Risk Management and Healthcare Policy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Risk Stratification for Cephalosporin-Induced Thrombocytopenia: Development and Validation of a Multidimensional Predictive Model in Older Adults

Xiuyan Li[1,*], Wanlin Lei[2,*], Maofeng Wang[2], Lili Xu[3]

[1]Intensive Care Unit, Affiliated Dongyang Hospital, Wenzhou Medical University, Dongyang, Zhejiang, 322100, People's Republic of China; [2]Department of Biomedical Sciences Laboratory, Affiliated Dongyang Hospital, Wenzhou Medical University, Dongyang, Zhejiang, 322100, People's Republic of China; [3]Department of Obstetrics, Affiliated Dongyang Hospital, Wenzhou Medical University, Dongyang, Zhejiang, 322100, People's Republic of China

*These authors contributed equally to this work

Correspondence: Maofeng Wang; Lili Xu, Email wzmcwmf@wmu.edu.cn; xulili41663@163.com

Objective: Third-generation cephalosporins, while widely prescribed, carry underquantified thrombocytopenia risks in older adults. This study aimed to develop and validate a clinical prediction model for cephalosporin-associated thrombocytopenia in hospitalized patients aged over 65 years.

Methods: A retrospective cohort (2019~2023) initially included 45,779 cephalosporin treated patients. After applying exclusion criteria, 12,917 patients were analyzed. Predictors were selected via LASSO regression, with backward elimination multivariate logistic regression constructing a nomogram. Model performance was assessed using AUC, calibration curves, and decision curve analysis (DCA) in training and testing sets.

Results: The final model identified eight predictors: baseline platelet count (PLT), red blood cell count (RBC), presence of tumor, renal insufficiency (RI), liver cirrhosis (LC), meropenem use, use of antifungal drugs (AD), and daily usage frequency (DUF). It demonstrated strong discrimination (training AUC 0.82 [95% CI 0.79–0.85]; testing AUC 0.80 [0.76–0.84]) and calibration (Brier score 0.057). DCA confirmed clinical utility across wide risk thresholds.

Conclusion: This nomogram tool enables rapid thrombocytopenia risk assessment in elderly patients receiving cephalosporins. Clinically, it guides antibiotic selection by quantifying comorbidity-drug interactions, and improves toxicity monitoring accuracy in complex geriatric cases with polypharmacy.

Keywords: thrombocytopenia, predictive model, geriatric inpatients, nomogram, third generation cephalosporins

Introduction

Third-generation cephalosporins, though effective against infections in elderly patients,[1,2] pose a heightened risk of drug-induced thrombocytopenia (TCP),[3] a bleeding-prone condition. Older adults are especially vulnerable due to comorbidities,[1] polypharmacy, and age-related declines in hepatic/renal function.[4,5] Current challenges involve integrating age-related physiological heterogeneity, variability in drug metabolism, and complex comorbidities to develop a clinically actionable, high-accuracy predictive model that balances antimicrobial efficacy and medication safety.

In the elderly, the risk of thrombocytopenia after third-generation cephalosporins is a concern. To better understand and predict this risk, several studies have developed predictive models.[6,7] Regarding the risk of thrombocytopenia after the use of antibiotic, studies have shown that drug-induced thrombocytopenia is a rare but serious side effect.[7–9] In one study, researchers analyzed the incidence and associated risk factors for thrombocytopenia in patients treated with cefoperazone/sulbactam. The results showed that treatment duration, daily dose, and other clinical factors such as baseline platelet count and liver function indicators were all closely related to the occurrence of thrombocytopenia.[10] Another study developed a predictive model to assess the risk of thrombocytopenia in elderly patients treated with linezolid. The model considered multiple factors, including

Received: 24 April 2025
Accepted: 16 June 2025
Published: 25 June 2025

patient age, renal function, and baseline platelet count, demonstrating good predictive performance.[11] In the case of chemotherapy-related thrombocytopenia, researchers have also developed predictive models to help identify high-risk patients. Studies show that tumor type, treatment line, and the use of specific drugs are significantly associated with the occurrence of thrombocytopenia.[12] The development and validation of these models provide valuable tools for clinicians to better manage and prevent thrombocytopenia during treatment. In addition, studies on immune thrombocytopenia (ITP) have provided relevant insights. Research has developed predictive models based on clinical laboratory parameters to aid in the diagnosis of ITP, demonstrating good predictive accuracy.[13] These studies highlight the importance of combining clinical and laboratory data for risk assessment during drug use. Researchers have also developed predictive models using machine learning techniques to enhance the accuracy and reliability of predictions. These models analyze large amounts of clinical data to identify key factors associated with thrombocytopenia, supporting clinical decision-making.[14]

While predictive models for drug-induced TCP have been established for antibiotics like linezolid and chemotherapeutic agents, limited studies specifically target third-generation cephalosporins in elderly populations, despite their distinct risk profiles (eg, age-related metabolic changes, polypharmacy). Current models for cephalosporins, such as cefoperazone/sulbactam, focus on general clinical factors but lack integration of geriatric-specific variables. Older adults are particularly vulnerable due to comorbidities, reduced hepatic/renal function, and polypharmacy, yet existing risk prediction models lack specificity for this population.

To bridge this gap, we developed and validated a novel model integrating geriatric-specific factors to predict TCP risk during third-generation cephalosporin therapy in elderly patients.

Methods

Study Population

This retrospective cohort study analyzed hospitalized patients who received third-generation cephalosporin therapy between January 2019 and December 2023, initially comprising 45,779 individuals. Inclusion criteria required documented administration of third-generation cephalosporins during hospitalization. Exclusion criteria: (1) age <65 years (n=22,270), (2) missing pre-treatment platelet count (n=3684), (3) pre-treatment platelet count $<100\times10^9$/L (n=2598) or $>400\times10^9$/L (n=818), and (4) missing post-treatment platelet count (n=3492). After exclusions, 12,917 patients were enrolled and randomly partitioned into a training set (n=9041, 70%) and a testing set (n=3876, 30%). Ethical approval for the study was obtained from the Ethics Committee of Affiliated Dongyang Hospital of Wenzhou Medical University (approval #2025-YX-012), and Ethics Committee of Affiliated Dongyang Hospital of Wenzhou Medical University waived the requirement for the written informed consent of the patients. All patient medical information was anonymized and deidentified before the analysis. This research involving human participants was conducted in accordance with the principles of the Declaration of Helsinki.

Outcome Definition

Thrombocytopenia[15] was defined as a hematologic event characterized by platelet counts descending below 100×10^9/L within 30 days post-initiation of third-generation cephalosporin treatment in hospitalized adults. Case ascertainment leveraged structured pharmacologic classification identifiers within the hospital's electronic medical record (EMR) platform, with explicit exclusion of individuals exhibiting baseline thrombocytopenia (pre-treatment platelet count $<100\times10^9$/L) or concurrent exposure to platelet-modulating therapies.

Risk Factors

Predictor selection was guided by a tripartite evidence-based framework: (i) literature-derived associations from post-marketing surveillance research, (ii) therapeutic relevance to antimicrobial safety surveillance, and (iii) accessibility of institutionalized biomarkers. De-identified clinical data were systematically retrieved from the hospital's electronic medical record system, capturing: demographic profiles (sex, age); behavioral determinants (tobacco/alcohol use histories); comorbid conditions spanning neoplastic, metabolic (diabetes mellitus), and cardiovascular disorders; hepatic/renal functional status; pharmacotherapeutic exposures (anticoagulant regimens, broad-spectrum antifungals); and

hematobiochemical indices - including nadir values of leukocyte, erythrocyte, and thrombocyte counts, complemented by serum albumin and lactate concentrations measured ≤30 days preceding cephalosporin administration. All pre-existing medical conditions were temporally constrained to antedate antibiotic initiation, thereby mitigating retrospective recall inaccuracies and standardizing baseline comparability across the observational cohort.

Data Preprocessing

The analysis employed a systematic preprocessing pipeline aligned with clinical informatics standards. From 29 potential predictors, variables demonstrating over 20% missing entries were eliminated through comprehensive missingness evaluation. For retained features with partial missing data (<20% gaps), we applied multivariate imputation via chained equations (MICE algorithm) with five-cycle predictive mean matching. The cohort underwent stratified partitioning (70% training, 30% validation) preserving outcome prevalence across subsets.[16]

Model Building

Feature selection was performed using least absolute shrinkage and selection operator (LASSO) regression, a penalized regularization method that effectively isolates clinically significant predictors.[17,18] These key predictors subsequently underwent refinement through backward elimination multivariate logistic regression guided by the Akaike information criterion (AIC). The finalized predictors informed the construction of a clinical nomogram to estimate thrombocytopenia risk probabilities.

Model Evaluation

Diagnostic accuracy was quantified using receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) serving as the primary discrimination metric. Model calibration was assessed through graphical probability alignment plots comparing predicted risks against empirical event rates. Clinical utility was rigorously tested via threshold-dependent decision curve analysis (DCA), evaluating net patient benefit across clinically relevant risk probability ranges. Comparative performance benchmarking against conventional clinical indicators was conducted to validate predictive superiority. Figure 1 presents the complete model development and validation phases.

Statistical Methods

All computational workflows were executed in R version 4.4.2. Categorical variables expressed as frequency counts with percentages; comparisons employed χ^2 or Fisher's exact tests. Continuous variables represented using parametric (mean ± SD, Student's *t*-test) or nonparametric (median with IQR, Mann–Whitney *U*-test) descriptors. Missing data were addressed through multivariate imputation by chained equations (MICE) with predictive mean matching using the *mice* package.[19] Baseline cohort characterization and intergroup comparisons were performed via the *compareGroups* toolkit to automate standardized effect size calculations. Feature selection leveraged regularized regression via *glmnet*'s LASSO algorithm, followed by multivariable logistic regression modeling using the *glm* function. Predictive performance evaluation included discrimination (ROC analysis via *pROC* and *fbroc*, incorporating DeLong's method for AUC comparison), calibration (logistic recalibration using *rms* and *riskRegression* with restricted cubic splines), and clinical utility (decision curve analysis and clinical impact curves implemented via *rmda* and *dcurves*). A nomogram was constructed using *regplot* for individualized risk visualization, while diagnostic accuracy metrics were quantified via *reportROC*.[20] All statistical tests were two-sided, and a significance level of $p < 0.05$ was considered statistically significant.

Results

Study Population Characteristics

The study cohort comprised a total of 12,917 subjects, among which 12,007 subjects did not have thrombocytopenia and 910 subjects had thrombocytopenia. Table 1 summarizes the baseline characteristics of these subjects. Significant differences were observed between the two groups in several variables. Females constituted a slightly higher proportion in the no thrombocytopenia group (39.29% vs 35.16%, p=0.015). Subjects with thrombocytopenia were older (median age 77.00 years vs 76.00 years, p<0.001) and had significantly lower platelet counts (PLT: 136×10^9/L vs 195×10^9/L,

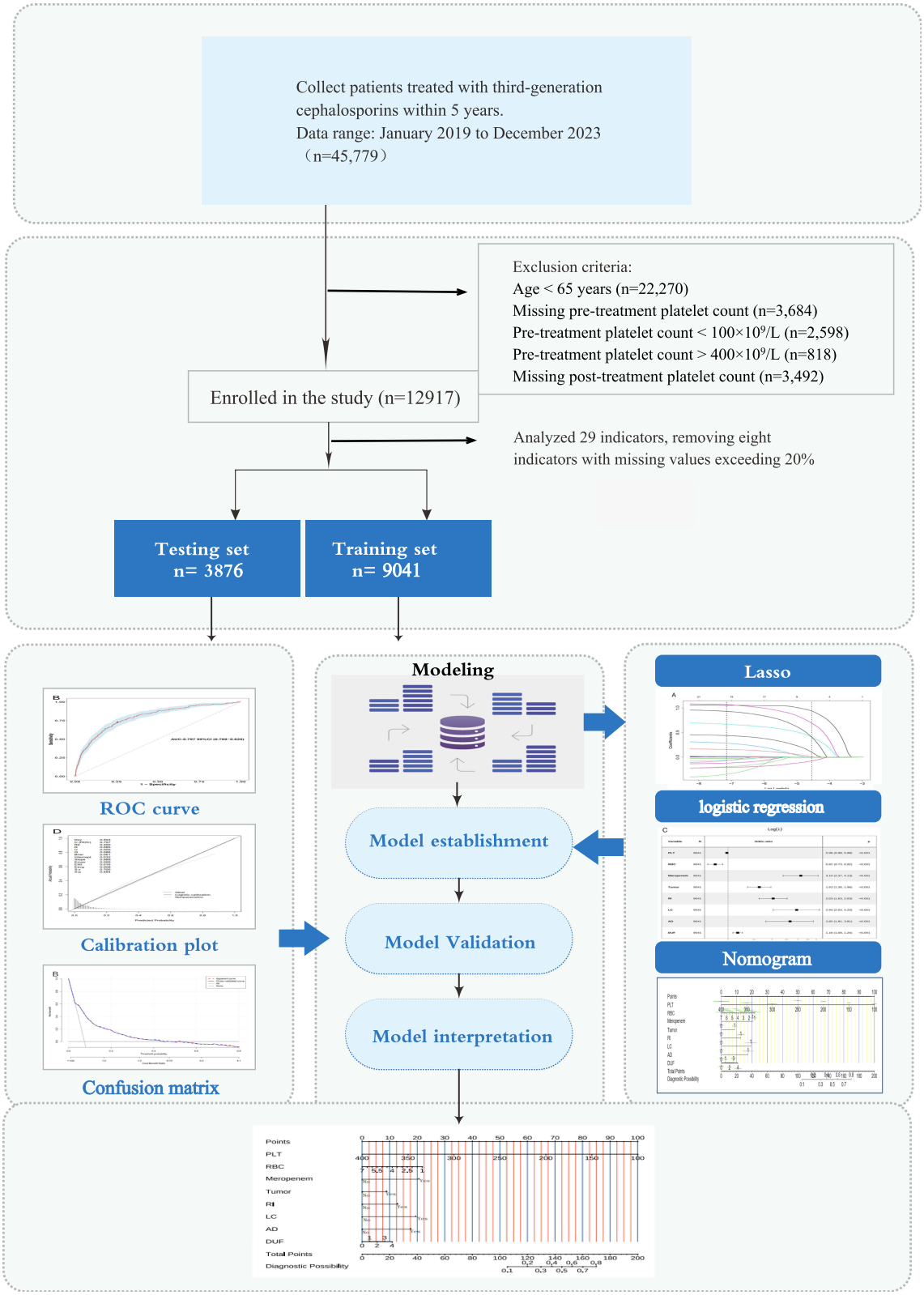

Figure 1 Study process flowchart.

Table 1 Baseline Characteristics of Subjects

Variables	Total N=12917	No Thrombocytopenia N=12007	Thrombocytopenia N=910	p
Sex				0.015
Female	5038 (39.00%)	4718 (39.29%)	320 (35.16%)	
Male	7879 (61.00%)	7289 (60.71%)	590 (64.84%)	
Age (years)	76.00 [70.00;83.00]	76.00 [70.00;83.00]	77.00 [71.00;84.00]	<0.001
PLT(10^9/L)	191 [153;237]	195 [157;240]	136 [118;173]	<0.001
CRE(μmol/L)	62.00 [51.00;77.00]	62.00 [51.00;77.00]	64.00 [50.00;81.75]	0.078
WBC(10^9/L)	7.49 [5.52;10.65]	7.52 [5.55;10.66]	7.11 [4.97;10.48]	<0.001
RBC(10^{12}/L)	4.08 [3.62;4.51]	4.09 [3.64;4.52]	3.91 [3.33;4.37]	<0.001
Meropenem, n (%)				<0.001
No	12299 (95.22%)	11533 (96.05%)	766 (84.18%)	
Yes	618 (4.78%)	474 (3.95%)	144 (15.82%)	
Ofloxacin, n (%)				0.956
No	11398 (88.24%)	10594 (88.23%)	804 (88.35%)	
Yes	1519 (11.76%)	1413 (11.77%)	106 (11.65%)	
Smoke, n (%)				0.078
No	248 (1.92%)	223 (1.86%)	25 (2.75%)	
Yes	12669 (98.08%)	11784 (98.14%)	885 (97.25%)	
Drink, n (%)				0.078
No	248 (1.92%)	223 (1.86%)	25 (2.75%)	
Yes	12669 (98.08%)	11784 (98.14%)	885 (97.25%)	
DM, n (%)				0.403
No	10476 (81.10%)	9748 (81.19%)	728 (80.00%)	
Yes	2441 (18.90%)	2259 (18.81%)	182 (20.00%)	
Hypertension, n (%)				0.229
No	5313 (41.13%)	4921 (40.98%)	392 (43.08%)	
Yes	7604 (58.87%)	7086 (59.02%)	518 (56.92%)	
Tumor, n (%)				<0.001
No	9289 (71.91%)	8706 (72.51%)	583 (64.07%)	
Yes	3628 (28.09%)	3301 (27.49%)	327 (35.93%)	
MI, n (%)				0.123
No	12409 (96.07%)	11544 (96.14%)	865 (95.05%)	
Yes	508 (3.93%)	463 (3.86%)	45 (4.95%)	
CI, n (%)				0.379
No	9053 (70.09%)	8403 (69.98%)	650 (71.43%)	
Yes	3864 (29.91%)	3604 (30.02%)	260 (28.57%)	
Anticoagulants, n (%)				<0.001
No	4821 (37.32%)	4563 (38.00%)	258 (28.35%)	
Yes	8096 (62.68%)	7444 (62.00%)	652 (71.65%)	
RI, n (%)				<0.001
No	11457 (88.70%)	10743 (89.47%)	714 (78.46%)	
Yes	1460 (11.30%)	1264 (10.53%)	196 (21.54%)	
LC, n (%)				<0.001
No	12611 (97.63%)	11776 (98.08%)	835 (91.76%)	
Yes	306 (2.37%)	231 (1.92%)	75 (8.24%)	
AD, n (%)				<0.001
No	12549 (97.15%)	11708 (97.51%)	841 (92.42%)	
Yes	368 (2.85%)	299 (2.49%)	69 (7.58%)	
DUF (n)	1.00 [0.00;3.00]	1.00 [0.00;3.00]	1.00 [0.00;3.00]	<0.001
Duration (day)	4.09 [0.01;6.90]	4.15 [0.01;6.89]	3.16 [0.01;7.00]	0.002

Abbreviations: PLT, Platelet count; CRE, Creatinine; WBC, White blood cell count; RBC, Red blood cell count; DM, Diabetes mellitus; MI, Myocardial infarction; CI, Cerebral infarction; RI, Renal insufficiency; LC, Liver cirrhosis; AD, Antifungal drugs; DUF, Daily usage frequency.

https://doi.org/10.2147/RMHP.S529488

p<0.001). Other notable differences included lower white blood cell counts (WBC: 7.11×10^9/L vs 7.52×10^9/L, p<0.001), red blood cell counts (RBC: 3.91×10^{12}/L vs 4.09×10^{12}/L, p<0.001), and higher usage of meropenem (15.82% vs 3.95%, p<0.001) and anticoagulants (71.65% vs 62.00%, p<0.001). Subjects with thrombocytopenia also exhibited a higher prevalence of renal insufficiency (RI: 21.54% vs 10.53%, p<0.001), liver cirrhosis (LC: 8.24% vs 1.92%, p<0.001), and antifungal drug usage (AD: 7.58% vs 2.49%, p<0.001). The cohort was divided into a training set (n=9041) and a testing set (n=3876) with comparable baseline characteristics (Table 2). No significant differences were found between the two sets in most variables. These similarities suggest that the training and testing sets were well-balanced, ensuring the reliability of the subsequent predictive model.

Table 2 The Baseline Characteristics of the Training and Testing Set

Variables	Total N=12917	Testing N=3876	Training N=9041	p
Sex				0.701
Female	5038 (39.0%)	1522 (39.3%)	3516 (38.9%)	
Male	7879 (61.0%)	2354 (60.7%)	5525 (61.1%)	
Age (years)	76.0 [70.0;83.0]	76.0 [70.0;83.0]	76.0 [70.0;83.0]	0.412
PLT(10^9/L)	191 [153;237]	189 [152;236]	191 [153;237]	0.271
CRE(μmol/L)	62.0 [51.0;77.0]	62.0 [51.0;78.0]	62.0 [51.0;77.0]	0.419
WBC(10^9/L)	7.5 [5.5;10.7]	7.5 [5.5;10.7]	7.5 [5.5;10.6]	0.977
RBC(10^{12}/L)	4.1 [3.6;4.5]	4.1 [3.6;4.5]	4.1 [3.6;4.5]	0.072
Meropenem, n (%)				0.086
No	12299 (95.2%)	3671 (94.7%)	8628 (95.4%)	
Yes	618 (4.8%)	205 (5.3%)	413 (4.6%)	
Ofloxacin, n (%)				0.486
No	11398 (88.2%)	3408 (87.9%)	7990 (88.4%)	
Yes	1519 (11.8%)	468 (12.1%)	1051 (11.6%)	
Smoke, n (%)				0.683
No	248 (1.9%)	71 (1.8%)	177 (2.0%)	
Yes	12669 (98.1%)	3805 (98.2%)	8864 (98.0%)	
Drink, n (%)				0.683
No	248 (1.9%)	71 (1.8%)	177 (2.0%)	
Yes	12669 (98.1%)	3805 (98.2%)	8864 (98.0%)	
DM, n (%)				0.404
No	10476 (81.1%)	3126 (80.7%)	7350 (81.3%)	
Yes	2441 (18.9%)	750 (19.3%)	1691 (18.7%)	
Hypertension, n (%)				0.354
No	5313 (41.1%)	1570 (40.5%)	3743 (41.4%)	
Yes	7604 (58.9%)	2306 (59.5%)	5298 (58.6%)	
Tumor, n (%)				0.971
No	9289 (71.9%)	2786 (71.9%)	6503 (71.9%)	
Yes	3628 (28.1%)	1090 (28.1%)	2538 (28.1%)	
MI, n (%)				1.000
No	12409 (96.1%)	3724 (96.1%)	8685 (96.1%)	
Yes	508 (3.9%)	152 (3.9%)	356 (3.9%)	
CI, n (%)				0.585
No	9053 (70.1%)	2703 (69.7%)	6350 (70.2%)	
Yes	3864 (29.9%)	1173 (30.3%)	2691 (29.8%)	
Anticoagulants, n (%)				0.785
No	4821 (37.3%)	1454 (37.5%)	3367 (37.2%)	
Yes	8096 (62.7%)	2422 (62.5%)	5674 (62.8%)	

(*Continued*)

Table 2 (Continued).

Variables	Total N=12917	Testing N=3876	Training N=9041	p
RI, n (%)				0.734
No	11457 (88.7%)	3444 (88.9%)	8013 (88.6%)	
Yes	1460 (11.3%)	432 (11.1%)	1028 (11.4%)	
LC, n (%)				0.273
No	12611 (97.6%)	3775 (97.4%)	8836 (97.7%)	
Yes	306 (2.4%)	101 (2.6%)	205 (2.3%)	
AD, n (%)				0.295
No	12549 (97.2%)	3756 (96.9%)	8793 (97.3%)	
Yes	368 (2.8%)	120 (3.1%)	248 (2.7%)	
DUF (n)	1.0 [0.0;3.0]	1.0 [0.0;3.0]	1.0 [0.0;3.0]	0.235
Duration (day)	4.1 [<0.1;6.9]	4.1 [<0.1;6.9]	4.1 [<0.1;6.9]	0.712

Abbreviations: PLT, Platelet count; CRE, Creatinine; WBC, White blood cell count; RBC, Red blood cell count; DM, Diabetes mellitus; MI, Myocardial infarction; CI, Cerebral infarction; RI, Renal insufficiency; LC, Liver cirrhosis; AD, Antifungal drugs; DUF, Daily usage frequency.

Selected Predictors and Construction Model

Through LASSO regression analysis employing tenfold cross-validation under the binomial family specification, eight variables demonstrating optimal predictive utility were retained in the final model using the lambda.1se regularization parameter. The variable selection trajectory (Figure 2A) and cross-validation error profile (Figure 2B) visually elucidate the shrinkage dynamics and stability of this feature refinement process. The final logistic regression model, presented in Figure 2C and Table 3, identified several variables significantly associated with thrombocytopenia. The odds of thrombocytopenia decreased with higher platelet counts (OR=0.982, 95% CI: 0.979–0.983, p<0.001) and red blood cell counts (OR=0.817, 95% CI: 0.726–0.918, p=0.001). Conversely, the use of meropenem (OR=3.14, 95% CI: 2.372–4.126, p<0.001), presence of tumor (OR=1.634, 95% CI: 1.356–1.963, p<0.001), renal insufficiency (OR=2.035, 95% CI: 1.628–2.530, p<0.001), liver cirrhosis (OR=2.942, 95% CI: 2.031–4.200, p<0.001), antifungal drug usage (OR=2.653, 95% CI: 1.810–3.814, p<0.001), and higher daily usage frequency (DUF) (OR=1.163, 95% CI: 1.078–1.254, p<0.001) were associated with increased odds of thrombocytopenia.

Model Visualization

We developed a comprehensive nomogram to predict the risk of thrombocytopenia in a large patient cohort. Figure 3 presents the nomogram, which incorporates significant predictors identified through rigorous statistical analysis. The nomogram incorporates several key predictors that significantly influence the risk of thrombocytopenia, including platelet count (PLT), red blood cell count (RBC), meropenem use, presence of tumor, renal insufficiency (RI), liver cirrhosis (LC), use of antifungal drugs (AD), and daily usage frequency (DUF). Figure 3 visually represents the nomogram, where the sum of points from all predictors is mapped to the total points axis. This total points value then corresponds to the predicted risk of thrombocytopenia on the risk axis. The graphic depiction enables clinicians to quickly assess a patient's risk level by simply summing the points for each relevant predictor. For instance, lower platelet counts and red blood cell counts contribute to higher points, indicating an increased risk of thrombocytopenia. Similarly, the presence of certain conditions like tumors, renal insufficiency, liver cirrhosis, and the use of specific medications such as meropenem and antifungal drugs also contribute points. Finally, the daily usage frequency of medications is taken into account, with higher frequencies associated with a greater risk.

Model Validation

The model demonstrated robust discriminative ability in both the training and validation cohorts. In the training cohort, the area under the receiver operating characteristic curve (AUC) was 0.803 (95% CI: 0.784–0.821), indicating strong

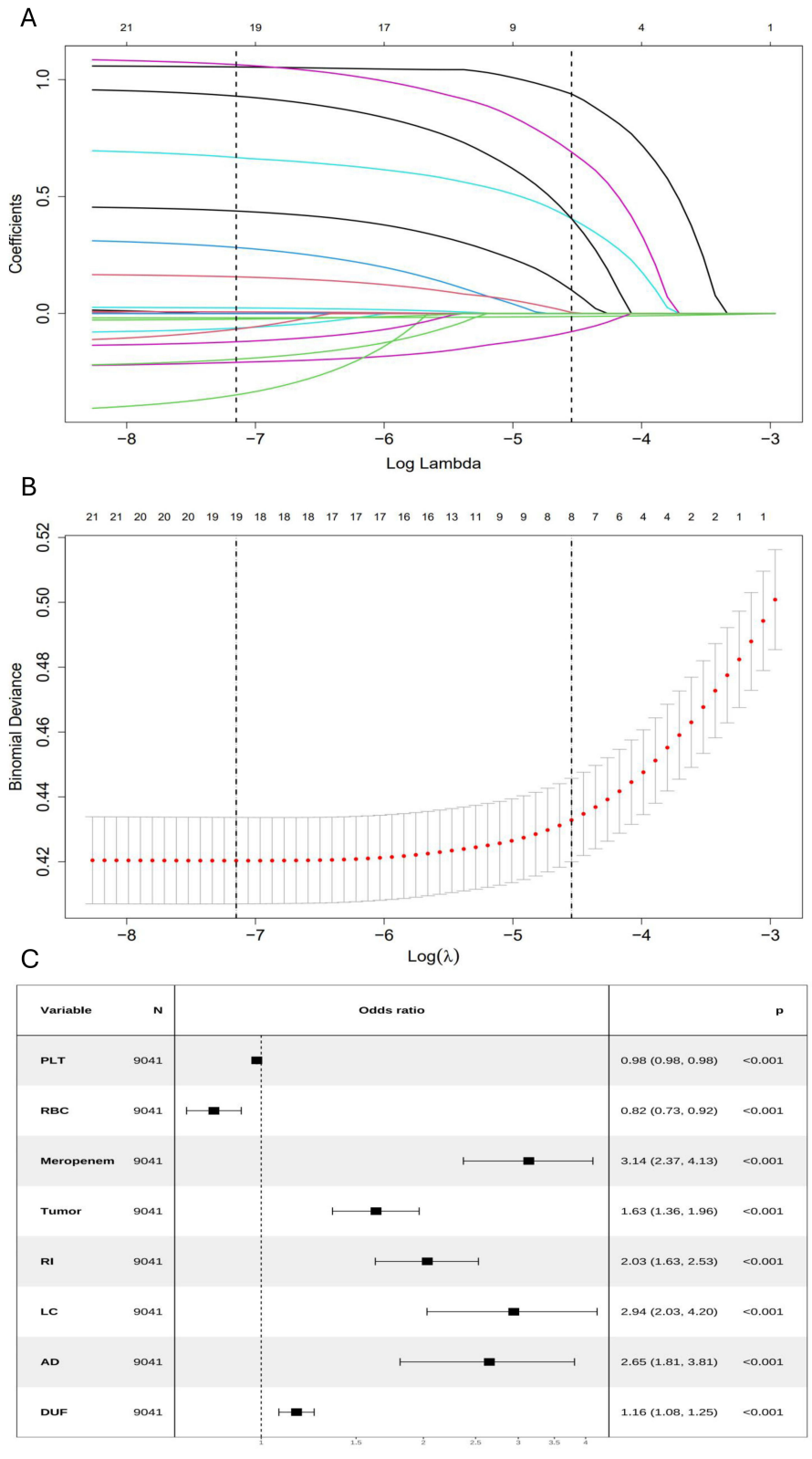

Figure 2 Variable selection was performed using LASSO and logistic regression. (**A**) Coefficient profiles plotted against log(lambda), showing variable selection (nonzero coefficients) and optimal lambda. (**B**) Optimal lambda (lambda.1se) selected via the 1-SE rule, marked by vertical dashed lines. (**C**) Forest plot.
Abbreviations: PLT, platelet count; RBC, Red blood cell count; RI, renal insufficiency; LC, liver cirrhosis; AD, Antifungal drugs; DUF, Daily usage frequency.

Table 3 Final Model Coefficients

Characteristics	B	SE	OR	CI	p
(Intercept)	0.771	0.29402	2.162	2.161 (1.213–3.843)	0.009
PLT(10^9/L)	−0.019	0.00108	0.982	0.981 (0.979–0.983)	<0.001
RBC(10^{12}/L)	−0.202	0.05964	0.817	0.816 (0.726–0.918)	0.001
Meropenem	1.144	0.14102	3.14	3.139 (2.372–4.126)	<0.001
Tumor	0.491	0.09444	1.634	1.633 (1.356–1.963)	<0.001
RI	0.71	0.11231	2.035	2.034 (1.628–2.530)	<0.001
LC	1.079	0.18504	2.942	2.942 (2.031–4.200)	<0.001
AD	0.976	0.18975	2.653	2.652 (1.810–3.814)	<0.001
DUF	0.151	0.03841	1.163	1.163 (1.078–1.254)	<0.001

Abbreviations: PLT, Platelet count; RBC, Red blood cell count; RI, Renal insufficiency; LC, Liver cirrhosis; AD, Antifungal drugs; DUF, Daily usage frequency.

separation between positive and negative cases (Figure 4A). The validation cohort exhibited comparable performance, with an AUC of 0.797 (95% CI: 0.769–0.825) (Figure 4B). Calibration analysis revealed strong agreement between predicted probabilities and observed outcomes. In the training cohort, the Brier score was 0.057, reflecting high accuracy of probabilistic predictions (Figure 4C). In the validation cohort, the calibration slope (0.989) and intercept (0.032) further supported excellent alignment with the ideal line, indicating minimal overfitting or underfitting (Figure 4D).

The decision curve analysis (DCA) demonstrated robust clinical utility of the predictive model across both the training and validation cohorts. In the training cohort, the net benefit of the model surpassed the "treat all" and "treat none" strategies across a wide range of threshold probabilities (Figure 5A). Similar results were observed in the validation cohort (Figure 5B). The cross-validated DCA curve in the validation set closely aligned with the apparent curve from the training set, indicating minimal overfitting and generalizability of the model. The clinical impact curves (CIC) illustrated the model's ability to

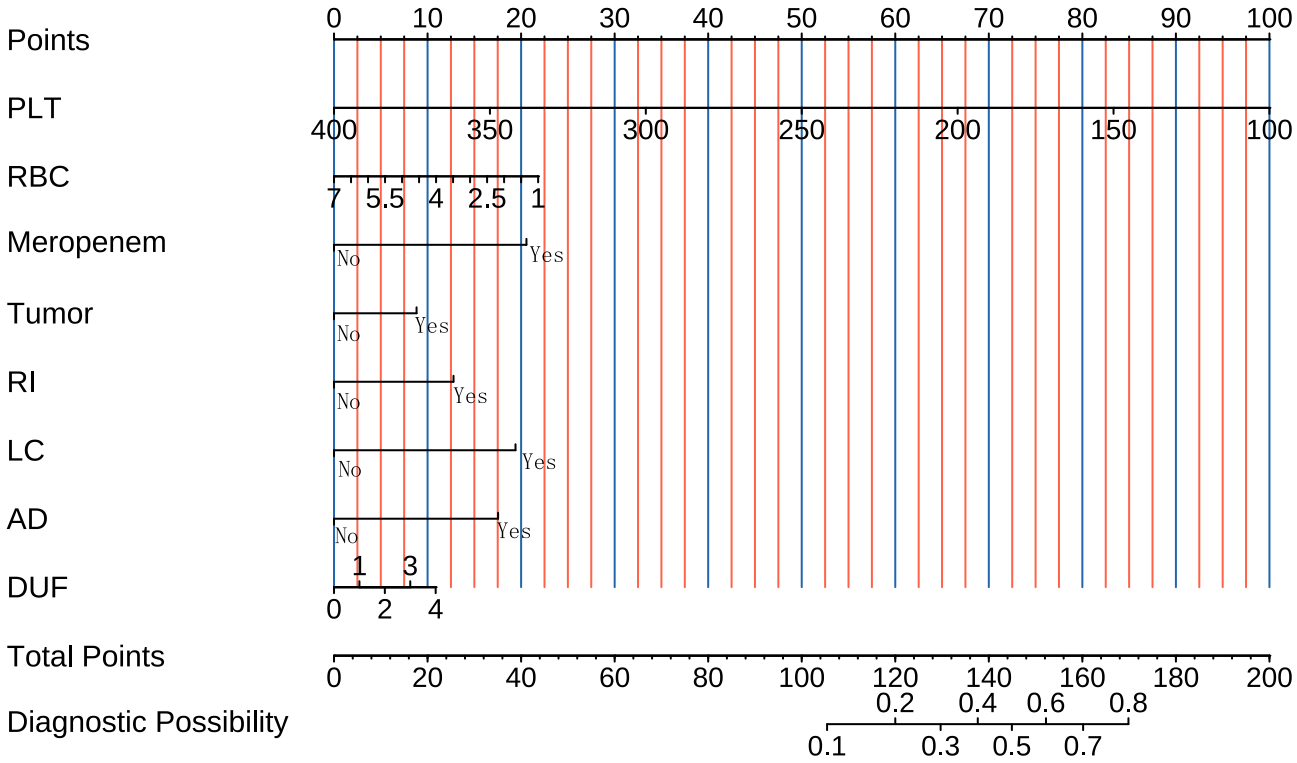

Figure 3 Nomogram for predicting thrombocytopenia.
Abbreviations: PLT, platelet count; RBC, Red blood cell count; RI, renal insufficiency; LC, liver cirrhosis; AD, Antifungal drugs; DUF, Daily usage frequency.

https://doi.org/10.2147/RMHP.S529488

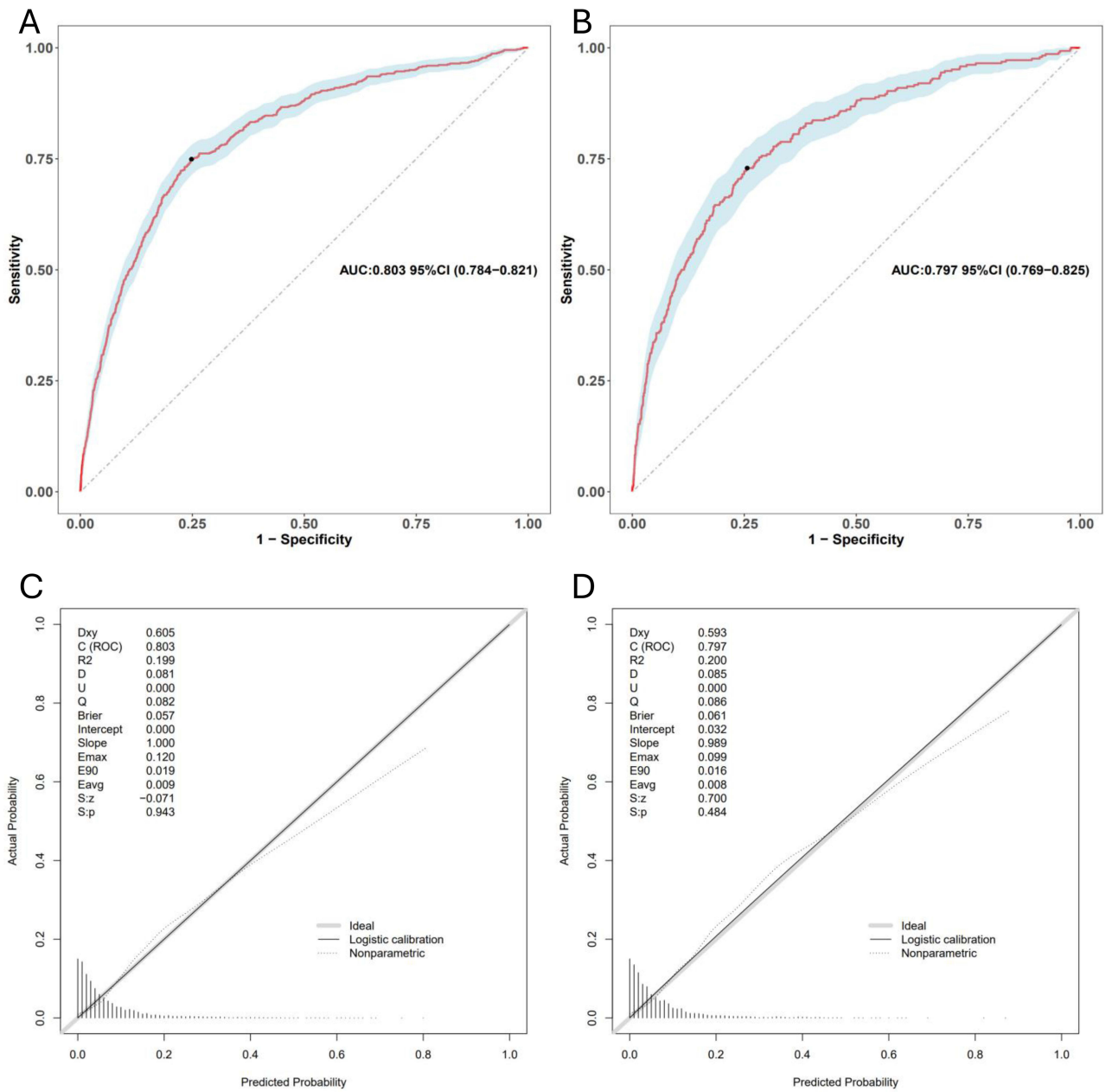

Figure 4 Receiver operating characteristic (ROC) curves and Calibration curves of the nomogram. (**A** and **B**) ROC curves for model performance in the training (**A**) and validation (**B**) sets. (**C** and **D**) Calibration curves comparing predicted bleeding risk (x-axis) with observed frequency (y-axis) in the training (**C**) and validation (**D**) sets. The gray dashed line (model performance) and black solid line (ideal prediction) indicate calibration accuracy.

stratify patients into risk groups that correlated strongly with observed outcomes. In the training cohort, the predicted number of high-risk patients closely matched the actual number of patients experiencing the event across threshold probabilities (Figure 5C). This alignment persisted in the validation cohort (Figure 5D), with overlapping curves confirming the model's reliability in identifying patients most likely to benefit from interventions. The net reduction curves (NRC) quantified the model's capacity to reduce unnecessary interventions while maintaining clinical effectiveness. In the training cohort, the model achieved a net reduction of 38 interventions per 100 patients at 0.1 threshold probability (Figure 5E). This reduction remained consistent in the validation cohort (35 interventions per 100 patients at the same threshold; Figure 5F), demonstrating its stability across datasets. The NRC further highlighted that the model's benefit-to-harm ratio remained favorable even

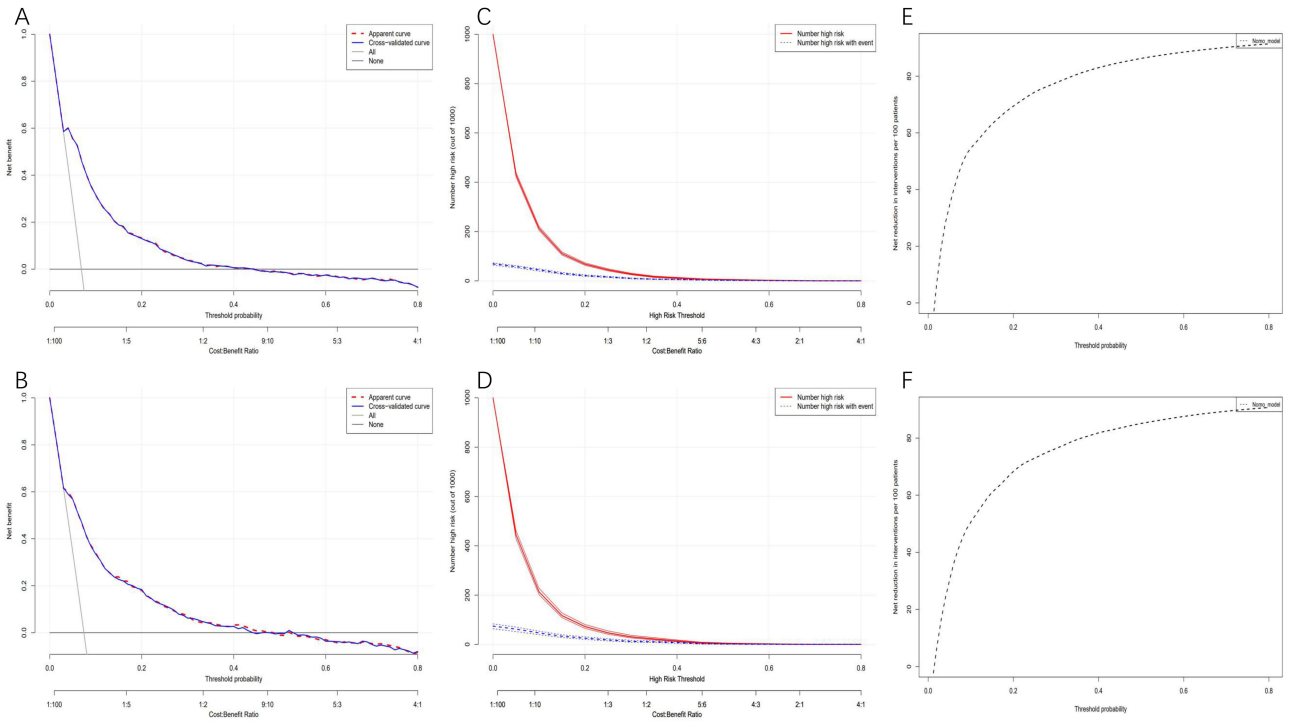

Figure 5 Clinical utility evaluation of the nomogram. (**A** and **B**) Decision curve analysis (DCA) in training (**A**) and validation (**B**) sets. Y-axis: net benefit; horizontal lines indicate "None" (treat no patients) and "All" (treat all) strategies; red curve: model performance. (**C** and **D**) Clinical impact curves (CIC) showing high-risk classified patients (red) versus true positives (blue) across threshold probabilities, in the training (**C**) and validation (**D**) sets. (**E** and **F**) Net reduction curves (NRC) quantifying reducible cases under varying diagnostic thresholds (x-axis), in the training (**E**) and validation (**F**) sets.

under stricter cost assumptions, supporting its applicability in resource-constrained settings. Across all analyses, the model exhibited comparable performance between the training and validation cohorts.

Model Comparison with a Single Indicator

The nomogram model demonstrated superior predictive accuracy compared to individual clinical or laboratory indicators, as illustrated in Figure 6. The nomogram achieved a significantly higher area under the receiver operating characteristic curve (AUC) of 0.803 compared to single indicators, such as PLT, RBC, and RI ($p < 0.001$ for all comparisons via DeLong's test).

Discussion

In this study, we developed and validated a logistic regression model incorporating eight predictors to evaluate the risk of TCP during cephalosporin therapy. Our model exhibited robust discriminative power (AUC: 0.80 training, 0.797 validation) and calibration accuracy (Brier score: 0.057). The clinically interpretable nomogram translates these predictors into actionable risk stratification, enabling individualized assessment of thrombocytopenia risk.

In the elderly, risk factors for thrombocytopenia after the use of third-generation cephalosporins may be associated with multiple factors. Baseline platelet count and red blood cell count are important predictive indicators. Postoperative thrombocytopenia is a common complication following cardiac surgery, especially in the elderly. This condition may be related to several variables before and during surgery, such as preoperative platelet count, and red blood cell transfusion.[21] Our findings align with and extend prior research on cephalosporin-associated thrombocytopenia in elderly populations. Cancer patients may experience an increased risk of thrombocytopenia due to their pathological state and drug interactions during treatment.[22] Liver cirrhosis patients, with impaired liver function, may have abnormal drug metabolism, increasing the incidence of drug-related adverse reactions, including thrombocytopenia.[23] Renal insufficiency is also a significant risk factor, as decreased kidney function can affect drug clearance, leading to accumulation in

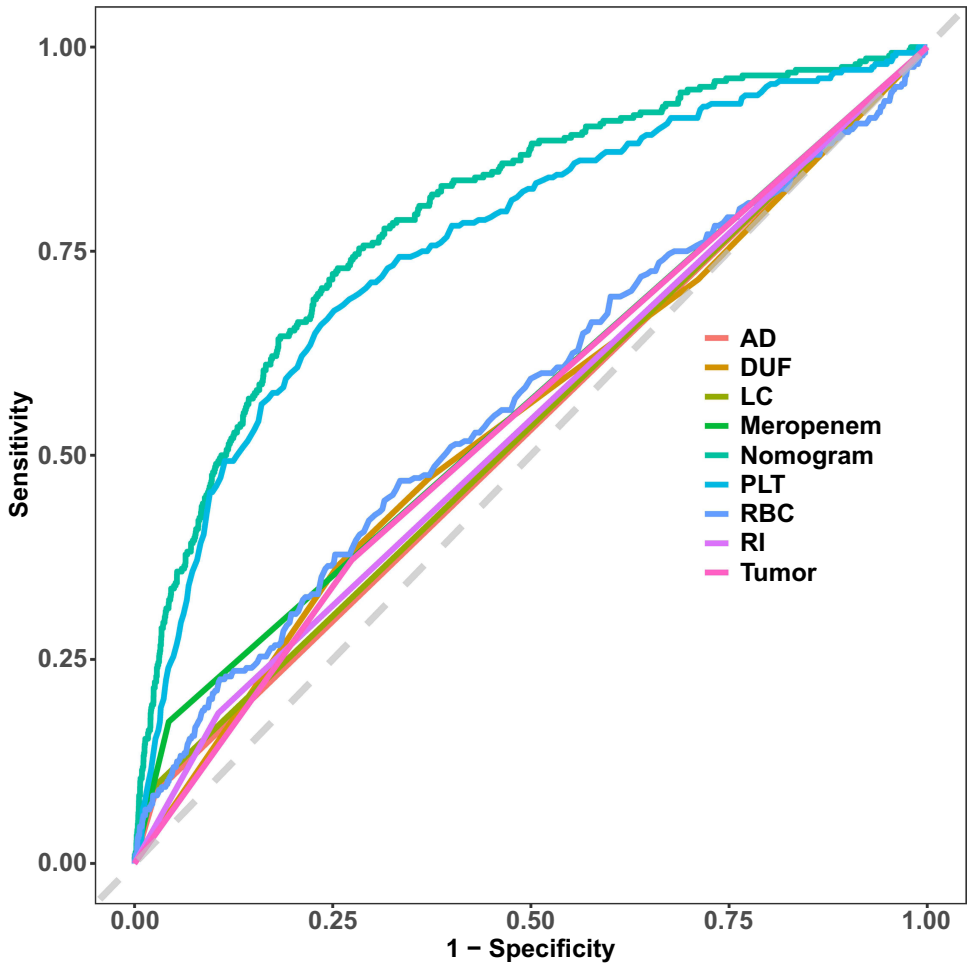

Figure 6 Comparison between the nomogram and individual indicators.
Abbreviations: PLT, platelet count; RBC, Red blood cell count; RI, renal insufficiency; LC, liver cirrhosis; AD, Antifungal drugs; DUF, Daily usage frequency.

the body and thus increasing the risk of adverse reactions.[24] Echoing prior evidence, our analysis confirmed cancer, liver cirrhosis, and renal insufficiency as pivotal risk predictors, highlighting the contribution of chronic disease burden to hematotoxicity through diminished physiological reserve and impaired drug clearance pathways.

Studies have shown that drug interactions and underlying health conditions in patients may increase this risk. Use of meropenem may be associated with thrombocytopenia. Meropenem is a broad-spectrum antibiotic commonly used to treat severe bacterial infections. However, studies have reported that meropenem can lead to hematological abnormalities such as thrombocytopenia.[25,26] In elderly patients, due to decreased metabolic function, particular attention should be paid to monitoring platelet levels when using meropenem. Antifungal drugs may also increase the risk of thrombocytopenia. Especially when antifungal drugs are used in combination with other medications, drug interactions can occur, affecting platelet production or survival.[27] Elderly patients should pay special attention to the combination of meropenem and antifungal drugs when using third-generation cephalosporins. The interactions between these drugs may increase the risk of thrombocytopenia, so monitoring and management should be strengthened during treatment to ensure patient safety. It has also been found in our research to be the important influencing factor. According to a previous study, the use of cefoperazone/sulbactam has been associated with an increased incidence of thrombocytopenia.[8] Researchers analyzed 6489 adult patients treated with cefoperazone/sulbactam and found that 2.4% of patients developed thrombocytopenia. Further multivariate analysis revealed that factors such as treatment duration exceeding 14 days, daily dose greater than or equal to 6 grams, and the use of non-invasive ventilators were risk factors for thrombocytopenia.[8] This may be attributed to the fact that in our model, daily usage frequency serves as a crucial indicator.

Our study advances cephalosporin safety monitoring by establishing a clinically actionable, geriatric-focused risk prediction tool. By integrating these predictors into an interpretable nomogram, we bridge the gap between population-level risk algorithms and individualized clinical decision-making—enabling real-time risk stratification without delaying empiric therapy. Our work refines two key implications for practice and research. First, it demonstrates that dynamic interactions between antibiotics and comorbidities are quantifiable and should inform antibiotic stewardship protocols. Second, our model's calibration accuracy supports its utility in geriatric pharmacovigilance, where polypharmacy and physiological heterogeneity often confound toxicity prediction.

While our model demonstrates robust predictive performance, its generalizability may be constrained by the single-center retrospective design and unmeasured confounders such as genetic predispositions or dynamic platelet trends. The proposed risk threshold, though clinically actionable, requires prospective validation to assess its impact on stewardship adherence and patient outcomes. Furthermore, gaps in documenting real-time dose changes and concurrent interventions during therapy necessitate integrating continuous data streams into clinical monitoring systems. Future studies should validate externally through multicenter cohorts to establish clinical utility, mechanistic exploration of predictor-biomarker relationships, and implementation frameworks that couple risk stratification with serial platelet monitoring to optimize cephalosporin safety in aging populations.

Conclusion

Our study establishes a validated logistic regression model integrating modifiable and non-modifiable predictors to stratify cephalosporin-associated thrombocytopenia risk in older adults. By enabling pre-symptomatic risk identification, the nomogram empowers clinicians to initiate preventive monitoring before hematologic decompensation, thereby reducing bleeding-related hospitalizations. Future implementation requires external validation, mechanistic studies on drug-comorbidity interplay, to balance cephalosporin efficacy with geriatric safety priorities.

Data Sharing Statement

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the Affiliated Dongyang Hospital of Wenzhou Medical University.

Ethics Approval

This study received approval from the Medical Ethics Committee of the Affiliated Dongyang Hospital of Wenzhou Medical University (approval #2025-YX-012). Informed consent was waived, and patient records/information were anonymized and deidentified before analysis.

Funding

This research was supported by the Zhejiang Provincial Natural Science Foundation of China under Grant No. LTGY23H200002.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflict of interest.

References

1. Chen Y, Liu H, Li C. Evaluating the clinical effectiveness of third-generation cephalosporins combined with levofloxacin for treating community-acquired pneumonia in elderly patients. *Altern Ther Health Med*. 2024:AT10283.
2. Malviya M, Kale-Pradhan P, Coyle M, Giuliano C, Johnson LB. Clinical and drug resistance characteristics of providencia infections. *Microorganisms*. 2024;12(10):2085. doi:10.3390/microorganisms12102085
3. Williamson DR, Albert M, Heels-Ansdell D, et al. Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. *Chest*. 2013;144(4):1207–1215. doi:10.1378/chest.13-0121

4. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. *Curr Med Chem*. 2010;17(6):571–584. doi:10.2174/092986710790416326
5. Cusack BJ. Pharmacokinetics in older persons. *Am J Geriatr Pharmacother*. 2004;2(4):274–302. doi:10.1016/j.amjopharm.2004.12.005
6. Bathini L, Jandoc R, Kuwornu P, et al. Clinical outcomes of failing to dose-reduce cephalosporin antibiotics in older adults with CKD. *Clin J Am Soc Nephrol*. 2019;14(2):197–205. doi:10.2215/cjn.10710918
7. Zhao X, Peng Q, Hu D, et al. Prediction of risk factors for linezolid-induced thrombocytopenia based on neural network model. *Front Pharmacol*. 2024;15:1292828. doi:10.3389/fphar.2024.1292828
8. Zhu B, Jin P, Li J, Zhu Y. Retrospective analysis of risk factors for cefoperazone/sulbactam-induced thrombocytopenia in adult Chinese patients: a six-year real-world study. *Infect Drug Resist*. 2024;17:3901–3911. doi:10.2147/idr.S475590
9. Tan SJ, Cockcroft M, Page-Sharp M, et al. Population pharmacokinetic study of ceftriaxone in elderly patients, using cystatin C-based estimates of renal function to account for frailty. *Antimicrob Agents Chemother*. 2020;64(10). doi:10.1128/aac.00874-20
10. Fu A, Ge F, Wang Y, et al. Development and internal validation of a model for predicting cefoperazone/sulbactam-associated coagulation disorders in Chinese inpatients. *BMC Pharmacol Toxicol*. 2024;25(1):41. doi:10.1186/s40360-024-00761-7
11. Qin Y, Chen Z, Gao S, Shen Y, Ye Y. Development and validation of a risk prediction model for linezolid-induced thrombocytopenia in elderly patients. *Eur J Hosp Pharm*. 2024;31(2):94–100. doi:10.1136/ejhpharm-2022-003258
12. Zhou S, Song B, Li C, et al. The predictive model for risk of chemotherapy-induced thrombocytopenia based on antineoplastic drugs for solid tumors in eastern China. *Sci Rep*. 2023;13(1):3185. doi:10.1038/s41598-023-27824-9
13. Zhong K, Pei Y, Yang Z, Zheng Q. Construction of a clinical prediction model for the diagnosis of immune thrombocytopenia based on clinical laboratory parameters. *J Cancer Res Clin Oncol*. 2024;150(9):412. doi:10.1007/s00432-024-05914-z
14. Maray I, Rodríguez-Ferreras A, Álvarez-Asteinza C, Alaguero-Calero M, Valledor P, Fernández J. Linezolid induced thrombocytopenia in critically ill patients: risk factors and development of a machine learning-based prediction model. *J Infect Chemother*. 2022;28(9):1249–1254. doi:10.1016/j.jiac.2022.05.004
15. Chen C, Guo DH, Cao X, et al. Risk factors for thrombocytopenia in adult Chinese patients receiving linezolid therapy. *Curr Ther Res Clin Exp*. 2012;73(6):195–206. doi:10.1016/j.curtheres.2012.07.002
16. Jing J, Wanling L, Maofeng W. A practical nomogram for predicting the bleeding risk in patients with a history of myocardial infarction treating with aspirin. *Clin Appl Thromb Hemost*. 2024;30:10760296241262789. doi:10.1177/10760296241262789
17. Jianling Q, Lulu J, Liuyi Q, et al. A nomogram for predicting the risk of pulmonary embolism in neurology department suspected PE patients: a 10-year retrospective analysis. *Front Neurol*. 2023;14:1139598. doi:10.3389/fneur.2023.1139598
18. Liang C, Wanling L, Maofeng W. LASSO-derived model for the prediction of bleeding in aspirin users. *Sci Rep*. 2024;14(1):12507. doi:10.1038/s41598-024-63437-6
19. Chen T, Lei W, Wang M. Predictive model of internal bleeding in elderly aspirin users using XGBoost machine learning. *Risk Manag Healthc Policy*. 2024;17:2255–2269. doi:10.2147/rmhp.S478826
20. Qian Y, Wanlin L, Maofeng W. Machine learning derived model for the prediction of bleeding in dual antiplatelet therapy patients. *Front Cardiovasc Med*. 2024;11:1402672. doi:10.3389/fcvm.2024.1402672
21. Zhao H, Zhang W, Liu Y, Peng W. Risk factors and prediction model for thrombocytopenia following coronary artery bypass graft surgery in elderly Chinese population. *J Thorac Dis*. 2024;16(1):273–284. doi:10.21037/jtd-23-1396
22. Thabit AK, Alghamdi AA, Alsaeed AK, et al. Linezolid-associated thrombocytopenia: assessment of risk factors in patients without hemato-oncologic diseases. *J Clin Med*. 2024;13(8):2380. doi:10.3390/jcm13082380
23. Huang CE, Chang JJ, Wu YY, et al. Different impacts of common risk factors associated with thrombocytopenia in patients with hepatitis B virus and hepatitis C virus infection. *Biomed J*. 2022;45(5):788–797. doi:10.1016/j.bj.2021.09.001
24. Huang Z, Liu Z, Zhuo L, et al. Risk factors for renal insufficiency and survival implications after radical nephrectomy and thrombectomy in renal cell carcinoma with tumor thrombus: a systematic review. *BMC Urol*. 2025;25(1):20. doi:10.1186/s12894-024-01664-9
25. Hussain K, Salat MS, Mohammad N, et al. Meropenem-induced pancytopenia in a preterm neonate: a case report. *J Med Case Rep*. 2021;15(1):25. doi:10.1186/s13256-020-02632-1
26. Cachia J, Torpiano P, Pace D. Meropenem-induced thrombocytopenia: a paediatric case. *BMJ Case Rep*. 2021;14(9):e243443. doi:10.1136/bcr-2021-243443
27. Kaya Kılıç E, Bulut C, Sönmezer M, et al. Risk factors for linezolid-associated thrombocytopenia and negative effect of carbapenem combination. *J Infect Dev Ctries*. 2019;13(10):886–891. doi:10.3855/jidc.10859