

# Effect of Platelet Parameters on Linezolid-Related Thrombocytopenia in Hospitalized Patients

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**Background:** Linezolid-induced thrombocytopenia incidence varies considerably. Linezolid-related thrombocytopenia in patients has received few studies which have investigated risk factors including platelet parameters except for platelet counts. The study aims to analyze the effect of platelet parameters, including mean platelet volume and platelet large cell ratio, on linezolid-related thrombocytopenia in patients.

**Methods:** The effect of platelet parameters on linezolid-related thrombocytopenia was identified by univariate and multivariate logistic regressions. A Kaplan–Meier survival analysis was carried out to compare the survival of patients who developed linezolid-related thrombocytopenia with patients who did not.

**Results:** Thrombocytopenia occurred at a rate of 41.5% (66/159) after linezolid therapy in hospitalized patients. Platelet parameters, including the difference in mean platelet volume (MPV/fL=0.08 (−1.2–0.9)vs-0.5 (−1.5–0.3), (OR, 0.459;  $P = 0.001$ ), the difference in platelet large cell ratio (PLCR/fL=0.9 (−5.1–6.2)vs-3.8 (−8.6–2.4), (OR, 1.156;  $P = 0.001$ ), baseline platelet counts (OR, 0.995;  $P = 0.006$ ) and duration of linezolid therapy  $\geq 10$ d (OR, 1.346;  $P = 0.007$ ), were significantly associated with linezolid-related thrombocytopenia in hospitalized patients. In addition, other risk factors which also are associated with linezolid-related thrombocytopenia include baseline red blood cells, co-medication with parecoxib and co-medication with caspofungin. Accumulated in-hospital mortality of patients with thrombocytopenia was significantly higher than that of patients without thrombocytopenia during linezolid treatment (19.7% vs 8.6%,  $P = 0.003$ ).

**Conclusion:** The difference in mean platelet volume, the difference in large platelet ratio, baseline platelet counts and duration of linezolid therapy  $\geq 10$ d significantly affected the development of linezolid-related thrombocytopenia in hospitalized patients.

**Keywords:** linezolid, platelet parameters, thrombocytopenia, risk factors

## Introduction

Linezolid is the first approved fully synthetic oxazolidinone antibacterial drug, in (vancomycin-resistant enterococci-resistant *Enterococcus*, VRE), methicillin-resistant *Staphylococcus aureus* (multi-drug-resistant *Staphylococcus aureus*, MRSA), *Mycobacterium tuberculosis* (*Mycobacterium tuberculosis*) infection and other diseases treatment playing a pivotal role in.<sup>1,2</sup> With the clinical application of linezolid, a wide range of thrombocytopenia caused by same (adverse drug reaction, ADR) has become increasingly prominent, and the risk of treatment failure in patients has increased.<sup>3</sup>

Thrombocytopenia, defined as a platelet count  $< 75\%$  of baseline count and  $< 100 \times 10^9/L$  after medication,<sup>3</sup> or defined as a  $\geq 10 \times 10^4$  cells/mm<sup>3</sup> decrease from the baseline or a  $\geq 30\%$  reduction,<sup>4</sup> is among the most common adverse events during linezolid treatment.<sup>5,6</sup> Due to the difference in inclusion criteria and/or exclusion criteria among prior studies, the incidence of thrombocytopenia varies considerably (2.4–78.6%).<sup>7–9</sup>

The utility of platelet parameters have been found to play an important role in discerning thrombocytopenia.<sup>10</sup> For example, platelet size, measured as MPV and PLCR, has been proved to have prognostic and diagnostic values in discriminating thrombocytopenia.<sup>11</sup> It also has been found to be a factor for discriminating hypoproliferative and hyperdestructive thrombocytopenia.<sup>12</sup> A strong positive correlation is found between MPV and quantities of granular megakaryocytes ( $P = 0.03$ ), whereas a negative relationship existed between MPV and platelet-form megakaryocytes

( $P = 0.028$ ).<sup>13</sup> MPV and PLCR were significantly higher in patients with immune thrombocytopenia than in patients with hypoproliferative thrombocytopenia ( $P < 0.0001$ ).<sup>14</sup> Although studies have reported that lower baseline platelet values,<sup>3</sup> lower body weight<sup>15</sup> and longer medication time<sup>16</sup> et al in patients are independent risk factors for linezolid-related thrombocytopenia, few studies have investigated platelet parameters as risk factors for linezolid-related thrombocytopenia.

Previous studies have reported thrombocytopenia induced by linezolid at various levels, improvement of treatment measures, clinical efficacy of linezolid, and predictors of linezolid-induced thrombocytopenia. However, studies are insufficient and often limited due to variability in study design and patient populations. Most studies included patients with a hematological neoplastic disease. Such a disease may considerably hamper the assessment of thrombocytopenia. In addition, some published studies on risk factors for linezolid-induced thrombocytopenia from Asian countries and several Western countries showed considerable inter-study variability in their findings.

Therefore, the purpose of this study is to identify the effect of platelet parameters on linezolid-related thrombocytopenia in hospitalized Chinese patients (patients with hematological malignancies are excluded) by analyzing risk factors of thrombocytopenia in hospitalized patients treated with linezolid.

## Materials and Methods

### Patients and Study Design

The study population included hospitalized patients treated with linezolid in a tertiary teaching hospital in China during the period from January 2020 to December 2021. Inclusion criteria: (1) patients received linezolid therapy during hospitalization; (2) patients with at least two of the following symptoms: i) body temperature  $> 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ ; ii) respiration rate ( $> 20$  times/min) or  $\text{PaCO}_2 < 32\text{mmHg}$ ; iii) heart rate  $> 90$  times/min; iv) peripheral white blood cell (WBC) count  $> 10 \times 10^9/\text{L}$ , peripheral WBC count  $< 4 \times 10^9/\text{L}$ , or normal peripheral WBC count but immature cells  $> 10\%$ . Exclusion criteria: (1) patients with incomplete data; or (2) pregnant patients.

For each included patient, a standardized electronic case report system was used by investigators to collect data including social demographic characteristics, clinical diagnosis, comorbidities, laboratory values, length of ICU and hospital stay. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, and the informed consent was waived since the study was retrospective and the data were collected anonymously.

### Definition

In the present study, thrombocytopenia was defined as a decrease in platelet count of  $\geq 25\%$  and a final count of  $< 100 \times 10^9/\text{L}$ .<sup>3</sup>

After 7 days of medication. In the present study, thrombocytopenia was defined as a decrease in platelet count of  $\geq 25\%$  and a final count of  $< 100 \times 10^9/\text{L}$ . 159 inpatients of 66 (41.5%) had thrombocytopenia after Linezolid treatment. Count the cases where the decrease in platelet count after medication is greater than or equal to 25% compared to the baseline examination value before medication, as shown in the Table 1.

### Statistical Analysis

Quantitative variables were summarized with mean  $\pm$  standard deviation (SD) or median with interquartile range (IQR) depending on normality of the distribution. Number (percentage) was used for qualitative variables. The Shapiro–Wilk

**Table 1** Status of Thrombocytopenia in Positive Cases

Reduction Grouping	n	Composition Ratio/%
25% ~ 40%	26	39.39
40% ~ 50%	30	45.45
> 50%	9	13.64

test was carried out to test normality. Independent *t* test or Mann–Whitney *U*-test was implemented for data comparison while appropriate and categorical variables are analyzed with Chi-square test or Fisher exact test. Variables with  $P < 0.1$  in the univariate analysis were included in the multivariate analysis. Before multivariate analysis, collinearity test was conducted to determine the collinearity among those factors. If tolerance (*T*)  $> 0.1$  or variance inflation factor (VIF)  $< 10$ , no collinearity existed among those factors. Then risk factors were confirmed according to the multivariate analysis. The odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were reported.

The cumulative incidence of in-hospital mortality, was compared through a Log rank test and presented with Kaplan–Meier curves.

All statistical analysis was performed on the Statistical Package for the Social Sciences version 19.0 (SPSS, Chicago, IL, USA). All tests were two-side, and  $P < 0.05$  was considered statistically significant.

## Results

### Demographics and Clinical Characteristics of Study Population

A total of 159 hospitalized patients received linezolid therapy from January 2020 to December 2021 were finally included in the study, of which male patients accounting for 67.3% (107/159). The patients' median age was 62 years, and 69 of 159 patients (43.3%) aged  $\geq 65$  years. The leading infection type was pulmonary infection (86.2%), followed by intra-abdominal infection (27.0%). Specific patient characteristics are shown in Table 2. Platelet count in patients with thrombocytopenia: Before medication:  $(159.1 \pm 57.3) \times 10^9/L$  and After medication:  $(105.6 \pm 51.3) \times 10^9/L$  in Figure 1.

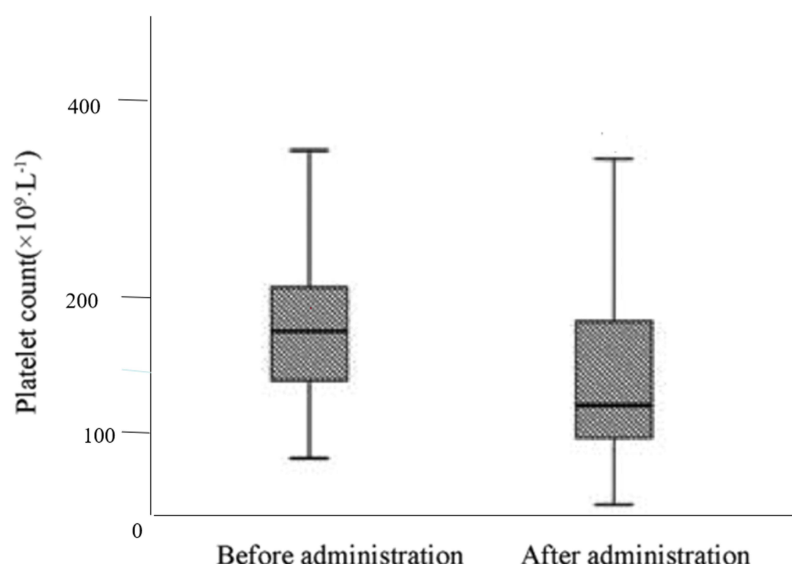
### Risk Factors Associated with Thrombocytopenia

Among the patients included, 66 (41.5%) patients developed thrombocytopenia. Table 3 shows the demographic data, comorbidities, laboratory tests and concomitant medications of hospitalized patients with linezolid-related thrombocytopenia and patients without thrombocytopenia.

**Table 2** Characteristics of Patients Enrolled in the Study

Characteristic	Study Population
Demographic analysis	
Age (median, IQR)	62 (17–89)
Age ( $\geq 65$ year), <i>n</i> (%)	69 (43.3)
Sex (male), <i>n</i> (%)	107 (67.3)
Length of hospital stay (median, IQR)	14 (7–25)
Thrombocytopenia, <i>n</i> (%)	66 (41.5)
Comorbidities, <i>n</i> (%)	
Renal insufficiency	105 (66.0)
Liver disease	157 (98.7)
MODS	76 (47.8)
Hypoproteinemia	64 (40.3)
CRRT, <i>n</i> (%)	87 (54.7)
Type of infection, <i>n</i> (%)	
Pulmonary infection	137 (86.2)
Intra-abdominal infection	43 (27)
Urinary tract infection	33 (20.8)
Bacteremia	12 (7.5)
Skin and skin structure infection	13 (8.2)
Other sites infection	20 (12.6)
Empirical medication	58 (36.5)
Hospitalized death, <i>n</i> (%)	21 (13.2)

**Abbreviations:** MODS, multiple organ dysfunction syndrome; CRRT, continuous renal replacement therapy; IQR, interquartile range.



**Figure 1** Trend in platelet counts before and following linezolid.

In the univariate analysis, renal insufficiency, CRRT, the difference in MPV, the difference in PLCR, baseline PLT counts, baseline RBC, baseline CREA, baseline ALT, lactic acid <2.5 mmol/L, combined use of parecoxib or/and caspofungin were associated with a higher risk of linezolid related thrombocytopenia in hospitalized patients ( $P < 0.1$ ). No significant difference was observed in the thrombocytopenia incidence in relation to other baseline levels and other concurrent medications, including baseline CREA, baseline ALT and CRRT et al [Table 3](#) details the information of the patients.

According to the univariate analysis, the collinearity of these potential prognostic variables was estimated. No multicollinearity was found with  $VIF < 10$ . Therefore, the aforementioned factors were included in the multivariate analysis. Finally, the multivariate analysis shows that the difference in MPV ( $OR$ , 0.459 [95% CI, 0.372–0.857];  $P = 0.001$ ), the

**Table 3** Univariate Logistic Regression Results for Risk Factors Developing Thrombocytopenia

Characteristic	Patients with Thrombocytopenia (n = 66)	Patients without Thrombocytopenia (n = 93)	P-value
Demographic analysis			
Age (median, IQR)	62 (48.5–72)	61 (47.5–74)	0.525 <sup>b</sup>
Sex (male), n (%)	43 (56.5)	64 (68.8)	0.911 <sup>c</sup>
Medication days (median, IQR)	6 (4–10)	6 (3–10)	0.442 <sup>b</sup>
Length of hospital stay (median, IQR)	14 (6–25)	14 (7–24)	0.879 <sup>b</sup>
Duration of linezolid therapy (median, IQR)	12 (8.5–17)	6 (3–10)	0.001 <sup>c</sup>
ICU admission, n (%)	36 (54.5)	48 (51.6)	0.972 <sup>c</sup>
Comorbidities, n (%)			
Renal insufficiency	58 (87.9)	93 (57.0)	0.049 <sup>c</sup>
Liver disease	65 (98.5)	92 (98.9)	0.936 <sup>c</sup>
Hypoproteinemia	31 (47.0)	33 (35.5)	0.186 <sup>c</sup>
MODS	32 (48.5)	43 (46.2)	0.638 <sup>c</sup>
Invasive procedure, n (%)			
CRRT	48 (72.7)	39 (41.9)	0.004 <sup>c</sup>
Laboratory values			
The difference of MPV, fL (median, IQR)	−0.08 (−1.2–0.9)	−0.5 (−1.5–0.3)	0.051 <sup>b</sup>
The difference of PLCR, (median, IQR)	0.9 (−5.1–6.2)	−3.8 (−8.6–2.4)	0.002 <sup>b</sup>

(Continued)

Table 3 (Continued).

Characteristic	Patients with Thrombocytopenia (n = 66)	Patients without Thrombocytopenia (n = 93)	P-value
Baseline PLT counts, $\times 10^9/L$ (median, IQR)	105.6 (68.8–153.2)	138.5 (50.1–212)	0.019 <sup>b</sup>
Baseline RBC, $\times 10^{12}/L$ (median, IQR)	2.9 (2.6–3.8)	3.5 (2.9–3.9)	0.005 <sup>b</sup>
Baseline ALB, g/L (median, IQR)	27.5 $\pm$ 6.4	28.2 $\pm$ 4.9	0.315 <sup>a</sup>
Baseline CREA, $\mu\text{mol/L}$ (median, IQR)	145 (62.1–293.5)	108.6 (43–221)	0.005 <sup>b</sup>
Baseline BUN, mmol/L (median, IQR)	11.3 (7.2–21.3)	10.2 (5.8–16.3)	0.285 <sup>b</sup>
Baseline ALT, U/L (median, IQR)	22.1 (13.9–52.6)	38 (21.5–93.2)	0.003 <sup>b</sup>
Baseline AST, U/L (median, IQR)	53.5 (21–100.2)	46 (25–109)	0.856 <sup>b</sup>
Baseline ALP, U/L (median, IQR)	99.5 (55.1–144.2)	97 (65–157.9)	0.527 <sup>b</sup>
Baseline total bilirubin, $\mu\text{mol/L}$ (median, IQR)	21.3 (8.2–49.3)	19.8 (11–45.6)	0.956 <sup>b</sup>
Co-medications, n (%)			
Proton pump inhibitor	45 (68.2)	72 (77.4)	0.631 <sup>c</sup>
Amiodarone	18 (27.2)	9 (9.6)	0.066 <sup>c</sup>
Aspirin	8 (12.2)	10 (10.7)	0.831 <sup>c</sup>
Calcium antagonist	9 (13.6)	12 (12.9)	0.572 <sup>c</sup>
Parecoxib	21 (31.8)	11 (11.8)	0.008 <sup>c</sup>
Caspofungin	26 (39.4)	24 (25.8)	0.018 <sup>c</sup>
Levofloxacin	8 (12.1)	13 (13.9)	0.539 <sup>c</sup>
Meropenem	37 (56.1)	42 (45.2)	0.817 <sup>c</sup>
Glucocorticoids	53 (80.3)	65 (70.0)	0.136 <sup>c</sup>
Hospitalized death, n (%)	13 (19.7)	8 (8.6)	0.003 <sup>c</sup>

Notes: <sup>a</sup>Independent t test. <sup>b</sup>Mann–Whitney U-test. <sup>c</sup>Pearson's Chi-squared test.

Abbreviations: MODS, multiple organ dysfunction syndrome; CRRT, continuous renal replacement therapy; the difference of MPV, the difference between mean platelet volume of starting and stopping linezolid; the difference of PLCR, the difference between platelet large cell ratio of starting and stopping linezolid; PLT, platelet; RBC, red blood cells; ALB, albumin; CREA, creatinine; BUN, blood urea nitrogen; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; IQR, interquartile range.

difference in PLCR (*OR*, 1.156 [95% CI, 1.078–1.359]; *P* = 0.001), baseline platelet counts (*OR*, 0.995 [95% CI, 0.991–0.998]; *P* = 0.006), baseline RBC (*OR*, 0.578 [95% CI, 0.459–0.916]; *P* = 0.005), co-medication with parecoxib (*OR*, 1.346 [95% CI, 0.951–1.528]; *P* = 0.007), duration of linezolid therapy  $\geq 10$  d (*OR*, 1.169 [95% CI, 0.857–1.421]; *P* = 0.001), co-medication with caspofungin (*OR*, 2.521 [95% CI, 1.056–6.238]; *P* = 0.001) were found to be independently associated with linezolid-related thrombocytopenia in hospitalized patients (Table 4).

Kaplan–Meier curves demonstrated a higher accumulated incidence of in-hospital mortality in patients suffered from linezolid-related thrombocytopenia than those who did not. *P* value is 0.003 from the Log rank test, as shown in Figure 2.

## Discussion

66 hospitalized patients developed thrombocytopenia after linezolid therapy.

A previous study by Shen et al, found that LI-TP was closely associated with the duration of linezolid treatment, with their ROC curve indicating that a treatment duration  $\geq 12$  days was more likely to cause thrombocytopenia. Nukui et al, reported that half of the patients in their study developed thrombocytopenia within days of linezolid treatment, which is consistent with our results that 49.3% of elderly patients developed LI-TP within 10 days of initiating linezolid treatment. Duration of linezolid therapy  $\geq 10$  days was considered a significant risk factor for LI-TP in elderly patients in this study. Several studies speculated that LI-TP is caused by inhibiting the proliferation of progenitor cells and the onset of the decrease in platelet count is delayed and reaches a nadir at around 2 weeks.

In the present study, we found that the difference in MPV and the difference in PLCR were independently risk factors influencing thrombocytopenia in patients. To our knowledge, this relationship has not been reported previously. It has been demonstrated that some morphological platelet indices, such as MPV, are valuable for distinguishing

**Table 4** Factors Independently Associated with Thrombocytopenia in Hospitalized Patients with Linezolid Therapy

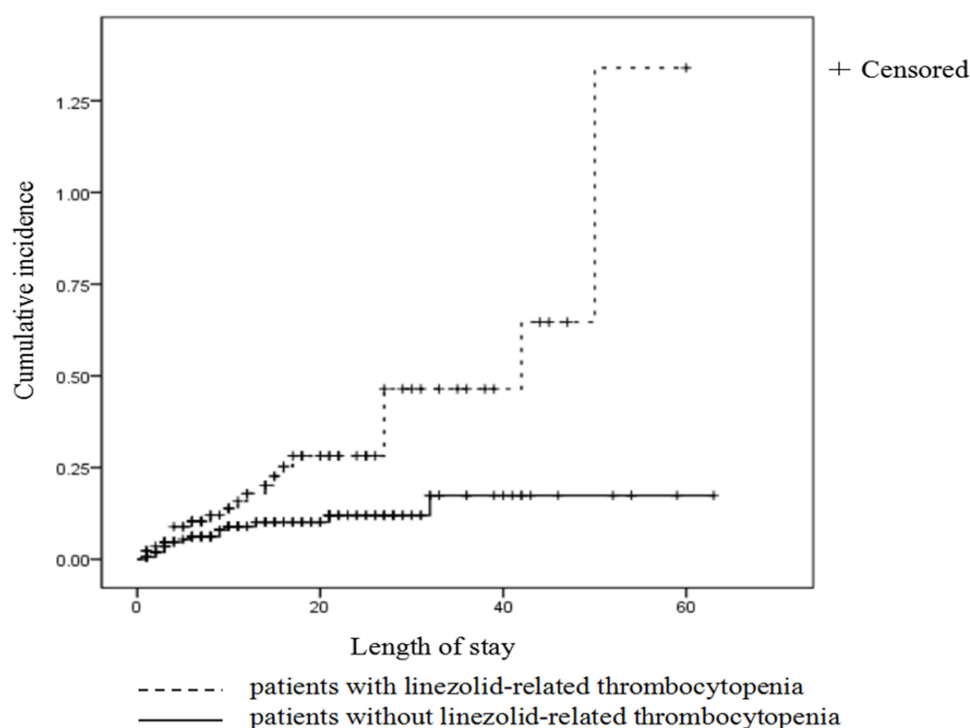
Variable	Estimate	s.e.	Wald's $\chi^2$	OR (95% CI)	P-value
Renal insufficiency	0.085	0.301	0.026	1.712 (0.531–2.675)	0.931
CRRT	0.283	0.361	0.797	1.486 (0.812–2.397)	0.452
<b>Duration of linezolid therapy <math>\geq 10</math> d</b>	<b>0.956</b>	<b>0.001</b>	<b>21.58</b>	<b>1.169 (0.857–1.421)</b>	<b>0.001</b>
<b>The difference of MPV</b>	<b>−0.006</b>	<b>0.201</b>	<b>15.632</b>	<b>0.459 (0.372–0.857)</b>	<b>0.001</b>
<b>The difference of PLCR</b>	<b>0.135</b>	<b>0.027</b>	<b>13.622</b>	<b>1.156 (1.078–1.359)</b>	<b>0.001</b>
<b>Baseline PLT counts, <math>\times 10^9/L</math></b>	<b>−0.005</b>	<b>0.001</b>	<b>7.855</b>	<b>0.995 (0.991–0.998)</b>	<b>0.006</b>
<b>Baseline RBC, <math>\times 10^{12}/L</math></b>	<b>−0.539</b>	<b>0.317</b>	<b>7.8</b>	<b>0.578 (0.459–0.916)</b>	<b>0.005</b>
<b>Caspofungin</b>	<b>0.975</b>	<b>0.318</b>	<b>5.94</b>	<b>2.521 (1.056–6.238)</b>	<b>0.025</b>
CREA, $\mu\text{mol/L}$	0.261	0.006	0.009	1.311 (0.998–1.561)	0.939
<b>Parecoxib</b>	<b>0.753</b>	<b>0.268</b>	<b>9.5</b>	<b>1.346 (0.951–1.528)</b>	<b>0.007</b>
ALT, U/L	0.001	0.005	0.312	1.000 (0.999–1.001)	0.683

**Note:** Bold part represents: a higher risk of linezolid related thrombocytopenia in hospitalized patients ( $P < 0.1$ ).

**Abbreviations:** CRRT, continuous renal replacement therapy; the difference of MPV, the difference between mean platelet volume of starting and stopping linezolid; the difference of PLCR, the difference between platelet large cell ratio of starting and stopping linezolid; PLT, platelet; RBC, red blood cells; CREA, creatinine; ALT, alanine transaminase.

thrombocytopenia. MPV is process in bone marrow.<sup>17</sup> Enlarged MPV can be used as a measurement of young platelets, indicating that the origin of thrombocytopenia was peripheral destruction.<sup>18</sup> Previous studies have shown that the mechanism for thrombocytopenia in patients was the increased platelet destruction caused by platelet desialylation.<sup>19</sup> Thus, we tentatively speculated that the mechanism of thrombocytopenia in patients treated with linezolid might be decreased platelet count generation.

In addition, an increase in PLCR may indicate the presence of platelet aggregates, micro-erythrocytes, and giant platelet.<sup>20</sup> Therefore, the increase in PLCR may be caused by the aggregation of platelets when they exert antimicrobial effect. Additionally, platelets generated from megakaryocytes in the bone marrow and released in the bloodstream

**Figure 2** Kaplan–Meier estimates of the cumulative incidence of in-hospital mortality.



through pseudopodial projections named proplatelets.<sup>21,22</sup> The increase in the ratio of large platelets indicates that the mechanism of small platelets formation was impaired and the maturity was lowered. Therefore, we speculated that linezolid related thrombocytopenia may be caused by the decreased platelet production and increased platelet aggregation reflected by the increase in PLCR. Future work should explore the potential pathophysiologic link between platelet parameters and platelet dysfunction.

A previous study pointed out that for the blood in patients with risk factors such as advanced age and low platelet baseline value, the risk of thrombocytopenia is higher.<sup>5,6</sup> The relation between plate reduction and the combination of the above risk factors and thrombocytopenia has not been reported so far. It is worth mentioning that previous studies have shown that compared with patients with lower platelet counts, the rate of thrombocytopenia in patients with higher baseline platelet counts is about 5 times higher.<sup>12</sup> Meanwhile, the data in this treatise point out that patients with high baseline platelet counts are more likely to have a large and rapid platelet drop within 7 days of medication. In addition, patients with less concomitant anti-infective drugs often have low level of infection, relatively high baseline platelet value, and are more likely to develop platelet drop in a short time.

The mechanism of thrombocytopenia caused by linezolid is still unclear. Given the recent advances in our understanding and the studies on the role of platelet indices in thrombocytopenia, we imply that the inhibition of the formation of platelets may be a mechanism of linezolid-related thrombocytopenia.

Previous studies have shown that lower baseline platelet count may be closely related to linezolid-associated thrombocytopenia.<sup>23,24</sup> Zhang et al reported that the ratio of platelet count (day 7/day 0) < 1 ( $OR = 10.021$ ;  $P = 0.012$ ) and the baseline platelet count ( $OR = 0.985$ ;  $P = 0.036$ ) were independent risk factors of thrombocytopenia at day 14 of linezolid therapy in patients with acute-on-chronic liver failure.<sup>25</sup> Choi et al reported that only baseline platelet count <  $150 \times 10^3/\text{mm}^3$  was an independent predictor of early-onset ( $\leq 6$  days) thrombocytopenia.<sup>26</sup> It seems to indicate that the occurrence of linezolid-related thrombocytopenia is dependent on baseline platelet counts.

Baseline red blood cells were found to be associated with thrombocytopenia in this study. The increased risk of thrombocytopenia could be related to linezolid-induced myelosuppression, leading to red cell aplasia<sup>27</sup> or abnormal erythroblast morphology.<sup>28</sup> Whereas Bernstein et al failed to find any association,<sup>29</sup> their conclusion may remain some uncertainties. Since some of their studies were based on case reports, the conclusions varied according to the difference in pathophysiological conditions. On the contrary, the present research identified the mechanism from the platelet indicators with a relatively large sample size. However, the assessment of the mechanism of linezolid-induced thrombocytopenia would be useful on the molecular level.

In the present study, the co-medication with parecoxib or/and caspofungin was a risk factor for thrombocytopenia which may be accounted for the variability in linezolid concentration caused by parecoxib, and may significantly alter plasma linezolid exposure.<sup>30</sup> Studies have shown that linezolid caused thrombocytopenia related to higher drug exposure.<sup>31</sup> In addition, caspofungin induced peripheral destruction of platelets acts as a likely contributor to linezolid induced thrombocytopenia.<sup>32</sup>

The patients included in this study were not monitored for blood drug concentration, but the dose of Linezolid and the change of blood drug concentration were related to the incidence of thrombocytopenia. According to relevant literature studies, thrombocytopenia is related to the valley concentration of Linezolid. The target concentration of Linezolid (2–8 mg/L), the higher the valley concentration, the higher the incidence of adverse reactions. Zuo M et al<sup>33–35</sup> found that creatinine clearance, hemodialysis, duration of Linezolid use, and valley concentration of Linezolid were independent risk factors for thrombocytopenia. The steady-state trough concentration of Linezolid was significantly correlated with thrombocytopenia. These studies all show that the thrombocytopenia caused by Linezolid is related to the dosage and trough concentration of the drug.

In-hospital mortality estimated by Kaplan–Meier method was higher in hospitalized patients with thrombocytopenia after linezolid treatment (19.7% vs 8.6%,  $P = 0.003$ ). The increased mortality in septic thrombocytopenic patients could be explained by increased serious thrombotic complications and platelet consumption reflected by thrombocytopenia or increased bleeding frequency/severity.<sup>36</sup> Therefore, linezolid-related thrombocytopenia is associated with higher mortality during sepsis.

Thrombocytopenia is one of the common indicators of poor prognosis in critically ill patients, and is associated with longer ICU hospital stays and higher mortality rates.<sup>37</sup> GURU K et al<sup>38</sup> et al showed that patients with thrombocytopenia at admission were treated with Linezolid, the mortality rate was three times that of patients without thrombocytopenia, and every 50% increase in platelet, accompanied by a 40% decrease in mortality rate. According to Du et al,<sup>39</sup> the main causes of death of critically ill patients who were treated with Linezolid included Respiratory failure, septic shock and organ failure. Previous studies have confirmed that thrombocytopenia is associated with multiple system and organ dysfunction such as ALI, ARDS, capillary leakage syndrome, acute renal failure, and septic shock.<sup>40,41</sup> Therefore, thrombocytopenia may lead to adverse outcomes such as patient death through multiple complex pathophysiological pathways. We look forward to more basic research to elucidate the mechanisms behind this.

In clinical work regarding linezolid-related thrombocytopenia, the harm of rare diseases and complex risk factors should be responded with the following proper prevention and treatment measures. ① Linezolid should only be used in the treatment or prophylaxis of confirmed or highly suspected infections caused by susceptible bacteria, In order to reduce the generation of drug-resistant bacteria and ensure the linezolid efficacy of amines. The use of linezolid in elderly and young patients with severe infections should be of particular concern. ② Reduce the combined use of antibacterial drugs as much as possible. ③ Blood routine tests are required before and during the medication. Monitoring is necessary to reduce the occurrence of serious adverse events. ④ In the event of linezolid-related thrombocytopenia, the use of drug should be discontinued immediately. Platelet counts generally return to normal/basal levels within 7 to 14 days. When platelet counts are significantly reduced, platelet transfusion, subcutaneous injection of human thrombopoietin and other treatments should be carried out.

There remain some limitations in the study. Firstly, the results lack molecular regulation of the mechanism of linezolid-related thrombocytopenia. Secondly, some factors may be missed since most of the factors considered in our study were based on literatures. Finally, the mechanism of linezolid-induced thrombocytopenia has not yet been elucidated, and there is still controversy over the topic. Therefore, further studies are required for the verification on cellular and molecular level. Despite of these limitations, the results may attribute to the study on the mechanism of linezolid-induced thrombocytopenia.

## Conclusion

Platelet parameters, including the difference in MPV, the difference in PLCR and baseline platelet counts were significantly associated with the occurrence of linezolid-related thrombocytopenia in patients. Platelet parameters have an important implication in linezolid-induced thrombocytopenia. Platelet parameters monitoring should be encouraged for optimizing the utilization of linezolid in hospitalized patients.

## Data Sharing Statement

The clinical data of patients used to support the findings of this study are included within the article.

## Ethical Approval

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) [XJTU1AF2019LSK-163] and complied with the Declaration of Helsinki.

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## Disclosure

The authors declare that there is no conflict of interest in this work.



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