Development and validation of a risk prediction model for linezolid-induced thrombocytopenia in elderly patients

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ABSTRACT

Objectives Linezolid is the first oxazolidinone antimicrobial agent developed for treating multidrug-resistant gram-positive bacterial infections. The study aimed to investigate the risk factors of linezolid (LI)-induced thrombocytopenia (LI-TP) and to develop and validate a risk prediction model to identify elderly patients at high risk of developing LI-TP during linezolid therapy.

Methods A retrospective cohort study was performed at Zhongshan Hospital, Fudan University, China. The study involved elderly Chinese patients aged ≥65 years administered with linezolid (600 mg) twice a day between January 2015 and April 2021. We collected the patients’ clinical characteristics and demographic data from electronic medical records, and compared the differences between LI-TP patients and those who had not developed thrombocytopenia (NO-TP) after linezolid treatment. The risk prediction model was developed based on the regression coefficient generated from logistic regression model.

Results A total of 343 inpatients were enrolled from January 2015 to August 2020 and were used as the training set. Among them, 67 (19.5%) developed LI-TP. Multivariate logistic regression analysis revealed that baseline platelet counts <150×10^9·L^-1 (odds ratio (OR)=3.576; p<0.001), age ≥75 years (OR=2.258; p=0.009), estimated glomerular filtration rate (eGFR <60 mL·(min·1.73 m^2)^-1 (OR=2.553; p=0.002), duration of linezolid therapy ≥10 d (OR=3.218; p<0.001), intensive care unit (ICU) admittance (OR=2.682; p=0.004), concomitant piperacillin-tazobactam (OR=3.863; p=0.006) were independent risk factors for LI-TP in elderly patients. The LI-TP risk prediction model was established using a scoring method based on the regression coefficient and exhibited a good discriminative performance and may be useful for clinicians to identify patients at high risk of developing LI-TP.

INTRODUCTION

Linezolid is the first oxazolidinone antimicrobial agent developed to clinically treat multi-drug-resistant gram-positive bacteria including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and vancomycin-resistant Staphylococcus (VRSA). It 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. However, linezolid is associated with various adverse reactions, such as bone marrow suppression that is mainly manifested as thrombocytopenia and anaemia. Previous studies suggest linezolid can suppress platelet precursor cell 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, leading to a decrease in platelet count. Various studies have shown that elderly patients are more likely to develop thrombocytopenia, due to their specific physiological status. Some studies have reported that LI-TP incidence ranged from 20.9% to 70.4% in elderly patients, which was accompanied by higher risks of mortality. The risk factors of linezolid-induced thrombocytopenia (LI-TP) in elderly populations have been reported in several studies, although findings conflict. For example, studies by Lq and Zheng 2013, Zhou et al., 2014 and Shen et al., 2020 found that only the baseline platelet count <200×10^9/L, duration of linezolid therapy and renal impairment were significant risk factors for LI-TP. Meantime, a study by Li J et al., reported that elderly patients admitted to ICU had a higher risk of LI-TP than those of a similar age who were not admitted to ICU. Elderly patients are predisposed to multiple diseases, which require treatment using complicated medications that exacerbate the LI-TP problem. However, the risk factors of LI-TP in elderly patients were inconsistent. Indeed, few studies have established risk prediction models of LI-TP for this special population.

This study’s objective was to identify the risk factors associated with LI-TP in elderly patients, to construct and validate a risk prediction model to evaluate the risks of thrombocytopenia in elderly patients while receiving linezolid therapy, and to help physicians identify patients with higher risks of developing LI-TP using this prediction model.

METHODS

Study design and recruitment criteria
This study was performed between January 2015 and April 2021. Clinical data for these patients was...
retrospectively collected from the medical records, with permission from the Ethical Committee of ZhongShan Hospital. Patients who were ≥65 years and who had been consequently administered with linezolid (600 mg, q12h; orally or intravenously) for three or more days were recruited. None of the patients had been previously treated with linezolid in the 2 weeks before the treatment, and each patient was included only once per admission. Patients were excluded from the study if they were diagnosed with haematological diseases, were experiencing bleeding, had platelet count monitoring less than three times, were receiving radiotherapy or chemotherapy, lacked baseline platelet counts, had baseline platelet counts less than 100×10^9·L^{-1} or had received blood transfusions 2 weeks before the initiation of linezolid therapy.

### Disease grading and definition

We used platelet counts to categorise 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 100×10^9·L^{-1}. Disease severity was divided into four levels as follows: grade I was 75~99×10^9·L^{-1}, grade II was 50~74×10^9·L^{-1}, grade III was 20~49×10^9·L^{-1} and grade IV was below 20×10^9·L^{-1}, according to guidelines from the National Institute of Allergy and Infectious Diseases (NIAID). The causality of the adverse events was determined using the Naranjo algorithm. In addition, we divided clinical outcomes associated with platelet counts into two levels: recovery and improvement. Recovery was defined as platelet counts returning to the baseline value during hospitalisation; improvement was defined as platelet counts that increased to 100×10^9·L^{-1} after termination of linezolid treatment during hospitalisation.

### Clinical and demographic characteristics

We collected the following clinical and demographic characteristics for each elderly patient: age, gender, weight, payment method, hospitalised department, laboratory variables, as well as concomitant medication. The baseline of platelet data was collected 2 weeks before the initiation of linezolid therapy.

Other records were also extracted if the patients were transferred to ICU, had surgery, mechanical ventilation, renal replacement therapy or bleeding. Moreover, we comprehensively analysed variables associated with linezolid treatment and combined medications, including duration of linezolid therapy and concomitant drug.

### Data analysis

The statistical analysis was carried out using SPSS version 23.0 (IBM, 187 Chicago, IL, USA). Continuous variables were described as the mean± standard deviation (SD) or median (interquartile range[IQR])and groups were compared using the student’s t-test or the Mann-Whitney U-test. A Chi-squared test or Fisher’s exact test were used to analyse the categorical variables. Furthermore, multivariate logistic regression analysis was used to determine the association between the independent variable and LI-TP. A risk prediction model was constructed according to the risk factors. 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. Sample size should be 10 times more than the number of independent variables.

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**Table 1** Demographic and clinical characteristics of elderly patients in the training 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, interquartile range; n, number.

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**Figure 1** Flowchart of patients included in this study. LI-TP, linezolid-induced thrombocytopenia; n, number; NO-TP, no development of thrombocytopenia; TP, thrombocytopenia.

**RESULTS**

**Patient characteristics**

A total of 343 patients were recruited in the training set (figure 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 (table 1). The elderly patients had a median weight of 60.0 (IQR 55.0~70.0) kg. Linezolid was administered at a dose of 600 mg q12h, with a median duration of 8.5 (IQR 6.0~13.0) days. Variations in platelet counts during linezolid therapy were used to assign the elderly patients into two groups, LI-TP and NO-TP. After the initiation of linezolid therapy, 19.5% (67/343)
of the patients developed thrombocytopenia. Of these, 68.7% (46/67) were male, with a median age of 75.0 (IQR 69.0–79.0) years.

**Univariate analysis in the training set**

Demographic and clinical characteristics of elderly patients were compared in the training set; the older the patient the more likely they were to develop LI-TP, especially those over 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. The baseline platelet counts and eGFR were significantly lower in LI-TP patients compared with those without, and the P value<0.001. Moreover, LI-TP patients were more likely to have a longer linezolid treatment than those without. In addition, patients transferred to the ICU exhibited a higher risk of LI-TP (table 2).

A further analysis of 33 types of drugs used during the linezolid treatment indicated 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 with the NO-TP group, a significantly higher number of LI-TP patients were receiving piperacillin-tazobactam (14.9% vs 5.4%; p=0.016).

**Establishment of LI-TP prediction model**

A total of seven categorised variables with p<0.05 in the univariate analyses were selected for multivariate logistic regression analysis. These were: age, baseline platelet counts, eGFR, duration of linezolid therapy, ICU admittance, concomitant with heparin.

| 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) | 0.704 |
| 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: | | | |
| Medical, n (%) | 24 (35.8) | 129 (46.7) | 0.116 |
| Surgical, n (%) | 23 (34.3) | 94 (34.1) | 0.116 |
| ICU, n (%) | 20 (29.9) | 53 (19.2) | 0.116 |
| Payment methods: | | | |
| Self-payment, n (%) | 23 (34.3) | 124 (44.9) | 0.116 |
| Basic national medical insurances, n (%) | 44 (65.7) | 152 (55.1) | 0.116 |
| Baseline laboratory data: | | | |
| Platelet count (10⁹·L⁻¹), median (IQR) | 168.0 (134.0–222.0) | 253.5 (187.3–343.0) | <0.001 |
| Platelet count <150×10⁹·L⁻¹, n (%) | 24 (35.8) | 33 (12.0) | <0.001 |
| Haemoglobin (g·L⁻¹), median (IQR) | 104.0 (83.0–112.0) | 99.0 (84.3–114.0) | 0.930 |
| Total bilirubin (μmol·L⁻¹), median (IQR) | 11.5 (6.5–21.0) | 10.1 (7.0–16.9) | 0.327 |
| Total albumin (g·L⁻¹), median (IQR) | 60.0 (54.0–64.0) | 61.0 (57.0–66.0) | 0.155 |
| Albumin (g·L⁻¹), median (IQR) | 32.0 (30.0–35.0) | 33.0 (30.0–36.0) | 0.401 |
| Alanine aminotransferase (U·L⁻¹), median (IQR) | 19.0 (12.0–45.0) | 22.5 (14.0–36.8) | 0.578 |
| Aspartate aminotransferase (U·L⁻¹), median (IQR) | 27.0 (17.0–47.0) | 26.0 (18.0–37.0) | 0.902 |
| eGFR(μL·(min·1.73 m²)⁻¹), median (IQR) | 55.0 (39.0–84.3) | 87.1 (53.0–96.0) | <0.001 |
| eGFR <60 mL·(min·1.73 m²)⁻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 (8.9) | 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 |

eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range.
and piperacillin-tazobactam. Multivariate logistic regression analysis revealed that baseline platelet counts below $150 \times 10^9 \text{L}^{-1}$, age $\geq 75$ years, eGFR lower than $60 \text{mL}(\text{min} \cdot 1.73 \text{m}^2)$, duration of linezolid therapy $\geq 10$ days, ICU admittance as well as concomitant with piperacillin-tazobactam were independent risk factors for LI-TP (table 4). Finally, a risk LI-TP prediction model was established based on the multiple logistic regression model. The equation we used was:

$$\text{Logit}(P) = -3.720 + 0.815 \times \text{Age} + 1.274 \times (\text{baseline platelet count}) + 0.937 \times \text{eGFR} + 1.169 \times (\text{duration of linezolid therapy}) + 0.987 \times (\text{ICU admittance}) + 1.352 \times \text{PTZ}$$

Where age $<75$ years $= 0$ and $\geq 75$ years $= 1$; baseline platelet count $\geq 150 \times 10^9 \text{L}^{-1} = 0$ and $<150 \times 10^9 \text{L}^{-1} = 1$; eGFR $\geq 60 \text{mL}(\text{min} \cdot 1.73 \text{m}^2) = 0$ and $<60 \text{mL}(\text{min} \cdot 1.73 \text{m}^2) = 1$; duration of linezolid therapy $<10$ days and $\geq 10$ days $= 1$; ICU admittance, yes $= 1$, no $= 0$; and PTZ, yes $= 1$, no $= 0$.

This risk prediction model in the training set showed a good discriminative performance to evaluate the development of thrombocytopenia, with an AUC of $0.795$ (95% CI: $0.740–0.851$, figure 2), and was well-calibrated based on the Hosmer-Lemeshow test with $\chi^2$ statistic of $5.376$ ($p=0.717$; online supplemental figure S1).

### 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 (online supplemental table S1). 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, so did the probability of thrombocytopenia (online supplemental figure S2). We categorised 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 (online supplemental figure S3). In the training set, the trend of higher risk level linking to a higher incidence of LI-TP was apparent.

The risk prediction model demonstrated excellent discriminatory performance in the validation population, with an AUC of $0.849$ (95% CI: $0.760$ to $0.939$). In the validation set, 19 (21.1\%) of 90 elderly patients developed thrombocytopenia during linezolid treatment, and the incidence of LI-TP of low-risk, moderate-risk, and high-risk levels were $6.1\%$, $33.3\%$, and $62.5\%$, respectively (online supplemental figure S2). This showed a clear trend of higher risk level associated with a higher incidence of LI-TP.

### LI-TP severity and treatment

The lowest platelet count in each patient was used to classify LI-TP severity. The incidence of LI-TP in patients with grade 3 and 4 thrombocytopenia was $22.4\%$ (15/67) and $12.0\%$ (8/67), respectively, with a mean time of 12.8±6.8 days for the 22 elderly patients (online supplemental table S2). Furthermore, there was a significant decreasing trend in platelet counts over time, with higher frequency of LI-TP after 10 days of treatment. The median platelet counts in patients with LI-TP at different time points are shown in online supplemental figure S4. The causality of LI-TP in each patient was estimated using the Naranjo algorithm, and these results are listed in online supplemental table S2). Adverse thrombocytopenic complications, including gastrointestinal bleeding, cutaneous bleeding, intracranial haemorrhage and pulmonary haemorrhage, were found in 25.4\% (17/67) of LI-TP patients. Medication adjustments, including the termination of linezolid therapy, were reported in 44.8\% (30/67) of LI-TP patients after TP onset, 28.4\% (19/67) of the patients took no treatment, 23.9\% (16/67) of the patients were administered with recombinant human thrombopoietin (rhTPO) for 3.0±2.4 days or recombinant human interleukin-11 (rhIL-11) for 5.7±3.7 days to improve platelet functions.

### Outcomes of LI-TP

The all-cause mortality in elderly patients with LI-TP was 38.8\% (26/67), which was significantly higher than that observed in patients without thrombocytopenia (15.2\%, $p<0.001$). Out of 67 patients, 26 patients were excluded as they died before recovery, as well as 10 patients who stopped monitoring platelet

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### Table 3 Comparison of concomitant drugs used between patients with linezolid-induced thrombocytopenia (LI-TP) and those without (NO-TP)

| Characteristics | LI-TP (67) | NO-TP (276) | P value |
|-----------------|------------|-------------|---------|
| 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   |
| ß-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   |
| Spirinolactone  | 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   |
| 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   |
| Polype nephosphatidylcholine | 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   |
| Benzodiazepine  | 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   |

ACEL, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitors.

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counts after the discontinuation of linezolid therapy. After discontinuation of linezolid therapy, recovery of platelet counts to the baseline value was recorded in 23 patients at an average time of 9.3 ± 4.9 days, and 8 patients exhibited improved platelet counts at an average time of 4.4 ± 1.6 days.

**DISCUSSION**

Increased use of linezolid to treat Gram-positive bacterial infections has induced the associated adverse drug reactions, especially thrombocytopenia and anaemia. Several studies reported the risk factors of LI-TP in elderly patients, including baseline platelet, duration of linezolid therapy and renal impairment. 

Elderly 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 particularly for elderly patients. Therefore, it is imperative to determine the risk factors, develop and validate a risk prediction model of LI-TP for elderly patients.

The incidence of LI-TP in elderly patients has been reported to range from 20.9% to 70.4%. The variations are attributed to the disparities in the definition of thrombocytopenia. In our study, we found that this occurrence of LI-TP was 19.5%, consistent with a study that used the same thrombocytopenia definition. For our definition, we adopted a platelet count lower than 100×10^9·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.

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 ≥12 days was more likely to cause thrombocytopenia. Nukuil et al., reported that half of the patients in their study developed thrombocytopenia within 11 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 ≥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.

Our results revealed a significant association between baseline platelet counts <150×10^9·L and thrombocytopenia development in elderly patients. This finding was consistent with Choi et al., who documented significantly low baseline platelet counts in patients with thrombocytopenia than in those without. Moreover, eGFR <60 mL·(min·1.73 m2) was also identified as an independent risk factor for LI-TP, which increases 2-fold in thrombocytopenia. Recent studies found the risk of LI-TP increased by 2-, 8-, and 9-folds in cases of mild, moderate, and severe renal insufficiency, respectively. Generally, ageing 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. On the other hand, the clearance of linezolid was closely associated with creatinine clearance, with AUC in linezolid shown to increase in thrombocytopenic patients with renal impairment.

Patients with renal insufficiency are likely to exhibit higher plasma linezolid concentrations and high risks of LI-TP.

Our study also revealed that ICU admittance was an important risk factor for LI-TP. Generally, 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 to the ICU were more likely to develop LI-TP.

Since elderly patients are mainly characterised by complicated therapeutic drug regimens, we analysed 33 different drug types administered alongside linezolid treatment to determine their impact on LI-TP, which was a larger number than those reported in other studies. 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. In this study, we identified that piperacillin-tazobactam was a significant risk factor of LI-TP in elderly patients by multivariate logistic analysis. Generally, piperacillin-tazobactam induced thrombocytopenia is considered immune-mediated. When drugs covalently link to a serum protein, they tend to form an immunogenic structure. Antibodies induced by this mechanism are usually specific to small molecule hapten, and are subsequently called hapten-dependent antibodies. Penicillin-like drugs, such as piperacillin, may trigger thrombocytopenia through this mechanism. Previous studies have also shown that antibodies are recognised and bind to platelets in the presence of soluble penicillin, thereby reducing platelet count. Elderly patients are more likely to have a rapid onset of immune thrombocytopenia.

Table 4  Risk factors of linezolid-induced thrombocytopenia

| Risk factors                        | β     | SE    | Wald χ² | P value | OR    | 95% CI         |
|------------------------------------|-------|-------|---------|---------|-------|---------------|
| Intercept                          | -3.720| 0.444 | 70.087  | <0.001  | 2.258 | 1.229 to 4.149|
| Age≥75 years                       | 0.815 | 0.310 | 6.890   | 0.009   | 2.533 | 1.262 to 5.103|
| Baseline platelet count <150×10^9·L| 1.274 | 0.349 | 13.318  | <0.001  | 3.576 | 1.804 to 7.088|
| eGFR <60 mL·(min·1.73 m2)          | 0.937 | 0.310 | 9.155   | 0.002   | 2.533 | 1.391 to 4.859|
| Duration of linezolid therapy ≥10 d| 1.169 | 0.324 | 12.988  | <0.001  | 3.218 | 1.704 to 6.076|
| ICU admittance                     | 0.987 | 0.345 | 8.198   | 0.004   | 2.682 | 1.365 to 5.269|
| PTZ                                | 1.352 | 0.490 | 7.621   | 0.006   | 3.863 | 1.480 to 10.085|

CI, confidence interval; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; OR, overall response; PTZ, piperacillin-tazobactam.

Figure 2  Receiver operating characteristic curves for the linezolid-induced thrombocytopenia risk model using the training set (A) and validation set (B). AUC, area under the curve; CI, confidence interval.
due to repeated use of piperacillin-tazobactam. Our finding shows that a combined application of piperacillin-tazobactam during the linezolid therapy enhances the risk of LI-TP.

Additionally, we found that the occurrence of LI-TP was not significantly associated with gender. A study by Zhou et al. 2014 indicated that male gender is not the significant risk factor for LI-TP, which is consistent with our result. However, the number of patients in these studies is small and more large-scale studies with more patients are needed to confirm our finding.

A previous study not particularly for elderly patients had constructed a prediction model of LI-TP with an AUC of 0.711 (95% CI: 0.664 to 0.757), but it did not conduct an extra validation set of the risk prediction model to verify the potential performance in decision-making guided by the risk score. Our study developed and validated a risk prediction 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 risks groups to predict LI-TP risk in elderly patients. This provided a more convenient method for clinicians to identify elderly patients with high risk of LI-TP for close monitoring.

Our study had some limitations. First, due to the retrospective nature of our study, we could not control for all possible confounding factors. Second, we did not determine the therapeutic drug monitor of linezolid, hence the association between concentration and thrombocytopenia cannot be ascertained. Thirdly, the sample size was relatively small to develop a classical risk prediction model, which may lead to instability of our model. However, the results of our model were robust with a good discriminative power.

CONCLUSION
In summary, the occurrence of LI-TP was approximately 20% in elderly Chinese patients. Platelet counts should be monitored closely in elderly patients experiencing prolonged linezolid therapy, higher age, renal insufficiency, ICU admittance, low baseline platelets, 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.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethical Committee of the Zhongshan Hospital, Fudan University (B2021-304). We did not need to obtain written informed consent from the patients whose records were used as the study had received a Retrospective Clinical Application from ZhongShan Hospital.

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Data availability statement Data are available upon reasonable request.

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Key messages
What is already known on this topic
► Linezolid-induced thrombocytopenia (LI-TP) is a common adverse drug reaction of linezolid. Elderly patients with special physiological status are more likely to develop LI-TP.
► However, few studies have established a risk prediction model of LI-TP in elderly patients.

What this study adds
► Significant risk factors associated with LI-TP were found to be baseline platelet counts below $150 \times 10^3\ \text{L}^{-1}$, age ≥75 years, eGFR lower than 60 mL·min$^{-1}$·1.73 m$^2$, duration of linezolid therapy ≥10 d, ICU admittance, as well as concomitant with piperacillin-tazobactam.
► A risk prediction model for LI-TP in elderly patients was developed and validated.

How this study might affect research, practice or policy
► Our model may help physicians to identify individual patients with high risk of LI-TP for close monitoring in practice.
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