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Development and validation of a risk prediction model for linezolid-induced anemia in elderly patients: a retrospective cohort study

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Hongling Ma, Zhaotang Gong, Rihan Wu and GuLeng SiRi

Abstract

Background: Linezolid-induced anemia (LI-AN) is a severe adverse reaction, but risk factors of the LI-AN for elderly patients have not been established.

Objectives: The objective of this study was to develop a nomogram capable of predicting LI-AN in elderly patients.

Design: This is a retrospective study to develop and validate a nomogram for anemia prediction in elderly patients treated with linezolid.

Methods: We retrospectively screened elderly patients treated with linezolid at Inner Mongolia People's Hospital from January 2020 to December 2023 and validated our findings using the MIMIC-IV 2.2 database. Anemia was defined as hemoglobin reduction to 75% of baseline value. Univariate and multivariable logistic regression models were used to identify predictors and construct the nomogram, which was evaluated using receiver operating characteristic (ROC) curve analysis, calibration plot, and decision curve analysis.

Results: A total of 231 patients were enrolled in this study. The training set comprised 151 individuals, and anemia occurred in 28 cases (18.54%). In the external validation set of 80 individuals, 26 (32.5%) were diagnosed with anemia. The predictors included duration of linezolid therapy, patient estimated glomerular filtration rate value, and sequential organ failure assessment score ⩾2. The ROC curve for the training set was 0.830 (95% CI: 0.750–0.910), while a similar ROC curve of 0.743 (95% CI: 0.621–0.865) was obtained for the validation set. The calibration curve demonstrated good correlation between predicted and observed results, indicating that this study effectively predicts risk factors associated with LI-AN in elderly patients.

Conclusion: The developed prediction model can provide valuable guidance for clinicians to prevent anemia and facilitate rational linezolid use in elderly patients.

Plain language summary

Study analyzing the clinical data of elderly patients using linezolid to better understand what factors may contribute to anemia in patients

Why was the study done? This study aimed to develop a tool that predicts the risk of anemia in elderly patients treated with linezolid, a medication that can cause severe side effects like low hemoglobin levels. Identifying factors that contribute to this adverse reaction can help doctors prevent it and ensure safer use of linezolid.

Correspondence to:
GuLeng SiRi
Department of Pharmacy, Inner Mongolia Autonomous Region People's Hospital, 20 Zhaowuda Road, Hohhot, Inner Mongolia 010017, China
srgl985@126.com

Hongling Ma

Rihan Wu
Department of Pharmacy, Inner Mongolia Autonomous Region People's Hospital, Hohhot, Inner Mongolia, China

Zhaotang Gong
Department of Pharmacy, Inner Mongolia Autonomous Region People's Hospital, Hohhot, Inner Mongolia, China

Department of Pharmacy, Inner Mongolia Medical University, Hohhot, Inner Mongolia, China

What did the researchers do? The researchers studied the medical records of elderly patients treated with linezolid at Inner Mongolia People's Hospital over a 4-year period. To better understand which factors are related to the occurrence of anemia, so we can find ways to predict the occurrence of problems.

What did the researchers find? Factors that increase the risk of anemia after using linezolid include the duration of use of linezolid, kidney function, and SOFA score, that is, the longer the use of linezolid, the worse the kidney function, the higher the SOFA score, and the more likely the patient is to develop anemia.

What do the findings mean? The researchers successfully created a tool, called a prediction model, which can help doctors predict the likelihood of anemia in elderly patients taking linezolid. This can guide clinicians in monitoring and managing patients more effectively, potentially reducing the occurrence of anemia and ensuring safer use of linezolid in elderly populations.

Keywords: anemia, clinical prediction model, linezolid, MIMIC-IV, rational use

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Introduction

Anemia is defined by a reduction in one or more key parameters of red blood cells as assessed by complete blood count, namely hemoglobin (Hb) concentration, hematocrit, or red blood cell count. Notably, a Hb concentration falling below the lower limit of normal serves as a primary clinical indicator. Several factors contribute to anemia in the elderly, encompassing malnutrition, kidney disease, chronic disease/inflammatory anemia, and drug-induced causes, the latter being particularly significant.[1] Currently, previous studies defined anemia as a 25% decrease in Hb from baseline during treatment.[2,3]

Linezolid is the first synthesized oxazolidinone antibiotic, which effectively inhibited bacterial protein synthesis by binding to a specific site on the 23S ribosomal RNA (rRNA) of the 50S subunit. This mechanism prevents the formation of a functional 70S initiation complex.[4] Linezolid is indicated for treating nosocomial and community-acquired pneumonia caused by Gram-positive bacteria, complex skin and soft tissue infections, as well as vancomycin-resistant enterococcus infections at a standard dose of 600 mg every 12 h.

A notable severe adverse effect associated with linezolid use is myelosuppression, including neutropenia, thrombocytopenia, and anemia, in particular, sideroblastic anemia is induced by linezolid.[5] Increasing attention has been focused on linezolid-induced anemia (LI-AN) in clinical research. While evidence-based medicine has fairly comprehensively investigated linezolid-induced thrombocytopenia (LI-TP), research into predictive models for LI-AN remains underdeveloped. Numerous previous studies had reported risk factors for LI-TP and developed predictive models accordingly.[6–13] Liu et al. and Qin et al. developed a risk prediction model for LI-TP in elderly patients, identifying estimated glomerular filtration rate (eGFR), ICU admission, baseline platelet count, and concomitant use of piperacillin-tazobactam as significant risk factors.[14,15] Onita et al. highlighted an increased risk of LI-TP with prolonged therapy duration.[16] Limited studies suggest that aspartate aminotransferase (AST) >80 U/L, eGFR <90 mL/min/1.73 m^2, and treatment duration >15 days are risk factors for LI-AN.[17,18] Qin et al. constructed a LI-AN prediction model specific to Chinese patients; however, this model lacked validation and exhibited limited predictive efficacy.[18]

Elderly patients often present with multiple comorbidities necessitating complex medication regimens, thereby increasing susceptibility to LI-AN. However, the risk factors for LI-AN

among elderly patients have shown inconsistency, and few studies have established predictive models specifically for this demographic. Therefore, this study aimed to develop a risk prediction model for LI-AN in elderly patients undergoing linezolid therapy, validated using the MIMIC-IV database to ensure the precision and clinical applicability. The prediction model aims to identify individuals at heightened risk of LI-AN and guides rational linezolid use of clinical practice.

Materials and methods

Study design and setting

We established and validated a nomogram on anemia prediction in elderly patients who treated with linezolid through a retrospective study. Data were collected in patients who received linezolid treatment between January 2020 and December 2023 from Inner Mongolia Autonomous Region people's Hospital's electronic medical records and the large US MIMIC-IV 2.2. The MIMIC-IV database is a publicly accessible and freely available repository of de-identified electronic medical files for Beth Israel Deaconess Medical Center patients who were admitted, including 509,200 patients admitted to the ICU from 2008 to 2019. Patients aged above 60 years who received linezolid therapy (600 mg, q 12 h) for ⩾3 days were included in the study. However, those diagnosed with leukemia, myelodysplastic syndrome, multiple myeloma, myelofibrosis, lymphoma, megaloblastic anemia, bleeding, receiving a blood transfusion, incomplete case information, or chemo/radiotherapy within 2 weeks prior to the initiation of linezolid therapy were excluded from the study. In addition, patients with the lower than normal Hb count before linezolid treatment (130 g/L for males and 115 g/L for females) were also excluded from the study. Anemia was defined as a 25% decrease in Hb from baseline during treatment. LI-AN was defined as linezolid-induced anemia. The reporting of this study conforms to the TRIPOD (Supplemental Material) statement. Approval for this research was obtained from the Medical Ethics Committee of Inner Mongolia Autonomous Region People's Hospital. Patient consent was waived due to the retrospective nature of the study.

Data collection

The clinical data of patients in the training set data were obtained by consulting the electronic medical record of the People's Hospital of Inner Mongolia Autonomous Region. Data extraction was performed using structured query language from MIMIC-IV 2.2 and using STATA 15.0 (Stata Corporation, College Station, TX, USA) for data cleaning, which was used as external validation data. The clinicopathological data of patients treated with linezolid were collected, such as sex, age, weight, comorbidity, site of infection, combination drugs, continuous renal replacement therapy, sequential organ failure assessment (SOFA) score, and duration of linezolid therapy. The laboratory data, included baseline Hb, serum albumin, total bilirubin, alanine aminotransferase, AST, white cells counts, percentage of neutrophils (NEUT), eGFR. We have established that the anemia in the study was an adverse effect of linezolid.

Nomogram construction

We performed univariate regression analysis. Variables with $p < 0.05$ in the univariate analysis were next included in the logistic multivariable analysis. We screened the meaningful indicators as candidate variable from the multivariable analysis to construct the model. Logistic regression analysis was used to estimate the odds ratio (OR) of each candidate variable and build the model. We constructed a nomogram for more intuitive presentation.

Validation of nomograms

We used the concordance index (C-index) to measure accuracy of the prediction results of the nomograms. The C-index range of 0.50–0.70 generally indicates a lower level of accuracy, while the range of 0.71–0.90 suggests a moderate level of accuracy. However, a value exceeding 0.90 is considered indicative of high accuracy. Calibration curves were used to compare the predicted results of the nomogram with the actual results. The decision curve analysis (DCA) was used to evaluate the clinical decision efficacy of the model.

Statistical analysis

Data were analyzed using the R version 4.3.2 (A professional free statistical software) and STATA 15.0. Measurement data conforming to normal distribution were expressed as mean ± standard deviation, and independent sample *t* test was used between groups. Measurement data with nonnormal distribution were expressed as median

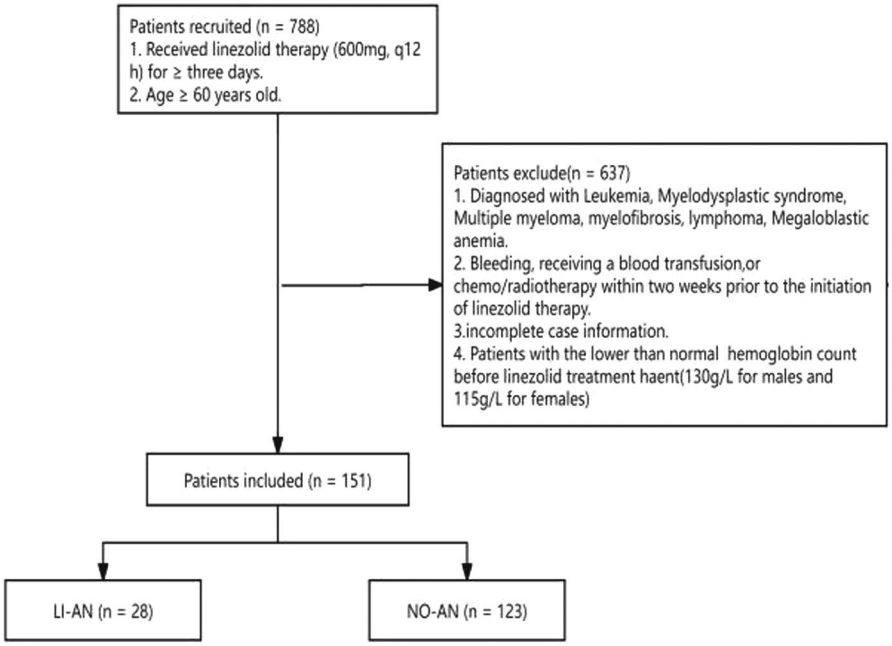

Figure 1. Flowchart of patients included in this study.

(interquartile range, IQR), and nonparametric test was used between groups. The Chi-square test or Fisher's exact test was used to analyze the categorical variables, which were described as numbers (percentages). All tests were two-tailed tests and $p < 0.05$ was statistically significant.

Results

Patient characteristics

A total of 151 patients were recruited in the training set (Figure 1). Their median age was 79.0 (IQR 71.5–87.5) years, with males accounting for 58.28% (88/151) of the total patients (Table 1). Linezolid was administered at a dose of 600 mg q 12 h, with a median duration of 8.0 (IQR 5.0, 10.5) days. Twenty-eight patients were defined as anemic, and the anemia incidence was 18.54%. Of these, 67.9% (19/28) were male, with a median age of 80.46 (IQR 72.5, 88.0) years. Eighty patients were recruited in the validation cohort, from the MIMIC-IV 2.2 database.

Univariate analysis in the training set

Univariate logistic regression analysis was used to screen the risk predictors. There were significant differences in eGFR (OR: 0.98, $p = 0.023$), SOFA score ≥ 2 (OR: 7.18, $p < 0.001$), duration of linezolid therapy (OR: 1.19, $p < 0.001$), but there was no significant difference in patient gender, infection, and accompanying diseases between patients with and without LI-AN.

Establishment of LI-AN prediction model and nomogram

Further, multivariable logistic regression analysis indicated that the variables ultimately included in the prediction model were eGFR (OR: 0.986, $p = 0.049$), SOFA score ≥ 2 (OR: 6.91, $p = 0.003$), duration of linezolid therapy (OR: 1.215, $p < 0.001$) (Table 2). Based on the aforementioned results, we constructed the nomogram with three factors (Figure 2). The nomogram demonstrated a positive correlation between the duration of linezolid treatment and the score, indicating an increased likelihood of LI-AN. Similarly, a lower eGFR value, SOFA score ≥ 2 were associated with higher scores. The cumulative sum of these four scores corresponds to the probability of LI-AN (Figure 2).

Performance assessment and validation of the nomogram

We evaluated the effectiveness of the nomogram in predicting anemia in both the training and validation cohorts, with an Area Under the Curve (AUC)

Table 1. Baseline characteristics of the study population.

Characteristics	Total ($n = 151$)	LI-AN ($n = 28$)	No LI-AN ($n = 123$)	p Value
Age (years), M (Q_1, Q_3)	79.00 (71.50, 87.50)	80.46 (72.5, 88.00)	79.36 (71.00, 87.25)	0.559
Male, *n* (%)	88 (58.28)	19 (67.9)	69 (56.1)	0.345
Duration (days), M (Q_1, Q_3)	8.00 (5.00, 10.50)	11.64 (8.00, 14.00)	7.82 (5.00, 10.00)	<0.001
SOFA score, *n* (%)				<0.001
<2	71 (47.02)	4 (14.3)	67 (54.4)	
⩾2	80 (52.98)	24 (85.7)	56 (45.5)	
CRRT, *n* (%)	1 (0.66)	1 (3.6)	0 (0)	0.185
Hemoglobin (g/L), mean ± SD	135.66 ± 12.92	139.54 ± 12.84	134.78 ± 12.83	0.084
Albumin(g/L), mean ± SD	31.92 ± 4.53	31.99 ± 4.11	31.90 ± 4.64	0.919
Total bilirubin (μmol/L), M (Q_1, Q_3)	11.95 (8.20, 16.14)	15.00 (9.35, 18.09)	12.42 (7.30, 15.35)	0.167
ALT (U/L), M (Q_1, Q_3)	19.40 (11.32, 32.80)	44.01 (15.33, 51.6)	35.50 (11.02, 32.35)	0.448
AST (U/L), M (Q_1, Q_3)	26.50 (17.15, 39.80)	37.86 (18.68, 40.38)	41.53 (16.78, 39.85)	0.454
eGFR, (mL/(min·1.73 m^2)), M (Q_1, Q_3)	68.02 (48.03, 92.81)	58.89 (32.16, 79.86)	81.73 (50.04, 93.90)	0.015
WBC × 10^9/L, *n* (%)				0.423
<4	5 (3.31)	0 (0)	5 (4.1)	
4–10	71 (47.02)	11 (39.3)	60 (48.8)	
⩾10	75 (49.67)	17 (60.7)	58 (47.2)	
NEUT (%), M (Q_1, Q_3)	84.90 (76.90, 89.65)	84.25 (80.73, 89.93)	81.53 (75.95, 89.73)	0.291
Concomitant disease, *n* (%)				
COPD	42 (27.81)	5 (17.9)	37 (30.1)	0.285
Hypertension	71 (47.02)	12 (42.9)	59 (48.0)	0.780
Diabetes	47 (31.13)	9 (32.1)	38 (30.9)	1.000
Coronary heart disease	77 (50.99)	14 (50.0)	63 (51.2)	1.000
Types of infection, *n* (%)				
Blood	18 (11.92)	3 (10.7)	15 (12.2)	1.000
Pulmonary	106 (70.20)	21 (75.0)	85 (69.14)	0.699
Urinary tract	38 (25.17)	4 (14.3)	34 (27.6)	0.219
Combination antibiotics, *n* (%)				
Carbapenems	60 (39.74)	19 (67.9)	41 (33.3)	0.002
Cephalosporin	4 (2.65)	0 (0.0)	4 (3.3)	0.753
Piperacillin-tazobactam	10 (6.62)	2 (7.1)	8 (6.8)	1.000
Quinolones	6 (3.97)	2 (7.1)	4 (3.3)	0.678

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; LI-AN, linezolid-induced anemia; NUET, percentage of neutrophils; SD, standard deviation; SOFA, sequential organ failure assessment; WBC, white blood cell.

Table 2. Results of the univariate and multivariable regression analysis of linezolid-related anemia.

Variable	Univariate analysis		Multivariable analysis	
	OR (95% CI)	***p* Value**	**OR (95% CI)**	***p* Value**
Age	1.01 (0.97–1.05)	0.586		
Sex	0.61 (0.25–1.44)	0.258		
Duration	1.19 (1.08–1.32)	<0.001	1.215 (1.093–1.350)	<0.001
SOFA score ⩾2	7.18 (2.35–21.92)	<0.001	6.91 (1.971–24.226)	0.003
CRRT	—	0.991		
Hemoglobin	1.03 (1.00–1.06)	0.122		
Albumin	1.00 (0.92–1.10)	0.924		
Total bilirubin	1.04 (0.99–1.09)	0.144		
ALT	1.00 (1.00–1.01)	0.540		
AST	1.00 (0.99–1.01)	0.817		
eGFR, [mL/(min·1.73 m^2)]	0.98 (0.97–1.00)	0.023	0.986 (0.971–1.000)	0.049
WBC × 10^9/L	—	0.989		
NEUT	1.02 (0.98–1.07)	0.246		
Concomitant disease, *n* (%)				
COPD	0.51 (0.18–1.43)	0.199		
Hypertension	0.81 (0.36–1.86)	0.625		
Diabetes	1.06 (0.44–2.56)	0.897		
Coronary heart disease	0.95 (0.42–2.16)	0.907		
Types of infection, *n* (%)				
Blood	0.86 (0.23–3.21)	0.827		
Pulmonary	1.34 (0.53–3.42)	0.539		
Urinary tract	0.44 (0.14–1.35)	0.150		
Combination antibiotics, *n* (%)				
Carbapenems	4.22 (1.76–10.15)	0.001		
Cephalosporin	—	0.990		
Piperacillin-tazobactam	1.11 (0.22–5.51)	0.902		
Quinolones	2.29 (0.40–13.16)	0.354		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; NEUT, percentage of neutrophils; OR, odds ratio; SOFA, sequential organ failure assessment; WBC, white blood cell.

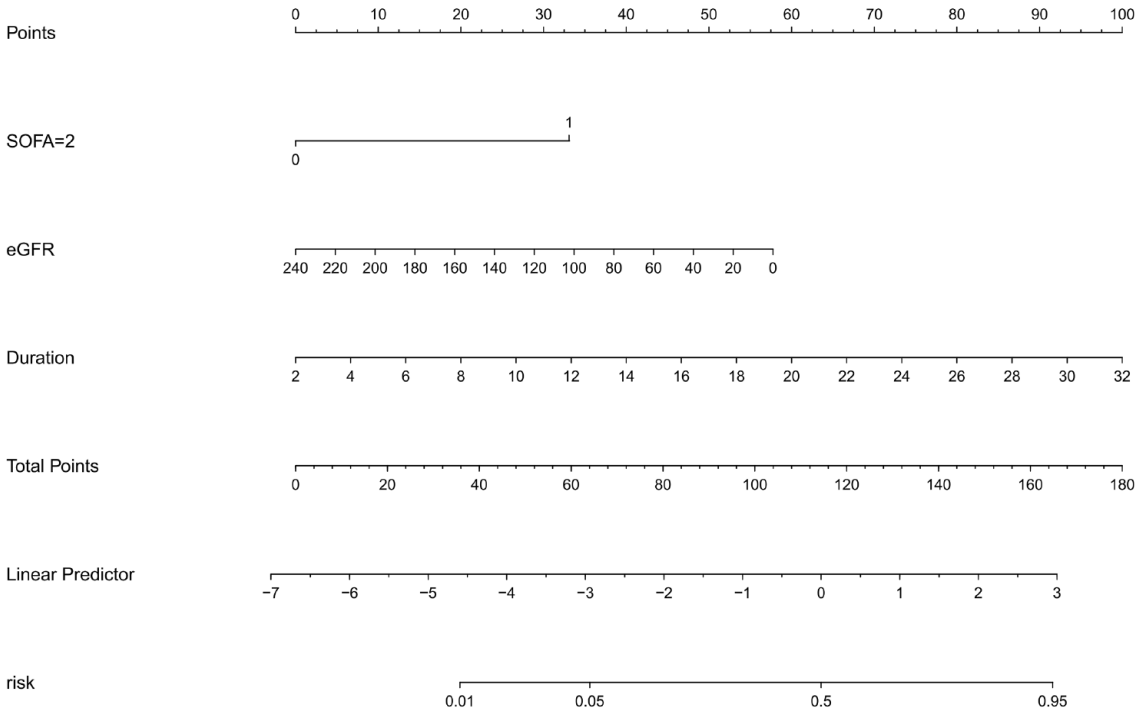

Figure 2. Nomogram with risk factors for linezolid-related anemia.

of 0.830 (95% CI: 0.750–0.910) for the training cohort and 0.743 (95% CI: 0.621–0.865) for the validation cohort (Figures 3 and 4). Furthermore, calibration curve analysis demonstrated a good concordance between the predicted probabilities and the observed anemia in the training cohort (Figure 5). The DCA demonstrated a clinically useful model with high accuracy between 5% and 95% probability of prediction (Figure 6).

LI-AN treatment measures

There was currently no established indication for LI-AN associated with any medication. However, the myelosuppression induced by linezolid is reversible, the potential recovery of Hb and blood cell count to pretreatment levels upon discontinuation of linezolid therapy. In this study, out of 28 patients who developed LI-AN, 75% (21/28) discontinued linezolid treatment; among these individuals, 42.8% (9/21) experienced a normalization of Hb levels after withdrawal, while incomplete test data were observed in 47.6% (10/21) cases following cessation of linezolid therapy. Additionally, timely administration of leukocyte-depleted packed red blood cells was provided to 9.5% (2/21) patients to prevent adverse vital signs.

Discussion

In this study, we identified risk factors associated with LI-AN in elderly patients, developed a robust clinical prediction model, and subsequently validated it using data from elderly

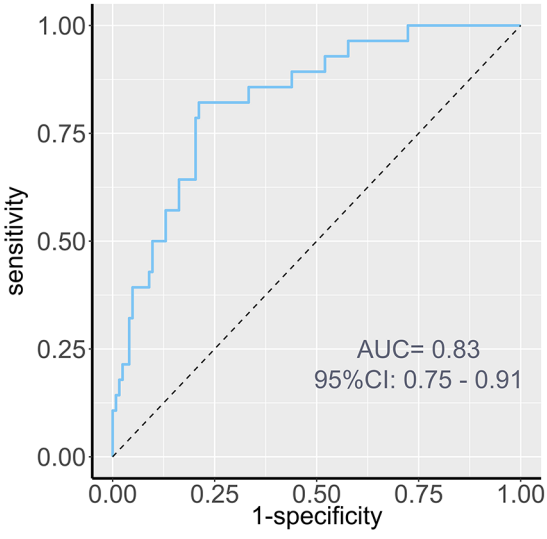

Figure 3. The ROC curves of the nomogram for linezolid-related anemia in training group.
ROC, receiver operating characteristic.

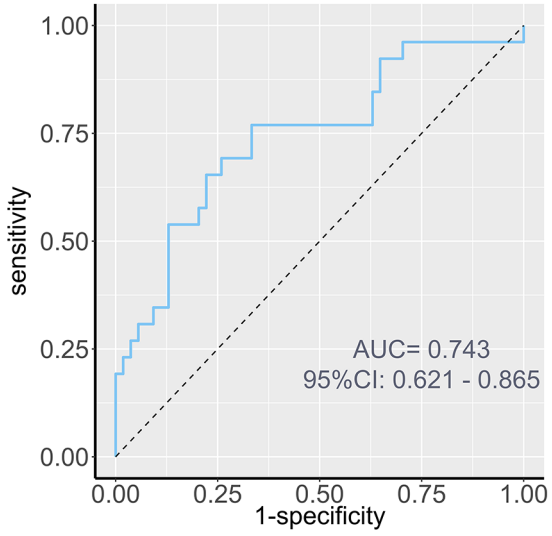

Figure 4. The ROC curves of the nomogram for linezolid-related anemia in validation.
ROC, receiver operating characteristic.

patients in the MIMIC-IV database. This predictive model demonstrates significant efficacy in forecasting the occurrence of anemia in elderly patients treated with linezolid for a minimum duration of 3 days, thereby providing substantial data support for the safe administration of linezolid in geriatric individuals. Key risk factors identified in this study include the duration of linezolid therapy, eGFR, and SOFA score ⩾2.

Hanai et al. demonstrated in their stud that the duration of linezolid treatment stands as the sole independent risk factor for LI-AN, with a notably higher incidence among patients treated for over 15 days.[17] Senneville et al. reported a median time from treatment initiation to anemia onset of 7.4 weeks (range 4–16).[2] Similarly, Qin et al. developed a prediction model that also identified prolonged linezolid duration as a risk factor for LI-AN.[18] Our investigation identified linezolid treatment exceeding 11 days as an independent risk factor for anemia in elderly patients, basically consistent with findings by Qin et al. (11.64 days vs 10 days). Monitoring Hb levels closely is advised when linezolid treatment extends beyond 11 days due to heightened anemia risk. Senneville et al. additionally noted that pretreatment Hb <10.5 g/dL (OR: 16.49, 95% CI 1.06–255, $p = 0.04$) was identified as a risk factor for LI-AN, contrasting with our study, which found no significant relationship between pre-treatment Hb levels and LI-AN.[2] Consistent with previous research on LI-AN, no relevant findings were identified.[17,18] Notably, our study observed higher baseline Hb levels among LI-AN group prior to treatment compared to controls (139.54 ± 12.84 vs 134.78 ± 12.83). Further exploration of the relationship between pretreatment Hb levels and LI-AN may be warranted.

Dai et al. studied that hepatic and/or renal insufficiency was a risk factor for linezolid-related anemia, and pointed out that patients with eGFR < 90 mL/min/1.73 m^2 were predisposed to develop LI-AN.[3] Other research has identified end-stage renal disease as an independent risk factor for anemia (OR: 4, 95% CI, 1.50–10.64, $p = 0.006$).[13] Our study further established a significant correlation between eGFR levels and Hb decline. Linezolid administration resulted in elevated serum concentrations in renal insufficiency patients, impacting hematopoietic function and potentially leading to anemia or

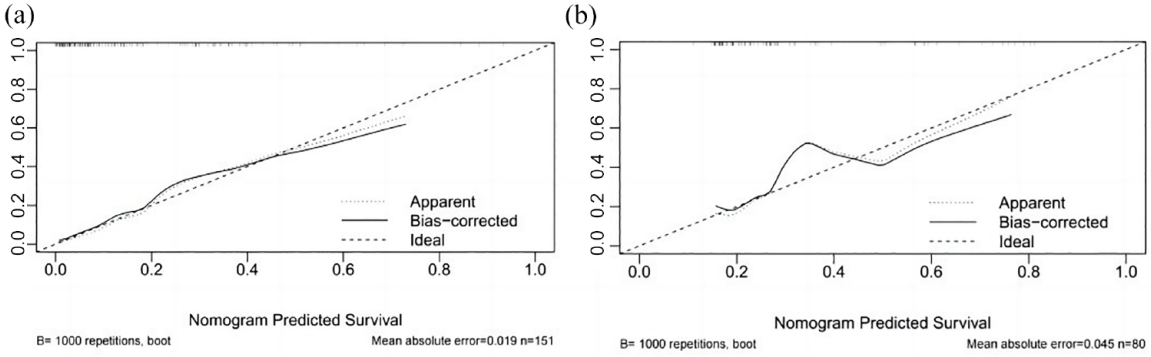

Figure 5. The calibration curves in the training group (a) and validation group (b).

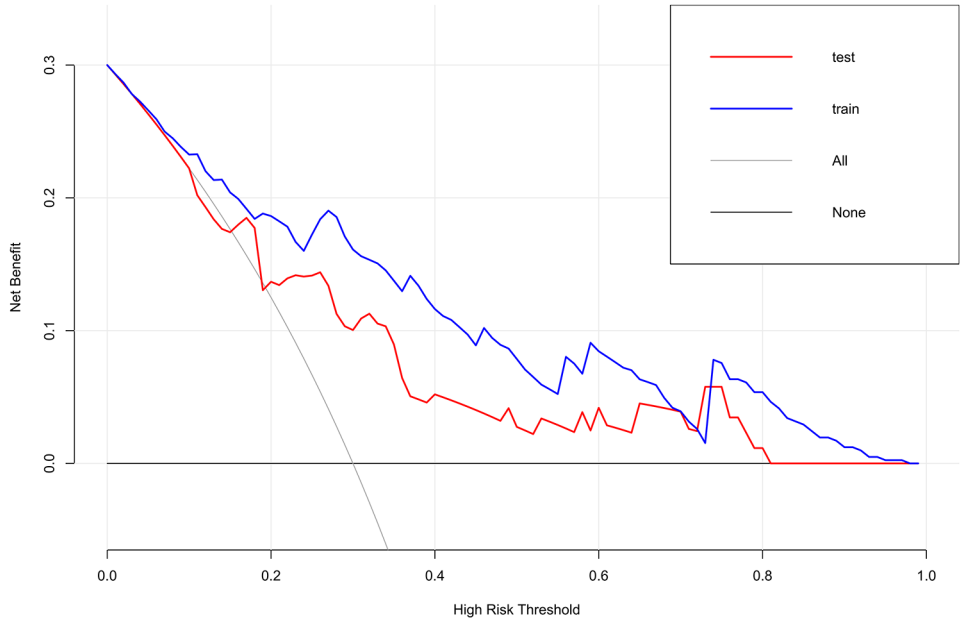

Figure 6. The DCA in the training group and validation group.
DCA, decision curve analysis.

thrombocytopenia. Close monitoring of Hb levels is recommended to promptly detect anemia. Dai et al. also identified AST >80 U/L as a risk factor for LI-AN.[3] Hepatic insufficiency might impair Hb synthesis. Takahashi et al. reported chronic liver disease as a possible risk factor for linezolid hematology toxicity (OR: 1.63, 95% CI 0.92–2.86, $p=0.092$).[19] However, our study may have inadvertently included a limited cohort of patients with hepatic impairment, possibly precluding any definitive association between liver function and LI-AN.

This study suggested that a SOFA score ⩾2 represents a risk factor for anemia. The SOFA score functions as a metric of disease severity and prognostic outlook in patients, particularly noting the onset of Sepsis in ICU-infected individuals when the SOFA score reaches ⩾2.[20] Sepsis precipitates acute organ dysfunction and circulatory compromise, potentially influencing the pharmacokinetics of linezolid and resulting in elevated drug concentrations that may predispose to LI-AN. One study indicated that bacteremia/infective endocarditis was also correlated with linezolid blood toxicity.[21] Our findings are substantiated by the fact that bacteremia or other infections can evoke a severe systemic response (sepsis) that results in LI-AN. Therefore, clinicians are advised to prudently evaluate the risk-to-benefit ratio of administering linezolid to elderly patients with higher SOFA scores, considering strategies such as treatment duration reduction or alternative drug selection to mitigate the incidence of anemia.

We developed a predictive model for LI-AN in a Chinese population and externally validated it using the MIMIC-IV database, enhancing the model's generalizability and reliability across different datasets. Our definition of LI-AN was stringent, focusing exclusively on elderly patients meeting specific inclusion criteria. External validation using a public database avoided the need to split the training set, reducing the risk of overfitting and enhancing the accuracy of validation results. The predictive model was robust and the results were reliable, which can be used in drug reaction prediction studies of real-world clinical adverse.

The aging population exhibits diminished drug tolerance and heightened susceptibility to adverse effects attributable to declining physiological function. Establishing a predictive model for LI-AN among the elderly holds substantial clinical significance. This model aids clinicians in the initial screening of geriatric patients undergoing linezolid therapy for infections, enabling assessment and prediction of their risk of developing anemia. By identifying those at higher risk,

clinicians can implement preemptive measures such as increasing Hb monitoring frequency or timely discontinuation of medication to minimize the incidence of adverse effects. Furthermore, the model aids in avoiding unnecessary tests and treatments; for instance, low-risk elderly patients may require fewer frequent blood tests, thus, conserving healthcare resources and reducing costs. Clinicians can leverage the predictive model's outcomes to weigh the pros and cons of treatment options, deciding whether to proceed with linezolid or opt for alternative therapies. This approach supports clinicians in making more scientific and rational decisions during the course of treatment.

Limitations

Our study have limitations. First, because of the retrospective design of this study, we were unable to control for all confounding factors. Second, although we performed external validation combined with external data, our study sample was small. Further multicenter prospective studies with large samples are needed to ensure adequate statistical power in the analysis.

Conclusion

This study established and validated a nomogram to predict the risk factors for LI-AN in elderly patients. The predict model provides valuable insights into risk identification and prevention of LI-AN in elderly patients. Through the predict model can guide the clinicians to rational linezolid use and avoid LI-AN.

Declarations

Ethics approval and consent to participate

Approval for this research was obtained from the Medical Ethics Committee of Inner Mongolia Autonomous Region People's Hospital. This study is a retrospective study that collects only existing medical records and data and will not involve direct intervention of any individual or collection of new information; therefore, patient consent was waived. We promise to strictly abide by the principles of privacy protection during the data collection and processing process and ensure that the personal information of all participants is not disclosed.

Consent for publication

Not applicable.

Author contributions

Hongling Ma: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Zhaotang Gong: Software; Writing – original draft; Writing – review & editing.

Rihan Wu: Data curation; Supervision; Writing – review & editing.

GuLeng SiRi: Conceptualization; Formal analysis; Methodology; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data are available from the corresponding author upon reasonable request.

ORCID iD

GuLeng SiRi https://orcid.org/0000-0003-0705-1153

Supplemental material

Supplemental material for this article is available online.

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