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Therapeutic drug monitoring of linezolid and exploring optimal regimens and a toxicity-related nomogram in elderly patients: a multicentre, prospective, non-interventional study

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Background: The concentrations of linezolid, its optimal regimen and the associated side effects in elderly patients remain unclear.

Methods: In this multicentre, prospective study, elderly patients receiving linezolid at four tertiary hospitals in Beijing between May 2021 and December 2022 were included. Linezolid concentrations and haematological toxicity were monitored dynamically. Risk factors for linezolid overexposure and moderate-to-severe linezolid-induced thrombocytopenia (M/S LIT) were analysed, and a predictive model of M/S LIT was developed.

Results: A total of 860 linezolid concentrations were measured in 313 patients. The median trough concentrations of linezolid were 24.4 (15.3, 35.8) mg/L at 36–72 h and 26.1 (17.0, 38.1) mg/L at 5–10 days ($P=0.132$). Severe linezolid exposure was independently associated with age, estimated glomerular filtration rate (eGFR) and the worst SOFA score ($SOFA_1$), and we further recommended dose regimens for elderly patients based on these findings. The incidences of linezolid-induced thrombocytopenia(LIT) and M/S LIT were 73.5% and 47.6%, respectively. M/S LIT was independently correlated with treatment duration, average trough concentration (TDM_a), baseline platelet count, eGFR and baseline SOFA score ($SOFA_0$). The developed nomogram predicted M/S LIT with an area under the curve of 0.767 (95% CI 0.715–0.820), a sensitivity of 71.1% and a specificity of 73.2%.

Conclusions: Linezolid trough concentrations increased dramatically in the elderly, by about 10 mg/L in patients aged 65–80 years, followed by a further increase of 10 mg/L for every 10 years of age. Therapeutic drug monitoring is recommended in elderly patients receiving linezolid. The developed nomogram may predict M/S LIT and guide dosage adjustments of linezolid.
Clinical trial registration number: ChiCTR2100045707

Introduction

Linezolid is a synthetic oxazolidinone antibiotic commonly used to treat Gram-positive bacterial infections, including vancomycin-resistant *Enterococcus* and MRSA.[1,2] The manufacturer's instructions suggest no significant change in linezolid pharmacokinetics and thus no need to adjust its dosage in elderly patients (≥65 years). However, Cattaneo *et al.*[3] found that linezolid trough concentrations were 3-fold higher in elderly (aged >80 years) compared with younger patients (aged <40 years) following treatment with the conventional 600 mg twice daily dose, and levels increased by 30% for every 10 years of age. Tinelli *et al.*[4] also found that linezolid trough concentrations exceeded the upper therapeutic safety threshold of 8 mg/L in patients aged ≥70 years. Numerous studies found that about 50% of patients developed linezolid-induced thrombocytopenia (LIT) when trough concentrations of linezolid reached 8 mg/L.[5–8] When the concentration was 8 mg/L and the MIC was 2 mg/L (few MRSA strains have MIC ≥ 2 mg/L),[5,9,10] the AUC_{0-24}/MIC exceeded the target value (100) required to ensure clinical efficacy according to pharmacokinetic/pharmacodynamic theory.[5,11] Kawasuji *et al.*[12] and Cojutti *et al.*[13] found that maintaining the trough concentration of linezolid at 2–8 mg/L reduced the occurrence of LIT and ensured the treatment course. Pea *et al.*[14] also found that adjusting the trough concentration to 2–7 mg/L significantly decreased the incidence of LIT and maintained the clinical efficacy rate to 98%. Therefore, maintaining the trough concentration of linezolid at 2–8 mg/L thus guaranteed its treatment effect and also reduced its hematological toxicity.

However, most elderly patients receive conventional doses of linezolid without therapeutic drug monitoring (TDM) in the real world, and data on linezolid trough concentrations and concomitant hematological toxicity in elderly patients are lacking. We conducted a multicentre, prospective study to collect relevant data, recommend dose regimens and establish a model to predict moderate-to-severe linezolid-induced thrombocytopenia (M/S LIT) to ensure the efficacy and safety of linezolid in elderly patients.

Materials and methods

Patients

This study included elderly patients treated at the First, Second, Fourth and Eighth Medical Centers of the Chinese People's Liberation Army General Hospital from May 2021 to December 2022. The inclusion criteria were patients aged ≥65 years, treated with intravenous or oral linezolid (Zyvox; Pfizer, USA) 1200 mg/day (600 mg twice daily). The exclusion criteria were previous use of linezolid within 1 month; concurrent chemotherapy or platelet transfusion; receiving renal replacement therapy; and repeated inclusion within 1 year. The enrolled patients were further divided into groups according to age: 65–80, 81–90 and >90 years. An additional 40 non-elderly patients (18–65 years old) were included.

Data collection

Basic information on the subjects included sex, age, underlying diseases, Charlson's comorbidity index, SOFA score, P-glycoprotein (P-gp) inhibitor use, infection site and prognosis.

Therapeutic drug monitoring

Trough plasma linezolid concentrations were detected using liquid chromatography–tandem mass spectrometry,[15] with linear detection from 0.8 to 100 mg/L and a lower limit of quantification of 0.8 mg/L. The observed intra- and interday assay imprecision and inaccuracy were <10%.

Peripheral blood (5 mL) was drawn from the patient's antecubital fossa into EDTA-containing Vacutainers® (Becton Dickinson, Milan, Italy) before linezolid administration in the morning and after drug withdrawal. All samples were centrifuged at 2500 ×*g* for 10 min, and 2 mL of supernatant was separated and stored at −20°C for subsequent detection. The blood concentrations measured after 3–6 doses of linezolid (36–72 h) and again at 5–10 days within 2 h of the next scheduled administration time were recorded as TDM_{36-72h} and TDM_{5-10d}, respectively. Blood concentrations 24 and 48–72 h after the last dose of linezolid (drug withdrawal) were recorded as TDM_{w24h} and $TDM_{w48-72h}$, respectively.

Definition

Thrombocytopenia was defined as a decrease in platelet count >30% of baseline levels from initiation of linezolid treatment to 72 h after withdrawal:[5,16,17] a decrease of 30%–49% was mild, 50%–69% moderate and ≥70% severe.[5] Erythropenia was defined as a decrease in erythrocyte count >10% of baseline from initiation of linezolid treatment to 72 h after withdrawal: a decrease of 10%–19% was mild, 20%–29% moderate and ≥30% severe. Hypohaemoglobinaemia was defined as a decrease in haemoglobin >10% of baseline levels: a decrease of 10%–19% was mild, 20%–29% moderate and ≥30% severe.

When the trough concentration was 30 mg/L, approximately 50% of patients developed moderate-to-severe thrombocytopenia, so patients with an average trough concentration of linezolid (TDM_a) ≥ 30 mg/L were included in the severe exposure group, and patients with TDM_a <30 mg/L were included in the non-severe exposure group. TDM_a was taken as the average concentration during treatment. The distributions of linezolid trough concentrations were defined as follows: desired therapeutic range, trough concentration 2–8 mg/L; underexposure, trough concentration <2 mg/L; overexposure, trough concentration >8 mg/L; and severe exposure, trough concentration ≥30 mg/L.[18]

Nomogram

The nomogram, also known as the alignment diagram, was developed by multivariate logistic regression analysis using R 3.6.2 to integrate meaningful predictors and draw them on the same plane in a certain proportion. The specific operation process and operation code are given in Supplementary material (available as Supplementary data at *JAC* Online). Calibration curves were drawn and decision curve analysis was performed using R 3.6.2 to evaluate the effectiveness and benefits of the nomogram.

Statistical analysis

Quantitative data with a normal distribution were expressed as mean and standard deviation and analysed by *t*-tests. Quantitative data with a non-normal distribution were presented as median and interquartile range and assessed by Mann–Whitney *U* test. Numerical data were compared using χ^2 or Fisher's exact probability test. Correlations between factors were determined by Spearman's analysis. Multivariate logistic regression analysis was used to identify factors affecting severe linezolid exposure and the independent factors influencing M/S LIT. Kaplan–Meier plots were used to show the probability of M/S LIT in relation to the duration of linezolid treatment. A receiver operating characteristic (ROC) curve was developed by R Base Package and used to evaluate the validity of the nomogram model. A validation set of elderly patients treated with linezolid at the aforementioned four tertiary hospitals from January 2023 to May 2023 was included. $P < 0.05$ was considered significant.

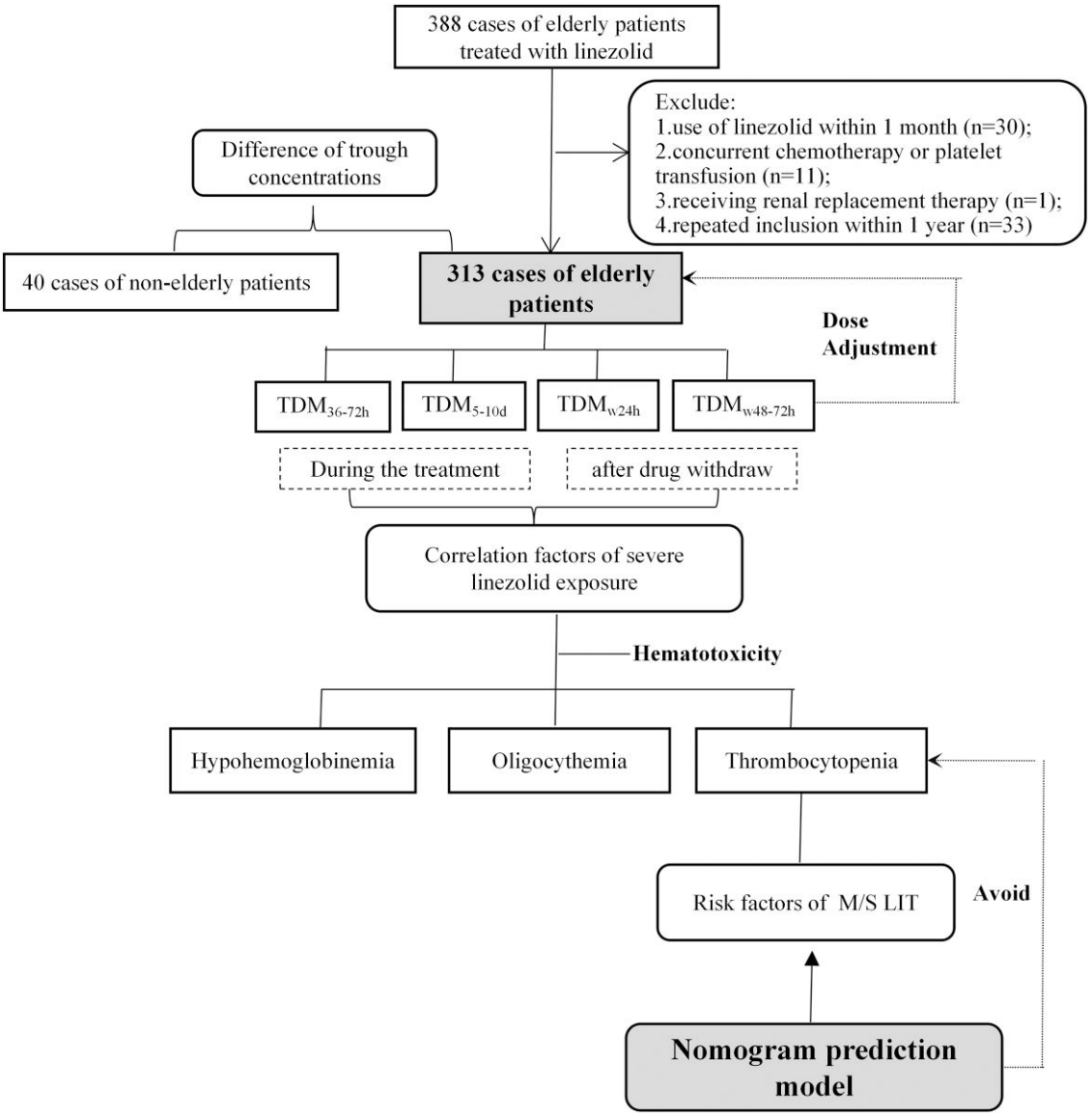

Figure 1. Flow chart of patient enrolment and study design. $TDM_{36–72h}$, 3–6 doses of linezolid (36–72 h); $TDM_{5–10d}$, 5–10 days of linezolid; TDM_{w24h}, 24 h after withdrawal; $TDM_{w48–72h}$, 48–72 h after withdrawal. M/S LIT, moderate-to-severe linezolid-induced thrombocytopenia.

Results

Linezolid trough concentrations in elderly and non-elderly patients

A total of 313 elderly patients and 40 non-elderly patients were included (Figure 1). The median trough concentrations of linezolid ($TDM_{5–10d}$) were 26.1 (17.0, 38.1) mg/L and 5.9 (3.9, 10.5) mg/L, respectively ($P < 0.0001$) (Supplementary data Table S1, Figure 2a). The basic information of 40 non-elderly patients is presented in Supplementary data Table S2.

Linezolid trough concentrations showed a positive moderate linear correlation with age ($R = 0.488$, $P < 0.0001$; Figure 2b) and a negative weak linear correlation with estimated glomerular filtration rate (eGFR) ($R = -0.347$, $P < 0.0001$; Figure 2b).

Dynamic monitoring of linezolid trough concentrations in the elderly

In total, 313 elderly patients were included, and 244 (78%), 273 (87.2%), 40 (12.8%) and 303 (96.8%) trough concentrations were included as $TDM_{36–72h}$, $TDM_{5–10d}$, TDM_{w24h} and $TDM_{w48–72h}$, respectively (Figure 2c).

The median $TDM_{36–72h}$ values were 24.4 (15.3, 35.8) mg/L in the total study population and 10.5 (4.8, 20.8), 21.1 (11.4, 29.5) and 29.9 (20.7, 40.7) mg/L in the 65–80, 81–90 and >90 groups, respectively ($P < 0.001$ among the three age groups; Table 1, Figure 2d). The median $TDM_{5–10d}$ values were 26.1 (17.0, 38.1), 11.9 (9.1, 23.3), 23.8 (14.8, 31.8) and 31.1 (21.9, 44.9) mg/L in the total study population and in the 65–80, 81–90 and >90 groups, respectively ($P < 0.0001$

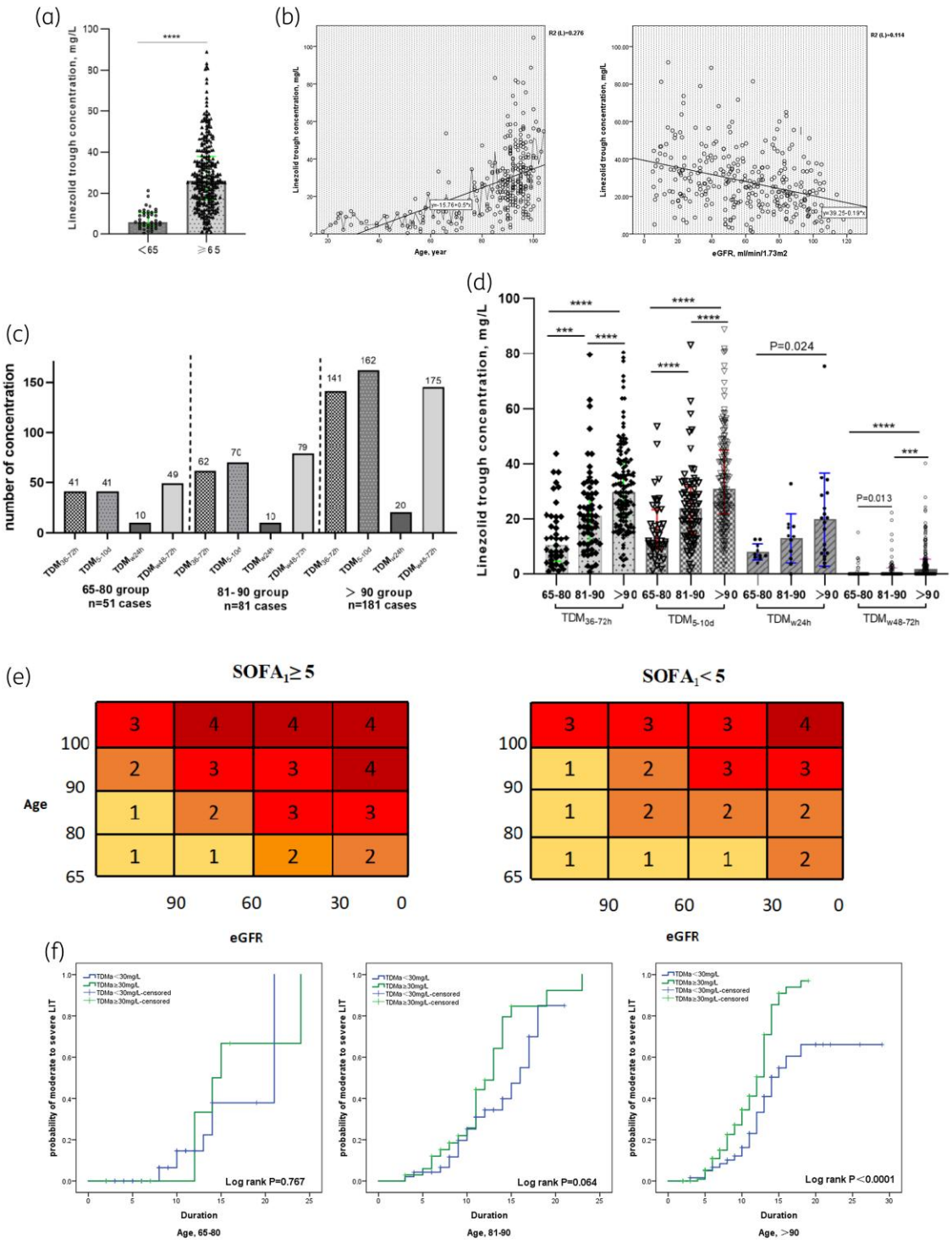

Figure 2. (a) Linezolid trough concentrations in 40 non-elderly and 313 elderly patients ($P < 0.0001$). (b) Linear correlations between trough concentrations of linezolid and age and eGFR. (c) Number of linezolid concentrations at different age groups. (d): Dynamic monitoring of linezolid concentrations at different ages. ***$P < 0.001$; ****$P < 0.0001$. (e) Based on multivariate analysis, four dose regimens were recommended: 1:600 mg + 300 mg daily; 2:300 mg twice daily; 3:600 mg once daily; and 4:300 mg once daily. (f) Kaplan–Meier plot showing the probability of M/S LIT in relation to linezolid duration at different age groups.

Table 1. Dynamic monitoring of linezolid concentrations in 313 elderly patients

	Groups			
TDM	65–80 ($n=51$)	81–90 ($n=81$)	>90 ($n=181$)	All ($n=313$)
TDM_{36-72h}, median (IQR)	10.5 (4.8, 20.8)	21.1 (11.4, 29.5)***	29.9 (20.7, 40.7)****####	24.4 (15.3, 35.8)
N (%)	41 (80.4)	62 (76.5)	141 (77.9)	244 (78.0)
<2 mg/L, *N* (%)	4 (9.8)	1 (1.6)	0 (0)	5 (2.0)
>8 mg/L, *N* (%)	26 (63.4)	54 (87.1)	136 (96.5)	216 (88.5)
≥30 mg/L, *N* (%)	6 (14.6)	14 (22.6)	69 (48.9)	89 (36.5)
TDM_{5-10d}, median (IQR)	11.9 (9.1, 23.3)	23.8 (14.8, 31.8)****	31.1 (21.9, 44.9)****####	26.1 (17.0, 38.1)
N (%)	41 (80.4)	70 (86.4)	162 (89.5)	273 (87.2)
<2 mg/L, *N* (%)	2 (4.9)	1 (1.4)	0 (0)	3 (1.1)
>8 mg/L, *N* (%)	33 (80.5)	65 (92.9)	159 (98.1)	257 (94.1)
≥30 mg/L, *N* (%)	4 (9.8)	19 (27.1)	84 (51.9)	107 (39.2)
TDM_{w24h}, median (IQR)	7.1 (6.1, 10.9)	13.1 (5.2, 17.3)	18.1 (7.7, 27.5)*	12.4 (4.9, 15.5)
N (%)	10 (19.6)	10 (12.3)	20 (11.0)	40 (12.8)
≥2 mg/L, *N* (%)	9 (90)	10 (100)	20 (100)	39 (97.5)
>8 mg/L, *N* (%)	4 (40)	7 (70)	14 (70)	25 (62.5)
$TDM_{w48-72h}$, median (IQR)	0	0 (0, 2.3)*	1.8 (0, 5.6)****###	0 (0, 3.6)
N (%)	49 (96.1)	79 (97.5)	175 (96.7)	303 (96.8)
≥2 mg/L, *N* (%)	8 (16.3)	22 (27.8)	85 (48.6)	115 (37.9)
>8 mg/L, *N* (%)	1 (2.0)	5 (6.3)	31 (17.1)	37 (12.2)

*Versus 65–80 group.

#>90 group versus 81–90 group; TDM, therapeutic drug monitoring. TDM_{36-72h}, 3–6 doses of linezolid (36–72 h); TDM_{5-10d}, 5–10 days of linezolid; TDM_{w24h}, 24 h after withdrawal; $TDM_{w48-72h}$, 48–72 h after withdrawal.

*<0.05; **<0.01; ***<0.001; ****<0.0001; ###<0.001; ####<0.0001.

among the three age groups; Table 1, Figure 2d). The median TDM_{w24h} values in the total study population and in the 65–80, 81–90 and >90 groups were 12.4 (4.9, 15.5), 7.1 (6.1, 10.9), 13.1 (5.2, 17.3) and 18.1 (7.7, 27.5) mg/L, respectively. TDM_{w24h} differed significantly between the 65–80 and >90 groups ($P=0.024$; Table 1, Figure 2d). The median $TDM_{w48-72h}$ values were 0 (0, 3.6), 0 (0, 2.3) and 1.8 (0, 5.6) mg/L in the total study population and in the 65–80, 81–90 and >90 groups, respectively, with significant differences among the groups ($P<0.05$) (Table 1, Figure 2d).

The median trough concentration after 5–10 days of linezolid therapy was slightly higher than that at 36–72 h in the total study population and in all age groups, but the differences were not significant ($P>0.05$; Table 1, Figure 2d).

Factors related to severe linezolid exposure

A total of 119 (38.0%) patients were included in the severe exposure (TDM_a ≥30 mg/L) group, and the remaining 194 (62.0%) patients were included in the non-severe exposure group. In multivariate analysis, severe linezolid exposure was independently associated with age (OR, 1.808; 95% CI, 1.245–2.626, per 10 years, $P=0.002$, Table 2), eGFR <60 mL/min/1.73 m^2 (OR, 2.067; 95% CI, 1.222–3.497, $P=0.007$, Table 2) and $SOFA_1 \geq 5$ (OR, 3.031; 95% CI, 1.415–6.494, $P=0.004$, Table 2).

Based on factors related to severe linezolid exposure and ORs, we further recommended dose regimens for elderly patients (Figure 2e): 600 and 300 mg at 12 h intervals (600 mg + 300 mg daily); 300 mg twice daily; 600 mg once daily; and 300 mg once daily.

Correlation between severe linezolid exposure and hematological toxicity

The incidence of LIT in the total study population was 73.5% (230/313), and the incidences of mild, moderate and severe LIT in the non-severe exposure were 26.8% (52/194), 27.3% (53/194) and 11.3% (22/194), respectively, and in the severe exposure groups were 24.4% (29/119), 31.9% (38/119) and 30.3% (36/119), respectively, with a significant difference between the two groups ($P<0.0001$, Table 3). In the non-severe-exposure group, 56.7% (110/194) of patients continued to decline after drug withdrawal, compared with 78.1% (93/119) in the severe exposure group ($P=0.003$; Table 3).

The incidence of hypohaemoglobinaemia was significantly higher in the severe exposure compared with the non-severe exposure group (72.3% versus 55.7%, respectively, $P=0.030$, Table 3), while the incidence of erythropenia was similar in both groups (70.6% versus 56.7%, respectively, $P=0.092$; Table 3).

A total of 51.1% (160/313) of patients stopped medication due to haematological toxicity, including 43.3% (84/194) and 63.9% (76/119) in the non-severe exposure and severe exposure groups, respectively ($P<0.0001$; Table 3).

Probability of M/S LIT in relation to linezolid duration

The incidence of M/S LIT increased gradually with increasing duration of linezolid administration in the 65–80 and 81–90 groups, but there was no difference between the non-severe exposure and severe exposure groups ($P>0.05$; Figure 2f). The incidence

Table 2. Univariate and multivariate analysis of severe linezolid exposure

Characteristics	All patients ($n=313$)	Groups		Univariate	Multivariate	
		Non-severe exposure group ($n=194$)	Severe exposure group ($n=119$)	P	OR (95% CI)	P
Age, per 10 years, x ± s	8.93 ± 0.97	8.68 ± 1.05	9.34 ± 0.67	<0.0001[b]	1.808 (1.245–2.626)	0.002
Age, *N* (%)				< 0.0001[a]		
65–80	51 (16.3)	46 (23.7)	5 (4.2)			
81–90	81 (25.9)	62 (32.0)	19 (16.0)			
>90	181 (57.8)	86 (44.3)	95 (79.8)			
Weight, kg, median (IQR)	65 (57, 74.5)	64 (57, 75)	65 (56, 74)	0.757[c]		
BMI, kg/m^2, median (IQR)	37.8 (34, 43)	37.5 (33, 43)	38.5 (34, 44)	0.997[c]		
Regimen, mg/kg, x ± s	19.0 ± 3.7	18.8 ± 3.5	19.3 ± 4.2	0.757[b]		
TDM_a, mg/L, median (IQR)	25.2 (16.5, 36.0)	18.3 (11.9, 24.1)	40.3 (34.4, 48.3)	<0.0001[c]		
$TDM_{w48-72h}$, mg/L, x ± s	2.0 ± 5.4	1.02 ± 3.49	3.61 ± 7.29	<0.0001[b]		
Gender, male, *N* (%)	263 (84.0)	161 (83.0)	102 (85.7)	0.523[a]		
Underlying disease, *N* (%) COPD	64 (20.4)	30 (15.5)	34 (28.6)	0.005[a]	1.629 (0.880–3.015)	0.120
Respiratory failure	58 (18.5)	34 (17.5)	24 (20.2)	0.559[a]		
Hypertension	217 (69.3)	130 (67)	87 (73.1)	0.256[a]		
Coronary heart disease	193 (61.7)	106 (54.6)	87 (73.1)	0.001[a]	1.495 (0.860–2.599)	0.154
Atrial fibrillation	37 (11.8)	22 (11.3)	15 (12.6)	0.737[a]		
Diabetes mellitus	132 (42.2)	79 (40.7)	53 (44.5)	0.507[a]		
CKD	124 (39.6)	62 (32.0)	62 (52.1)	< 0.0001[a]		
Chronic liver disease	16 (5.1)	12 (6.2)	4 (3.4)	0.278[a]		
Neurological disease	122 (39.0)	71 (36.6)	51 (42.9)	0.270[a]		
Malignancy	73 (23.3)	48 (24.7)	25 (21)	0.448[a]		
CCI, median (IQR)	3 (5, 7)	5 (3, 8)	5 (4, 7)	0.739[c]		
Invasive ventilation, *N* (%)	67 (21.4)	35 (18.0)	32 (26.9)	0.064[a]	1.010 (0.548–1.861)	0.974
P-gp inhibitor, *N* (%)	83 (26.5)	44 (22.7)	39 (32.8)	0.050[a]	1.171 (0.662–2.073)	0.588
Linezolid within 3 months, *N* (%)	73 (23.3)	40 (20.6)	33 (27.7)	0.149[a]		
Infection site, *N* (%)				0.729[a]		
Pulmonary infection	279 (89.1)	172 (88.7)	107 (89.9)			
Others	34 (10.9)	22 (11.3)	12 (10.1)			
30-Day mortality, *N* (%)	16 (5.1)	7 (3.6)	9 (7.6)	0.123[a]		
Laboratory findings						
Albumin, g/L, x ± s	34.0 ± 5.2	34.1 ± 5.1	33.9 ± 5.33	0.756[b]		
Creatinine, μmol/L, Median (IQR)	81 (61, 128)	77 (55, 110)	93 (71, 149)	<0.0001[c]		
eGFR, ml/min/1.73 m^2, median (IQR)	61.7 (36.4, 84.0)	68.5 (48.0, 89.9)	50 (23.6, 72.9)	<0.0001[c]		
Bilirubin, μmol/L, Median (IQR)	10.9 (7.4, 16.2)	10.2 (7.2, 15.6)	11.6 (8.0, 17.3)	0.122[c]		
ALT, U/L, median (IQR)	15.3 (9.6, 24.9)	15.6 (9.7, 28.2)	14.4 (9.4, 23.4)	0.258[c]		
AKI, *N* (%)	30 (9.6)	17 (8.8)	13 (10.9)	0.528[a]		
eGFR < 60 mL/min/1.73 m^2, *N* (%)	149 (47.6)	71 (36.6)	78 (65.5)	<0.0001[a]	2.067 (1.222–3.497)	0.007
$SOFA_1$, median (IQR)	5 (3, 9)	5 (3, 8)	7 (5, 10)	<0.0001[c]		

Continued

Table 2. *Continued*

Characteristics	All patients ($n=313$)	Groups		Univariate	Multivariate	
		Non-severe exposure group ($n=194$)	Severe exposure group ($n=119$)	*P*	OR (95% CI)	*P*
$SOFA_1 \geq 5$, *N* (%)	229 (73.2)	121 (62.4)	108 (90.8)	<0.0001[a]	3.031 (1.415–6.494)	0.004
Treatment, *N* (%)						
Plasma transfusion	79 (25.2)	44 (22.7)	35 (29.4)	0.183[a]		
Thrombopoietin	30 (9.6)	16 (8.2)	14 (11.8)	0.305[a]		
Erythropoietin	21 (6.7)	12 (6.2)	9 (7.6)	0.636[a]		
Vasoactive drug	68 (21.7)	40 (20.6)	28 (23.5)	0.544[a]		
Combination of antibiotics, *N* (%)						
Carbapenems	215 (68.7)	136 (70.1)	79 (66.4)	0.491[a]		
Cephalosporin	98 (31.3)	58 (29.9)	40 (33.6)	0.491[a]		
Antifungal drug	92 (29.4)	56 (28.9)	36 (30.3)	0.794[a]		

Weight and BMI were from 212 patients.
TDM_a, average trough concentration; CCI, Charlson's comorbidity index; $SOFA_1$, the worst SOFA; TDM, therapeutic drug monitoring.
[a]χ^2 test.
[b]*t*-test.
[c]Mann–Whitney *U* test.

of M/S LIT also increased gradually with increased duration of linezolid administration in the >90 group, and the incidence was significantly higher in the severe exposure compared with the non-severe exposure group from the 6th day of administration ($P<0.0001$; Figure 2f).

Risk factors for M/S LIT in the elderly

A total of 164 patients (52.4%) with no or mild LIT were included in the control group, and 149 patients (47.6%) with M/S LIT were included in the M/S LIT group.

Multivariate logistic regression analysis identified linezolid duration ≥12 days (OR, 2.413; 95% CI, 1.422–4.093, $P=0.001$), TDM_a ≥30 mg/L (OR, 2.684; 95% CI, 1.612–4.468, $P<0.0001$), $Plt_0 > 200\times10^9$/L (OR, 2.264; 95% CI, 1.366–3.751, $P=0.002$), eGFR <60 mL/min/1.73 m^2 (OR, 1.945; 95% CI, 1.143–3.310, $P=0.014$) and $SOFA_0 \geq 5$ (OR, 2.108; 95% CI, 1.264–3.517, $P=0.004$) as independent risk factors for M/S LIT in elderly patients (Table 4).

Nomogram to predict M/S LIT in the elderly

Based on logistic regression results, we established a nomogram model to predict M/S LIT (Figure 3a). The calibration curve showed that the nomogram was consistent with the ideal condition (Figure 3b). Decision curve analysis indicated that our nomogram added more net benefit than either the all-positive or all-negative situation over a large threshold range (0.1–1.0; Figure 3c).

The predictive performance of the nomogram was analysed by ROC curves. The optimal cutoffs and corresponding sensitivity and specificity are listed in Supplementary data Table S3. The AUC of total score in the nomogram was 0.767 (95% CI, 0.715–0.820, $P<0.0001$; Figure 3d) with a sensitivity of 71.1% and a specificity of 73.2%. The ROC curve identified a median time of 12 days until the development of M/S LIT.

Clinical use of nomogram

Each patient's scores for $SOFA_0$, duration, TDM_a, Plt_0 and eGFR were calculated and added to obtain a total score, corresponding to the M/S LIT incidence. Assuming a threshold incidence of 50%, the corresponding total score was 173. $SOFA_0$, Plt_0 and eGFR were fixed, and the occurrence of M/S LIT could be reduced by adjusting the duration and TDM_a. For example, for a $SOFA_0$ score = 53, Plt_0 score = 40, eGFR score = 30 and use for 14 days (duration score = 42), the TDM_a score needed to be <8 (173-53-40-30-42) and the corresponding TDM_a thus needed to be <7 mg/L. In another example, for $SOFA_0$ score = 53, Plt_0 score = 40, eGFR score = 30 and a monitored trough concentration of 20 mg/L (TDM_a score = 22), linezolid should be used for <9 days (duration score = 28) to reduce the occurrence of M/S LIT. If a long course of linezolid is expected, the dosage should be reduced.

External model validation

We confirmed the reliability of the nomogram model in a validation set of 80 elderly patients treated with intravenous or oral linezolid at the above four tertiary hospitals from January 2023 to May 2023. Trough concentrations were measured after 3 days of linezolid administration. The mean age of patients

Table 3. Correlation between severe linezolid exposure and haematological toxicities

	All patients ($n=313$)	Groups: Non-severe exposure group ($n=194$)	Groups: Severe exposure group ($n=119$)	P
Platelet				
Baseline, 10^9/L, x±s	207±78	205±77	211±80	0.486[b]
At withdrawal time, 10^9/L, median (IQR)	116 (88, 165)	127 (91, 174)	104 (81, 143)	0.004[c]
After withdrawal,10^9/L, median (IQR)	99 (65, 153)	111 (74, 172)	82 (51, 116)	<0.0001[c]
Continued to decline, *N* (%)	203 (64.8)	110 (56.7)	93 (78.1)	0.003[a]
Percentage decline, %, median (IQR)	48 (29, 65)	43 (18, 60)	57 (41, 72)	<0.0001[c]
Thrombocytopenia, *N* (%)	230 (73.5)	127 (65.4)	103 (86.6)	<0.0001[a]
Mild	81 (25.9)	52 (26.8)	29 (24.4)	
Moderate	91 (29.1)	53 (27.3)	38 (31.9)	
Severe	58 (18.5)	22 (11.3)	36 (30.3)	
Erythrocyte				
Baseline, 10^9/L, x±s	3.54±0.67	3.52±0.68	3.58+0.65	0.390[b]
At withdrawal time, 10^9/L, median (IQR)	3.14 (2.77, 3.54)	3.21 (2.77, 3.52)	3.05 (2.76, 3.56)	0.496[c]
After withdrawal, 10^9/L, median(IQR)	3.08 (2.68, 3.44)	3.10 (2.68, 3.45)	3.02 (2.66, 3.44)	0.524[c]
Continued to decline, *N* (%)	176 (56.2)	104 (53.6)	72 (60.5)	0.994[a]
Percentage decline, %, median(IQR)	13 (6, 22)	11 (5, 21)	15 (8, 23)	0.037[c]
Oligocythaemia, *N* (%)	194 (62.0)	110 (56.7)	84 (70.6)	0.092[a]
Mild	98 (31.3)	54 (27.8)	44 (37.0)	
Moderate	60 (19.2)	36 (18.6)	24 (20.2)	
Severe	36 (11.5)	20 (10.3)	16 (13.4)	
Haemoglobin				
Baseline, g/L, x±s	108±19	107±20	110±17	0.234[b]
At withdrawal time, 10^9/L, median (IQR)	98 (86, 109)	100 (87, 108)	94 (86, 110)	0.704[c]
After withdrawal, g/L, median (IQR)	95 (84, 106)	96 (84, 106)	93 (84, 106)	0.549[c]
Continued to decline, *N* (%)	177 (56.5)	104 (53.6)	73 (61.3)	0.871[a]
Percentage decline, %, median(IQR)	13 (5, 22)	12 (3, 21)	15 (8, 22)	0.026[c]
Hypohaemoglobinaemia, *N* (%)	194 (62.0)	108 (55.7)	86 (72.3)	0.030[a]
Mild	96 (30.7)	52 (26.8)	44 (37.0)	
Moderate	66 (21.1)	37 (19.1)	29 (24.4)	
Severe	32 (10.2)	19 (9.8)	13 (10.9)	
Withdrawal due to haematological toxicity, *N* (%)	160 (51.1)	84 (43.3)	76 (63.9)	<0.0001[a]

[a]χ^2 test.
[b]*t*-test.
[c]Mann–Whitney *U* test.

included in the validation set was 93.0±6.2 years, the median TDM_a was 29.0 mg/L (21.9, 40.5), the median Plt_0 was 196×10^9/L (159×10^9, 245×10^9), and the median eGFR was 63.8 mL/min/1.73 m^2 (38.9, 80.9). Thirty-six patients (45.0%) had SOFA scores of ≥5 (Supplementary data Table S4). The total points for individuals were calculated, and an additive effect with an AUC of 0.754 (95% CI, 0.643–0.866, $P<0.001$) was also obtained in the validation set, suggesting that the nomogram model had good sensitivity and specificity for predicting M/S LIT in the elderly.

Discussion

The current study found higher than expected trough concentrations of linezolid in the elderly. The steady-state trough concentration in patients aged 65–80 years was 11.9 (9.1, 23.3) mg/L, and this increased by a further 10 mg/L for approximately every 10 years of age. Overexposure occurred in nearly 90% of patients and severe exposure in more than one-third of patients, associated with an incidence of LIT of 73.5% in elderly patients. Our analysis also showed that linezolid approached a steady concentration after 3–6 doses (36–72 h), suggesting that its trough concentration and antimicrobial efficacy could be assessed at 36–72 h of administration. Based on multivariate analysis of severe linezolid exposure, four dose regimens were recommended to ensure medication safety.[19] Notably, we developed a nomogram model to predict the risk of M/S LIT to help clinicians adjust the dosage and duration of linezolid as required.

In our study, the steady trough concentration of linezolid in the elderly was 26.1 (17.0, 38.1) mg/L, which was about four-fold higher than that in non-elderly patients. This was similar to the

Table 4. Univariate analysis and multivariate analysis of risk factors for moderate-to-severe LIT in the elderly patients

Characteristics	All patients ($n=313$)	Groups		Univariate	Multivariate	
		Control ($n=164$)	M/S LIT ($n=149$)	*P*	OR (95% CI)	*P*
Age, year, x ± s	89.29 ± 9.74	87.56 ± 10.67	91.19 ± 8.22	0.006[b]		
Age, *N* (%)				0.002[a]		
65–80	51 (16.3)	38 (23.2)	13 (8.7)			
81–90	81 (25.9)	39 (23.8)	42 (28.2)			
>90	181 (57.8)	87 (53.0)	94 (63.1)			
Gender, male, *N* (%)	263 (84.0)	138 (84.1)	125 (83.9)	0.951[a]		
Continued to decline, *N* (%)	203 (64.8)	91 (55.5)	112 (75.2)	0.014[a]		
TDM						
TDM_{36-72h}, mg/L, median (IQR)	24.4 (15.3, 35.8)	19.5 (10.6, 31.7)	29.1 (19.3, 37.4)	<0.0001[c]		
TDM_{5-10d}, mg/L, median (IQR)	26.1 (17.0, 38.1)	21.4 (11.9, 30.7)	31.8 (23.3, 45.7)	<0.0001[c]		
TDM_a, mg/L, median(IQR)	25.2 (16.5, 36.0)	21.7 (12.5, 32.4)	29.9 (21.2, 42.1)	<0.0001[c]	2.684 (1.612, 4.468)	<0.0001
$TDM_a \geq 30$, mg/L, *N* (%)	119 (38.0)	45 (27.4)	74 (49.7)	<0.0001[a]		
$TDM_{w48-72h}$, mg/L, x ± s	0 (0, 3.6)	0 (0, 2.9)	1.7 (0, 4.4)	<0.0001[c]		
$TDM_{w48-72h} > 2$ mg/L, *N* (%)	115 (36.7)	47 (28.7)	68 (45.6)	0.002[a]		
Duration, day, median (IQR)	10 (7, 13)	10 (6, 12)	11 (8, 14)	0.003[c]		
Duration ≥12 day, *N* (%)	120 (38.3)	50 (30.5)	70 (47.0)	0.003[a]	2.413 (1.422, 4.093)	0.001
Underlying disease, *N* (%)						
COPD	64 (20.4)	30 (18.3)	34 (22.8)	0.321[a]		
Respiratory failure	58 (18.5)	24 (14.6)	34 (22.8)	0.063[a]		
Hypertension	217 (69.3)	110 (67.1)	107 (71.8)	0.364[a]		
Coronary heart disease	193 (61.7)	96 (58.5)	97 (65.1)	0.233[a]		
Atrial fibrillation	37 (11.8)	20 (12.2)	17 (11.4)	0.477[a]		
Diabetes mellitus	132 (42.2)	74 (45.1)	58 (38.9)	0.268[a]		
CKD	124 (39.6)	50 (30.5)	74 (49.7)	0.001[a]		
Chronic liver disease	16 (5.1)	11 (6.7)	5 (3.4)	0.175[a]		
Neurological disease	122 (39.0)	61 (37.2)	61 (40.9)	0.498[a]		
Malignancy	73 (23.3)	45 (27.4)	28 (18.8)	0.109[a]		
CCI, median (IQR)	5 (3, 7)	5 (3, 7)	5 (3, 7)	0.277[c]		
Invasive ventilation, *N* (%)	67 (21.4)	26 (15.9)	41 (27.5)	0.012[a]		
P-gp inhibitor, *N* (%)	83 (26.5)	35 (21.3)	48 (32.2)	0.030[a]		
Linezolid within 3 months, *N* (%)	73 (23.3)	30 (18.3)	43 (28.9)	0.027[a]		
Tigacycline with 1 month, *N* (%)	106 (33.9)	50 (30.5)	56 (37.6)	0.185[a]		
Infection site, *N* (%)				0.128[a]		
Pulmonary infection	279 (89.1)	142 (86.6)	137 (91.9)			
Others	34 (10.9)	22 (13.4)	12 (8.1)			
30-day mortality, *N* (%)	16 (5.1)	5 (3.0)	11 (7.4)	0.082[a]		
Laboratory findings						
Albumin, g/L, x ± s	34.0 ± 5.2	33.9 ± 5.6	34.1 ± 4.7	0.998[b]		
Creatinine, μmol/L, median (IQR)	90 (64, 138)	81 (54, 118)	100 (70, 165)	<0.0001[c]		
eGFR, ml/min/1.73 m^2, median (IQR)	62 (36, 84)	69 (47, 90)	52 (30, 79)	<0.0001[c]		
Bilirubin, μmol/L, median (IQR)	12.5 (8.2, 19.8)	11.8 (7.7, 17.9)	13.5 (8.9, 21)	0.098[c]		
ALT, U/L, median (IQR)	18 (11, 35)	16 (10, 33)	20 (11, 40)	0.053[c]		
PLT_0, 10^9/L, median (IQR)	200 (156, 243)	186 (145, 223)	210 (167, 267)	<0.0001[c]		
$PLT_0 > 200 \times 10^9$/L, *N* (%)	157 (50.2)	67 (40.9)	90 (60.4)	0.001[a]	2.264 (1.366, 3.751)	0.002
AKI, *N* (%)	30 (9.6)	15 (9.1)	15 (10.1)	0.782[a]		
eGFR < 60 mL/min/1.73 m^2, *N* (%)	149 (47.6)	62 (37.8)	87 (58.4)	<0.0001[a]	1.945 (1.143, 3.310)	0.014
$SOFA_0$, median (IQR)	4 (2, 7)	3 (2, 6)	5 (3, 8)	<0.0001[c]		
$SOFA_0 \geq 5$, *N* (%)	142 (45.4)	59 (36.0)	83 (55.7)	<0.0001[a]	2.108 (1.264, 3.517)	0.004
Treatment, *N* (%)						
Plasma transfusion	79 (25.2)	37 (22.6)	42 (28.2)	0.252[a]		
Thrombopoietin	30 (9.6)	12 (7.3)	18 (12.1)	0.153[a]		

Continued

Table 4. *Continued*

Characteristics	All patients ($n=313$)	Groups		Univariate	Multivariate	
		Control ($n=164$)	M/S LIT ($n=149$)	*P*	OR (95% CI)	*P*
Erythropoietin	21 (6.7)	7 (4.3)	14 (9.4)	0.075[a]		
Vasoactive drug	68 (21.7)	29 (17.7)	39 (26.2)	0.069[a]		
Combination of antibiotics, *N* (%)						
Carbapenems	215 (68.7)	107 (65.2)	108 (72.5)	0.168[a]		
Cephalosporin	98 (31.3)	57 (34.8)	41 (27.5)	0.168[a]		
Antifungal drug	92 (29.4)	46 (28.0)	46 (30.9)	0.584[a]		

M/S LIT, moderate-to-severe linezolid-induced thrombocytopenia; TDM_{36-72h}, 3–6 doses of linezolid (36–72 h); TDM_{5-10d}, 5–10 days of linezolid; TDM_a, average trough concentration; $TDM_{w48-72h}$, 48–72 h after withdrawal; CCI, Charlson's comorbidity index; P-gp, P-glycoprotein; PLT_0, baseline platelet; $SOFA_0$, baseline SOFA.
[a]χ^2 test.
[b]*t*-test.
[c]Mann–Whitney *U* test.

preliminary results of Cattaneo *et al.*[20]; however, the median trough concentration of linezolid in the elderly in their study was 8.2–9.3 mg/L, which was significantly lower than in our study. This may be related to the small number of elderly patients included in their study (about 90 cases) and their younger age (aged 45–73 years). Tinelli *et al.*[4] found a trough concentration of linezolid of 13.0 (11.9, 16.0) mg/L in elderly patients aged ≥70 years, which was also significantly lower than in the current study, possibly because 47.6% of patients in our study had a decreased GFR (eGFR <60 mL/min/1.73 m^2) and 57.8% were very elderly (age >90 years). We found no significant difference between trough concentrations after 3–6 doses of linezolid (36–72 h) and the steady-state trough concentrations (5–10 days), suggesting that linezolid approached steady-state levels at 36–72 h of administration in elderly patients. In the real world, although the half-life of linezolid in elderly patients is larger and the time to reach steady state might be longer, clinicians can still evaluate the concentration and efficacy of linezolid at 36–72 h. We included 181 patients over >90 years old, which, to the best of our knowledge, represents the largest sample of very elderly patients studied to date. This study also revealed that nearly 100% of patients aged >90 years had overexposure to linezolid and about 50.0% had severe exposure, which corresponded to the high incidence of M/S LIT of 51.9%. Overall, these results suggest that the dose of linezolid is too high in elderly patients, and there is thus an urgent need to adjust the administration schedule based on TDM. In addition, we speculated that linezolid may be suitable for MRSA bloodstream infections in elderly patients,[21–23] although further clinical studies are needed to confirm this.

Previous studies did not examine linezolid clearance concentration or myelosuppression after withdrawal. We monitored these parameters dynamically and showed that 97.5% (39/40) of patients still had therapeutic levels 24 h after linezolid withdrawal, and 62.5% (25/40) of patients had overexposure, while 37.9% (115/303) of patients had therapeutic concentrations 48–72 h after linezolid withdrawal, and 12.2% (37/303) had overexposure. This could explain why platelets continued to decline in 64.8% (203/313) of patients after linezolid withdrawal, and began to recover 3 days later. In addition, 51.1% (160/313) of elderly patients stopped linezolid due to linezolid-related hematological toxicity, which seriously affected the treatment course but has rarely been reported in previous studies.

Linezolid trough concentrations in the elderly were closely correlated with age, renal function (eGFR <60 mL/min/1.73 m^2) and SOFA score in the current study. The correlations with age and renal function have been confirmed in a series of studies,[3–6,12,16,18,20,24] but we also found that linezolid trough concentrations were associated with the worst SOFA score during medication. Elderly patients with $SOFA_1 \geq 5$ had a 2.031-fold increased risk of severe linezolid exposure. However, Zoller *et al.*[25] found no correlation between linezolid trough concentrations and APACHE II score, possibly because the subjects in that previous study were all severely infected. We were unable to find any other studies that reported the correlation between SOFA score and linezolid trough concentration. It is appreciated that, based on multivariate analysis of risk factors for severe linezolid exposure, we recommended four reduced linezolid dose regimens (Figure 2e).[19] We offered a protocol for how to proceed with linezolid reduction in elderly patients, but the effectiveness of the dose regimens needs to be tested in a large sample in clinical practice.

Linezolid is a substrate for P-gp, and the concurrent use of P-gp inhibitors may thus increase linezolid exposure. Pea *et al.*[26] found that concurrent use of powerful P-gp inhibitors (omeprazole, amiodarone and amlodipine) was a risk factor for linezolid overexposure. The current study did not support an effect of P-gp inhibitors (calcium antagonists, proton pump inhibitors, amiodarone) on trough concentrations of linezolid in the elderly, consistent with the study of Galar *et al.*[16] Clarithromycin, rifampicin, cyclosporine and CYP2J2 inhibitors may also affect linezolid concentrations,[14,27–31] but none of the subjects in the present study used these drugs and therefore no conclusions could be drawn.

Linezolid overexposure causes thrombocytopenia, which can affect the duration of medication and treatment effect.

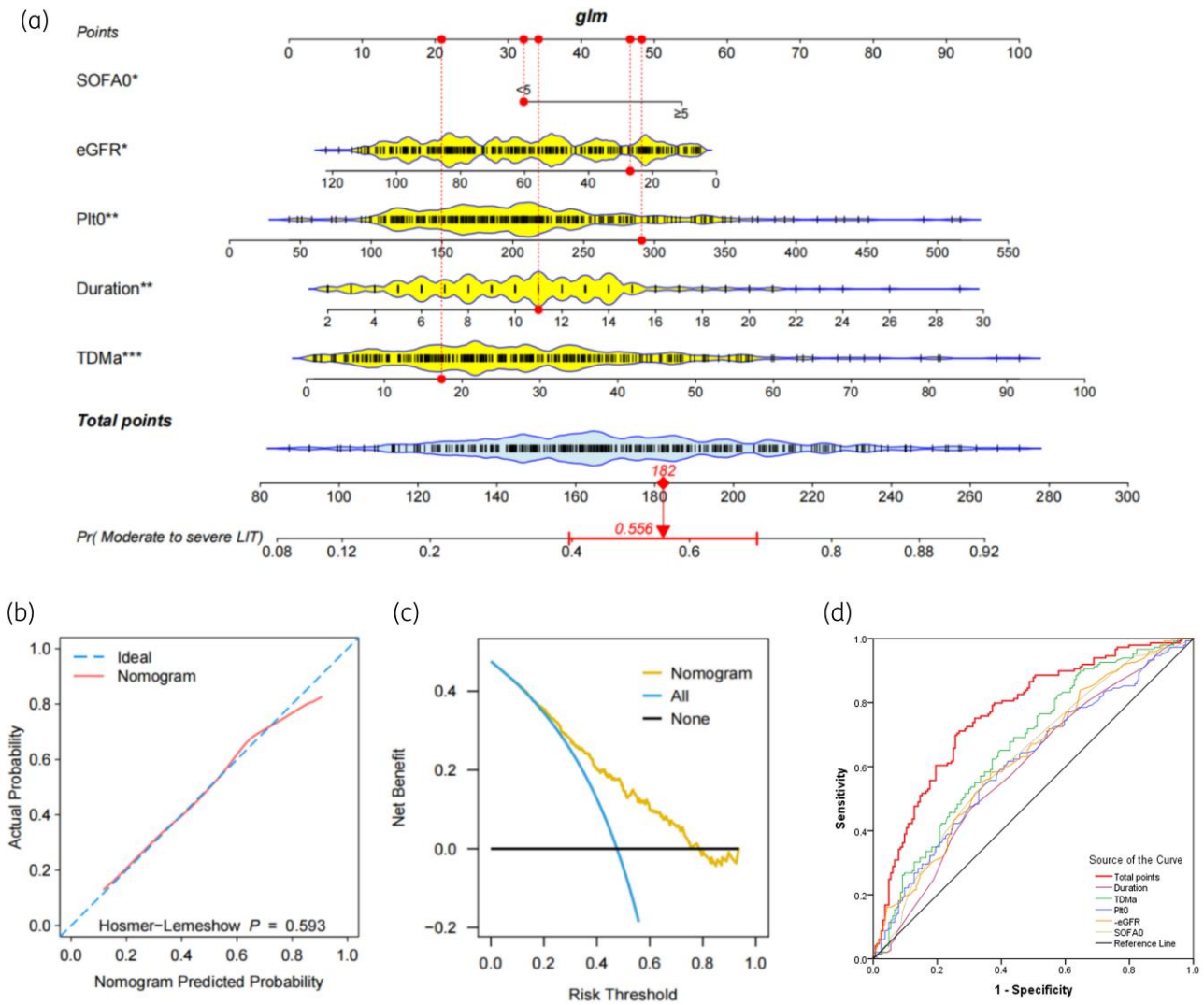

Figure 3. (a) Factors significant in multivariate analysis were used to develop a nomogram to predict the probability of M/S LIT. For example (indicated by a solid circle and arrow), $SOFA_0$, eGFR, Plt_0, duration and TDM_a in an elderly patient were 4, 25 mL/min/1.73 m^2, 290×10^9/L, 11 days and 18 mg/L, respectively. The scores for their $SOFA_0$, eGFR, Plt_0, duration and TDM_a were approximately 32, 47, 48, 34 and 21, respectively. Hence, the total point for this patient was 182, which indicated a probability of 0.556 for developing M/S LIT. As 0.556 was relatively neutral, linezolid could be used for 11 days at a trough concentration of 18 mg/L in this patient. However, if we want to prolong the duration of linezolid, we can reduce the dosage and trough concentration to reduce the risk of M/S LIT. (b) Calibration curves of nomograms in terms of agreement between the predicted risk and actual observed outcomes. The solid line was close to the diagonal dotted line, indicating good prediction effect. (c) Decision curve analysis of the nomogram for M/S LIT. (d) ROC curve to evaluate the predictive value of nomogram model and other factors for predicting moderate to severe LIT in the elderly population. AUC of warning model was 0.767 (95% CI 0.715–0.820, $P<0.0001$). M/S LIT, moderate-to-severe linezolid-induced thrombocytopenia.

The incidence of M/S LIT in the present study was 47.6%, with M/S LIT occurring earlier and more frequently with increasing linezolid trough concentrations, especially in patients aged >90 years. Current evidence indicates that inhibition of mitochondrial protein synthesis is the underlying cause due to the interaction of linezolid with mitochondrial ribosomes, and megakaryocytes have been confirmed as the preferred targets for linezolid cytotoxicity.[32] M/S LIT was independently correlated with treatment duration, TDM_a, Plt_0, eGFR and $SOFA_0$. We therefore developed a nomogram risk prediction model based on the aforementioned results, which allowed adjustments of the dosage and duration of linezolid treatment. This is the first nomogram model combined with TDM to graphically represent the independent risk factors for M/S LIT.

This study had some limitations. First, 32.3% (101/313) of the elderly patients were chronically bedridden, and their weight and body mass index (BMI) could not be assessed. We therefore assessed the effects of weight and BMI on linezolid concentration in a subset of patients. We found that the linezolid concentration was not associated with weight and BMI, which was consistent with previous findings.[18,33] In addition, eGFR could not provide an accurate estimation of creatinine clearance in long-term

bedridden patients. This could be a bias that could cause misinterpretation. Second, elderly patients were often infected with multiple pathogens and some patients lacked pathogenicity evidence, and the therapeutic effect of linezolid was therefore not evaluated. Third, the duration of linezolid treatment in this study was too short to evaluate its long-term effects, due to its toxicity. Finally, large studies and population PK models in elderly patients are needed to refine the recommended dose regimens.

Conclusions

Our study revealed that elderly patients administered routine doses of linezolid experienced severe drug overexposure and a high rate of thrombocytopenia, which has not previously been appreciated. There is an urgent need for TDM, optimal dose regimens and a nomogram model to rationally adjust the dose of linezolid to ensure its curative effect and reduce the incidence of M/S LIT.

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Transparency declarations

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Chinese People's Liberation Army (PLA) General Hospital (ethical approval number: S2020-206-01), and written informed consent was obtained from all the participants or legal agents.

Supplementary data

Supplementary Tables S1–S4 are available as Supplementary data at *JAC* Online.

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