Infection and Drug Resistance

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ORIGINAL RESEARCH

Using Machine Learning to Predict Linezolid-Associated Thrombocytopenia

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Objective: Using artificial intelligence and machine learning to predict linezolid-induced thrombocytopenia helps identify related risk factors in patients.

Methods: Between January 2020 and December 2023, 284 patients receiving linezolid from Beijing Chaoyang Hospital were enrolled. The data underwent filtering to ensure completeness and quality. The filtered data were then randomly divided into training and validation sets at a 3:1 ratio using stratified sampling. Four machine learning methods-logistic regression, Lasso regression, support vector machine (SVM), and random forest-were employed to develop predictive models on the training set, with optimal hyperparameters determined through grid search. Model performance was assessed via 10 - fold cross - validation on the training set, and the model with the highest AUC was selected. The chosen model was further validated on the independent validation set, with AUC, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) calculated.

Results: During treatment with linezolid, 42 (14.8%) of the 284 patients developed thrombocytopenia, with an average onset of 12.0 ±5.6 days after starting linezolid therapy. The random forest model demonstrated the best performance, with an AUC of 0.902 (95% CI 0.814–0.991) in the validation set. This model achieved a sensitivity of 81.8%, specificity of 86.9%, positive predictive value (PPV) of 52.9%, and negative predictive value (NPV) of 96.4%.

Conclusion: We developed a machine learning model to predict linezolid-associated thrombocytopenia, with the random forest model achieving an AUC of 0.902. This model can help clinicians assess patient risk and optimize treatment plans. Future work should validate the model in multicenter studies and explore its integration into clinical decision support systems.

Keywords: linezolid, thrombocytopenia, machine learning, risk factors

Introduction

Linezolid, the first fully synthetic oxazolidinone antibacterial drug, is widely used for treating severe Gram-positive bacterial infections, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).[1,2] However, its increasing clinical use has led to a higher incidence of adverse reactions,[3–7] particularly thrombocytopenia, which is defined as a reduction in platelet count to $<100\times10^9$/L or a decrease of ≥25% from baseline. This adverse effect can increase the risk of bleeding and necessitate premature discontinuation of treatment, posing a significant challenge in clinical practice.[8–13] While several risk factors for linezolid-associated thrombocytopenia (LAT) have been identified, including age, duration of linezolid use, and renal function, current risk prediction models often lack sufficient accuracy and comprehensiveness. Additionally, most existing studies have focused on single-method approaches for model construction, limiting comparative insights and the development of more robust predictive tools.

In recent years, artificial intelligence and machine learning have shown great potential in predicting adverse drug reactions and have been increasingly applied in the medical field.[14–16] These technologies can analyze complex datasets to identify meaningful patterns and develop predictive models with higher accuracy.[17–19] However, there is still a gap in

Received: 11 February 2025
Accepted: 9 May 2025
Published: 23 May 2025

utilizing machine learning to comprehensively predict LAT, especially in integrating multiple risk factors and comparing different modeling approaches.

This study aims to fill this gap by employing multiple machine learning algorithms to develop and compare predictive models for LAT. By leveraging a comprehensive dataset and advanced analytical techniques, we seek to enhance the accuracy and reliability of LAT prediction, ultimately contributing to safer and more effective use of linezolid in clinical settings.

Materials and Methods

Patients and Study Design

Ethical approval for this study was obtained from the Institutional Review Board of our institute (Approval No. 2024-KE-337). This retrospective study adheres to the principles outlined in the Declaration of Helsinki. A total of 284 patients treated with linezolid at our hospital from January 2020 to December 2023 were included in the study. Inclusion criteria: (1) The patient received linezolid treatment during hospitalization; (2) Clinical data, including sex, age (≥18 years), admission and discharge dates, infection type, and serological parameters, were collected for statistical analysis. The serological parameters included platelet count (PLT), large platelet ratio (P-LCR), platelet distribution width (PDW), mean platelet volume (MPV), white blood cell count (WBC $>100\times10^9$/L), total protein (TP), albumin (ALB), serum prealbumin (PA), hemoglobin (Hb), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), creatinine (CREA), and blood urea nitrogen (BUN). Exclusion criteria: (1) Patients with incomplete data; (2) Patients who had pre-existing thrombocytopenia; (3) Patients who received platelet transfusions within three days before starting linezolid treatment. Ultimately, 42 patients were assigned to the thrombocytopenia group, and 242 patients to the normal group. Data were randomly divided into training and validation sets.

Definition

According to the latest version of the Common Terminology Criteria for Adverse Events (CTCAE), version 5, thrombocytopenia is defined as either a platelet count $<100\times10^9$/L or a decrease of more than 25% from the baseline platelet count.

For disease assessment, thrombocytopenia is classified into four levels based on the platelet count: Level 1 ($75–100\times10^9$/L), Level 2 ($50–75\times10^9$/L), Level 3 ($25–50\times10^9$/L), and Level 4 ($<25\times10^9$/L).

Statistical Analysis

This study used R software (version 4.3.2, https://www.R-project.org) and various machine learning R software packages (caret, glmnet, e1071, randomForest, pROC, tidyverse) for statistical analysis. We first assessed the completeness of the dataset. By discarding features with excessive missing values, we ultimately retained 10 features for modeling. Subsequently, we filtered outpatient records with missing values across these retained features. This left a total of 284 records, including 42 samples with thrombocytopenia. These samples were then randomly split into test and verification sets in a 3:1 ratio, employing stratified sampling to ensure that the proportion of thrombocytopenia samples remained consistent across both sets. To identify the most suitable machine learning model, we constructed four models—logistic regression, random forest, support vector machine (SVM), and lasso regression—on the training set. For each model, we performed a grid search to determine optimal hyperparameters and evaluated robust performance using 10-fold cross-validation (Table 1). The model with the highest AUC on the test set was selected as the final model, and its performance was subsequently assessed on the test set.

Results

Demographics and Clinical Characteristics of Study Population

284 patients (197 male and 87 female) were treated with linezolid between January 2020 and December 2023, meeting all the required criteria. During treatment, 42 patients (14.8%) developed thrombocytopenia, with the onset occurring after an average of 12.0 ± 5.6 days of linezolid administration. The ages of the patients ranged from 18 to 97 years, with

Table 1 The Hyperparametric Fine-Tuning Parameters of Each Model

Model	Method	Grid Search (Search Area)	Best tune (Tuning Value)
Logistic model	glmnet (alpha=0)	Lambda = seq(0.01, 0.1, by = 0.01)	Lambda=0.01
Random forest	rf	mtry = c(2, 4, 6, 8)	mtry=2
SVM	svmRadial	C = c(0.1, 1, 10),sigma = c(0.01, 0.1, 1)	C=10, sigma=0.1
Lasso	glmnet(alpha=1)	Lambda = seq(0.01, 0.1, by = 0.01)	Lambda=0.03

a median age of 67 years. Of the 284 patients, 150 (52.8%) were aged ≥65 years. The primary indications for linezolid therapy included bacterial pneumonia (92 patients, 32.4%) and postoperative infections (52 patients, 18.3%). Furthermore, the respiratory department was the leading user of linezolid, with 79 patients (27.8%) receiving the treatment, aligning with the primary indications for its use. In patients who developed thrombocytopenia, platelet counts were recorded as follows: before linezolid treatment (Pre-linezolid), the count was $(191.1\pm84.7)\times10^9$/L, and after linezolid treatment (Post-linezolid), it decreased to $(152.8\pm71.6)\times10^9$/L, as shown in Figure 1. It can be seen from Figure 1 that linezolid can cause thrombocytopenia, P<0.0001, with statistical significance. The clinical parameters for the entire study population, as well as for both study groups, are presented in detail in Table 2.

Risk Factors Associated with Thrombocytopenia

In the univariate analysis, age, PLT, PDW, MPV, P-LCR, BUN, CREA, and WBC were identified as high-risk factors for thrombocytopenia following linezolid treatment ($P < 0.05$). However, no significant differences were observed in the occurrence of thrombocytopenia based on sex or the duration of linezolid treatment. The results of the univariate logistic regression analysis are presented in Table 3.

Machine Learning

The data were divided into training and validation groups at a 3:1 ratio, selecting 10 features: sex, age, duration of treatment, PLT, PDW, MPV, P-LCR, BUN, CREA, and WBC. Age may be associated with various mechanisms underlying linezolid-induced thrombocytopenia. As age increases, the hematopoietic function of the bone marrow tends to decline, which may heighten the marrow's sensitivity to linezolid and consequently increase the likelihood of bone marrow depression, thereby affecting platelet production. Additionally, the immune system function in the elderly is

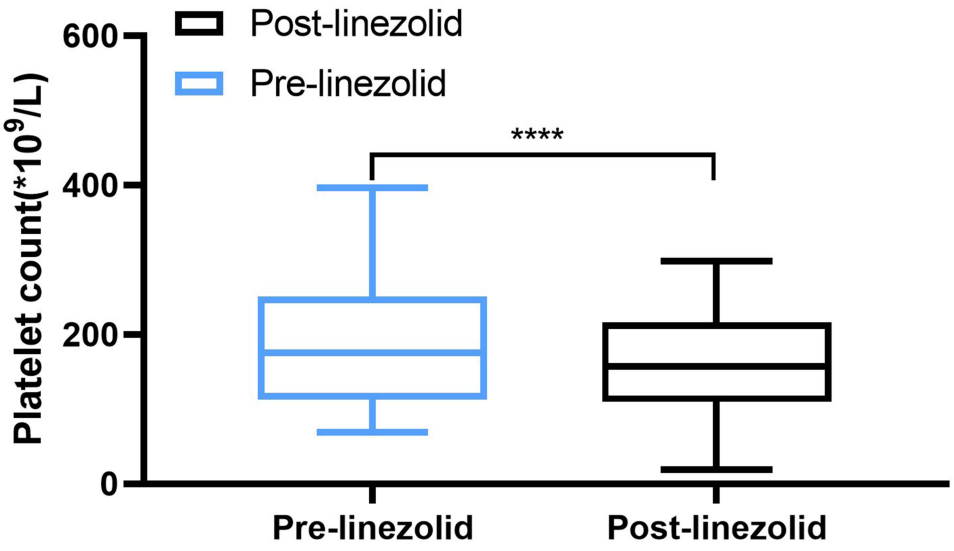

Figure 1 Trend in platelet counts before and following linezolid. ****: P<0.0001, mean ± SD: 191.1±84.7 (Pre-linezolid); 152.8±71.6 (Post-linezolid).

https://doi.org/10.2147/IDR.S479658

Table 2 The Distribution of Each Variable That Meets the Screening Condition

Name	Levels	Normal (N=242)	Thrombocytopenia (N=42)	*P*-value
Gender	Female	78(32.2%)	10(23.8%)	>0.999
	Male	164(67.8%)	32(76.2%)	
Age (median)	Mean±SD	66±17.7	70±17.0	0.171
Hierarchical diagnosis	I(76~100×10^9/L)	N/A	19(45.2%)	N/A
	II(50~75×10^9/L)	N/A	12(28.6%)	N/A
	III(26~49×10^9/L)	N/A	6(14.3%)	N/A
	IV(0~25×10^9/L)	N/A	5(11.9%)	N/A
PLT	Mean±SD	240.0±127.6	98±59.2	<0.001
P-LCR	Mean±SD	27.7±9.6	40.5±9.6	<0.001
PDW	Mean±SD	11.3±3.8	14.8±3.6	<0.001
MPV	Mean±SD	10.4±1.5	11.9±6.8	<0.001
WBC	Mean±SD	9.3±6.5	10.8±8.8	<0.001
TP	Mean±SD	58.6±7.9	52.7±8.8	0.007
ALB	Mean±SD	32.0±11.1	30.1±5.6	<0.001
PA	Mean±SD	0.2±0.1	0.1±0.1	<0.001
Hb	Mean±SD	88.0±18.9	79.0±46.3	<0.001
APTT	Mean±SD	31.4±10.2	40.1±16.3	<0.001
PT	Mean±SD	13.5±4.8	14.4±5.3	0.138
CREA	Mean±SD	60.6±87.4	109.2±89.2	0.009
BUN	Mean±SD	8.0±9.0	14.7±11.1	<0.001

Abbreviations: PLT, platelet count; P-LCR, large platelet ratio; PDW, platelet distribution width; MPV, mean platelet volume; WBC, white blood cell count; TP, total protein; ALB, albumin; PA, serum prealbumin; Hb, hemoglobin; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international standardized ratio; CREA, creatinine; BUN, blood urea nitrogen.

Table 3 Results After Univariate Logistic Regression Analysis

Variables	Single Factor Logistic	
	OR	P
Sex	1.58	0.321
Age	1.02	0.045
Span	1.02	0.424
PLT	0.99	<0.001*
PDW	1.20	<0.001*
MPV	1.48	<0.001*
P-LCR	1.08	<0.001*
BUN	1.05	<0.001*
CREA	1.00	<0.001*
WBC	1.06	<0.001*

Note: *means the statistical significance is more obvious.

Abbreviations: PLT, platelet count; P-LCR, large platelet ratio; PDW, platelet distribution width; MPV, mean platelet volume; WBC, white blood cell count; CREA, creatinine; BUN, blood urea nitrogen.

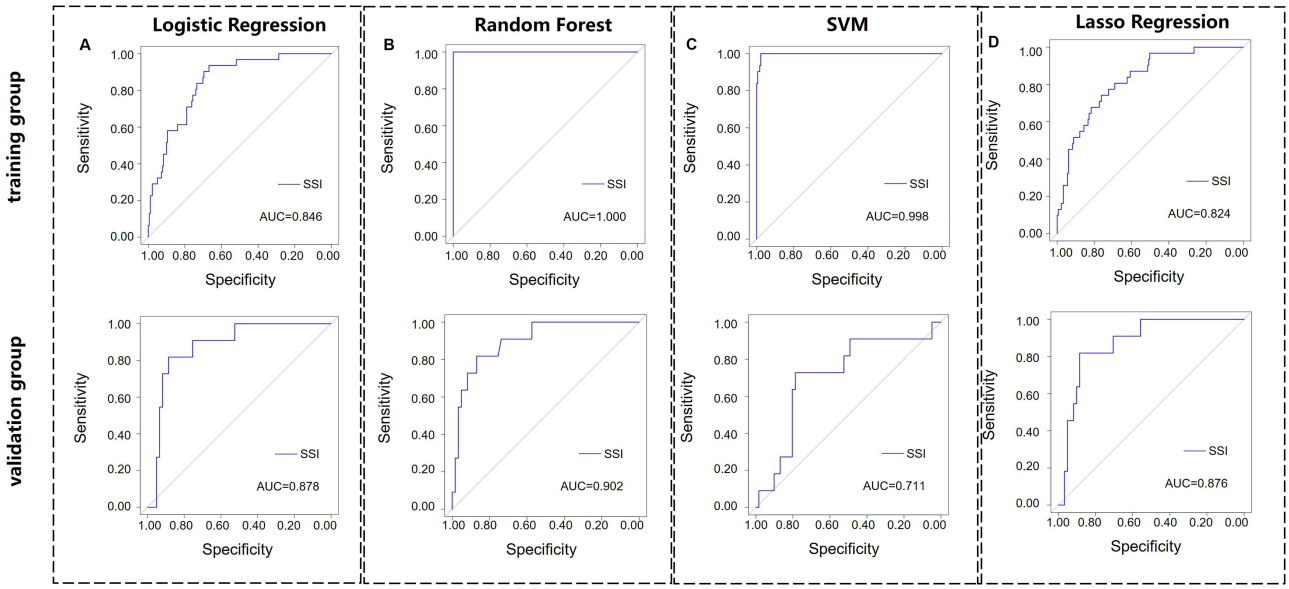

Figure 2 The ROC curve of four prediction models: (**A**) logistic regression, (**B**) random forest, (**C**) SVM, and (**D**) lasso regression.

often compromised, making immune-mediated platelet destruction more probable. Moreover, the body's antioxidant capacity typically weakens with age, leading to relatively elevated oxidative stress levels and greater susceptibility to oxidative stress damage induced by linezolid, which may ultimately result in thrombocytopenia. A low platelet count is an independent risk factor for linezolid-induced thrombocytopenia. When the baseline platelet count is low, it indicates that the patient has an insufficient platelet reserve in the body. Once exposed to linezolid, such patients are more likely to develop thrombocytopenia. This can occur through several mechanisms, including bone marrow suppression that reduces platelet production, immune-mediated platelet destruction, oxidative stress, or inhibition of megakaryocyte release. BUN primarily reflects kidney function status. In renal insufficiency, the metabolism and excretion of linezolid may be impaired, leading to drug accumulation in the body. This can increase the risk of myelosuppression, immune-mediated damage, and oxidative stress, thereby exacerbating thrombocytopenia. WBC count may be associated with the immune-mediated mechanism of linezolid-induced thrombocytopenia. WBCs are involved in the immune response, and abnormal WBC counts may indicate immune dysfunction. This can lead to the production of autoantibodies against platelets, resulting in immune-mediated platelet destruction. LAT activity usually indicates cell damage or destruction. In the context of linezolid-induced thrombocytopenia, increased LAT activity may be related to platelet injury caused by oxidative stress, or it may indirectly reflect bone marrow cell damage due to myelosuppression.

Four predictive models were developed using logistic regression, Lasso regression, SVM, and random forest techniques, as shown in Figure 2. Table 4 presents the variables identified as most significant through these four methods. Table 5 compares the performance of the models, with the random forest model selected as the best (F1 score: 0.643, precision-recall curves see Figure 3). The random forest model demonstrated an AUC of 0.902 (95% CI 0.814–0.991), sensitivity of 81.8%, specificity of 86.9%, positive predictive value of 52.9%, and negative predictive value of 96.4%.

Discussion

Risk Factors

In this study, logistic regression was used to analyze high-risk factors for linezolid-associated thrombocytopenia (LAT), and machine learning algorithms were employed to develop predictive models based on various predictors. 42 hospitalized patients developed thrombocytopenia following linezolid treatment.

In clinical practice, thrombocytopenia can result from various factors, with drugs playing a significant role. Linezolid is a common culprit in drug-induced thrombocytopenia. In this study, the incidence of linezolid-induced

https://doi.org/10.2147/IDR.S479658

Table 4 Risk Factors Screened by Four Machine Learning Algorithms

Logistic	Lasso	SVM	RF
PLT	Sex	PLT	Age
PDW	Age		PLT
MPV	span		P-LCR
P-LCR	PLT		BUN
BUN	P-LCR		CREA
CREA	CREA		WBC
WBC	WBC		

Abbreviations: PLT, platelet count; P-LCR, large platelet ratio; PDW, platelet distribution width; MPV, mean platelet volume; WBC, white blood cell count; CREA, creatinine; BUN, blood urea nitrogen.

Table 5 Performance Indicators of the Four Machine Learning Algorithms on the Validation Group

	AUC (95% CI)	Threshold	Sensitivity	Specificity	PPV	NPV
Logistic	0.878 (0.780–0.975)	0.2	81.8%	88.5%	56.2%	96.4%
Random Forest	0.902 (0.814–0.991)	0.2	81.8%	86.9%	52.9%	96.4%
SVM	0.711 (0.539–0.883)	0.2	72.7%	78.7%	38.1%	94.1%
Lasso	0.876 (0.781–0.971)	0.2	81.8%	88.5%	56.3%	96.4%

Abbreviations: CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

thrombocytopenia was 14.8%, consistent with findings from previous studies.[17,20] Age is a physiological factor affecting linezolid plasma concentrations. Elderly patients, due to multiple underlying conditions and compromised liver and kidney function, are more prone to drug accumulation, leading to higher plasma drug levels and an increased risk of thrombocytopenia. The univariate analysis in this study confirmed that age is a significant risk factor for thrombocytopenia.

Our findings also identified several additional risk factors for LAT, including PLT, PDW, MPV, P-LCR, BUN, CREA, and WBC. A low baseline platelet count has long been recognized as a risk factor for LAT. Given that LAT is defined by a platelet count drop of at least 100×10^9/L or a 25% reduction, a lower starting platelet count makes it more likely for patients to meet the criteria for LAT. Pharmacokinetic studies of linezolid indicate that 30% of the drug is excreted unchanged by the kidneys. In cases of renal impairment, the clearance of linezolid decreases by 20%, leading to higher plasma levels, which can increase the risk of LAT. This study also found that BUN and CREA were associated with LAT, corroborating previous research linking renal function impairment to LAT.

Model Strengths

In this study, we developed four machine learning models to predict LAT. Many studies have investigated risk factors for thrombocytopenia following linezolid treatment and have employed machine learning to construct predictive models. A study by Qin et al[21] used logistic regression to develop and validate a risk prediction model for elderly patients at risk for thrombocytopenia during linezolid therapy. The model identified baseline platelet count, age, eGFR, duration of linezolid therapy, ICU admission, and concurrent use of piperacillin-tazobactam as independent risk factors, with AUC values of 0.795 (95% CI: 0.740–0.851) and 0.849 (95% CI: 0.760–0.939), respectively. Another study by Gou et al[22]

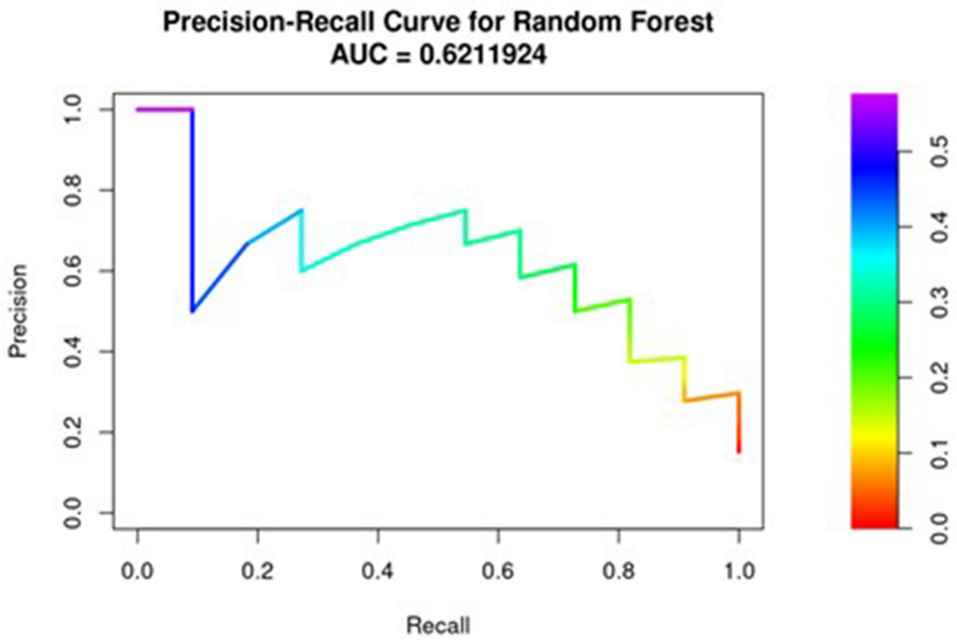

Figure 3 Precision-recall curves for Random Forest.

used logistic regression to create a combined factor risk prediction model for thrombocytopenia, incorporating treatment duration, eGFR, and creatinine clearance (CCr), with an AUC of 0.875 (95% CI: 0.822–0.927). Anu Patel et al[14] applied machine learning, specifically random forest classification, to predict hematological adverse events in patients treated with linezolid, achieving an AUC of 0.905. These studies have enhanced our understanding of thrombocytopenia associated with linezolid and provided valuable predictive models to assist clinicians in identifying and managing this adverse reaction.

There are some differences between this study and reported literatures in feature selection methods, model construction methods, dataset differences, sample size and research design. In this study, various machine learning methods were used for feature selection, and a variety of prediction models were constructed. Finally, random forest model was selected as the optimal model, and its AUC value reached 0.902, showing high prediction accuracy. However, the sample size of this study is relatively small, and it is a single-center retrospective study, which may have certain limitations. The reference mainly uses logistic regression model to build the risk prediction model, and its AUC value is up to 0.849, which is slightly lower than our study, but its sample size is large, and it focuses on the special population of elderly patients. Moreover, the wide AUC confidence interval of random forest model is mainly caused by insufficient sample size. This limitation affects the accuracy of the model performance estimation and the reliability of the decision, which can be mitigated by increasing the sample size, optimizing the model and data processing.

The practical significance and application effects of linezolid risk prediction model in clinical practice are as follows: 1. Improve treatment safety: Through the prediction model, doctors can assess the risk of adverse reactions in patients before treatment, so as to take preventive measures to improve the safety of treatment. 2. Optimize the treatment plan: According to the predicted results, doctors can adjust the treatment plan, such as changing drugs, adjusting doses, strengthening monitoring, etc., in order to reduce the occurrence of adverse reactions. 3. Promote precision medicine: The application of predictive models helps to realize precision medicine, that is, to develop personalized treatment plans according to the individual characteristics of patients.

Linezolid is a special-use antibiotic, and its clinical indications should be strictly controlled to prevent misuse. The standard dosing regimen for linezolid in adults is 600 mg q12h. For patients with mild to moderate renal insufficiency, dose adjustment is generally not required. However, studies have demonstrated that in special populations, such as those with renal dysfunction, linezolid can lead to the accumulation of its primary metabolite, hydroxyethyl amino

acetic acid. This accumulation may increase the risk of adverse reactions associated with linezolid. Therefore, it is recommended to monitor the blood concentration of linezolid in these patients to ensure therapeutic efficacy and minimize potential toxicity. Thrombocytopenia is a common adverse reaction to linezolid, particularly in elderly patients who require long-term treatment (≥7 days). For these patients, enhanced monitoring is recommended. During treatment, attention should be given to changes in blood routine and coagulation parameters, and clinicians should watch for signs of bleeding, such as petechiae, blood in sputum, gum bleeding, and occult blood in stools. When linezolid is co-administered with P-glycoprotein (P-gp) inhibitors, it is advisable to monitor the blood concentration of linezolid, maintaining trough levels between 2 and 8 mg/L to effectively control infection and reduce the risk of thrombocytopenia.

Limitations

Despite the use of multiple methods to construct a high-performing predictive model, this study has several limitations. First, as a single-center, retrospective study, it lacked drug concentration monitoring data and did not thoroughly investigate the relationship between liver and kidney function, drug exposure, and adverse reactions. Second, the sample size was relatively small, with only 42 patients who developed thrombocytopenia. Third, the retrospective design introduces the potential for selection bias and subjective biases, which could affect the robustness of the results.

Conclusion

In our study, we utilized four machine learning methods to develop predictive models, after careful comparison, selected the optimal one. The linezolid risk prediction model improved the accuracy and selectivity of the model through comprehensive screening of various methods, and provided a powerful tool for clinicians to assess patient risk before treatment with linezolid. This model has significant clinical application value in improving treatment safety, optimizing treatment plan and promoting precision medicine. However, limitations in study design and sample size suggest the need for future studies to conduct multicenter prospective studies to further validate the model's stability and generalizability, and to integrate the model into electronic health records or clinical decision support systems for real-time risk assessment.

Data Sharing Statement

The clinical data of patients used to support the findings of this study are included within the article.

Ethical Approval

The study was approved by the Ethics Committee of the Beijing Chaoyang Hospital Hospital [2024-KE-337] and complied with the Declaration of Helsinki. Beijing Chaoyang Hospital has agreed to waive the requirement for informed consent. The results of this study are intended for use in clinical research and analysis only and will not be used for clinical intervention. The risk to the subjects is no greater than minimal and waiving informed consent will not have an adverse effect on their rights or health. In addition, the subjects' personal information will be erased from the study and the de-identification process has been carried out to effectively protect their privacy and personal identification information.

Funding

Funding was provided by Beijing Chao-Yang Hospital Golden Seeds Foundation grant number CYZ202327.

Disclosure

The authors declare that they have no competing interests.

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