META-ANALYSIS

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

Changcheng Shi1,2 | Junbo Xia3 | Jian Ye3 | Yaping Xie4 | Weizhong Jin3 | Wei Zhang3 | Liusheng Wang3 | Xuping Ding3 | Nengming Lin1,2 | Limin Wang2,3

1Department of Clinical Pharmacy, Affiliated Hangzhou First People’s Hospital, Zhejiang University School of Medicine, Hangzhou, China
2Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Affiliated Hangzhou First People’s Hospital, Zhejiang University School of Medicine, Hangzhou, China
3Department of Respiratory Medicine, Affiliated Hangzhou First People’s Hospital, Zhejiang University School of Medicine, Hangzhou, China
4Department of Hematology, Affiliated Hangzhou First People’s Hospital, Zhejiang University School of Medicine, Hangzhou, China

Correspondence
Nengming Lin, PhD, Department of Clinical Pharmacy, Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Affiliated Hangzhou First People’s Hospital, Zhejiang University School of Medicine, No. 261 Huansha Road, Hangzhou, China.
Email: lnm1013@zju.edu.cn
Limin Wang, MD, Department of Respiratory Medicine, Key Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Affiliated Hangzhou First People’s Hospital, Zhejiang University School of Medicine, No. 261 Huansha Road, Hangzhou, China.
Email: lemonwlm@163.com

Funding information
Hangzhou Agricultural and Social Development Project, Grant/Award Number: 20201203B214; Hangzhou Health Science and Technology Planning Project, Grant/Award Number: A202000058; Health Science and Technology Program of Zhejiang Province, Grant/Award Number: 2021KY237

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.

Changcheng Shi, Junbo Xia, Jian Ye and Yaping Xie contributed equally to this work and should be considered co-first authors.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. British Journal of Clinical Pharmacology published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.
**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 thrombocytopenia, which may lead to platelet transfusions, bleeding, and even an increased risk of mortality.\(^4,5\) Cases of thrombocytopenia 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 linezolid-induced thrombocytopenia (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 thrombocytopenia risk in patients taking linezolid.

**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 thrombocytopenia was given; and (3) data for renal function and thrombocytopenia 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 thrombocytopenia. The secondary outcomes included the following: (1) comparison of the thrombocytopenia risk between patients with and without severe RI, (2) comparison of the thrombocytopenia 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 thrombocytopenia. 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 thrombocytopenia 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 thrombocytopenia, and (5) indicators 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. 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. 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 $\geq 7$ 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\(^5,7\,12,16\,18,20,22,32\) 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.\(^1\) 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 $<100 - 150 \times 10^9/L$ and/or a $\geq 50\%$ 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\(^5,7,9,18,20,22,26,28\) 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\(^5,10,12,16,17,22,29\) and five\(^9,10,12,16,17,22\) 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\(^1\) 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
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., 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 thrombocytopenia risk in patients with linezolid. The odds of thrombocytopenia 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 thrombocytopenia than in patients without thrombocytopenia. These findings strongly indicate that worse renal function correlates with a greater risk of LIT.

The occurrence of thrombocytopenia reported in previous phase III trials was low, affecting approximately 2.4% of patients treated with linezolid therapy. However, much higher thrombocytopenia 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. 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 thrombocytopenia rates, as lower body weight, advanced age and worse conditions 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, oxidative damage to platelets, platelet destruction through immune-mediated processes and mitochondrial protein synthesis inhibition. 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. Of note, the in vivo study also
| Study   | Study design | Study period | Location | $n$ | Female, % | Age, years* | Linezolid therapy | Route | CLD Rate, % | Definition                                                                 |
|---------|--------------|--------------|----------|-----|-----------|-------------|--------------------|-------|-------------|----------------------------------------------------------------------------|
| Bi 2013 | Ret, SC      | 2008–2010    | China    | 50  | 28.0      | 81.4        | 13.0               | IV    | Yes         | PLT count < 100 × $10^{9}$/L and ≥ 25% decrease in PLT count from the baseline |
| Cazavet 2020 | Ret, SC | 2010–2014    | France   | 72  | 23.6      | 62.0        | 9.00               | IV    | Yes         | PLT count < 100 × $10^{9}$/L                                                                                                   |
| Chen 2012 | Ret, SC     | 2010         | China    | 254 | 33.5      | 59.0        | 9.43               | IV/PO | Yes         | PLT count < 100 × $10^{9}$/L or ≥ 25% decrease in PLT count from the baseline                                               |
| Choi 2019 | Ret, SC      | 2005–2016    | Korea    | 264 | 41.7      | 63.4        | 13.3               | IV    | NA          | PLT count < 100 × $10^{9}$/L                                                                                                   |
| Crass 2019 | Ret, SC | 2007–2018    | USA      | 341 | 41.6      | 54.0        | NA                 | IV/PO | Yes         | PLT count < 112.5 × $10^{9}$/L or ≥ 25% decrease in PLT count from the baseline                                               |
| Dai 2014   | Ret, SC      | 2012–2017    | China    | 145 | 27.6      | 66.1        | 12.0               | IV/PO | NA          | PLT count < 125 × $10^{9}$/L and ≥ 25% decrease in PLT count from the baseline                                               |
| Dong 2014  | Ret, SC      | 2008–2013    | China    | 70  | 25.7      | 58.6        | 11.3               | IV    | Yes         | PLT count < 100 × $10^{9}$/L and ≥ 25% decrease in PLT count from the baseline                                               |
| Fujii 2013 | Ret, SC      | 2011         | Japan    | 91  | 22.0      | 68.0        | 8.22               | IV    | Yes         | ≥ 30% decrease in PLT count from the baseline                                                                              |
| González-Del 2017 | Ret, SC | 2015         | Spain    | 549 | 44.8      | 73.3        | NA                 | NA    | NA          | > 25% decrease in PLT count from the baseline                                                                              |
| Hanai 2016 | Ret, SC      | 2004–2014    | Japan    | 221 | 23.5      | 64.6        | 14.4               | IV/PO | NA          | PLT count < 100 × $10^{9}$/L and ≥ 30% decrease in PLT count from the baseline                                               |
| Hirano 2014 | Ret, SC     | 2010–2012    | Japan    | 75  | 28.0      | 64.9        | 12.5               | IV/PO | Yes         | PLT count < 100 × $10^{9}$/L or ≥ 30% decrease in PLT count from the baseline                                               |
| Ichie 2015 | Ret, SC      | 2008–2013    | Japan    | 47  | 29.8      | 64.0        | 13.4               | IV    | Yes         | ≥ 30% (or 100 × $10^{9}$/L) decrease in PLT count from the baseline                                                          |
| Ishida 2013 | Ret, SC     | 2007–2012    | Japan    | 81  | 42.0      | 69.1        | 16.0               | IV    | Yes         | PLT count < 100 × $10^{9}$/L or ≥ 30% decrease in PLT count from the baseline                                               |
| Kaya 2019  | Ret, SC      | 2007–2017    | Turkey   | 371 | 46.6      | 63.6        | 12.8               | IV/PO | Yes         | PLT count < 100 × $10^{9}$/L or ≥ 25% decrease in PLT count from the baseline                                               |
| Kim 2019   | Ret, SC      | 2005–2015    | Korea    | 60  | 25.0      | 69.8        | 11.5               | NA    | NA          | PLT count < 150 × $10^{9}$/L or ≥ 50% decrease in PLT count from the baseline                                               |
| Lima 2020  | Ret, SC      | 2015–2017    | Brazil   | 66  | 43.9      | 62.0        | 10.0               | IV    | Yes         | PLT count < 100 × $10^{9}$/L or ≥ 20% decrease in PLT count from the baseline                                               |
| Lin 2006   | Ret, SC      | 2002–2004    | China    | 62  | 35.5      | 56.9        | 16.9               | IV    | Yes         | PLT count < 100 × $10^{9}$/L or ≥ 25% decrease in PLT count from the baseline                                               |
| Niwa 2014  | Ret, SC      | 2006–2009    | Japan    | 50  | 36.0      | 63.0        | NA                 | IV    | Yes         | PLT count < 100 × $10^{9}$/L or ≥ 25% decrease in PLT count from the baseline                                               |
| Nukui 2013 | Pro, SC      | 2009–2011    | Japan    | 30  | 30.0      | 46.0        | 12.0               | IV/PO | Yes         | > 25% decrease in PLT count from the baseline                                                                              |
| Rabon 2018 | Ret, SC      | 2014–2016    | USA      | 159 | 42.1      | 55.0        | NA                 | NA    | NA          | PLT count < 150 × $10^{9}$/L or ≥ 50% decrease in PLT count from the baseline                                               |
demonstrated that thrombocytopaenia was enhanced by RI, 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 ($C_{\text{min}}$) was observed in patients with thrombocytopaenia than in patients without thrombocytopaenia. Nukui et al. found that the thrombocytopaenia rate was significantly greater in patients with a linezolid $C_{\text{min}} > 7.5 \, \mu\text{g/mL}$. Linezolid $C_{\text{min}}$ thresholds of 6.3, 6.53, 7.85 and 8.2 mg/L 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. 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. 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 $\leq 40 \, \text{mL/min}$ was significantly associated with linezolid overexposure, defined as $C_{\text{min}} > 8 \, \text{mg/L}$. Souza et al. found that a decreased eGFR was a significant risk factor for higher linezolid $C_{\text{min}}$ values. In a study conducted in Spain, patients with an eGFR $<40 \, \text{mL/min}$ had a 4.27-fold higher risk of having $C_{\text{min}} > 8 \, \text{mg/L}$ than those with an eGFR $>80 \, \text{mL/min}$. A large retrospective study involving 1049 patients conducted in Italy found that Ccr $\leq 40 \, \text{mL/min}$ was associated with an approximately 1.46-fold risk of linezolid overexposure, defined as $C_{\text{min}} > 7 \, \text{mg/L}$. Souza et al. found that the median linezolid concentration in patients with RI (defined as an eGFR $<60 \, \text{mL/min/1.73 m}^2$) was 1.6-fold higher than that in patients without RI. 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. 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 $<40 \, \text{mL/min}$ and haemodialysis than in those with normal renal function. Similarly, Souza et al. recently found that compared

| Study | Study design | Study period | Location | n | Female, % | Age, years | Route | CLD | Rate, % | Definition |
|-------|-------------|--------------|----------|---|-----------|------------|-------|-----|---------|------------|
| Sato 2020 | Ret, SC    | 2011–2014    | Japan    | 37 | 45.9      | 57.4       | IV/PO | NA  | 45.9 | PLT count < 100 $\times 10^9$/L or ≥50% decrease in PLT count from the baseline |
| Takahashi 2011 | Ret, SC | 2007–2009 | Japan | 331 | 33.2 | 58.0 | IV/PO | Yes | 38.7 | ≥30% decrease in PLT count from the baseline |
| Tanaka 2021 | Ret, SC | 2015–2018 | Japan | 63 | 42.9 | 63.0 | IV | NA | 39.7 | PLT count < 100 $\times 10^9$/L |
| Wu 2006 | Ret, SC | 2002–2004 | China | 91 | 36.3 | 61.5 | IV/PO | Yes | 53.8 | PLT count < 100 $\times 10^9$/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.

Values are expressed as mean unless specified otherwise.

Thrombocytopaenia was defined as platelet count < 100 $\times 10^9$/L.
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. 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. The results of the

table 2 subgroup analyses of the association between renal impairment and thrombocytopaenia caused by linezolid

| Subgroup                          | Unadjusted analysis | Adjusted analysis |
|-----------------------------------|---------------------|------------------|
|                                   | No. of studies | OR (95% CI) | P-value | I² | No. of studies | OR (95% CI) | P-value | I² |
| 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 | 37.2 | 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    |

FIGURE 2 Forest plot of the association between renal impairment and thrombocytopaenia
FIGURE 3  Forest plot of the association between severe renal impairment and thrombocytopaenia

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Choi 2019 | 3.85 (2.21, 6.73) | 21.23 |
| Dong 2014 | 2.37 (0.69, 8.14) | 9.36 |
| Fujii 2013 | 0.85 (0.28, 2.59) | 10.78 |
| Hanai 2016 | 8.10 (3.51, 18.70) | 15.09 |
| Hirano 2014 | 3.35 (1.16, 9.70) | 11.45 |
| Lima 2020 | 3.19 (0.79, 12.90) | 7.82 |
| Niwa 2014 | 3.89 (0.83, 18.20) | 6.70 |
| Rabon 2018 | 2.12 (1.04, 4.34) | 17.56 |
| Subtotal ($I^2 = 42.6\%, P = 0.095$) | 3.06 (1.95, 4.80) | 100.00 |

Adjusted

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Bi 2013 | 1.06 (0.22, 5.15) | 11.45 |
| Choi 2019 | 4.19 (1.59, 11.06) | 30.25 |
| Ishida 2013 | 2.13 (0.50, 9.07) | 13.57 |
| Niwa 2014 | 0.64 (0.05, 7.57) | 4.52 |
| Rabon 2018 | 2.34 (1.01, 5.43) | 40.22 |
| Subtotal ($I^2 = 0.0\%, P = 0.496$) | 2.38 (1.39, 4.05) | 100.00 |

NOTE: Weights are from random effects analysis

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

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Hanai 2016 | 3.64 (1.39, 9.56) | 15.90 |
| Kim 2019 | 1.36 (0.37, 5.04) | 8.67 |
| Niwa 2014 | 1.18 (0.20, 6.79) | 4.76 |
| Rabon 2018 | 3.00 (1.01, 8.92) | 12.46 |
| Takahashi 2011 | 2.18 (1.22, 3.87) | 44.35 |
| Wu 2006 | 4.89 (1.74, 13.71) | 13.87 |
| Subtotal ($I^2 = 0.0\%, P = 0.543$) | 2.57 (1.75, 3.77) | 100.00 |

Adjusted

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Hanai 2016 | 3.32 (1.14, 9.67) | 49.23 |
| Hirano 2014 | 0.90 (0.10, 6.20) | 16.00 |
| Wu 2006 | 6.14 (1.63, 23.26) | 34.77 |
| Subtotal ($I^2 = 15.1\%, P = 0.308$) | 3.34 (1.41, 7.88) | 100.00 |

NOTE: Weights are from random effects analysis
study showed no significant difference in clearance of the linezolid between individuals with different levels of renal function.\textsuperscript{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.\textsuperscript{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\textsubscript{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.\textsuperscript{52} Considering the difficulty in determining AUC\textsubscript{24} values, linezolid C\textsubscript{min} is used as a surrogate marker of AUC\textsubscript{24} in clinical practice. To achieve optimal effectiveness while minimizing the risk of adverse events, C\textsubscript{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.\textsuperscript{53} Their analysis indicated that a daily dose of 600 mg was suitable for efficacy (defined as AUC\textsubscript{24}/MIC >100) against MRSA isolates with an MIC of 2 μg/mL in patients with a Ccr of ≤30 mL/min.\textsuperscript{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.\textsuperscript{54} Matsumoto et al.\textsuperscript{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\textsubscript{min} value of 4 mg/L when the Ccr is 30 mL/min. In 2019, Crass et al.\textsuperscript{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\textsubscript{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\textsubscript{min} > 8 mg/L. A reduced dose of 300 mg every 12 h is recommended to best balance efficacy and toxicity in patients with eGFR < 60 mL/min.\textsuperscript{7} More recently, a Japanese study reported that all patients (n = 13) receiving a dose of 300 mg every 12 h obtained C\textsubscript{min} ≥ 2 mg/L.\textsuperscript{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,\textsuperscript{56} body weight,\textsuperscript{56,57} and liver function,\textsuperscript{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, it is crucial to adjust the linezolid dose based on individual characteristics.
function, these patients may benefit from therapeutic drug monitoring (TDM). The study by Pea et al.\textsuperscript{42} showed that TDM-guided dose reductions allowed recovery from toxicity without compromising efficacy in approximately one-third of patients experiencing thrombocytopenia. A similar result was observed in a recent study by Kawasui et al.\textsuperscript{55} Furthermore, the authors found that dose adjustment was required for 90.5% of the episodes in patients with $\text{Ccr} \leq 60 \text{ mL/min}$, and the application of TDM could decrease the risk of clinical failure.\textsuperscript{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 thrombocytopenia 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.\textsuperscript{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 covariates differed across the included studies, and such covariates might play an important role in the development of thrombocytopenia. Third, different definitions of thrombocytopenia were used in different studies. We tried to perform a subgroup analysis by the thrombocytopenia 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 thrombocytopenia. A reduced linezolid dose should be considered in renal insufficiency patients at a low risk of treatment failure, ideally guided by TDM.

ACKNOWLEDGEMENTS

This study was supported by Hangzhou Health Science and Technology Planning Project (grant number: A20200058), Health Science and Technology Program of Zhejiang Province (grant number: 2021KY237), and Hangzhou Agricultural and Social Development Project (grant number: 202012038214).

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., 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.

ORCID

Changcheng Shi https://orcid.org/0000-0003-1616-3958
Nengming Lin https://orcid.org/0000-0001-5202-802X

REFERENCES

1. Clemett D, Markham A. Linezolid. Drugs. 2000;59(4):815–827.
2. Roger C, Roberts JA, Muller L. Clinical pharmacokinetics and pharmacodynamics of oxazolidinones. Clin Pharmacokinet. 2018;57(5):559-575.
3. Wang Y, Zou Y, Xie J, et al. Linezolid versus vancomycin for the treatment of suspected methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a systematic review employing meta-analysis. Eur J Clin Pharmacol. 2015;71(1):107-115.
4. Attassi K, Hershberger E, Alam R, Zervos MJ. Thrombocytopenia associated with linezolid therapy. Clin Infect Dis. 2002;34(5):695-698.
5. Kim HS, Lee E, Cho YJ, Lee YJ, Rhie SJ. Linezolid-induced thrombocytopenia increases mortality risk in intensive care unit patients, a 10 year retrospective study. J Clin Pharm Ther. 2019;44(1):84-90.
6. Cossu AP, Musu M, Mura P, De Giudici LM, Finco G. Linezolid-induced thrombocytopenia in impaired renal function: is it time for a dose adjustment? A case report and review of literature. Eur J Clin Pharmacol. 2014;70(1):23-28.
7. Crass RL, Cojutti PG, Pai MP, Pea F. Reappraisal of linezolid dosing in renal impairment to improve safety. Antimicrob Agents Chemother. 2019;63:e00605-e00619.
8. Lima LS, Brito EDCA, Mattos K, Parisotto EB, Perdomo RT, Weber SS. A retrospective cohort study to screen linezolid-induced thrombocytopenia in adult patients hospitalized in the Midwestern Region of Brazil. Hematol Transfus Cell Ther. 2020;42(3):230-237.
9. Takahashi Y, Takesue Y, Nakajima K, et al. Risk factors associated with the development of thrombocytopenia in patients who received linezolid therapy. J Infect Chemother. 2011;17(3):382-387.
10. Bi LQ, Zhou J, Huang M, Zhou SM. Efficacy of linezolid on gram-positive bacterial infection in elderly patients and the risk factors associated with thrombocytopenia. Pak J Med Sci. 2013;29(3):837-842.
11. Dong HY, Xie J, Chen LH, Wang TT, Zhao YR, Dong YL. Therapeutic drug monitoring and receiver operating characteristic curve prediction may reduce the development of linezolid-associated thrombocytopenia in critically ill patients. Eur J Clin Microbiol Infect Dis. 2014;33(6):1029-1035.
12. Niwa T, Watanabe T, Suzuki A, et al. Reduction of linezolid-associated thrombocytopenia by the dose adjustment based on the risk factors such as basal platelet count and body weight. Diagn Microbiol Infect Dis. 2014;79(1):93-97.
13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603-605.

14. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14(1):135.

15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.

16. Cazavet J, Bounes FV, Ruiz S, et al. Risk factor analysis for linezolid-associated thrombocytopenia in critically ill patients. *Eur J Clin Microbiol Infect Dis*. 2020;39(3):527-538.

17. Chen C, Guo DH, Cao X, et al. Risk factors for thrombocytopenia in adult Chinese patients receiving linezolid therapy. *Curr Ther Res Clin Exp*. 2012;73(6):195-206.

18. Choi GW, Lee JY, Chang MJ, et al. Risk factors for linezolid-induced thrombocytopenia in patients without haematoma-oncologic diseases. *Basic Clin Pharmacol Toxicol*. 2019;124(2):228-234.

19. Dai Y, Jiang S, Chen X, et al. Analysis of the risk factors of linezolid-related haematological toxicity in Chinese patients. *J Clin Pharm Ther*. 2021;46(3):807-813.

20. Fuji S, Takahashi S, Makino S, et al. Impact of vancomycin or linezolid therapy on development of renal dysfunction and thrombocytopenia in Japanese patients. *Chemotherapy*. 2013;59(5):319-324.

21. González-Del Castillo J, Candel FJ, Manzano-Lorenzo R, Arias L, García-Lamberechts EJ, Martín-Sánchez FJ. Predictive score of haematological toxicity in patients treated with linezolid. *Eur J Clin Microbiol Infect Dis*. 2017;36(8):1511-1517.

22. Hanai Y, Matsuo K, Ogawa M, et al. A retrospective study of the risk factors for linezolid-induced thrombocytopenia and anemia. *J Infect Chemother*. 2016;22(8):536-542.

23. Hirano R, Sakamoto Y, Tachibana N, Ohnishi M. Retrospective analysis of the risk factors for linezolid-induced thrombocytopenia in adult Japanese patients. *Int J Clin Pharmacol*. 2014;36(4):795-799.

24. Ichie T, Suzuki D, Yasui K, et al. The association between risk factors and time of onset for thrombocytopenia in Japanese patients receiving linezolid therapy: a retrospective analysis. *J Clin Pharm Ther*. 2015;40(3):279-284.

25. Ichie T, Suzuki D, Makino S, et al. Impact of vancomycin or linezolid therapy on development of renal dysfunction and thrombocytopenia in Japanese patients. *Chemotherapy*. 2013;59(5):319-324.

26. Ishida S, Maeda K, Nishio C, Nakai Y. Risk factors of linezolid-induced thrombocytopenia. *Jpn J Chemother*. 2012;67(8):2034-2042.

27. Fang J, Chen C, Wu Y, et al. Does the conventional dosage of linezolid necessitate therapeutic drug monitoring?—Experience from a prospective observational study. *Ann Transl Med*. 2020;8(7):493.

28. Matsumoto K, Shimégi A, Takeshi A, et al. Analysis of thrombocytopenic effects and population pharmacokinetics of linezolid: a dosage strategy according to the trough concentration target and renal function in adult patients. *Int J Antimicrob Agents*. 2014;44(3):242-247.

29. Boak LM, Rayner CR, Grayson ML, et al. Clinical population pharmacokinetics and toxicodynamics of linezolid. *Antimicrob Agents Chemother*. 2014;58(4):2334-2343.

30. Slatter JG, Stalker DJ, Feenstra KL, et al. Pharmacokinetics, metabolism, and excretion of linezolid following an oral dose of [14C]linezolid to healthy human subjects. *Drug Metab Dispos*. 2001;29(8):1136-1145.

31. Galan A, Valero M, Muñoz P, et al. Systematic therapeutic drug monitoring for linezolid: variability and clinical impact. *Antimicrob Agents Chemother*. 2017;61(10):e00687-17.

32. Morata L, De la Calle C, Gómez-Cerquera JM, et al. Risk factors associated with high linezolid trough plasma concentrations. *Expert Opin Pharmacother*. 2016;17(9):1183-1187.

33. Pea F, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. *J Antimicrob Chemother*. 2012;67(8):2034-2042.

34. Nishijo N, Tsuji Y, Matsunaga K, et al. Mechanism underlying linezolid-induced thrombocytopenia in a chronic kidney failure mouse model. *J Pharmacol Pharmacother*. 2017;8(1):9-13.

35. Ichie T, Suzuki D, Yasui K, et al. The association between risk factors and time of onset for thrombocytopenia in Japanese patients receiving linezolid therapy: a retrospective analysis. *J Clin Pharm Ther*. 2015;40(3):279-284.

36. Ichie T, Suzuki D, Makino S, et al. Impact of vancomycin or linezolid therapy on development of renal dysfunction and thrombocytopenia in Japanese patients. *Chemotherapy*. 2013;59(5):319-324.

37. Ishida S, Maeda K, Nishio C, Nakai Y. Risk factors of linezolid-induced thrombocytopenia. *Jpn J Chemother*. 2012;67(8):2034-2042.

38. Fang J, Chen C, Wu Y, et al. Does the conventional dosage of linezolid necessitate therapeutic drug monitoring?—Experience from a prospective observational study. *Ann Transl Med*. 2020;8(7):493.

39. Morata L, De la Calle C, Gómez-Cerquera JM, et al. Risk factors associated with high linezolid trough plasma concentrations. *Expert Opin Pharmacother*. 2016;17(9):1183-1187.

40. Pea F, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. *J Antimicrob Chemother*. 2012;67(8):2034-2042.

41. Slatter JG, Stalker DJ, Feenstra KL, et al. Pharmacokinetics, metabolism, and excretion of linezolid following an oral dose of [14C]linezolid to healthy human subjects. *Drug Metab Dispos*. 2001;29(8):1136-1145.

42. Galan A, Valero M, Muñoz P, et al. Systematic therapeutic drug monitoring for linezolid: variability and clinical impact. *Antimicrob Agents Chemother*. 2017;61(10):e00687-17.

43. Morata L, De la Calle C, Gómez-Cerquera JM, et al. Risk factors associated with high linezolid trough plasma concentrations. *Expert Opin Pharmacother*. 2016;17(9):1183-1187.

44. Pea F, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. *J Antimicrob Chemother*. 2012;67(8):2034-2042.
53. Sasaki T, Takane H, Ogawa K, et al. Population pharmacokinetic and pharmacodynamic analysis of linezolid and a hematologic side effect, thrombocytopenia, in Japanese patients. *Antimicrob Agents Chemother*. 2011;55(5):1867-1873.

54. Taguchi K, Miyakawa T, Ohmura T, et al. A reduced linezolid dosage maintains favorable efficacy with minimal hematologic toxicity in a methicillin-resistant *Staphylococcus aureus*-infected patient with renal insufficiency. *Scand J Infect Dis*. 2013;45(1):77-80.

55. Kawasuji H, Tsuji Y, Ogami C, et al. Proposal of initial and maintenance dosing regimens with linezolid for renal impairment patients. *BMC Pharmacol Toxicol*. 2021;22(1):13.

56. Abe S, Chiba K, Cirincione B, Grasela TH, Ito K, Suwa T. Population pharmacokinetic analysis of linezolid in patients with infectious disease: application to lower body weight and elderly patients. *J Clin Pharmacol*. 2009;49(9):1071-1078.

57. Tsuji Y, Yukawa E, Hiraki Y, et al. Population pharmacokinetic analysis of linezolid in low body weight patients with renal dysfunction. *J Clin Pharmacol*. 2013;53(9):967-973.

58. Riley RD, Moons KGM, Snell KIE, et al. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ*. 2019;364:k4597.

**SUPPORTING INFORMATION**

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

---

**How to cite this article:** Shi C, Xia J, Ye J, et al. Effect of renal function on the risk of thrombocytopaenia in patients receiving linezolid therapy: A systematic review and meta-analysis. *Br J Clin Pharmacol*. 2022;88(2):464-475. [https://doi.org/10.1111/bcp.14965](https://doi.org/10.1111/bcp.14965)