Development and Validation of a Risk Prediction Model of Linezolid-induced Thrombocytopenia in Elderly Patients

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Research Article

Keywords: linezolid, thrombocytopenia, elderly patient, risk factors, risk prediction model

Posted Date: June 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-582799/v1

Abstract

Background Linezolid is an oxazolidinone antimicrobial agent developed for treating multi-drug-resistant gram-positive bacterial infections.

Objective This study aimed at investigating risk factors of linezolid (LI)-induced thrombocytopenia (LI-TP) and establishing a risk predictive model for LI-TP.

Setting ZhongShan Hospital, FuDan University, China.

Method A retrospective study was performed in patients aged ≥ 65 years receiving linezolid therapy from January 2015 to April 2021. Clinical characteristics and demographic data were collected and compared between patients with LI-TP and those without.

Main outcome measures Incidence and risk factors of LI-TP in elderly patients.

Results A total of 343 inpatients were included as the train set from January 2015 to August 2020. Among them, 67 (19.5%) developed LI-TP. Multivariate logistic regression analysis revealed that baseline platelet counts < $150\times10^{9}\cdot L^{-1}$ (OR=3.576; *P*< 0.001), age ≥ 75 years (OR=2.258; *P*=0.009), eGFR< 60 $mL\cdot(min\cdot1.73m^{2})^{-1}$ (OR=2.553; *P*=0.002), duration of linezolid therapy ≥ 10 d (OR=3.218; *P*<0.001), ICU admittance (OR=2.682; *P*=0.004), and concomitant with piperacillin-tazobactam (PTZ) (OR=3.863; *P*=0.006) were independent risk factors for LI-TP. The risk predictive model was established and exhibited a moderate discriminative power, with an AUC of 0.795 [95%CI 0.740-0.851] and 0.849 [95%CI 0.760-0.939] in train set (n=343) and validation set (n=90), respectively.

Conclusion The risk factors of LI-TP in elderly patients were duration of linezolid therapy, age, eGFR, ICU admittance, baseline platelet counts, and concomitant with PTZ. A risk predictive model based on these risk factors may be useful to identify patients with high risk of LI-TP.

Impacts On Practice

Using the risk predictive model presented in this study, geriatric patients with linezolid therapy may predict the risks of thrombocytopenia during the hospitalization.

This predictive model can identify individual patients with high risk of linezolid-induced thrombocytopenia, and this special population should be paid more attention.

This risk predictive model may help physicians to make clinical decision, shorten the length of hospitalization of patients, and lower the costs of medical resources.

Introduction

Linezolid is the first oxazolidinone antimicrobial agent developed for clinical treatment of multi-drug-resistant gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and vancomycin-resistant *Staphylococcus* (VRSA) [1]. Functionally, linezolid binds bacterial 23S site of ribosomal RNA on the 50S subunit to prevent the formation of 70S initiation complex, thereby inhibiting protein synthesis and bacterial replication [2]. However, linezolid is associated with various adverse reactions, such as bone marrow suppression that is mainly manifested as thrombocytopenia and anemia [3, 4]. Previous studies have suggested that linezolid can suppress platelet precursor cells synthesis, thereby inhibiting platelet production. Moreover, it has also been documented that linezolid binds to glycoproteins on the platelet membrane surface, to form an immune complex. This complex is then transferred to the endoplasmic reticulum cortex where it gets cleared, leading to a decrease in platelet count [5–7]. Various studies have shown that aging patients are more likely to develop thrombocytopenia, due to their specific physiological status [8, 9]. Some studies had reported that LI-TP incidence ranged from 20.9–70.4% in elderly patients, which was accompanied with higher risks of mortality [10–12]. The risk factors of linezolid-induced thrombocytopenia (LI-TP) in elderly population have been reported in several studies, although the findings are conflicting. For example, published articles found that the baseline platelet count < 200×10^9/L, duration of linezolid therapy and renal impairment were significant risk factors for LI-TP [11, 13, 14], while the study of Li J et al reported that elderly patients admitted into ICU had a higher risk of LI-TP than those without [15]. Elderly patients are predisposed to multiple diseases, which require treatment using complicated medications that exacerbate the LI-TP problem. With the aging population increasing of Chinese society, LI-TP in elderly patients requires more attention. However, the risk factors of LI-TP in elderly patients were not consistent, and few studies had established risk predictive models of LI-TP for this special population.

Aim of the study

The objective of this study was to identify the risk factors associated with LI-TP, to construct and validate a risk predictive model to evaluate the risks of thrombocytopenia in geriatric patients while receiving linezolid therapy, and to help physicians to identify patient with higher risk of LI-TP using this predictive model.

Ethics approval

The study was approved by the Ethical Committee of Zhongshan Hospital, Fudan University (B2021-304).

Methods

Study design and recruitment criteria

This was a retrospective study involving linezolid-administered (orally or intravenously) elderly patients at Zhongshan Hospital, Fudan University. This study was performed between January 2015 and April 2021. Clinical data for these patients were collected from the medical records, with permission from the Ethical

Committee of the ZhongShan Hospital. Patients who were ≥ 65 years and had been administered with linezolid at a standard dose of 600 mg, q 12h for three or more days were recruited. While those diagnosed with hematological diseases (haemato-oncologic disease, myelosuppression, and disseminated intravascular coagulation), bleeding, with less than three times of monitoring on platelet counts, receiving radiotherapy or chemotherapy, who lacked baseline platelet counts, who had baseline platelet counts less than $100\times10^{9}\cdot L^{-1}$ or receiving blood transfusions 2 weeks before the initiation of linezolid therapy, were excluded from the study.

Definition of thrombocytopenia

Platelet counts were used to categorize the included patients into two groups: the linezolid-induced thrombocytopenia (LI-TP) group and the no development of thrombocytopenia (NO-TP) group. Thrombocytopenia was defined as a reduction in platelet counts to levels below $100\times10^{9}\cdot L^{-1}$.

Clinical and demographic characteristics

We collected the following clinical and demographic characteristics for each elderly patient: age, gender, weight, payment method (self-payment and medical insurance), hospitalized department (medical, surgical, and ICU), laboratory variables [baseline platelet counts, hemoglobin, total bilirubin, total albumin, serum albumin, alanine aminotransferase, aspartate aminotransferase, and estimated glomerular filtration rate (eGFR)], as well as concomitant disease [hypertension, diabetes, chronic heart disease (CHD), chronic obstructive pulmonary disease (COPD), and cancer]. Other records were also extracted, if the patients were transferred to ICU, had surgery, mechanical ventilation, renal replacement therapy or bleeding. Moreover, we comprehensively analyzed variables associated with linezolid treatment and combined medications, including duration of linezolid therapy, concomitance with antibiotics (carbapenems, quinolones, aminoglycosides, cephalosporin, piperacillin-tazobactam (PTZ), macrolides, compound sulfamethoxazole), vasoactive drugs [nitrates, β-blockers, dihydropyridines, angiotensin receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEI)], anticoagulant agents (heparin, warfarin), antiplatelet agents (aspirin, clopidogrel), azole antifungal agents, nonsteroidal anti-inflammatory drugs (NSAIDS), spironolactone, hydrochlorothiazide, furosemide, proton-pump inhibitors (PPI), polyene phosphatidylcholine, glutathione, ursodeoxycholic acid, magnesium isoglycyrrhizinate (MGL), benzodiazepines, opioid agonist, tamsulosin, β2-agonist, theophylline, rifampin, and isoniazid.

Data analysis

The statistical analysis was carried out using SPSS version 23.0 (IBM, 187 Chicago, IL, USA). The Kolmogorov-Smirnov test was performed to evaluate whether the data were normally or non-normally distributed. Normally distributed continuous variables were described as the mean ± standard deviation (SD), and the student's *t*-test was used to compare the LI-TP group and NO-TP group. Non-normally distributed continuous variables were expressed as the median (interquartile range, IQR), and groups were compared using the Mann-Whitney *U*-test. Chi-squared test or Fisher's exact test were used to analyze the categorical variables which were described as numbers (percentages). Furthermore, multivariate logistic

regression analysis was used to determine the association between the independent variables and linezolid-induced thrombocytopenia. A risk predictive model was constructed according to the variables retained in the final model. A risk score was developed according to the regression coefficient. To evaluate the discrimination of the risk model, receiver operating characteristic (ROC) curves were constructed, and area under the curve (AUC) was calculated. The goodness of fit was assessed with the Hosmer-Lemeshow test. All *P* values were two-sided, and a *P* value of less than 0.05 was considered significant.

Results

Patient Characteristics

A total of 343 patients were recruited in the train set (Fig. 1). Their median age was 72.0 (IQR 68.0 ~ 78.0) years, with males accounting for 70.6% (242/343) of the total population. The elderly patients had a median weight of 60.0 (IQR 55.0 ~ 70.0) kg, ranging from 37 to 170 kg. Linezolid was administered at a dose of 600 mg q12h, with a median duration of 8.5 (IQR 6.0 ~ 13.0) days, ranging from 3 ~ 40 days. Variations in platelet counts during linezolid therapy were used to assign the elderly patients into two groups, LI-TP and NO-TP (Table 1). After the initiation of linezolid therapy, 19.5% (67/343) of the patients developed thrombocytopenia. 68.7% (46/67) of them were male, with a median age of 75.0 (IQR 69.0 ~ 79.0) years.

Table 1
Demographic and clinical characteristics of the elderly patients in the train set

Characteristics	Total patients (n = 343)
Age (years), median (IQR)	72.0 (68.0 ~ 78.0)
Male, n (%)	242 (70.6)
Weight (kg), median (IQR)	60.0 (55.0 ~ 70.0)
Length of stay (days), median (IQR)	27.5 (17.5 ~ 44.0)
Duration of linezolid therapy (days), median (IQR)	8.5 (6.0 ~ 13.0)
Type of infection	
Pulmonary, n (%)	185 (53.9)
Intra-abdominal, n (%)	40 (11.7)
Blood, n (%)	32 (9.3)
Skin and soft tissue, n (%)	28 (8.2)
Urinary tract, n (%)	15 (4.4)
Bone and joint, n (%)	9 (2.6)
Central nervous system, n (%)	7 (2.0)
Others, n (%)	27 (6.4)
Bacterial species	Total pathogens isolated (n = 157)
Staphylococcus aureus, n (%)	65 (41.4)
Enterococcus faecium, n (%)	24 (15.3)
Enterococcus faecalis, n (%)	16 (10.2)
Tuberculosis mycobacterium spp., n (%)	26 (16.6)
Streptococcus, n (%)	9 (5.7)
Staphylococcus epidermidis, n (%)	5 (3.2)
Nocardia, n (%)	4 (2.5)
Others, n (%)	8 (5.1)
IQR, Inter Quartile Range.	

Univariate analysis in the train set

Demographic and clinical characteristics of elderly patients were compared in the train set, and patients with higher age were more likely to develop LI-TP, especially those aged ≥ 75 years old. No significant differences were found in terms of gender and weight, as well as in the accompanying diseases between patients with and without LI-TP. With regard to laboratory indicators, the baseline platelet counts and eGFR were significantly low in LI-TP patients compared to those without, and both of the *P* value < 0.001. Moreover, there were also no significant differences between the two groups with regards to whether they had undergone surgery or not, had mechanical ventilation or not, the hospital department they were in, and the mode of payment they had used. LI-TP patients were more likely to have a longer duration of linezolid therapy than those without. In addition, patients who were transferred to the ICU exhibited a higher risk of LI-TP (Table 2).

Table 2
Comparison of demographic and clinical characteristics between patients with linezolid-induced thrombocytopenia (LI-TP) and those without (NO-TP)

Characteristics	LI-TP (67)	NO-TP (276)	*P* value
Age (years), median (IQR)	75.0 (69.0 ~ 79.0)	71.0 (68.0 ~ 78.0)	**0.018**
65 ~ 74 years, n (%)	33 (49.3)	190 (68.8)	**0.003**
≥ 75 years	34 (50.7)	86 (31.2)	
Male, n (%)	46 (68.7)	196 (71.0)	0.704
Weight (kg), median (IQR)	60.0 (55.0 ~ 70.0)	59.5 (55.0 ~ 69.0)	0.288
Surgery, n (%)	26 (38.8)	103 (37.3)	0.822
ICU admittance, n (%)	50 (74.6)	144 (52.2)	**0.001**
Mechanical ventilation, n (%)	26 (38.8)	76 (27.5)	0.070
In-patient department:			0.116
Medical, n (%)	24 (35.8)	129 (46.7)	
Surgical, n (%)	23 (34.3)	94 (34.1)	
ICU, n (%)	20 (29.9)	53 (19.2)	
Payment methods:			0.116
Self-payment, n (%)	23 (34.3)	124 (44.9)	
Basic national medical insurances, n (%)	44 (65.7)	152 (55.1)	
Baseline laboratory data:			
Platelet count ($10^9 \cdot L^{-1}$), median (IQR)	168.0 (134.0 ~ 222.0)	253.5 (187.3 ~ 343.0)	**< 0.001**
Platelet count < $150 \times 10^9 \cdot L^{-1}$, n (%)	24 (35.8)	33 (12.0)	**< 0.001**
Hemoglobin ($g \cdot L^{-1}$), median (IQR)	104.0 (83.0 ~ 112.0)	99.0 (84.3 ~ 114.0)	0.930
Total bilirubin ($\mu mol \cdot L^{-1}$) , median (IQR)	11.5 (6.5 ~ 21.0)	10.1 (7.0 ~ 16.9)	0.327

LI-TP, linezolid-induce thrombocytopenia; NO-TP, no development of thrombocytopenia; ICU, Intensive Care Unit; IQR, Inter Quartile Range; eGFR, estimated Glomerular Filtration Rate; ACEI, Angiotensin-converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers; NSAID, Nonsteroidal Anti-inflammatory Drugs; PPI, Proton-Pump Inhibitors.

Characteristics	LI-TP (67)	NO-TP (276)	*P* value
Total albumin ($g \cdot L^{-1}$), median (IQR)	60.0 (54.0 ~ 64.0)	61.0 (57.0 ~ 66.0)	0.155
Albumin ($g \cdot L^{-1}$), median (IQR)	32.0 (30.0 ~ 35.0)	33.0 (30.0 ~ 36.0)	0.401
Alanine aminotransferase ($U \cdot L^{-1}$), median (IQR)	19.0 (12.0 ~ 45.0)	22.5 (14.0 ~ 36.8)	0.578
Aspartate aminotransferase ($U \cdot L^{-1}$), median (IQR)	27.0 (17.0 ~ 47.0)	26.0 (18.0 ~ 37.0)	0.902
eGFR [$mL \cdot (min \cdot 1.73m^2)^{-1}$], median (IQR)	55.0 (39.0 ~ 84.3)	87.1 (53.0 ~ 96.0)	**< 0.001**
eGFR < 60 $mL \cdot (min \cdot 1.73m^2)^{-1}$, n (%)	37 (55.2)	83 (30.1)	**< 0.001**
Concomitant disease, n (%)			
Hypertension	36 (53.7)	126 (45.7)	0.235
Diabetes	27 (40.3)	109 (39.5)	0.904
Chronic heart disease	36 (53.7)	113 (40.9)	0.058
Chronic obstructive pulmonary disease	8 (11.9)	27 (9.8)	0.601
Cancer	20 (29.9)	76 (27.5)	0.705
Type of infection, n (%)			
Pulmonary	32 (47.8)	153 (55.4)	0.258
Intra-abdominal	10 (14.9)	30 (10.9)	0.353
Urinary tract	5 (7.5)	10 (3.6)	0.296
Skin and soft tissue	5 (7.5)	23 (8.3)	0.815
Blood	9 (13.4)	23 (8.3)	0.198
Bone and joint	1 (1.5)	8 (2.9)	0.826
Central nervous system	1 (1.5)	6 (2.2)	1.000
Others	4 (6.0)	23 (8.3)	0.519

LI-TP, linezolid-induce thrombocytopenia; NO-TP, no development of thrombocytopenia; ICU, Intensive Care Unit; IQR, Inter Quartile Range; eGFR, estimated Glomerular Filtration Rate; ACEI, Angiotensin-converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers; NSAID, Nonsteroidal Anti-inflammatory Drugs; PPI, Proton-Pump Inhibitors.

Characteristics	LI-TP (67)	NO-TP (276)	*P* value
Duration of linezolid therapy (days), median (IQR)	13.0 (8.5 ~ 17.0)	8.0 (5.0 ~ 12.0)	**< 0.001**
Duration of linezolid therapy ≧ 10 d, n (%)	34 (50.7)	98 (35.5)	**0.021**
Vancomycin within preceding 2 weeks, n (%)	17 (25.4)	65 (23.7)	0.777
Concomitant drugs, n (%)			
Nitrate	17 (25.4)	50 (18.1)	0.179
ACEI	1 (1.5)	14 (5.1)	0.341
ARB	12 (17.9)	40 (14.5)	0.484
Dihydropyridine	23 (34.3)	85 (30.8)	0.577
β-blocker	25 (37.3)	100 (36.2)	0.869
Tamsulosin	2 (3.0)	24 (8.7)	0.113
β2-agonist	9 (13.4)	29 (10.5)	0.494
Theophylline	8 (11.9)	25 (9.1)	0.473
Hydrochlorothiazide	7 (10.4)	14 (5.1)	0.173
Spironolactone	17 (25.4)	68 (24.6)	0.900
Furosemide	25 (37.3)	87 (31.5)	0.364
Heparin	39 (58.2)	123 (44.6)	**0.045**
Warfarin	6 (9.0)	25 (9.1)	0.979
Aspirin	12 (17.9)	45 (16.3)	0.751
Clopidogrel	9 (13.4)	30 (10.9)	0.553
PPI	46 (68.7)	180 (65.2)	0.594
Piperacillin-tazobactam	10 (14.9)	15 (5.4)	**0.016**
Cephalosporin	25 (37.3)	91 (33.0)	0.500
Carbapenem	44 (65.7)	174 (63.0)	0.688

LI-TP, linezolid-induce thrombocytopenia; NO-TP, no development of thrombocytopenia; ICU, Intensive Care Unit; IQR, Inter Quartile Range; eGFR, estimated Glomerular Filtration Rate; ACEI, Angiotensin-converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers; NSAID, Nonsteroidal Anti-inflammatory Drugs; PPI, Proton-Pump Inhibitors.

Characteristics	LI-TP (67)	NO-TP (276)	*P* value
Aminoglycoside	4 (6.0)	31 (11.2)	0.202
Quinolone	21 (31.3)	80 (29.0)	0.704
Macrolide	3 (4.5)	14 (5.1)	1.000
Compound sulfamethoxazole	6 (9.0)	13 (4.7)	0.287
Azole antifungal agent	14 (20.9)	61 (22.1)	0.830
NSAID	18 (26.9)	78 (28.3)	0.820
Polyene phosphatidylcholine	4 (6.0)	26 (9.4)	0.370
Glutathione	23 (34.3)	104 (37.7)	0.610
Ursodeoxycholic acid	3 (4.5)	6 (2.2)	0.527
Magnesium isoglycyrrhizinate	8 (11.9)	31 (11.2)	0.870
Benzodiazepines	15 (22.4)	58 (21.0)	0.805
Opioid Agonist	15 (22.4)	41 (14.9)	0.135
Rifampin	6 (9.0)	23 (8.3)	0.870
Isoniazid	4 (6.0)	24 (8.7)	0.465

LI-TP, linezolid-induce thrombocytopenia; NO-TP, no development of thrombocytopenia; ICU, Intensive Care Unit; IQR, Inter Quartile Range; eGFR, estimated Glomerular Filtration Rate; ACEI, Angiotensin-converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers; NSAID, Nonsteroidal Anti-inflammatory Drugs; PPI, Proton-Pump Inhibitors.

A further analysis of 33 types of drugs used by elderly patients during the linezolid treatment showed that LI-TP was more likely to occur in patients treated with heparin (44.6% vs. 58.2%; $P = 0.045$) (Table 3). In addition, compared to the NO-TP group, a significantly higher number of LI-TP patients were receiving PTZ (14.9% vs. 5.4%; $P = 0.016$).

Table 3
Risk factors of linezolid-induced thrombocytopenia

Risk factors	β	SE	Wald χ^2	P value	OR	95%CI
Intercept	-3.720	0.444	70.087	< 0.001		
Age ≥ 75 years	0.815	0.310	6.890	0.009	2.258	1.229 ~ 4.149
Baseline platelet count < $150\times10^9\cdot L^{-1}$	1.274	0.349	13.318	< 0.001	3.576	1.804 ~ 7.088
eGFR < 60 $mL\cdot(min\cdot1.73m^2)^{-1}$	0.937	0.310	9.155	0.002	2.553	1.391 ~ 4.686
Duration of linezolid therapy ≥ 10 d	1.169	0.324	12.988	< 0.001	3.218	1.704 ~ 6.076
ICU admittance	0.987	0.345	8.198	0.004	2.682	1.365 ~ 5.269
PTZ	1.352	0.490	7.621	0.006	3.863	1.480 ~ 10.085

OR, Odds Ratio; CI, Confidence Interval; eGFR, estimated Glomerular Filtration Rate, PTZ, piperacillin-tazobactam.

Establishment of LI-TP prediction model

A total of 7 categorized variables with $P < 0.05$ in the univariate analyses were chosen to enter into multivariate logistic regression analysis, including: age, baseline platelet counts, eGFR, duration of linezolid therapy, ICU admittance, concomitant with heparin and PTZ. Multivariate logistic regression analysis revealed that baseline platelet counts < $150\times10^9\cdot L^{-1}$ [odds ratio (OR) = 3.576; $P < 0.001$], age ≥ 75 years (OR = 2.258; $P = 0.009$), eGFR < 60 $mL\cdot(min\cdot1.73m^2)^{-1}$ (OR = 2.553; $P = 0.002$), duration of linezolid therapy ≥ 10 d (OR = 3.218; $P < 0.001$), ICU admittance (OR = 2.682; $P = 0.004$) as well as concomitant with PTZ (OR = 3.863; $P = 0.006$) were independent risk factors for LI-TP (Table 4). Finally, a risk predictive model for LI-TP was established based on the multiple logistic regression analysis. The formulation was exhibited as below:

Logit (P) = -3.720 + 0.815 × Age + 1.274 × (Baseline platelet count) + 0.937 × eGFR + 1.169 × (Duration of linezolid therapy) + 0.987 × (ICU admittance) + 1.352 × PTZ

Where Age ≥ 75 years, yes = 1, no = 0; Baseline platelet count < $150\times10^9\cdot L^{-1}$, yes = 1, no = 0; eGFR < 60 $mL\cdot(min\cdot1.73m^2)^{-1}$, yes = 1, no = 0; Duration of linezolid therapy ≥ 10 d, yes = 1, no = 0; ICU admittance, yes = 1, no = 0; and PTZ, yes = 1, no = 0.

Table 4
Risk scores for developing thrombocytopenia

Risk factors	Score
Age	
< 75 years	0
≥ 75 years	2
Baseline platelet count	
$\geq 150\times10^{9}\cdot L^{-1}$	0
$< 150\times10^{9}\cdot L^{-1}$	3
eGFR	
$\geq 60\ mL\cdot(min\cdot1.73m^{2})^{-1}$	0
$< 60\ mL\cdot(min\cdot1.73m^{2})^{-1}$	2
Duration of linezolid therapy	
< 10 d	0
≥ 10 d	3
ICU admittance	
No	0
Yes	2
PTZ	
No	0
Yes	3

eGFR, estimated Glomerular Filtration Rate; PTZ, Piperacillin-tazobactam.

This risk predictive model in the train set showed a moderate discriminative performance to evaluate the development of thrombocytopenia, with an AUC of 0.795 (95% CI 0.740 ~ 0.851), and was well-calibrated based on the Hosmer and Lemeshow test with χ^2 statistic of 5.376 (P = 0.717).

Risk score development and Model validation

To facilitate the clinical use, we calculated the risk score of each risk factor according to the LI-TP risk evaluation model (Table 5). The total risk score ranged from 0 to 16, with corresponding predicted probabilities of LI-TP ranging from 2.4 to 94.3%. As the risk score increased, the probability of

thrombocytopenia was elevated. We categorized elderly patients based on this score into low (0–4 points), moderate (5–8 points) and high risk (≥ 9 points). The incidence of thrombocytopenia based on this classification was 8.1%, 26.6% and 60.0% for low, moderate and high risk, respectively. In the train set, the trend of higher risk level linking to a higher incidence of LI-TP was apparent.

The risk prediction model demonstrated good discriminative performance in the validation population, with an AUC of 0.849 (95%CI 0.760–0.939). In the validation set, 19 (21.1%) of 90 elderly patients developed thrombocytopenia during the linezolid treatment, and the incidence of LI-TP of the low-risk, moderate-risk, and high-risk levels were, respectively, 6.1%, 33.3%, and 62.5%, which showed a clear trend of higher risk level associated with a higher incidence of LI-TP.

Discussion

Increased use of linezolid for the treatment of multiple-drug resistant bacterial infections has induced the associated adverse drug reactions, especially in thrombocytopenia and anemia. Several studies reported the risk factors of LI-TP in elderly patients including baseline platelet, duration of linezolid therapy and renal impairment [12–14], while the conclusions of the studies were not consistent. Geriatric patients are often predisposed to multiple diseases and usually require complex medications that may increase the risk of LI-TP. However, few studies had constructed a LI-TP risk prediction model in this special population. Therefore, it is imperative to determine the risk factors, develop and validate a risk predictive model of LI-TP particularly for elderly patients.

In this present study, we performed a retrospective survey in elderly patients who were treated with a fixed dose 600 mg, q 12h of linezolid at Zhongshan Hospital, to identify risk factors contributing to thrombocytopenia after the initiation of linezolid treatment. The incidence of LI-TP in elderly patients has been reported to range from 20.9–70.4% [10–12]. The variations are attributed to the disparities in the definition of thrombocytopenia. In our study, the occurrence of LI-TP was 19.5%, consistent with a study that used the same thrombocytopenia definition [14]. For our definition, we adopted a platelet count lower than $100\times10^{9}\cdot L$ as the cut-off value, because this value is closely associated with increased ICU stay time and higher mortality, and can be used as a reference value for treatment adjustment [16–18].

Previous study found that LI-TP was closely associated with the duration of linezolid therapy, with their ROC curve indicating that duration of linezolid therapy ≥ 12 days was more likely to cause thrombocytopenia than those receiving linezolid therapy less than 12 days [14]. In addition, Nukuil et al. reported that 50% of the patients developed thrombocytopenia within 11 days of linezolid treatment, consistent with our results in which 49.3% of elderly patients developed LI-TP within 10 days after the initiation of linezolid treatment [19]. Duration of linezolid therapy ≥ 10 days was considered to be a significant risk factor for LI-TP in elderly patients in our study.

Our results revealed a significant association between baseline platelet counts $< 150\times10^{9}\cdot L^{-1}$ and thrombocytopenia development in elderly patients. This finding was consistent with Choi who

documented significantly lower baseline platelet counts in patients with thrombocytopenia than in those without [20]. With regard to the influence of laboratory variables, eGFR < 60 mL·(min·1.73m^2)$^{-1}$, which increases 2-fold in thrombocytopenia, was also identified as an independent risk factor for LI-TP. Aging affects the function of multiple organs, which may alter drug excretion. Therefore, a decline in renal function among elderly patients may elevate the risk of thrombocytopenia. Several studies found that the risks of LI-TP increased by 2, 8, and 9 folds in cases of mild, moderate, and severe renal insufficiency, respectively [21, 22]. On the other hand, the clearance of linezolid was closely associated with creatinine clearance, with area under the plasm concentration-time curve in linezolid shown to increase in thrombocytopenic patients with renal impairment [23]. Patients with renal insufficiency are likely to exhibit higher plasm linezolid concentrations and higher risks of LI-TP [19]. Therefore, physicians may pay more attentions to elderly patients with eGFR < 60 mL· (min·1.73m^2)$^{-1}$ to prevent the risk of thrombocytopenia.

Our multivariate logistic analysis revealed that ICU admittance was an important risk factor for LI-TP. The possible explanation may be that elderly patients in ICU often experience multiple organ failure and severe disease states, which may affect the pharmacokinetics of linezolid, leading to higher-than-expected drug concentration, and thrombocytopenia development. This may be the reason why elderly patients admitted in the ICU were more likely to develop LI-TP.

Since elderly patients are mainly characterized by complicated therapeutic drug regimens, we analyzed 33 different drug types administered alongside linezolid treatment to determine their impact on LI-TP, which was a larger number than that reported in other studies [8–9, 24]. Previous studies analyzing the risks associated with concomitant medications have shown that heparin are independent risk factors for LI-TP [25]. In this study, concomitance with heparin was also significantly different between LI-TP group and NO-TP groups in univariate analysis. However, multiple logistic regression analysis did not find this to be an independent risk factors, possibly due to the complicated concomitant diseases and medications associated with elderly patients. Choi et al reported that patients treated with a combination of linezolid and piperacillin-tazobactam were more likely to develop thrombocytopenia (28.6% vs. 17.6%, OR = 1.87, P < 0.05) in univariate logistic analysis [20]. While in our study, we identified that piperacillin-tazobactam to be a significant risk factor of LI-TP in geriatric patients by multivariate logistic analysis. Piperacillin-tazobactam induced thrombocytopenia is considered to be immune-mediated. This is because, when drugs covalently link to a serum protein, they tend to form an immunogenic structure and antibodies induced by this mechanism are usually specific to small molecule haptens, and are subsequently called hapten-dependant antibodies. Penicillin-like drugs, such as piperacillin, may trigger thrombocytopenia through this mechanism[26]. Elderly patients are more likely to have a rapid onset of immune thrombocytopenia due to repeated use of piperacillin-tazobactam [27]. Our finding shows that a combined application of piperacillin-tazobactam during the linezolid therapy enhances the risk of LI-TP, affirming the need to closely monitor platelet counts in elderly patients while receiving linezolid treatment.

Previous study had established a risk predictive model for LI-TP with an AUC of 0.711 (95%CI 0.664–0.757) in adult patients, but the model had not been externally verified [28]. Our study developed and

validated a risk predictive model of LI-TP for elderly patients with the AUC of 0.795 (95%CI 0.740 ~ 0.851) and 0.849 (95%CI 0.760 ~ 0.939) respectively, and the risk scores were further classified into three levels of low-, moderate-, and high-risk groups to predict the risks of LI-TP in elderly patients. This provided a more convenient method for clinicians to identify geriatric patients with high risk of LI-TP for closely monitoring.

Our study also had some limitations. Firstly, due to the retrospective nature of our study, we could not control for all possible confounding factors among elderly patients. Secondly, we did not determine the therapeutic drug monitor of linezolid, hence the association between linezolid concentration and thrombocytopenia cannot be ascertained. Thirdly, the sample size was relatively small to develop a classical risk predictive model, which may lead to the instability of our model. However, the results of our model were well-performed, which had a good discrimination power. Therefore, we want to share our exploratory results and expect our risk prediction model can be validated in the future.

Conclusion

In summary, the incidence of LI-TP was approximately 20% in elderly Chinese patients. Platelet counts should be monitored closely in elderly patients with longer linezolid therapy, higher age, renal insufficiency, ICU admittance, lower baseline platelet, and concomitant with piperacillin-tazobactam. A logistic regression model based on the above predictors showed good predictive power, and the establishment of risk score may help clinicians to identify elderly patients with high risk of LI-TP conveniently while receiving linezolid therapy.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Yan Qin, Yanrong Ye and Qianzhou Lv designed the study. Yan Qin and Yun Shen performed the research. Yan Qin and Zhe Chen worked on the data analysis. Yan Qin and Shuai Gao collected the data. Xiaoyu Li and Kunming Pan helped in solving statistical problems and professional questions encountered during the work. Yan Qin wrote the manuscript, Yanrong Ye and Yun Shen revised the manuscript.

Acknowledgements

This study was supported by the Youth Fund of ZhongShan hospital, FuDan University, (No. 2020ZSQN53).

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Table

Table 5 is not available with this version.

Figures

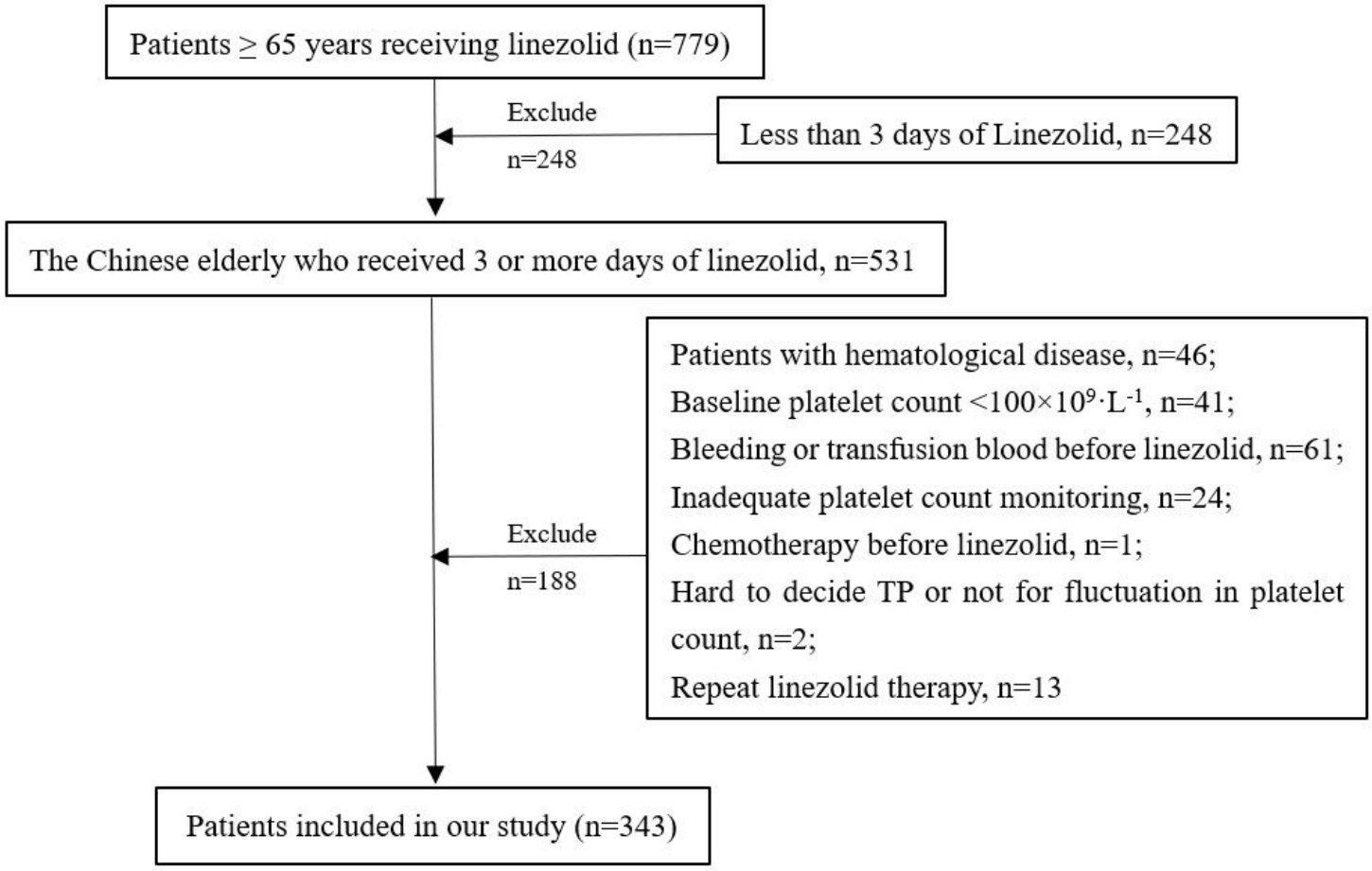

Figure 1

Flowchart of patients included in this study LI-TP, linezolid-induce thrombocytopenia; NO-TP, no development of thrombocytopenia.

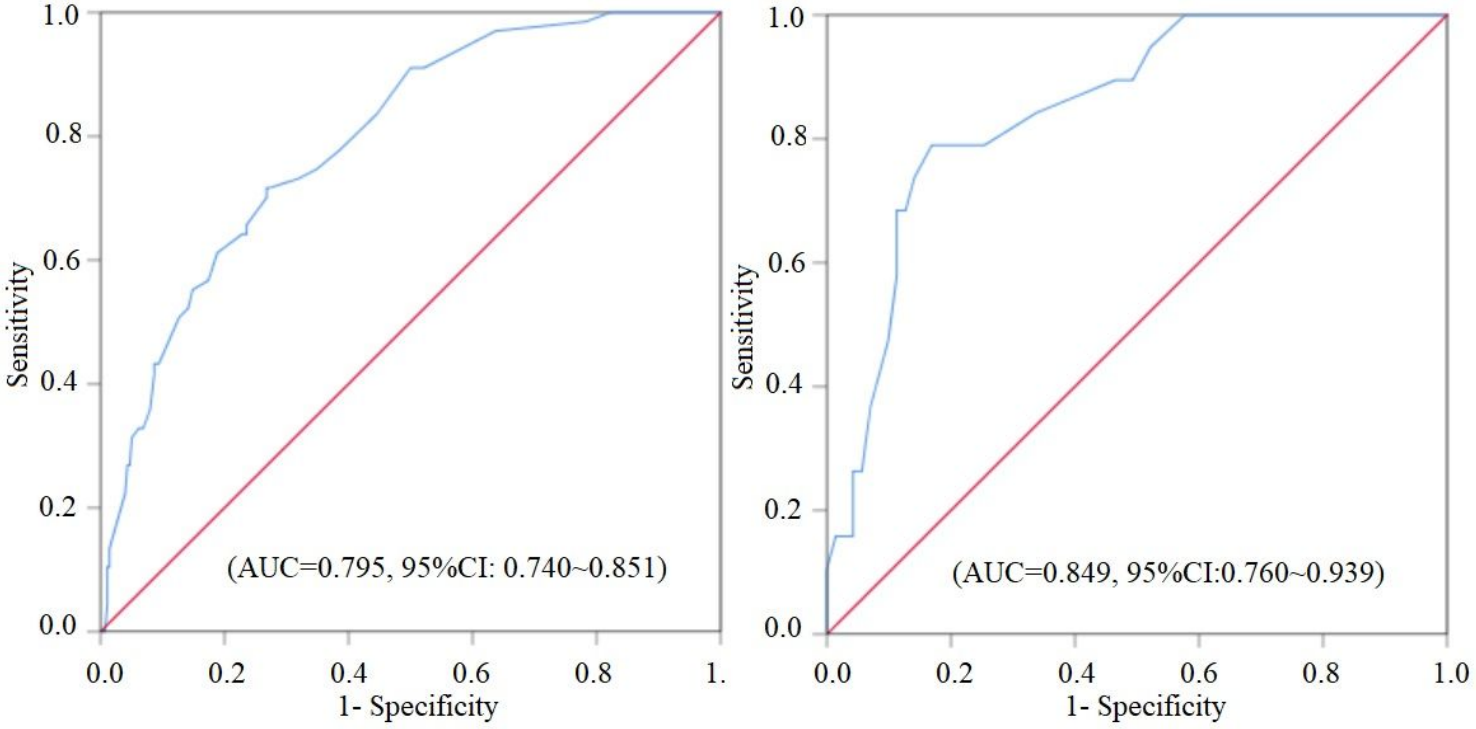

Figure 2

Receiver operating characteristic curves for the linezolid-induced thrombocytopenia risk model using the train set (A) and validation set (B). AUC, area under the curve; 95% CI, 95% confidence interval.