BMC Pharmacology and Toxicology

RESEARCH

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Development and validation of a nomogram to predict linezolid-induced thrombocytopenia in hospitalized adults

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Abstract

Background Linezolid (LZD) is used to treat infectious diseases caused by Gram-positive bacteria, but thrombocytopenia is one of the main adverse reactions to LZD administration. Early prediction of linezolid-induced thrombocytopenia (LI-TP) is of great importance to improve the clinical outcomes and prognoses. The aim of this study was to develop and validate a prediction model for LI-TP.

Methods A retrospective cohort of hospitalized adults receiving LZD therapy (January 2014–June 2022) was analyzed. Independent risk factors for LI-TP were identified via logistic regression in the training set ($n=757$). A nomogram model for LI-TP were developed based on independent risk factors, and verified in validation set ($n=123$).

Results The incidence of LI-TP was 13.5% (102/757). A logistic regression model was developed based on the seven independent risk factors, including age (≥ 60 y), duration of LZD therapy (> 11 d), bPLT ($< 308\times10^9$/L), ALT (> 100 IU/L), Ccr (< 67.5 mL/min), and concomitant use with VPA or Tac ($p<0.01$) and transformed into a quantifiable nomogram. The nomogram demonstrated strong discrimination with AUCs of 0.760 in training (95% CI: 0.709–0.812, $P<0.001$) and 0.767 in validation (95% CI: 0.635–0.899, $P<0.001$). The calibration curves and Hosmer-Lemeshow tests confirmed good reliability and specificity of the nomogram model.

Conclusion This nomogram provides a practical tool for stratifying LI-TP risk, which provide an important reference for enabling timely clinical interventions to enhance LZD safety.

Keywords Linezolid, Thrombocytopenia, Prediction model, Adverse reaction, Risk factors

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Background

Linezolid (LZD), classified as an oxazolidone antibiotic, is used to treat infectious diseases, including sepsis, bacterial pneumonia, skin and soft tissue infections, caused by Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* [1]. Currently, LZD is known as one of the most important anti-infection drugs and has been used in more than 60 countries. Although widely used in clinic, LZD administration caused many adverse reactions, such as hematotoxicity, gastrointestinal disorders and cutaneous reactions [2, 3]. Hematotoxicity includes anemia, eosinophilia, myelosuppression, neutropenia, cell aplasia and thrombocytopenia [4]. Thrombocytopenia (TP), with a reported incidence of 15–50%, is considered one of the major adverse events caused by LZD administration [5, 6]. Linezolid- induced thrombocytopenia (LI-TP) occurred in 2.4% of patients in a phase III trial, and two other previous studies reported rates of 3.3% [7] and 6.4% [8] among hospitalized patients respectively. Serious patients experience active gastrointestinal bleeding [9] or even death [10, 11]. Therefore, occurrence of LI-TP should be more attention.

There have been studies on the risk factors for LI-TP, which suggested that LI-TP was associated with prolonged treatment duration [12], renal insufficiency [13–16], chronic liver disease [15], a low baseline platelet count [17], daily per kg dose [5, 18], body weight [19, 20] and hypoalbuminemia [19]. However, data on the incidence and predictors of LI-TP are inadequate because of the diversity of patients or study designs. More importantly, the occurrence of LI-TP involves the comprehensive effect of risk factors rather than individual risk factors, which need to develop a prediction model. Studies have established prediction models for LI-TP in neonatal sepsis patients [21], critically ill patients [22] and elderly patients [23], but there are differences in methods and conclusions. Few studies have predicted the risk of LI-TP in adult patients by prediction models transformed into quantifiable nomograms.

The purposes of our study were to develop a prediction model that could be transformed into a quantifiable nomogram based on risk factors for LI-TP to predict the occurrence of LI-TP and then verify the prediction efficacy of the model to improve the safety of LZD administration in clinic.

Methods

Study design and definition

This was a retrospective study conducted at the First Affiliated Hospital of Army Medical University. Data were collected from patients treated with LZD (purchased from Fresenius Kabi Norge AS licensed by Pfizer AS) between January 2014 and June 2022. Patients enrolled between January 2014 and October 2020 were used for the training set, while patients enrolled between November 2020 and June 2022 were used for the validation set (Fig. 1).

The inclusion criteria were as follows: patients who were ≥ 18 years old who were administered LZD (600 mg every 12 h) for ≥ 5 days. The exclusion criteria were as follows: (1) patients who were diagnosed with haematooncologic diseases or myelosuppression as the original disease; (2) patients who were bleeding or received blood transfusions within one month before LZD therapy; (3) patients who underwent chemotherapy or radiotherapy within two weeks before LZD therapy; (4) patients with incomplete case information; (5) patients with a baseline platelet count that was not measured within 1 week before LZD therapy; (6) patients with a baseline platelet count greater than 450×10^9/L or less than 150×10^9/L; and (7) patients whose platelet counts were not routinely monitored during LZD therapy (Fig. 1).

Thrombocytopenia was defined as a platelet count less than 150×10^9/L [24]. The severity of thrombocytopenia was classified into the following categories based on the nadir platelet count [25]: mild, $101–149 \times 10^9$/L, moderate, $51–100 \times 10^9$/L, and severe, $\leq 50 \times 10^9$/L. Creatinine clearance (Ccr) was calculated by the Cockcroft-Gault equation based on serum creatinine levels.

Blood collection and analysis

Blood samples were collected via venipuncture using EDTA anticoagulant tubes. Platelet counts were measured using the SYSMEX XN-9000 automated hematology analyzer. Other laboratory parameters, including ALT, AST, and creatinine clearance (Ccr), were measured using standard laboratory techniques.

Patient groups and data collection

Patients were divided into two groups: the LI-TP group and the no thrombocytopenia (NO-TP) group. The characteristics, laboratory data and concomitant medications of patients were collected. The characteristics included age, sex, body weight and duration of LZD therapy (DLT), and the baseline laboratory data that were measured before treatment with LZD within 1 to 7 days included baseline platelet count (bPLT), hemoglobin (HGB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin (ALB), total bilirubin (TBIL), D-dimer, prothrombin time (PT), creatinine clearance (Ccr), blood sugar level (BSL), and concomitant medication that was reported for thrombocytopenia during the use of LZD, including piperacillin-tazobactam (PPC-TZBT), meloxicillin-sulbactam (MLC/SBT), cefoperazone-sulbactam (CFZ/SBT), ceftazidime (CAZ), aspirin, valproate (VPA) and tacrolimus (Tac) [26].

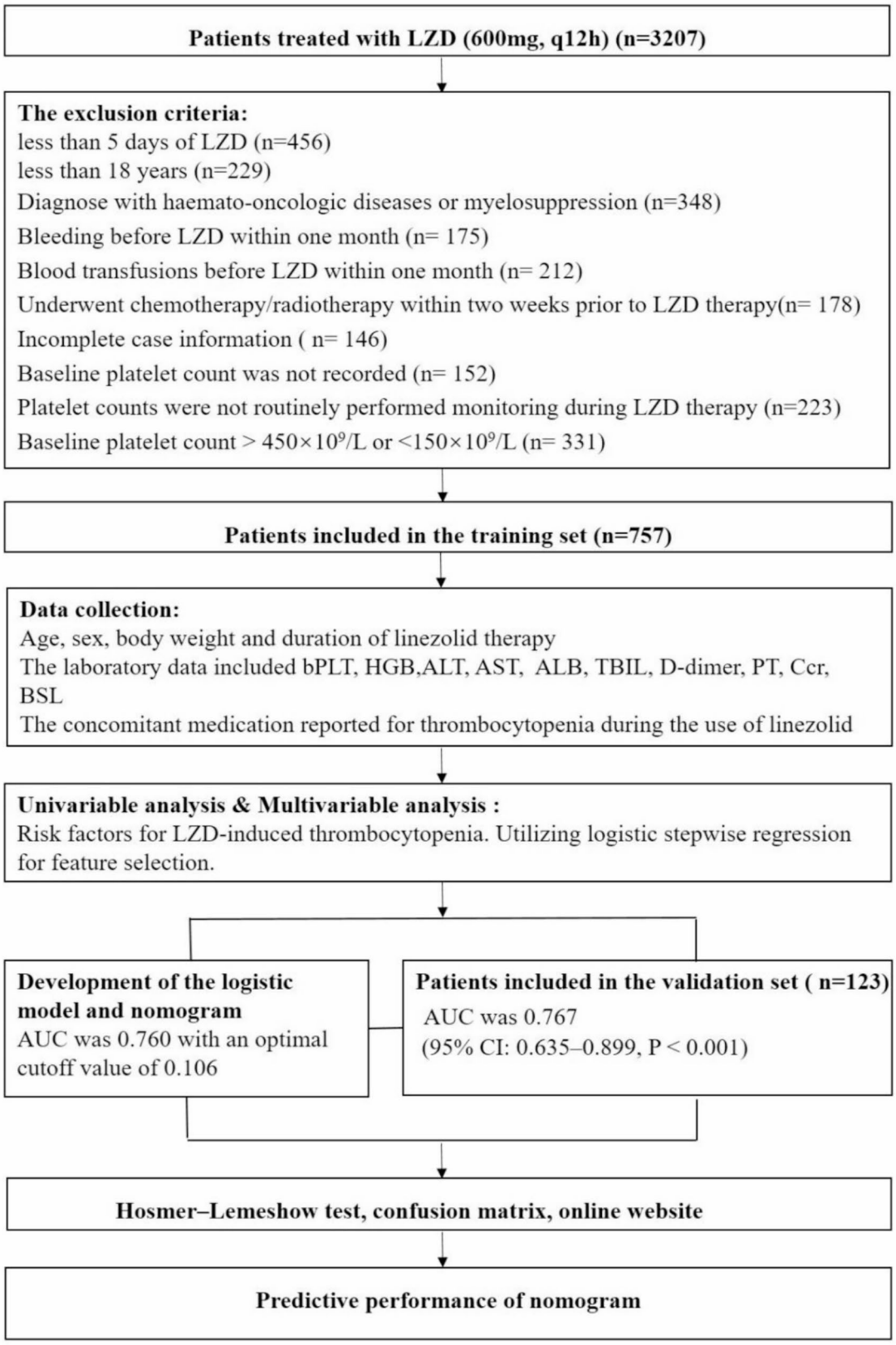

Fig. 1 The flow charts of the study process. LZD: linezolid; n: number

Statistical analysis

The normality of descriptive data was assessed using the Shapiro-Wilk test. Normally distributed data are presented as mean ± standard deviation (SD), while non-normally distributed data are expressed as median (interquartile range). Categorical variables are reported as frequency (n) and percentage (%), with group's comparisons performed using the χ^2 test or Fisher's exact test. For risk factor analysis, continuous variables (age, weight, treatment days, baseline platelet count, and creatinine clearance) were dichotomized based on cutoff values determined by the maximum Youden index and subsequently included in the analysis. Univariable and multivariable analyses were conducted to identify risk factors for LI-TP. Variables with a univariable *P*-value < 0.05 were incorporated into the multivariable model for stepwise regression analysis. Model performance in both training and validation sets was evaluated using receiver operating characteristic (ROC) curves, calibration curves, and confusion matrices. Survival curves for each risk factor were generated and compared using the Kaplan-Meier method and log-rank test. All P-values were two-tailed, and statistical significance was defined as $P < 0.05$. Data analysis was performed using SPSS 27.0 (IBM, Armonk, NY, USA) and R software (version 4.2.2, http://www.r-project.org/).

Results

Demographic and clinical characteristics of patients

In the 3207 cases of training set, 757 patients were included based on the inclusion criteria (Fig. 1). Male and female patients comprised 73.18% (554/757) and 26.82% (203/757), respectively, and their median age was 51 (41, 65) years, with 33.55% (254/757) of patients aged ≥ 60 years. The median body weight was 60 (59, 67), with 33.42% (253/757) of patients weighing ≥ 62 kg. The median duration of LZD therapy and baseline platelet level were 9 (7, 13) days and 251 (199,314) $\times 10^9$/L, respectively (Table 1).

Table 1 Demographic and clinical characteristics of 757 patients treated with LZD

Characteristic	Total patients (*n* = 757)	NO-TP (*n* = 655)	LI-TP (*n* = 102)	χ^2	*P*
Demographic					
Gender				0.007	0.932
Male, n (%)	554(73.18)	479(73.13)	75(73.53)		
Female, n (%)	203(26.82)	176(26.87)	27(26.47)		
Age (years), median (IQR)	51(41,65)	50(40,63)	61(44.75,73.25)	19.875	<0.01
Age ≥ 60 years, n (%)	254(33.55)	200(30.53)	54(52.94)		
Weight (kg), median (IQR)	60(59, 67)	60(60,67.5)	60(55,67.5)	4.207	0.04
Weight ≥ 62 kg, n (%)	253(33.42)	228(34.81)	25(24.51)		
Duration of linezolid therapy (DLT, days), median (IQR)	9(7,13)	9(7,13)	10.5(7,14)	5.273	0.022
Duration of linezolid therapy > 11 days, n (%)	272(35.93)	225(34.35)	47(46.08)		
Baseline laboratory data					
Platelets (10^3/mm^3), median (IQR)	251(199,314)	254(203,322)	238.5(185,278.5)	16.969	<0.01
Platelets < 308 × 10^3/mm^3, n (%)	548(72.39)	457(69.771)	91(89.22)		
Hemoglobin < 10 g/dL, n (%)	241(31.84)	213(32.519)	28(27.45)	1.045	0.307
Alanine aminotransferase (ALT) > 100 IU/L, n (%)	48(6.34)	35(5.344)	13(12.75)	8.141	0.004
Aspartate aminotransferase (AST) > 80 IU/L, n (%)	74(9.78)	57(8.70)	17(16.67)	6.347	0.012
Total bilirubin > 1.2 mg/dL, n (%)	122(16.12)	105(16.03)	17(16.67)	0.026	0.871
Serum albumin < 2.5 g/dL, n (%)	68(8.98)	59(9.01)	9(8.82)	0.004	0.952
Prothrombin time > 17 s, n (%)	11(1.45)	7(1.069)	4(3.92)	-	0.048
D-dimer > 10.55 mg/L, n (%)	25(3.30)	21(3.21)	4(3.92)	-	0.764
Blood sugar level (BSL) > 200mmol/L, n (%)	548(72.39)	34(5.19)	10(9.80)	3.431	0.064
Creatinine clearance (Ccr) < 67.5 mL/min, n (%)	241(31.84)	507(77.40)	56(54.90)	23.447	< 0.001
Concomitant medication, n (%)					
Piperacillin-Tazobactam	53(7.00)	47(7.18)	6(5.88)	0.227	0.634
Meloxicillin-Sulbactam	10(1.32)	9(1.37)	1(0.98)	-	1.000
Cefperazone-Sulbactam	68(8.98)	54(8.24)	14(13.73)	3.243	0.072
Ceftazidime	60(7.93)	54(8.24)	6(5.88)	0.675	0.411
Aspirin	18(2.38)	17(2.60)	1(0.98)	-	0.493
Sodium valproate (VPA)	29(3.83)	21(3.21)	8(7.84)	-	0.045
Tacrolimus (Tac)	13(1.72)	6(0.92)	7(6.86)	-	< 0.001

IQR, interquartile range; SD, standard deviation

Among 757 patients in the training set, 102 (13.5%) developed LI-TP, predominantly mild ($101–149 \times 10^9$/L). 44.12% (45/102) of patients terminated LZD therapy, whereas 55.88% (57/102) of the remaining patients did not take any measures. The all-cause mortality rate in the LI-TP group was 1.96% (2/102). The most common combination drug that caused thrombocytopenia during LZD therapy was cefoperazone-sulbactam (8.98%), followed by ceftazidime (7.93%) (Table 1). Platelet counts after the last dose of LZD were monitored in 62.7% (64/102) of patients who discontinued LZD therapy and returned to normal in all patients. None of the patients required platelet or red blood cell transfusion.

Risk factors for LZD induced thrombocytopenia

Univariate analysis was performed to determine the risk factors for LI-TP among abnormal clinical characteristics, demographic characteristics and concomitant medication use. The following ten variables were associated with LI-TP: age (≥60 y) (odds ratio (OR) [95% CI]: 2.559 [1.677–3.906]; $p<0.001$), body weight (>62 kg) (OR [95% CI]: 0.608 [0.377–0.982]; $p=0.042$), duration of LZD therapy (>11 d) (OR [95% CI]: 1.633 [1.072–2.489]; $p=0.023$), bPLT ($<308 \times 10^9$/L) (OR [95% CI]: 3.584 [1.876–6.849]; $p<0.001$), ALT (>100 IU/L) (OR [95% CI]: 2.587 [1.318–5.078]; $p=0.006$), AST (>80 IU/L) (OR [95% CI]: 2.098 [1.166–3.775]; $p=0.013$), PT (>17 s) (OR [95% CI]: 3.778 [1.086–13.145]; $p=0.037$), Ccr (<67.5 mL/min) (OR [95% CI]: 2.814 [1.829–4.329]; $p<0.001$), and concomitant use with VPA (OR [95% CI]: 2.569 [1.106–5.967]; $p=0.028$) or Tac (OR [95% CI]: 7.97 [2.623–24.22]; $p<0.001$).

Independent risk factors for LZD induced thrombocytopenia

Logistic regression analysis was used to analyze the independent risk factors for LI-TP. Seven independent risk factors were identified: age (≥60 y) (OR [95% CI]: 3.08 [1.84–5.18]; $p<0.001$), duration of LZD therapy (>11 d) (OR [95% CI]: 1.79 [1.13–2.84]; $p=0.013$), bPLT ($<308 \times 10^9$/L) (OR [95% CI]: 3.87 [2.05–8.02]; $p<0.001$), ALT (>100 IU/L) (OR [95% CI]: 3.83 [1.76-8.00]; $p<0.001$), Ccr (<67.5 mL/min) (OR [95% CI]: 1.92[1.15–3.21]; $p=0.012$), and concomitant use with VPA (OR [95% CI]: 3.48 [1.29–8.64]; $p=0.009$) or Tac (OR [95% CI]: 8.61 [2.52–30.44]; $p<0.001$) (Fig. 2A).

To determine the temporal correlation between the seven independent risk factors and LI-TP, Kaplan–Meier analysis was performed for the seven independent risk factors and revealed a higher cumulative incidence of LI-TP among patients aged ≥60 years, with a bPLT $<308 \times 10^9$/L, ALT >100 IU/L, and Ccr <67.5 mL/min, and concomitant use with VPA or Tac (Fig. 2B-G).

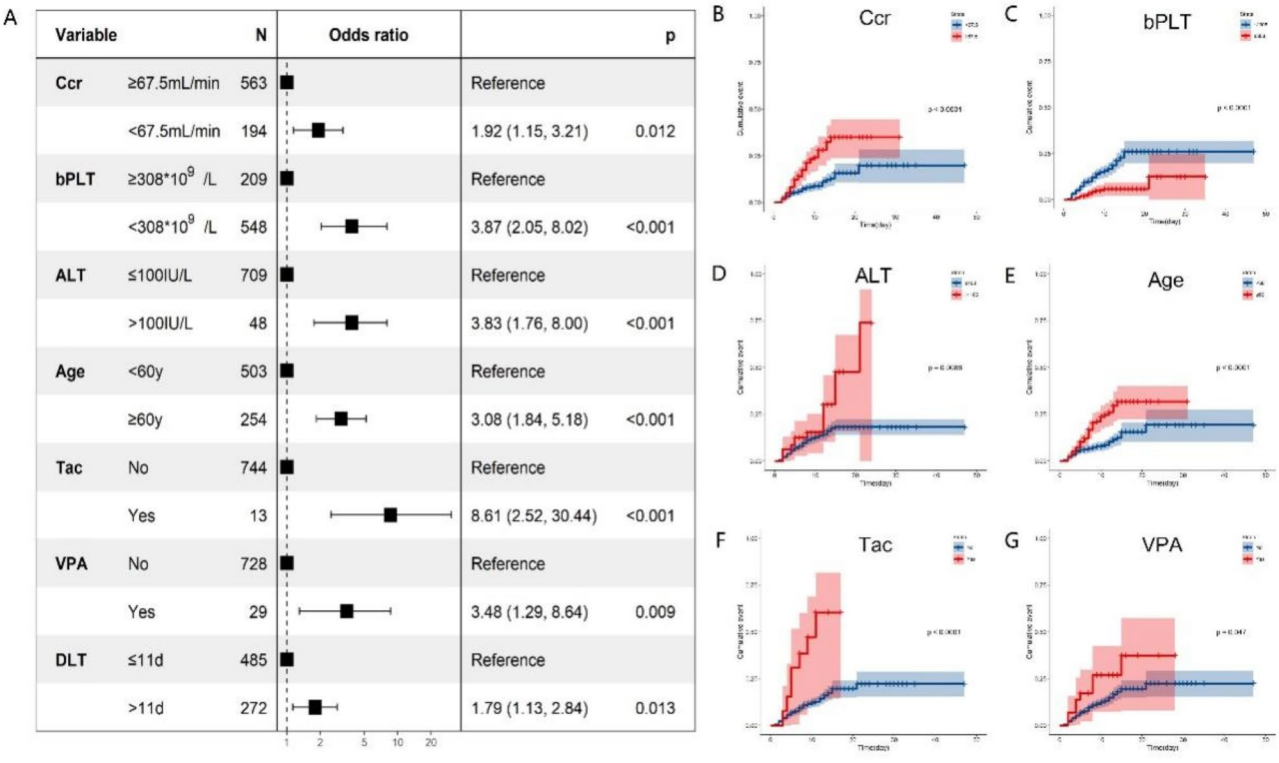

Fig. 2 Independent risk factors for LI-TP. (**A**) Risk factors associated with LI-TP by multivariate analysis (**B**-**G**) Kaplan–Meier estimates of the cumulative incidence of LI-TP, stratified by (**B**) baseline creatinine clearance (Ccr), (**C**) baseline platelet count (bPLT), (**D**) baseline alanine aminotransferase (ALT), (**E**) Age, (**F**) concomitant with tacrolimus (Tac), and (**G**) concomitant with valproate (VPA)

Development and validation of the logistic model and nomogram

We used logit (P) to establish a logistic regression model based on the independent risk factors in the training set. To facilitate a more intuitive understanding of the impact of independent risk factors for LI-TP, we established a nomogram according to the selected variables in the training set (Fig. 3C). The predictive performance of this nomogram was assessed by ROC analysis and calibration curve analysis. The area under the curve (AUC) of the model was 0.760 (95% CI: 0.709–0.812, $P < 0.001$), with an optimal cutoff of 0.106 (logit P -2.132) (Fig. 3A-B).

The validation set was used to verify nomogram performance. In the validation set (123 cases), 23 patients experienced LI-TP and 100 patients did not. The Hosmer–Lemeshow test ($P = 0.6654$) and calibration curve showed that the nomogram had good predictive performance (Fig. 4A). The AUC was 0.767 (95% CI: 0.635–0.899, $P < 0.001$) in the validation set (Fig. 4B). The predictive value of the model was evaluated by the confusion matrix drawn by the cut-off value of the maximum Youden index in the training and validation sets, and the relevant diagnostic indicators were calculated. The sensitivity and specificity were 0.7549 and 0.6687 in the training set, and 0.72 and 0.7083 in validation set, respectively (Fig. 4C-D).

We also have added the optimal prediction model on a web page, providing a reliable prediction tool for clinical medical professionals and researchers. The website address is https://mystudio.shinyapps.io/thrombocytopenia/.

The equation was as follows: $\text{LogitP} = 1.124 \times \text{Age}\ (>60\text{y}) + 0.583 \times \text{DLT}\ (>11\text{d}) + 1.352 \times \text{bPLT}\ (<308 \times 10^9/\text{L}) + 1.343 \times \text{ALT}\ (>100\ \text{IU/L}) + 0.655 \times \text{Ccr}\ (<67.5\ \text{mL/min}) + 1.246 \times \text{VAP}\ (\text{yes}) + 2.153 \times \text{Tac(yes)} - 5.837$.

Discussion

The incidence of LI-TP would severely limit the administration of LZD. In our study, the independent risk factors for LI-TP were identified. Meanwhile, a nomogram based on the independent risk factors was constructed. Finally, the performance of the nomogram was verified showing that the model had good predictive performance.

The incidence of adverse drug reactions (ADRs) is an important issue in the process of drug administration. Our study found that the cumulative incidence of LI-TP was 13.5%, which was lower than that in published studies (39.7-48.3%) [20, 27, 28]. This may be related to the definition of thrombocytopenia as a reduction of >25–50% from the baseline platelet count in other studies. Our study also found that all patients experienced mild declines in thrombocytopenia, similar to the findings in other studies [27, 29], and the platelet counts returned to normal after the cessation of LZD, indicating that physicians or pharmacists might have begun to pay attention to LI-TP and stopped it in time when they found a downward trend in platelet counts.

To predict the risk of LI-TP, we analyzed the independent risk factors for LI-TP, which included 7 independent risk factors: Ccr, ALT, age, bPLT, duration of LZD therapy, and concomitant use with VPA or Tac, which was consistent with those of other studies [11, 20, 30]. However, our conclusion was different in terms of the optimal cutoff value of each independent risk factor compared to those in other studies, which may be related to the following factors. First, different optimal cutoff values would lead to artificial bias in research results if they were divided artificially into different categories. For example, the following values were included in the risk factor analysis when the renal function of patients was classified into 3 categories based on Ccr: Ccr < 30 mL/min, Ccr of 30–59 mL/min, and Ccr ≥ 60 mL/min [11]. On the other hand, one of the definitions of thrombocytopenia is a reduction of >25-50% from the baseline platelet count, which might artificially increase the number of patients with thrombocytopenia [27, 31]. Different from other studies, it was more objective to determine the optimal cutoff value for each independent risk factor by statistical methods in our study.

A duration of LZD therapy > 11 days was significantly associated with the risk of LI-TP, which was consistent with the findings of published studies [6, 11, 30]. Current studies suggest that the mechanism of LI-TP is associated with myelosuppression [26]. As a result, thrombocytopenia usually does not occur at the start of treatment because drugs have no effect on the platelets already released in the bloodstream. However, platelet counts gradually decrease when the drugs inhibit bone marrow cells with high replication activity, including stem cells and megakaryocyte progenitors. This may be the cause of thrombocytopenia after continuous use of LZD.

LI-TP was found to be closely related to renal function. Approximately 30–40% of LZD is eliminated in urine at a conventional dose (600 mg every 12 h) [32, 33]. Renal function is associated with LZD blood concentration, which is closely related to ADRs when renal impairment occurs [34–36]. Impaired renal function increases the odds of developing thrombocytopenia 2- and 3- and 6-fold among patients treated with LZD with renal impairment and end-stage renal disease, respectively [14, 37, 38]. Related studies have also found that renal impairment is an independent risk factor for LI-TP, which is consistent with our conclusion [30, 39]. Therefore, when Ccr is less than 67.5 mL/min, platelet counts should be monitored regularly in patients with renal insufficiency. Since an exposure-response relationship for thrombocytopenia has been established in patients receiving LZD,

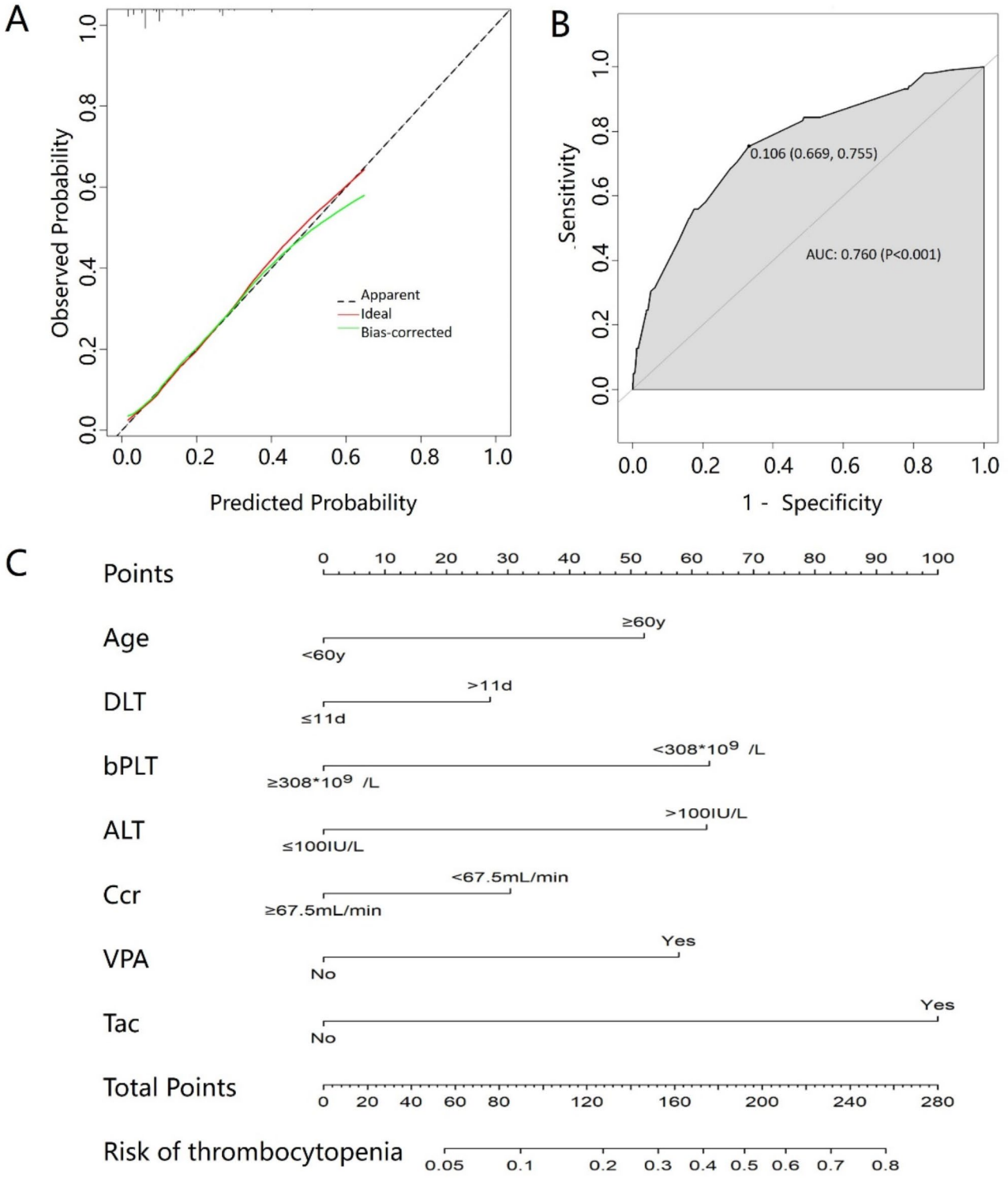

Fig. 3 Discrimination and calibration of the logistic model to predict the risk of LI-TP in the training set. (**A**) Calibration curves, (**B**) AUC and (**C**) nomogram. DLT: duration of LZD therapy; bPLT: baseline platelet count; ALT: baseline alanine aminotransferase; Ccr: baseline creatinine clearance; VPA: concomitant with valproate; Tac: concomitant with tacrolimus

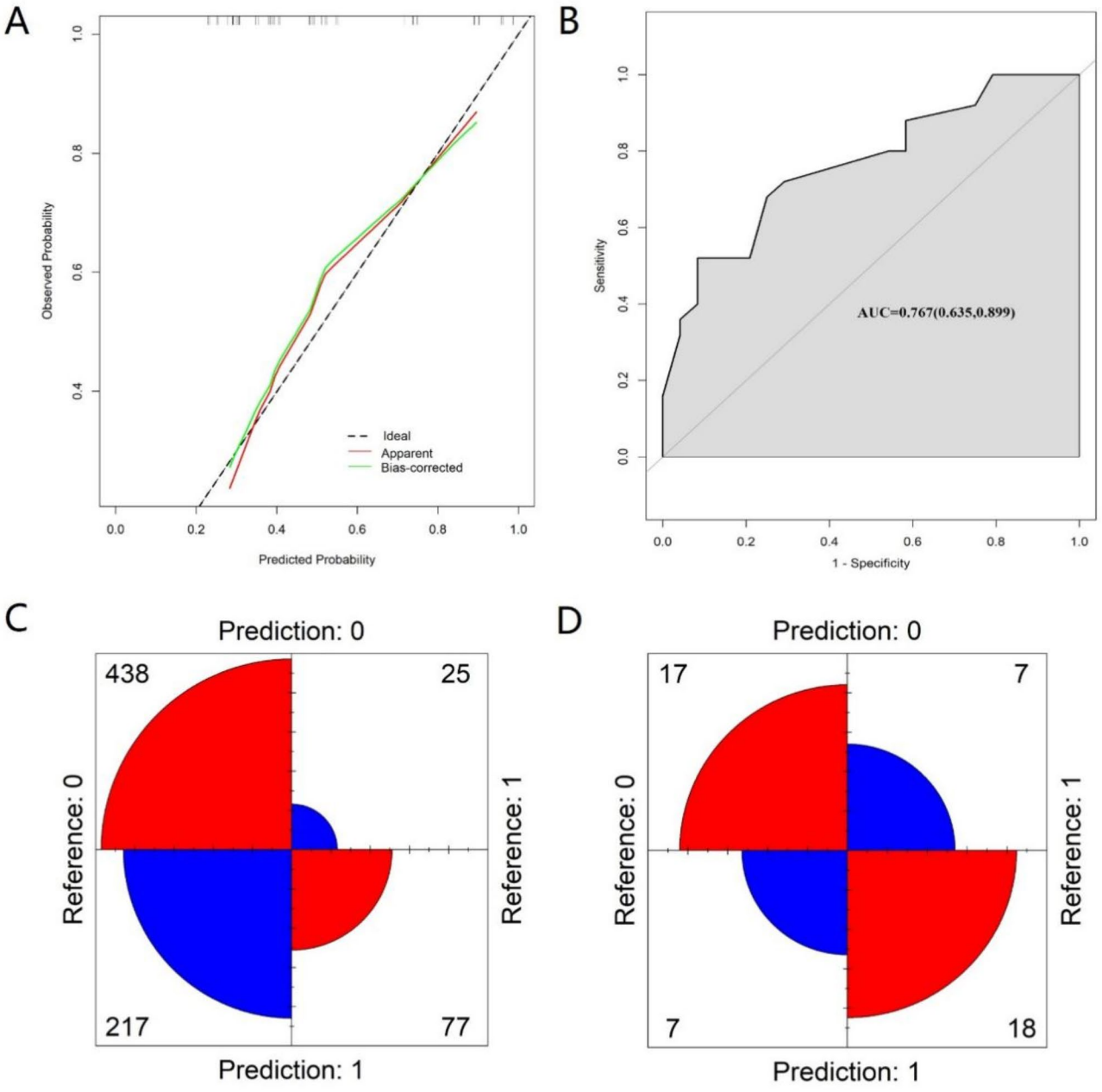

Fig. 4 Discrimination and evaluation of logistic model predicting LI-TP. (**A**-**B**) Discrimination and calibration of logistic model predicting LI-TP in the validation set including (**A**) calibration curves and (**B**) AUC. AUC: Area under the ROC curve. (**C**-**D**) Evaluation of predictive value of logistic model by confusion matrix in the training set (**C**) and validation set (**D**)

we could estimate the area under the concentration-versus-time curve (AUC) or the overall exposure area with respect to the risk of toxicity by measuring the trough concentration (C_{min}) [40, 41]. Related research has indicated that the incidence of thrombocytopenia increases significantly when C_{min} exceeds 7.5 mg/L [35]. Among hemodialysis patients, the risk of thrombocytopenia could be reduced by lowering the initial dose and lowering the plasma concentration [42]. Based on the above research, monitoring platelet counts and C_{min} could predict the toxicity of LI-TP, especially in patients with renal impairment.

The liver is the main site of drug metabolism and clearance, which dysfunction could lead to changes in drug disposition [43]. Some studies have shown that liver dysfunction decreases the clearance of LZD in critically ill patients [44, 45], and there is a high incidence of LI-TP among patients with acute and chronic liver failure [46], which might be related to exposure to supratherapeutic concentrations and adverse events such as

thrombocytopenia [47]. There is a risk of overexposure when patients with liver dysfunction receive standard-dose LZD (600 mg every 12 h), but LZD could be safely administered at reduced doses (300 mg every 12 h) with a minimum steady-state concentration ($C_{min, ss}$) of 2 to 8 g/ml [48], which suggests that we can reduce the incidence of adverse reactions by adjusting the dosage of LZD for patients with liver dysfunction. Our study also showed that increased ALT levels but not total bilirubin were associated with a higher risk of LI-TP, which may be consistent with previous studies that showed patients with liver dysfunction were more prone to thrombocytopenia due to a higher blood concentration of LZD [15].

To analyze the effect of drug combinations on thrombocytopenia, we collected information on drugs combined with LZD that have been reported for drug-related thrombocytopenia. Our results found that concomitant valproate or tacrolimus use was an independent risk factor for thrombocytopenia. Thrombocytopenia was the most common ADRs in patients taking valproate, with an incidence of 5–60% [49]. The possible mechanism of valproate-induced thrombocytopenia has been hypothesized to a dose-dependent direct toxic effect of platelet production on bone marrow and destruction of peripheral platelets because of the formation of autoantibodies against platelets [50]. Notably, concomitant Tac use increased 8.6-fold of LI-TP risk, underscoring the potential risk of its combination with LZD. Tacrolimus could induce thrombocytopenia by accelerating peripheral platelet destruction [26]. As previously mentioned, the mechanism of LI-TP was associated with myelosuppression [51]. Based on these studies, there are different mechanisms for thrombocytopenia between LZD, valproate or tacrolimus, which might accumulate the risk of thrombocytopenia. Other drugs that are known to cause TP have not been identified as risk factors for LI-TP, which may be related to the small number of patients treated with these drugs.

The AUCs of the combined predictors were 0.760 and 0.767 based on the logistic regression model in the training set and validation set, respectively, indicating that the LI-TP prediction model had good predictive performance. The logistic regression model with an optimal cutoff point of 0.106 was converted into a quantifiable nomogram so that clinicians could easily and quickly predict the risk of LI-TP based on the seven combined predictors before LZD treatment. If the cutoff point predicted by the nomogram is greater than 0.106, which indicates that the patient is at high risk for LI-TP, clinicians should take appropriate measures, such as replacing LZD with other drugs, monitoring platelet levels regularly or adjusting the administration schedule by monitoring LZD concentrations to prevent thrombocytopenia. Our study showed that the nomogram could be used as an effective tool to identify patients with high risk of LI-TP.

Limitations

This study has some limitations, including its retrospective design and the lack of external validation from different hospitals or regions. Additionally, we did not monitor LZD blood concentrations, which could provide further insights into the relationship between drug exposure and thrombocytopenia. Future studies should focus on multi-center studies and prospective validation to further validate the model utility in clinical practice. Additionally, the nomogram can also be integrated into electronic health records (EHRs) or clinical decision support systems (CDSS) to provide real-time risk assessment for LI-TP.

Conclusions

Our results showed that LI-TP was associated with seven independent risk factors: older age, prolonged treatment with LZD, elevated ALT level, renal impairment, low baseline platelet count, and the concomitant use of valproate or tacrolimus. The nomogram model based on the identified seven independent risk factors had good predictive performance. The quantifiable nomogram transformed from the logistic regression model can enable clinicians to easily and quickly predict LI-TP before LZD treatment, which provides an important reference for reducing the occurrence of LI-TP in the clinic.

Acknowledgements

We would like to thank all the physicians who participated in this study for their assistance in the enrollment and follow-up of patients.

Author contributions

Conceptualization, Y. Y., Y. F. and Y. J.; methodology, X. H.; software, X. H.; validation, Y. R., H. W., P. F. and P. W.; formal analysis, Z. D., X. L. and N. W.; investigation, Y. Y.; resources, F. S.; data curation, X. H.; writing—original draft preparation, Y. Y.; writing—review and editing, Y. F. and Y. J.; visualization, X. H.; supervision, Y. J.; project administration, Y. J.; funding acquisition, Y.Y. and Y. J.; All authors have read and agreed to the published version of the manuscript.

Funding

The authors received funding for this work from General Project of Chongqing Science and Health Joint Medical Scientific Research Project (2024MSXM177), the Future Medicine Youth Innovation Team Project of Chongqing Medical University (W0081), Key Project of Chongqing Science and Health Joint Medical Scientific Research Project (2022ZDXM020) and Chongqing Clinical Pharmacy Key Specialty Construction Project.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Army Medical University with a waiver of the requirement for informed consent (KY2023015) and adhered to the principles outlined in the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 16 July 2024 / Accepted: 21 February 2025
Published online: 27 February 2025

References

1. Vrioni G, et al. MALDI-TOF mass spectrometry technology for detecting biomarkers of antimicrobial resistance: current achievements and future perspectives. Ann Transl Med. 2018;6(12):240.
2. Birmingham MC, et al. Linezolid for the treatment of multidrug-resistant, gram-positive infections: experience from a compassionate-use program. Clin Infect Dis. 2003;36(2):159–68.
3. Tajima M, et al. Linezolid-Induced thrombocytopenia is caused by suppression of platelet production via phosphorylation of myosin light chain 2. Biol Pharm Bull. 2016;39(11):1846–51.
4. Nie X, et al. Evaluation of reporting quality for observational studies using routinely collected health data in pharmacovigilance. Expert Opin Drug Saf. 2018;17(7):661–8.
5. Niwa T, et al. Retrospective cohort chart review study of factors associated with the development of thrombocytopenia in adult Japanese patients who received intravenous linezolid therapy. Clin Ther. 2009;31(10):2126–33.
6. Hirano R, et al. Retrospective analysis of the risk factors for linezolid-induced thrombocytopenia in adult Japanese patients. Int J Clin Pharm. 2014;36(4):795–9.
7. Patel N, et al. A comparative evaluation of adverse platelet outcomes among Veterans' affairs patients receiving linezolid or Vancomycin. J Antimicrob Chemother. 2012;67(3):727–35.
8. Rao N, et al. Similar hematologic effects of long-term linezolid and Vancomycin therapy in a prospective observational study of patients with orthopedic infections. Clin Infect Dis. 2004;38(8):1058–64.
9. Lam S. Linezolid-associated thrombocytopenia. Consult Pharm. 2012;27(7):504–8.
10. Xiao B, et al. Lactic acidosis and thrombocytopenia associated with linezolid therapy: A case report. Am J Case Rep. 2018;19:1117–20.
11. Choi GW, et al. Risk factors for linezolid-induced thrombocytopenia in patients without haemato-oncologic diseases. Basic Clin Pharmacol Toxicol. 2019;124(2):228–34.
12. Green SL, Maddox JC, Huttenbach ED. Linezolid and reversible myelosuppression. JAMA. 2001;285(10):1291.
13. Lin YH, et al. High frequency of linezolid-associated thrombocytopenia among patients with renal insufficiency. Int J Antimicrob Agents. 2006;28(4):345–51.
14. Wu VC, et al. High frequency of linezolid-associated thrombocytopenia and anemia among patients with end-stage renal disease. Clin Infect Dis. 2006;42(1):66–72.
15. Sasaki T, et al. Population Pharmacokinetic and pharmacodynamic analysis of linezolid and a hematologic side effect, thrombocytopenia, in Japanese patients. Antimicrob Agents Chemother. 2011;55(5):1867–73.
16. Cossu AP, et al. 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):23–8.
17. Grau S, et al. Linezolid: low pre-treatment platelet values could increase the risk of thrombocytopenia. J Antimicrob Chemother. 2005;56(2):440–1.
18. Natsumoto B, et al. Risk factors for linezolid-associated thrombocytopenia in adult patients. Infection. 2014;42(6):1007–12.
19. Chen C, et al. Risk factors for thrombocytopenia in adult Chinese patients receiving linezolid therapy. Curr Ther Res Clin Exp. 2012;73(6):195–206.
20. Dong HY, et al. 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):1029–35.
21. Duan L, et al. A regression model to predict linezolid induced thrombocytopenia in neonatal Sepsis patients: A Ten-Year retrospective cohort study. Front Pharmacol. 2022;13:710099.
22. Maray I, et al. Linezolid induced thrombocytopenia in critically ill patients: risk factors and development of a machine learning-based prediction model. J Infect Chemother. 2022;28(9):1249–54.
23. Qin Y et al. Development and validation of a risk prediction model for linezolid-induced thrombocytopenia in elderly patients. Eur J Hosp Pharm. 2022.
24. Lee EJ, Lee AI. Thrombocytopenia Prim Care. 2016;43(4):543–57.
25. Williamson DR, et al. Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. Chest. 2013;144(4):1207–15.
26. Danese E, et al. Drug-Induced thrombocytopenia: mechanisms and laboratory diagnostics. Semin Thromb Hemost. 2020;46(3):264–74.
27. Kim HS, et al. 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.
28. Tanaka R, et al. A retrospective test for a possible relationship between linezolid-induced thrombocytopenia and hyponatraemia. J Clin Pharm Ther. 2021;46(2):343–51.
29. Cazavet J, et al. Risk factor analysis for linezolid-associated thrombocytopenia in critically ill patients. Eur J Clin Microbiol Infect Dis. 2020;39(3):527–38.
30. Takahashi Y, et al. Risk factors associated with the development of thrombocytopenia in patients who received linezolid therapy. J Infect Chemother. 2011;17(3):382–7.
31. Kaya Kilic E, et al. Risk factors for linezolid-associated thrombocytopenia and negative effect of carbapenem combination. J Infect Dev Ctries. 2019;13(10):886–91.
32. Slatter JG, et al. Pharmacokinetics, metabolism, and excretion of linezolid following an oral dose of [(14)C]linezolid to healthy human subjects. Drug Metab Dispos. 2001;29(8):1136–45.
33. Stalker DJ, et al. Pharmacokinetics and tolerance of single- and multiple-dose oral or intravenous linezolid, an Oxazolidinone antibiotic, in healthy volunteers. J Antimicrob Chemother. 2003;51(5):1239–46.
34. Matsumoto K, et al. Renal function as a predictor of linezolid-induced thrombocytopenia. Int J Antimicrob Agents. 2009;33(1):98–9.
35. Nukui Y, et al. High plasma linezolid concentration and impaired renal function affect development of linezolid-induced thrombocytopenia. J Antimicrob Chemother. 2013;68(9):2128–33.
36. Rao GG, et al. Therapeutic drug monitoring can improve linezolid dosing regimens in current clinical practice: A review of linezolid pharmacokinetics and pharmacodynamics. Ther Drug Monit. 2020;42(1):83–92.
37. Hanai Y, et al. A retrospective study of the risk factors for linezolid-induced thrombocytopenia and anemia. J Infect Chemother. 2016;22(8):536–42.
38. Crass RL, et al. Reappraisal of linezolid dosing in renal impairment to improve safety. Antimicrob Agents Chemother. 2019;63(8).
39. Zhao H, et al. A nomogram incorporating linezolid and metabolite concentrations for predicting linezolid induced thrombocytopenia in patients with renal impairment. Sci Rep. 2024;14(1):26064.
40. Pea F, et al. Therapeutic drug monitoring May improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother. 2012;67(8):2034–42.
41. Cattaneo D, Alffenaar JW, Neely M. Drug monitoring and individual dose optimization of antimicrobial drugs: Oxazolidinones. Expert Opin Drug Metab Toxicol. 2016;12(5):533–44.
42. Kawasuji H et al. Initially reduced linezolid dosing regimen to prevent thrombocytopenia in Hemodialysis patients. Antibiot (Basel). 2021;10(5).
43. Gallagher J, Biesboer AN, Killian AJ. Pharmacologic issues in liver disease. Crit Care Clin. 2016;32(3):397–410.
44. Sazdanovic P, et al. Pharmacokinetics of linezolid in critically ill patients. Expert Opin Drug Metab Toxicol. 2016;12(6):595–600.
45. Wicha SG, et al. Linezolid in liver failure: exploring the value of the maximal liver function capacity (LiMAx) test in a Pharmacokinetic pilot study. Int J Antimicrob Agents. 2017;50(4):557–63.
46. Zhang YM, et al. High frequency of thrombocytopenia in patients with acute-on-chronic liver failure treated with linezolid. Hepatobiliary Pancreat Dis Int. 2015;14(3):287–92.
47. Luque S, et al. Linezolid dosing in patients with liver cirrhosis: standard dosing risk toxicity. Ther Drug Monit. 2019;41(6):732–9.
48. Zhang SH, et al. Population pharmacokinetics and dosage optimization of linezolid in patients with liver dysfunction. Antimicrob Agents Chemother. 2020;64(6).
49. Gerstner T, et al. Valproate-associated coagulopathies are frequent and variable in children. Epilepsia. 2006;47(7):1136–43.

50. Nasreddine W, Beydoun A. Valproate-induced thrombocytopenia: a prospective monotherapy study. Epilepsia. 2008;49(3):438–45.
51. Kuter DJ, Tillotson GS. Hematologic effects of antimicrobials: focus on the Oxazolidinone linezolid. Pharmacotherapy. 2001;21(8):1010–3.

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