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META-ANALYSIS

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Effect of renal function on the risk of thrombocytopaenia in patients receiving linezolid therapy: A systematic review and meta-analysis

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Aims: The association of renal function and linezolid-induced thrombocytopaenia (LIT) remains controversial. We performed a meta-analysis to determine whether impaired renal function is associated with an increased LIT risk.

Methods: We conducted a systematic search of PubMed, EMBASE and the Cochrane Library from inception to February 2021 for eligible studies evaluating the relationship between renal function and LIT. Indicators of renal function included renal impairment (RI), severe RI, haemodialysis status, creatinine clearance rate (Ccr) and estimated glomerular filtration rate (eGFR). Unadjusted and adjusted estimates and 95% confidence intervals (CIs) were calculated separately using a random-effect model.

Results: A total of 24 studies with 3580 patients were included in the meta-analysis. RI patients had an increased LIT risk compared to non-RI patients in both the unadjusted (OR 3.54; 95% CI 2.27, 5.54; $I^2 = 77.7\%$) and adjusted analyses (OR 2.51; 95% CI 1.82, 3.45; $I^2 = 17.9\%$). This association persisted in the subset of studies involving only patients receiving a fixed conventional dose (600 mg every 12 h) and other subgroup analyses by ethnicity, sample size and study quality. Moreover, the LIT risk was significantly higher in patients with severe RI and haemodialysis than in patients without severe RI and haemodialysis. The eGFR and Ccr were significantly lower in LIT patients than in non-LIT patients.

Conclusions: Impaired renal function is associated with an increased risk of LIT. A reduced linezolid dose may be considered in RI patients at a low risk of treatment failure, ideally guided by therapeutic drug monitoring.

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KEYWORDS
dose, linezolid, meta-analysis, renal impairment, thrombocytopaenia

1 | INTRODUCTION

Linezolid is an oxazolidinone antibiotic widely used in the management of infections caused by drug-resistant pathogens, especially methicillin-resistant *Staphylococcus aureus* (MRSA).[1] This agent has favourable pharmacokinetic properties, such as availability in both intravenous and oral formulations, high oral bioavailability (approximately 100%), and excellent penetration in various tissues.[2] Moreover, linezolid shows a lower risk of nephrotoxicity than vancomycin, which remains the gold standard for the management of MRSA infections.[3] A dose adjustment of linezolid is not required when renal function is impaired according to the current package insert. These advantages make linezolid an attractive choice for patients with impaired renal function in daily practice.

The major safety concern with the use of linezolid is thrombocytopaenia, which may lead to platelet transfusions, bleeding, and even an increased risk of mortality.[4,5] Cases of thrombocytopaenia after linezolid therapy have been increasingly documented in patients with renal impairment (RI).[6] However, there are conflicting results on the effect of renal function on the risk of developing of linezolid-induced thrombocytopaenia (LIT) in the current literature. Several studies have reported that impaired renal function is an independent predictor for LIT,[5,7–9] while others have shown that there is no effect.[10–12] To date, no meta-analysis has been performed on this topic. The aim of this systematic review and meta-analysis was to comprehensively evaluate the effect of renal function on the thrombocytopaenia risk in patients taking linezolid.

2 | METHODS

The systematic review and meta-analysis was registered in PROSPERO (CRD42021239865).

2.1 | Literature search strategy

PubMed, EMBASE and the Cochrane Library were searched from inception to February 2021. The literature search was conducted using the following combinations of terms: "linezolid" AND "thrombocytopenia OR thrombopenia OR platelet OR thrombocytopenic" AND "renal OR kidney OR creatinine clearance OR glomerular filtration rate OR serum creatinine OR hemodialysis OR risk factor OR predictor". Additional eligible publications were identified from the references of the included studies.

2.2 | Inclusion and exclusion criteria

Randomized controlled trials and observational studies evaluating the association between renal function and the risk of LIT were included in the meta-analysis. The exclusion criteria were: (1) reviews, case reports, conference abstracts, and duplicate studies; (2) no definition of thrombocytopaenia was given; and (3) data for renal function and thrombocytopaenia were not available. Moreover, paediatric studies recruiting patients age < 12 years were excluded, as the fixed conventional dose (600 mg every 12 h) was authorized for only patients aged ≥12 years.

2.3 | Outcomes and definitions

The primary outcome was the association between RI and the risk of thrombocytopaenia. The secondary outcomes included the following: (1) comparison of the thrombocytopaenia risk between patients with and without severe RI, (2) comparison of the thrombocytopaenia risk between patients with and without haemodialysis, and (3) comparison of the baseline estimated glomerular filtration rate (eGFR) or creatinine clearance rate (Ccr) between patients with and without thrombocytopaenia. RI was defined as Ccr <60 or 50 mL/min, eGFR <60 or 50 mL/min/1.73 m^2 or serum creatinine >1.5 mg/dL. Severe RI was defined as Ccr <30 mL/min, eGFR <30 mL/min/1.73 m^2 or serum creatinine >2.0 mg/dL. The definition of thrombocytopaenia was based on the definitions used in the individual studies.

2.4 | Data extraction and quality assessment

The following data were abstracted by two investigators independently: (1) study information (author, publication year, study period, location, design and number of patients enrolled), (2) patient characteristics (age and sex), (3) details of linezolid therapy (route, dose and duration), (4) definition and prevalence of thrombocytopaenia, and (5) indictors of renal function. Because only observational studies were available for inclusion, the quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). Each study was scored from 0 to 9 according to eight items within three domains: selection, comparability and exposure (or outcome).[13] Any disagreements were resolved by consensus.

2.5 | Data synthesis and statistical analysis

The results are presented as odds ratios (ORs) for dichotomous data and as weighted mean differences (WMDs) for continuous data, both with 95% confidence intervals (CIs). Unadjusted and adjusted estimates were pooled separately using a random-effect model. For articles that provided data as medians and ranges (or interquartile ranges), the means and standard deviations were calculated according to the formulas in Wan et al.[14] Heterogeneity was assessed using the chi-squared test and I^2 statistics. $P < .10$ was used to indicate significant heterogeneity. I^2 values of 25%, 50% and 75% were used to indicate low, moderate and high heterogeneity, respectively.[15] Leave-one-out sensitivity analyses were performed to evaluate the influence of each study on the overall estimate. Additionally, subgroup analyses for the primary outcome stratified by the following factors were performed: ethnicity (Asian patients *vs*. Western patients), linezolid dose (fixed conventional dose *vs*. dose information unavailable), sample size (large studies with $n \geq 100$ *vs*. small studies with $n < 100$), and quality of studies (high quality with NOS ≥ 7 *vs*. low quality with NOS < 7). Publication bias was examined by constructing a funnel plot and Egger's test. All analyses were performed using Stata 15.0 software (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Literature search

The search process identified 696 publications (Supplementary Table S1), and a total of 24 observational studies[5,7–12,16–32] met the inclusion criteria. The literature selection process is shown in Figure 1. The characteristics of the studies included in the meta-analysis are presented in Table 1. Eighteen studies were conducted in Asia,[*] and six[7,8,16,21,26,29] were conducted in Western countries. The included studies comprised a total of 3580 patients, with a study mean or median age between 46 and 81 years. The sample size of each included study ranged from 30 to 549 patients, and the reported incidence of LIT ranged from 13.9% to 60.5%. A fixed conventional dose of linezolid (600 mg every 12 h) was administered in most of the studies, and details of the dose were unavailable in eight studies.[†] The mean or median duration of linezolid therapy ranged from 8.2 to 16.9 days. The definitions of thrombocytopaenia varied extensively from study to study. Thrombocytopaenia was defined variably as a platelet count <100–150 × 10^9/L and/or a ≥20–50% decrease in the platelet count from baseline. The median NOS score was 6 (range 4–8). The study quality assessment is presented in Supplementary Table S2.

3.2 | Primary outcome

Unadjusted and adjusted estimates of LIT in RI patients versus non-RI patients were presented in twelve[5,7–9,18,20–23,26–28] and six[5,7–9,18,21] studies, respectively (Supplementary Tables S3 and S4). Compared to patients without RI, those with RI had a higher risk of LIT in both the unadjusted (OR 3.54; 95% CI 2.27, 5.54; $I^2 = 77.7\%$) and adjusted (OR 2.51; 95% CI 1.82, 3.45; $I^2 = 17.9\%$) analyses (Figure 2). In the pooled analyses, a higher LIT risk associated with RI was also observed in the subset of studies involving only patients receiving a fixed conventional linezolid dose (600 mg every 12 h), in both the unadjusted (OR 2.59; 95% CI 1.64, 4.10; $I^2 = 60.8\%$) and adjusted analyses (OR 2.69; 95% CI 1.83, 3.95; $I^2 = 0\%$). Subgroup analyses based on ethnicity showed higher ORs of LIT development in studies from Asian countries than in studies from Western countries, in both the unadjusted and adjusted analyses. Moreover, subgroup analyses by sample size and study quality did not substantially alter the results of the main analyses (Table 2).

3.3 | Secondary outcomes

Unadjusted and adjusted estimates of LIT in severe RI patients *vs*. non-severe RI patients were presented in eight[‡] and five[10,12,18,25,29] studies, respectively (Supplementary Tables S5 and S6). Compared to patients without severe RI, those with severe RI had a higher risk of LIT in both the unadjusted (OR 3.06; 95% CI 1.95, 4.80; $I^2 = 42.6\%$) and adjusted (OR 2.38; 95% CI 1.39, 4.05; $I^2 = 0\%$) analyses (Figure 3).

Unadjusted and adjusted estimates of LIT in patients with haemodialysis *vs*. patients without haemodialysis were presented in six[5,9,12,22,29,32] and three[22,23,32] studies, respectively (Supplementary Tables S7 and S8). Compared to patients without haemodialysis, those with haemodialysis had a higher risk of LIT in both the unadjusted (OR 2.57; 95% CI 1.75, 3.77; $I^2 = 0\%$) and adjusted (OR 3.34; 95% CI 1.41, 7.88; $I^2 = 15.1\%$) analyses (Figure 4).

Ten studies[§] reported the comparison of the baseline Ccr between thrombocytopaenia and non-thrombocytopaenia patients (Supplementary Table S9). The pooled analysis showed that the mean baseline Ccr was significantly lower in patients with LIT than in patients without LIT (WMD −28.25; 95% CI −41.02, −15.47; $I^2 = 73.5\%$). Five studies[5,16,19,25,26] reported the comparison of the baseline eGFR between thrombocytopaenia and non-thrombocytopaenia patients (Supplementary Table S9). The pooled analysis showed that the mean baseline eGFR was significantly lower in patients with LIT than in patients without LIT (WMD −13.57; 95% CI −22.50, −4.65; $I^2 = 23.2\%$) (Figure 5).

3.4 | Sensitivity analyses and publication bias

Leave-one-out sensitivity analysis for the primary outcome showed no significant change compared to the original estimates (Supplementary Table S10). Sensitivity analyses for most of the secondary outcomes showed the results of the main analyses were not

*5,9–12,17–20,22–25,27,28,30–32

†5,18,19,21,22,29–31

‡8,11,12,18,20,22,23,29

§8,10,12,16,17,22–24,30,31

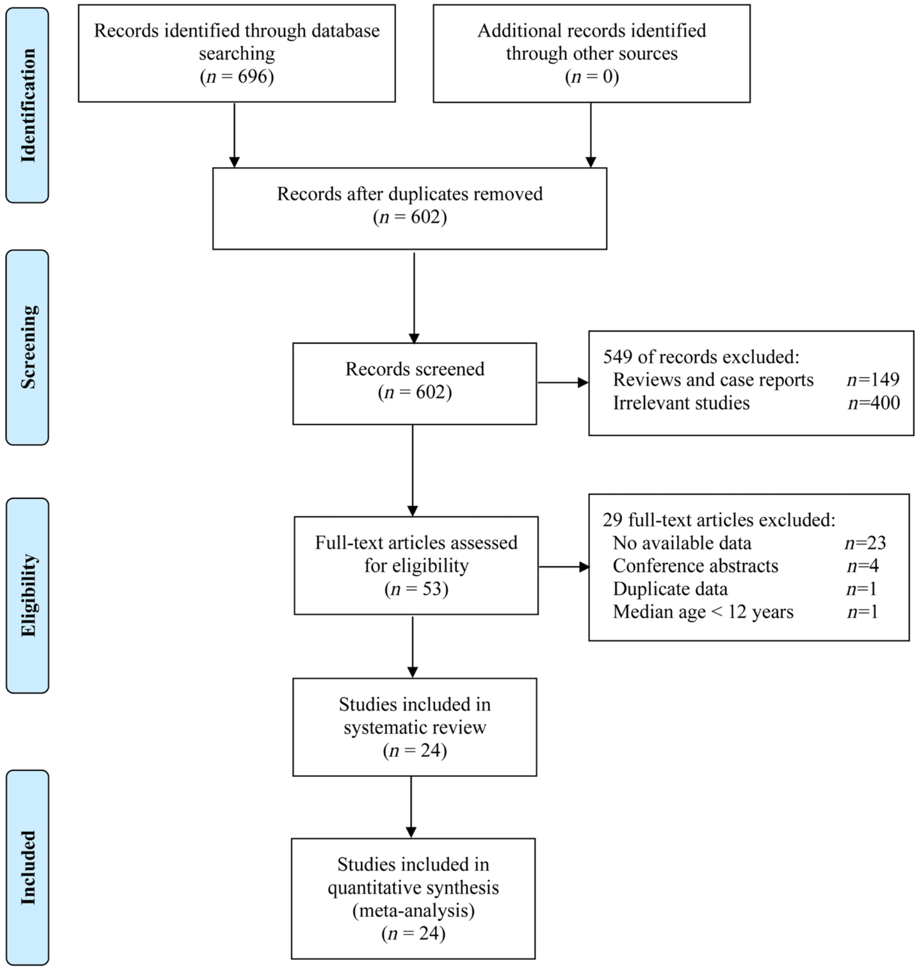

FIGURE 1 Flow diagram of the literature search and selection process

substantially altered (Supplementary Tables S11–S13). Although the significance of the adjusted estimates of LIT risk in severe RI patients *vs*. non-severe RI patients was lost after omitting the study by Choi *et al*.,[18] the trend towards a higher LIT risk in patients with severe RI was evident (OR 1.86; 95% CI 0.98, 3.52; $I^2 = 0\%$) (Supplementary Table S11). Sensitivity analysis for the adjusted LIT risk in patients with haemodialysis *vs*. patients without haemodialysis was not performed due to the limited included studies ($n = 3$). Egger's test showed no significant publication bias (Supplementary Table S14) and funnel plots are presented in Supplementary Figures S1–S4.

4 | DISCUSSION

To the best of our knowledge, the present study is the first meta-analysis evaluating the effect of renal function on the thrombocytopaenia risk in patients with linezolid. The odds of thrombocytopaenia development in patients with RI, severe RI or haemodialysis are more than double those in patients without RI, severe RI or haemodialysis, respectively. Furthermore, the Ccr and eGFR were significantly lower in patients with thrombocytopaenia than in patients without thrombocytopaenia. These findings strongly indicate that worse renal function correlates with a greater risk of LIT.

The occurrence of thrombocytopaenia reported in previous phase III trials was low, affecting approximately 2.4% of patients treated with linezolid therapy.[33] However, much higher thrombocytopaenia rates, ranging from 13.9% to 60.5%, were observed in the studies included in the present meta-analysis. We noticed that the patients enrolled in these phase III trials were mainly Western patients with a mean age of 51 years, and approximately 40% of the patients received the oral formulation and had non-severe conditions.[33] However, the patients enrolled in the present meta-analysis were mainly Asian patients with a lower body weight and patients who were older and had worse conditions than the patients in the previous phase III trials. These population discrepancies can partly explain the difference in the reported thrombocytopaenia rates, as lower body weight,[11,12] advanced age[34] and worse conditions[11,32] have been shown to be associated with the risk of LIT.

Currently, the mechanisms through which LIT occurs remain unclear. The mechanisms that have been proposed include the inhibition of the release of platelets from mature megakaryoblasts,[35] oxidative damage to platelets,[36] platelet destruction through immune-mediated processes[37,38] and mitochondrial protein synthesis inhibition.[39] Nishijo et al. performed an in vivo study using a chronic renal failure mouse model and suggested that LIT was not caused by a nonimmune-mediated mechanism.[40] Of note, the in vivo study also

TABLE 1 Characteristics of the included studies

Study	Study design	Study period	Location	*n*	Female, %	Age, years[a]	Linezolid therapy			Thrombocytopaenia	
							Duration, days[a]	Route	CLD	Rate, %	Definition
Bi 2013[10]	Ret, SC	2008–2010	China	50	28.0	81.4	13.0	IV	Yes	48.0	PLT count < 100 × 10^9/L and ≥ 25% decrease in PLT count from the baseline
Cazavet 2020[16]	Ret, SC	2010–2014	France	72	23.6	62.0[b]	9.00[b]	IV	Yes	13.9	PLT count < 100 × 10^9/L
Chen 2012[17]	Ret, SC	2010	China	254	33.5	59.0	9.43	IV/PO	Yes	27.2[c], 50.0[d]	PLT count < 100 × 10^9/L or ≥ 25% decrease in PLT count from the baseline
Choi 2019[18]	Ret, SC	2005–2016	Korea	264	41.7	63.4	13.3	IV	NA	29.2	PLT count < 100 × 10^9/L
Crass 2019[7]	Ret, SC	2007–2018	USA	341	41.6	54.0	NA	IV/PO	Yes	27.0	PLT count < 112.5 × 10^9/L or ≥ 25% decrease in PLT count from the baseline
Dai 2021[19]	Ret, SC	2012–2017	China	145	27.6	66.1	12.0[b]	IV/PO	NA	35.9	PLT count < 125 × 10^9/L and ≥ 25% decrease in PLT count from the baseline
Dong 2014[11]	Ret, SC	2008–2013	China	70	25.7	58.6	11.3	IV	Yes	44.3	PLT count < 100 × 10^9/L and ≥ 25% decrease in PLT count from the baseline
Fujii 2013[20]	Ret, SC	2011	Japan	91	22.0	68.0	8.22	IV	Yes	40.7	≥ 30% decrease in PLT count from the baseline
González-Del 2017[21]	Ret, SC	2015	Spain	549	44.8	73.3	NA	NA	NA	30.1	> 25% decrease in PLT count from the baseline
Hanai 2016[22]	Ret, SC	2004–2014	Japan	221	23.5	64.6	14.4	IV/PO	NA	48.4	> 30% decrease in PLT count from the baseline
Hirano 2014[23]	Ret, SC	2010–2012	Japan	75	28.0	64.9	12.5	IV/PO	Yes	38.7	PLT count < 100 × 10^9/L or ≥ 30% decrease in PLT count from the baseline
Ichie 2015[24]	Ret, SC	2008–2013	Japan	47	29.8	64.0	13.4	IV	Yes	53.2	≥ 30% (or 100 × 10^9/L) decrease in PLT count from the baseline
Ishida 2013[25]	Ret, SC	2007–2012	Japan	81	42.0	69.1	16.0	IV	Yes	60.5	PLT count < 100 × 10^9/L or ≥ 30% decrease in PLT count from the baseline
Kaya 2019[26]	Ret, SC	2007–2017	Turkey	371	46.6	63.6	12.8	IV/PO	Yes	29.9	PLT count < 100 × 10^9/L or ≥ 25% decrease in PLT count from the baseline
Kim 2019[5]	Ret, SC	2005–2015	Korea	60	25.0	69.8	11.5	NA	NA	48.3	PLT count < 150 × 10^9/L or ≥ 50% decrease in PLT count from the baseline
Lima 2020[8]	Ret, SC	2015–2017	Brazil	66	43.9	62.0	10.0	IV	Yes	18.2	PLT count < 100 × 10^9/L and ≥ 20% decrease in PLT count from the baseline
Lin 2006[27]	Ret, SC	2002–2004	China	62	35.5	56.9	16.9	IV	Yes	43.5	PLT count < 100 × 10^9/L or ≥ 25% decrease in PLT count from the baseline
Niwa 2014[12]	Ret, SC	2006–2009	Japan	50	36.0	63.0[b]	NA	IV	Yes	18.0	PLT count < 100 × 10^9/L and ≥ 25% decrease in PLT count from the baseline
Nukui 2013[28]	Pro, SC	2009–2011	Japan	30	30.0	46.0[b]	12.0[b]	IV/PO	Yes	56.7	> 25% decrease in PLT count from the baseline
Rabon 2018[29]	Ret, SC	2014–2016	USA	159	42.1	55.0[b]	NA	NA	NA	35.8	PLT count < 150 × 10^9/L or ≥ 50% decrease in PLT count from the baseline

TABLE 1 (Continued)

							Linezolid therapy		Thrombocytopaenia		
Study	Study design	Study period	Location	*n*	Female, %	Age, years[a]	Duration, days[a]	Route	CLD	Rate, %	Definition
Sato 2020[30]	Ret, SC	2011–2014	Japan	37	45.9	57.4	17.0[b]	IV/PO	NA	45.9	PLT count < 100 × 10^9/L or ≥ 50% decrease in PLT count from the baseline
Takahashi 2011[9]	Ret, SC	2007–2009	Japan	331	33.2	58.0	10.5	IV/PO	Yes	38.7	≥ 30% (or 100 × 10^9/L) decrease in PLT count from the baseline
Tanaka 2021[31]	Ret, SC	2015–2018	Japan	63	42.9	63.0[b]	12.0[b]	IV	NA	39.7	≥ 30% decrease in PLT count from the baseline
Wu 2006[32]	Ret, SC	2002–2004	China	91	36.3	61.5	16.2	IV/PO	Yes	53.8	PLT count < 100 × 10^9/L

Abbreviations: CLD, conventional linezolid dose (600 mg every 12 h); IV, intravenous administration; MC, multicentre; pts, patients; PO, oral administration; PLT, platelet; Pro, prospective study; Ret, retrospective study; SC, single centre.

[a]Values are expressed as mean unless specified otherwise.

[b]Values are expressed as median.

[c]Thrombocytopaenia was defined as platelet count < 100 × 10^9/L.

[d]Thrombocytopaenia was defined as ≥ 25% decrease in PLT count from the baseline.

demonstrated that thrombocytopaenia was enhanced by RI,[40] supporting the conclusions of the present meta-analysis.

Numerous clinical studies have evaluated the exposure–toxicity relationship of linezolid. A significantly higher linezolid trough concentration (C_{min}) was observed in patients with thrombocytopaenia than in patients without thrombocytopaenia.[41] Nukui et al. found that the thrombocytopaenia rate was significantly greater in patients with a linezolid C_{min} > 7.5 μg/mL.[28] Linezolid C_{min} thresholds of 6.3,[11] 6.53,[42] 7.85[43] and 8.2 mg/L[44] have all been correlated with a 50% probability of thrombocytopaenia development in various studies. Boak et al. found that linezolid exposure above 8 mg/L decreased the synthesis of platelet precursor cells by half using a newly developed population pharmacokinetic/toxicodynamic model.[45] These findings established that higher linezolid concentrations are correlated with an increased probability of thrombocytopaenia caused by linezolid.

Linezolid is eliminated by both renal and nonrenal mechanisms. Approximately 65% of linezolid is nonrenally cleared, and approximately 30% of the linezolid is cleared unchanged through the kidney in individuals with normal renal function.[46] In the presence of impaired renal function, there is a significant decrease in linezolid clearance and a high risk of overexposure. A prospective observational study involving 84 Chinese patients treated with a conventional linezolid dose found that a Ccr of ≤40 mL/min was significantly associated with linezolid overexposure, defined as C_{min} > 8 mg/L.[43] Galar et al. found that a decreased eGFR was a significant risk factor for higher linezolid C_{min} values.[47] In a study conducted in Spain, patients with an eGFR <40 mL/min had a 4.27-fold higher risk of having C_{min} > 8 mg/L than those with an eGFR >80 mL/min.[48] A large retrospective study involving 1049 patients conducted in Italy found that Ccr ≤ 40 mL/min was associated with an approximately 1.46-fold risk of linezolid overexposure, defined as C_{min} > 7 mg/L.[49] Souza et al. found that the median linezolid concentration in patients with RI (defined as an eGFR < 60 mL/min/1.73 m^2) was 1.6-fold higher than that in patients without RI.[50] Therefore, it is reasonable to speculate that the pharmacokinetic changes and the accumulation of linezolid contributed to the high risk of LIT in patients with impaired renal function. In the present study, subgroup analysis based on ethnicity was performed. Compared with studies from Asian countries, both the unadjusted and adjusted ORs of the development of LIT were higher in studies from Western countries when RI existed. This finding may be explained by the difference in body weight between Asian and Western populations, as Asian patients displayed a lower body weight and were more likely to achieve supratherapeutic exposure with the same dose.

Linezolid is metabolized via the oxidation of the morpholine ring into two major metabolites, PNU-142300 and PNU-142586.[50] Although these two metabolites do not appear to have significant antimicrobial activity, special attention should be paid to the accumulation of linezolid metabolites in individuals with impaired renal function. In an early single-dose pharmacokinetic study, the exposure to the two major metabolites was determined to be greater in patients with a Ccr <40 mL/min and haemodialysis than in those with normal renal function.[51] Similarly, Souza et al. recently found that compared

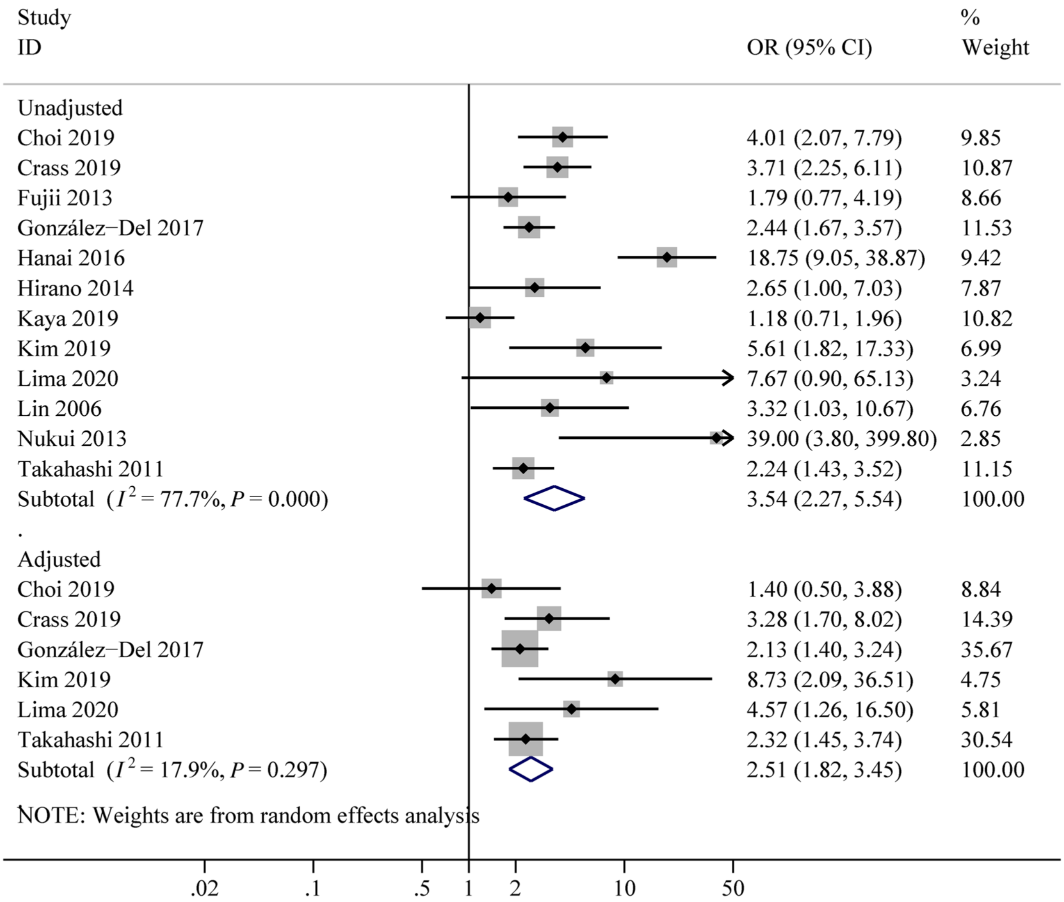

FIGURE 2 Forest plot of the association between renal impairment and thrombocytopaenia

TABLE 2 Subgroup analyses of the association between renal impairment and thrombocytopaenia caused by linezolid

	Unadjusted analysis				Adjusted analysis			
Subgroup	No. of studies	OR (95% CI)	*P*-value	I^2	No. of studies	OR (95% CI)	*P*-value	I^2
Ethnicity								
Asian patients	7	5.12 (2.45, 10.7)	<0.001	74.8	3	2.60 (1.20, 5.60)	0.015	52.5
Western patients	5	2.32 (1.53, 3.52)	<0.001	65.1	3	2.47 (1.73, 3.53)	<0.001	0
Conventional linezolid dose								
Yes	8	2.59 (1.64, 4.10)	<0.001	60.8	3	2.69 (1.83, 3.95)	<0.001	0
Not available	4	5.51 (2.15, 14.12)	<0.001	87.5	3	2.48 (1.16, 5.33)	0.02	53.8
Sample size								
Large	6	3.35 (1.84, 6.12)	<0.001	87.8	4	2.25 (1.70, 2.98)	<0.001	0
Small	6	3.72 (1.96, 7.07)	<0.001	37.3	2	6.10 (2.34, 15.88)	<0.001	0
Study quality								
High	5	5.33 (2.71, 10.46)	<0.001	75.1	3	3.10 (1.28, 7.51)	0.012	53.6
Low	7	2.28 (1.49, 3.50)	<0.001	56.6	3	2.30 (1.70, 3.13)	<0.001	0

to patients with normal renal function, the serum levels of PNU-142300 and PNU-142586 in patients with impaired renal function were 3.3- and 2.8-fold higher, respectively.[50] It may be possible that the accumulation of linezolid metabolites may contribute to the increased LIT rate. The involvement of linezolid metabolites in the development of thrombocytopaenia should be further investigated.

The recommendation for patients with impaired renal function who do not require a dose adjustment of linezolid was initially based on a previous single-dose pharmacokinetic study.[51] The results of the

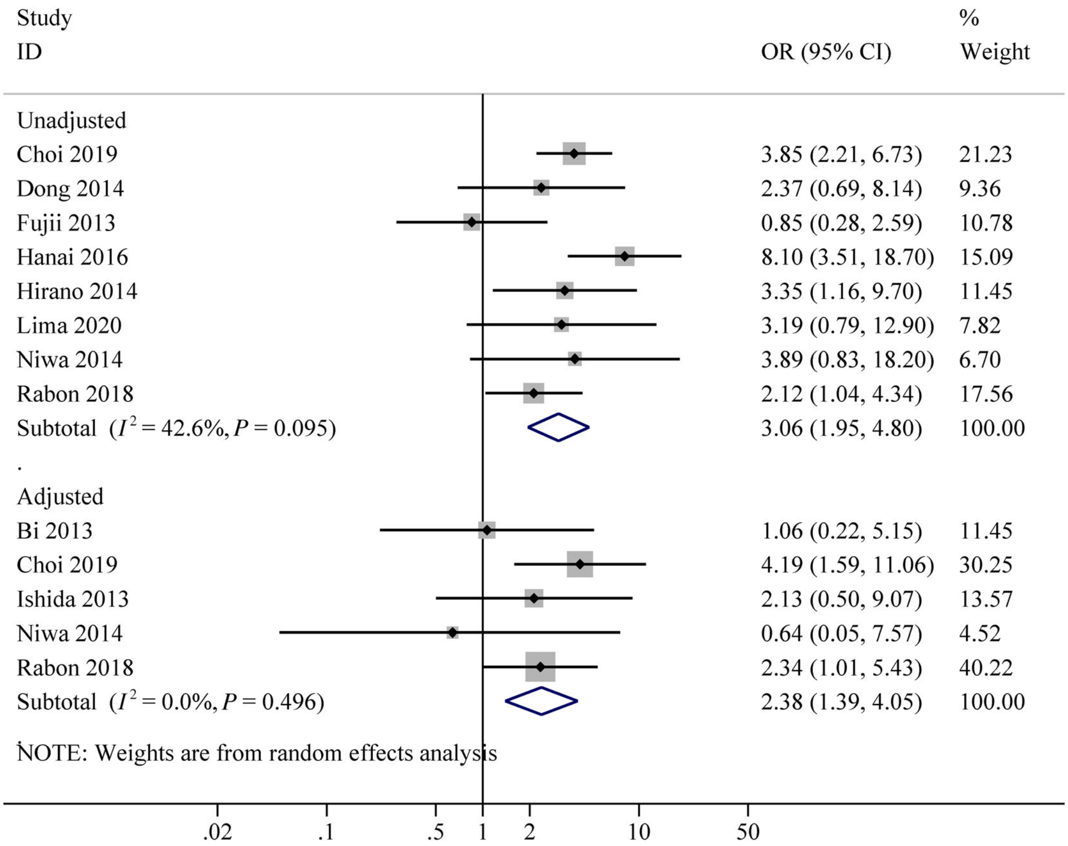

FIGURE 3 Forest plot of the association between severe renal impairment and thrombocytopaenia

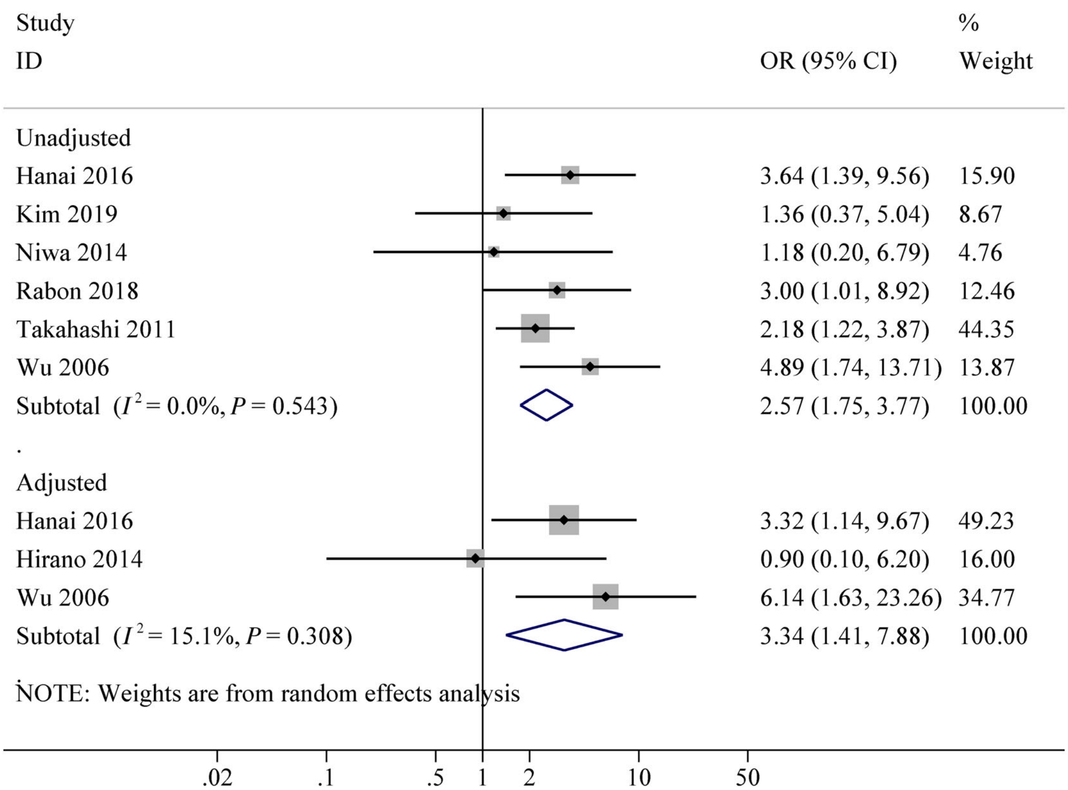

FIGURE 4 Forest plot of the association between haemodialysis status and thrombocytopaenia

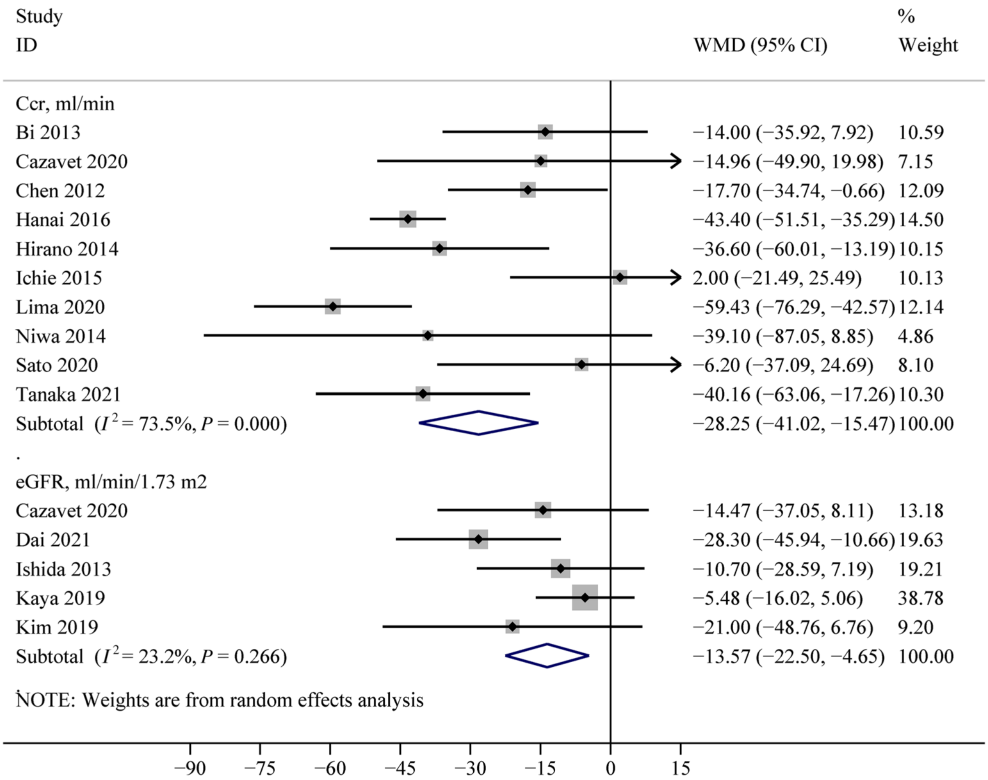

FIGURE 5 Forest plot of the comparison of indicators of renal function between thrombocytopaenia and non-thrombocytopaenia patients

study showed no significant difference in clearance of the linezolid between individuals with different levels of renal function.[51] However, an increasing number of studies have consistently demonstrated that renal function can significantly affect the pharmacokinetics (PK) of linezolid, as mentioned above. To investigate the correlation between RI and thrombocytopaenia in patients treated with a fixed conventional linezolid dose, subgroup analysis based on linezolid dose was performed in the current study. The results showed that among patients treated with a fixed conventional linezolid dose, those with RI still exhibited a significantly higher risk of thrombocytopaenia. Therefore, we questioned the rationality of the recommended dose for patients with impaired renal function in the package insert, as suggested by other authors.[6,7]

To establish optimal dose recommendations, the pharmacokinetics (PK) linked to patients and the pharmacodynamics (PD) linked to pathogenic bacteria should be considered. A ratio of the area under the curve for 24 h (AUC_{24}) to the minimum inhibitory concentration (MIC) between 80 and 120 has been shown to be the PK/PD target for the clinical effectiveness of linezolid therapy.[52] Considering the difficulty in determining AUC_{24} values, linezolid C_{min} is used as a surrogate marker of AUC_{24} in clinical practice. To achieve optimal effectiveness while minimizing the risk of adverse events, C_{min} values between 2 and 8 mg/L are recommended.

Several studies aiming to establish the optimal dose of linezolid for patients with impaired renal function have been published. Sasaki et al. conducted a population PK/PD analysis using data from 50 Japanese patients.[53] Their analysis indicated that a daily dose of 600 mg was suitable for efficacy (defined as AUC_{24}/MIC >100) against MRSA isolates with an MIC of 2 μg/mL in patients with a Ccr of ≤30 mL/min.[53] Later, Taguchi et al. reported a MRSA-infected patient with a Ccr of ≤30 mL/min who did not initially tolerate the authorized linezolid dose (600 mg every 12 h) due to thrombocytopaenia but was successfully treated without the occurrence of thrombocytopaenia after decreasing the dose by half.[54] Matsumoto et al.[44] developed a nomogram to calculate the initial daily dose of linezolid based on the Ccr value and through concentration. According to the nomogram, a daily dose of 600 mg is required to achieve a C_{min} value of 4 mg/L when the Ccr is 30 mL/min. In 2019, Crass et al.[7] developed a population PK model using data from 603 adult patients with 1309 plasma concentrations and performed a Monte Carlo simulation to identify the probability of achieving a linezolid C_{min} of 2–8 mg/L with different renal functions and dose regimens. The results demonstrated that with eGFR < 60 mL/min, more than half of the simulated patients receiving the conventional dose (600 mg every 12 h) attained C_{min} > 8 mg/L.[7] A reduced dose of 300 mg every 12 h is recommended to best balance efficacy and toxicity in patients with eGFR < 60 mL/min.[7] More recently, a Japanese study reported that all patients (n = 13) receiving a dose of 300 mg every 12 h obtained C_{min} ≥ 2 mg/L.[55] Taking these studies into account, we suggest that a reduced dose regimen, 300 mg every 12 hours, may be considered in patients with impaired renal function if the risk of treatment failure is low.

Of note, many other factors, including age,[56] body weight[56,57] and liver function,[53] have been found to impact linezolid PK. Due to the high variability of pharmacokinetic parameters and the greater susceptibility to thrombocytopaenia of patients with impaired renal function, these patients may benefit from therapeutic drug monitoring (TDM). The study by Pea et al.[42] showed that TDM-guided dose reductions allowed recovery from toxicity without compromising efficacy in approximately one-third of patients experiencing thrombocytopaenia. A similar result was observed in a recent study by Kawasuji et al.[55] Furthermore, the authors found that dose adjustment was required for 90.5% of the episodes in patients with Ccr ≤ 60 mL/min, and the application of TDM could decrease the risk of clinical failure.[55] Therefore, we recommend the application of TDM to guide the linezolid dose adjustment among patients with impaired renal function if the TDM service is available.

The present study has several strengths. First, this is the first meta-analysis that focused on the association between renal function and the development of thrombocytopaenia caused by linezolid. Our findings highlight the risk of LIT in patients with impaired renal function. Second, the unadjusted and adjusted analyses were performed separately, as recommended by the guidelines for the meta-analysis of prognostic factors.[58] These consistent results further reinforce the conclusions of the present study. Third, our work may help healthcare providers take a new look at the current recommended dose for patients with impaired renal function and may promote further research in the field of dose optimization.

There are several limitations of the present study. First, all studies included in the meta-analysis were designed as observational studies. Patient characteristics, such as baseline platelet counts, duration of linezolid therapy, or body weight stratified by renal function status, were not provided in most of the included studies, which made it difficult to evaluate whether these characteristics contributed to the observed effects. Second, the adjusted covariables differed across the included studies, and such covariables might play an important role in the development of thrombocytopaenia. Third, different definitions of thrombocytopaenia were used in different studies. We tried to perform a subgroup analysis by the thrombocytopaenia definition but failed because of the limited number of studies available for each definition. Fourth, most of the included studies were from Asian countries, accounting for 76%. More studies recruiting Western populations are needed, although a subset of the studies from Western countries showed similar results to those in the main analysis for the primary outcome.

5 | CONCLUSION

Our findings indicate that worse renal function correlates with a greater LIT risk. Patients with impaired renal function may be at a high risk of being overexposed to linezolid, eventually increasing the risk of experiencing thrombocytopaenia. A reduced linezolid dose should be considered in renal insufficiency patients at a low risk of treatment failure, ideally guided by TDM.

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COMPETING INTERESTS

All authors declare that they have no conflicts of interest.

CONTRIBUTORS

N.L. and L.W. developed the study concept and designed the research. C.S., W.J. and W.Z. conducted the electronic searches, study selection and extraction. C.S., J.X., J.Y., Y.X., L.W. and X.D. performed data analysis. C.S. wrote the manuscript. All authors read and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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