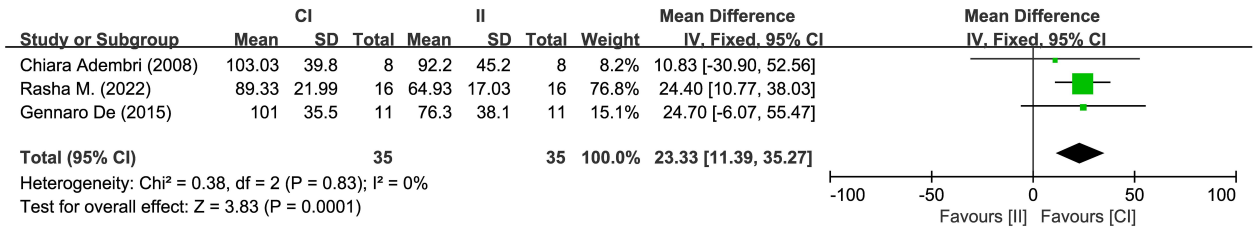

FIGURE 3
Forest plot comparing the AUC/MIC between CI and II ($n = 3$) using WMD as the primary effect measure.

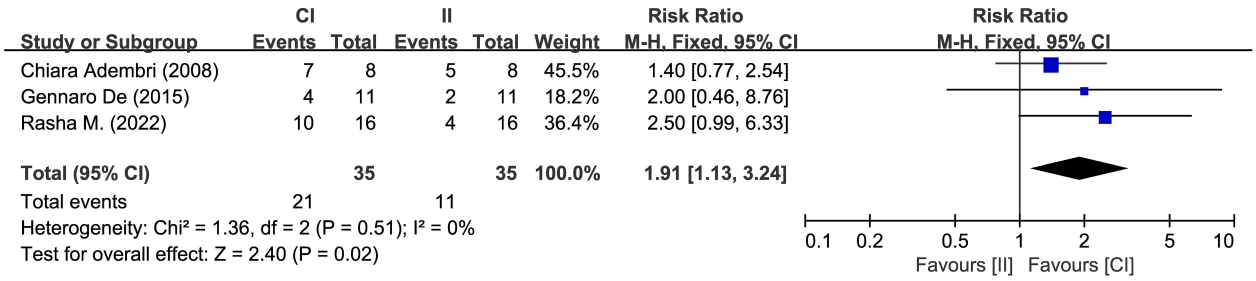

FIGURE 4
Forest plot comparing the PTA of AUC/MIC between CI and II ($n = 3$).

of bias (Supplementary Figure 4) and performing a leave-one-out analysis (Supplementary Table 1–S4). A sensitivity analysis excluding very small studies was not performed because three small RCTs were included ($n = 16$, 22, and 32). Sensitivity analyses yielded results consistent with the primary analysis. However, given the limited number of contributing studies, these findings should be interpreted cautiously.

For the LIT outcome, however, the meta-analysis included only two studies, one of which was judged to be at high risk of bias. Therefore, sensitivity analysis excluding the high-risk study and performing a leave-one-out analysis could not be performed. The only feasible sensitivity analysis, which involved changing the statistical model, yielded consistent results before and after the change (before: RR = 0.71, 95% CI: 0.39–1.28, $P = 0.25$; after: RR = 0.69, 95% CI: 0.38–1.26, $P = 0.23$).

4 Discussion

Linezolid, a time-dependent antimicrobial agent with a long PAE (7), was highly active against resistant staphylococci, including MRSA and MRSE, which remained highly susceptible to it (2). A T > MIC of at least 40% was associated with efficacy, with a target of ≥ 85% described in the literature (11), while an AUC/MIC ratio of > 80 was generally considered indicative of adequate clinical response (25). However, because the reporting formats of the original data in the included studies were inconsistent, uniformly formatted free-drug %T > MIC data were not available; therefore, T > MIC was not included in the pooled analysis of this meta-analysis. Therefore, the mechanistic link between CI and improved clinical outcomes remained inferential rather than directly demonstrated (10).

From a pharmacokinetic perspective, if total daily dose, drug clearance, and MIC had been comparable between the two

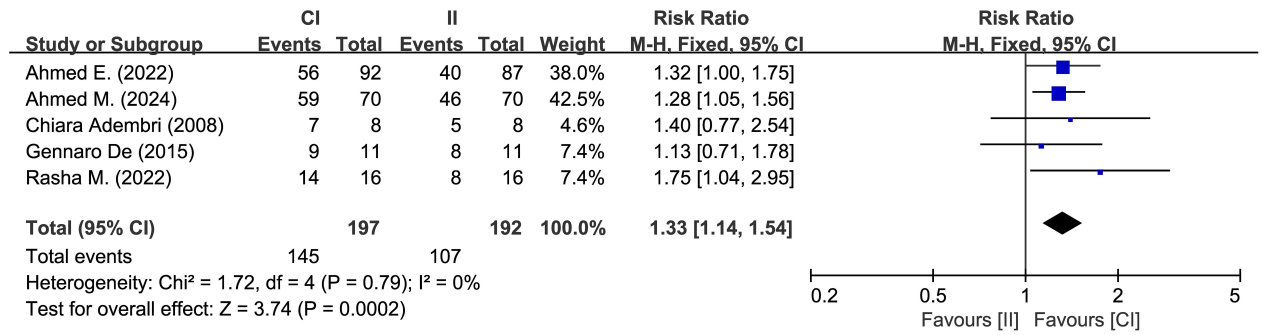

FIGURE 5
Forest plot summary of the unadjusted risk ratios (RRs) comparing clinical cure in patients treated with CI vs II ($n = 5$).

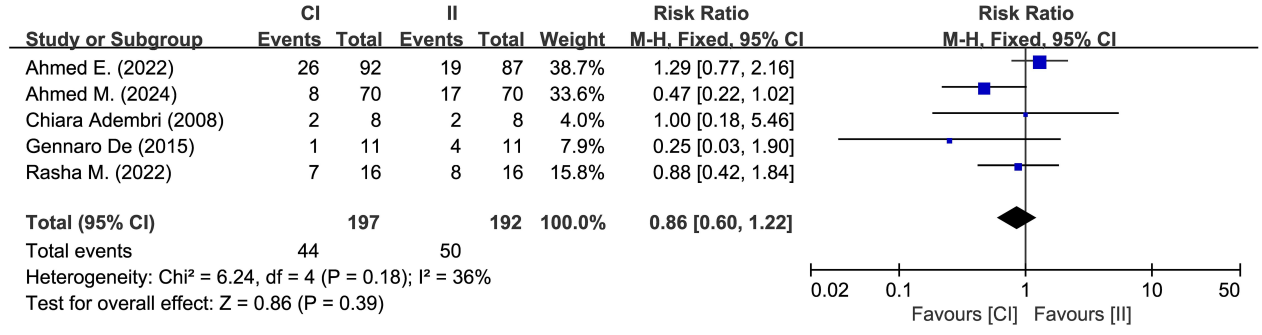

FIGURE 6
Forest plot summary of the unadjusted RRs comparing mortality in patients treated with CI vs II ($n = 5$).

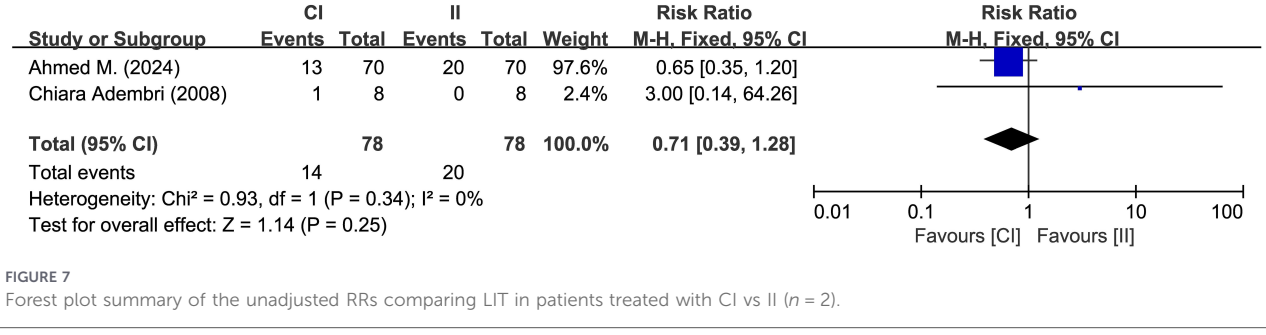

FIGURE 7
Forest plot summary of the unadjusted RRs comparing LIT in patients treated with CI vs II ($n = 2$).

groups, steady-state AUC/MIC would theoretically have been similar (11, 25, 26). However, a significant difference in AUC/MIC was observed between the CI and II groups (WMD = 23.33, 95% CI: 11.39–35.27, $P < 0.001$). This difference was primarily attributed to the different dosing regimens (CI vs. II). In addition, variations in renal function (20) and disease severity (23) across study populations might have affected drug clearance and consequently the AUC. Finally, given the small number of included studies and participants, caution was warranted when interpreting the observed difference in AUC/MIC, and further studies with standardized PK sampling and homogeneous populations were needed to confirm these findings.

In the present study, CI was associated with superior PK/PD profiles compared with II, as reflected by significantly higher PTA rates (RR = 1.91, 95% CI: 1.13–3.24, $P = 0.02$) and clinical cure rates (RR = 1.33, 95% CI: 1.14–1.54, $P < 0.001$). These findings suggested that CI might confer clinical benefits in patients at risk of underexposure, such as those with augmented renal clearance or infections caused by high-MIC pathogens. However, no significant difference in mortality was observed (RR = 0.86, 95% CI: 0.60–1.22, $P = 0.39$), indicating that improved PK/PD target attainment did not necessarily translate into a survival benefit.

From a clinical pharmacology viewpoint, our results indicated that CI was associated with higher PK/PD target attainment than II (27). One proposed advantage of CI is that it avoids the elevated peak plasma concentrations (C_{max}) typically occurring with intermittent infusion, a phenomenon mechanistically associated

with mitochondrial damage and the ensuing LIT (28, 29). In our meta-analysis, no statistically significant difference in thrombocytopenia was observed, although the point estimate favored CI (RR = 0.71, 95% CI: 0.39–1.28, $P = 0.25$). However, this mechanism was not directly assessed in our meta-analysis; therefore, it was discussed only as a hypothesis-generating explanation.

Several limitations of this study merit consideration. First, most studies failed to specify the duration of linezolid therapy, raising the possibility that regimen-related differences in exposure time could have biased the results. Second, the geographic concentration of the included trials (Egypt and Italy) limited the generalizability of our findings. Third, several of the component studies had limited statistical power due to small sample sizes. Fourth, publication bias could not be excluded because only five RCTs precluded funnel plot asymmetry testing. Fifth, grey literature and clinical trial registries were not specifically searched. Because the included RCTs predominantly enrolled critically ill patients, whether CI conferred similar benefits in non-critically ill patients, those with normal renal function, or those infected with low-MIC pathogens remained uncertain. Consequently, larger-scale, methodologically standardized clinical trials stratified by renal function, disease severity, pathogen MIC, and other relevant factors were required to identify the patient populations most likely to benefit from CI.

5 Conclusion

The present systematic review and meta-analysis demonstrated that CI yielded a higher PK/PD target attainment (high-certainty evidence) and clinical cure (moderate-certainty evidence) compared with II. However, better PK/PD target attainment translated into better patient outcomes remained uncertain. Therefore, additional well-powered, methodologically rigorous RCTs are warranted to corroborate our results.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

YD: Investigation, Data curation, Methodology, Conceptualization, Writing – review & editing, Formal analysis, Writing – original draft, Visualization, Funding acquisition. XW: Investigation, Writing – original draft, Funding acquisition. YZ: Writing – review & editing, Methodology, Conceptualization, Visualization. RL: Writing – original draft, Conceptualization. HY: Writing – original draft, Investigation. XL: Writing – original draft, Formal analysis, Data curation. JC: Writing – original draft, Conceptualization. FC: Writing – review & editing, Conceptualization, Methodology.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2026.1971024/full#supplementary-material

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