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ORIGINAL RESEARCH

Construction and Validation of a Nomogram Prediction Model for the Risk of Cefoperazone Sodium/Sulbactam Sodium-Related Coagulation Disorders

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Objective: To construct and validate a nomogram prediction model for the risk of cefoperazone sodium/sulbactam sodium (CPZ/SAM)-related coagulation disorders in hospitalized patients.

Methods: Patients treated with CPZ/SAM from January 2022 to December 2024 were enrolled and divided into a coagulation disorder group and a control group based on the occurrence of coagulation disorders. Clinical data were collected to identify risk factors and construct a nomogram model, which was validated using the Hosmer-Lemeshow goodness-of-fit test, receiver operating characteristic (ROC) curve, decision curve analysis (DCA), and clinical impact curve.

Results: A total of 439 patients were included, with 86 cases (19.59%) in the coagulation disorder group and 353 cases in the control group. Multivariate analysis identified malnutrition, recent bleeding history, prolonged treatment duration with CPZ/SAM, combination use with carbapenems, and elevated serum creatinine as independent risk factors. The constructed nomogram had an AUC of 0.845, demonstrating good calibration ability (χ^2=2.312, P=0.891), providing moderate net benefit in predicting the incidence of coagulation disorders, with consistent agreement between predicted and actual probabilities.

Conclusion: The nomogram model effectively identifies high-risk patients, indicating that attention should be paid to the risk of coagulation disorders in patients with the above risk factors during CPZ/SAM treatment.

Keywords: cefoperazone sodium/sulbactam sodium, coagulation disorders, predictive model, nomogram, antimicrobial stewardship

Introduction

Cefoperazone sodium/sulbactam sodium (CPZ/SAM), a broad-spectrum β-lactam/β-lactamase inhibitor combination, is extensively utilized for moderate to severe infections primarily caused by Gram-negative bacteria, such as intra-abdominal, pulmonary, and bloodstream infections.[1] Its bactericidal action stems from cefoperazone's inhibition of bacterial cell wall synthesis, complemented by sulbactam's protection against β-lactamase degradation, ensuring robust antimicrobial activity and tissue penetration.[2] A significant adverse reaction associated with CPZ/SAM is vitamin K-dependent coagulation disorder, potentially leading to prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT). In severe instances, this can manifest as gastrointestinal bleeding, epistaxis, or even intracranial hemorrhage, thereby elevating patient mortality risk.[3,4] The proposed mechanism involves the N-methylthiotetrazole (NMTT) side chain in cefoperazone, which inhibits vitamin K epoxide reductase. This inhibition curtails the synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X, consequently inducing coagulation dysfunction.[5]

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Although vitamin K supplementation can effectively prevent such adverse reactions, blind prophylactic use may lead to waste of medical resources and increased risk of allergies, making accurate identification of high-risk patients crucial.[6] While previous studies have explored associations between individual risk factors such as malnutrition, hepatic or renal dysfunction, and treatment duration with coagulation disorders,[7,8] there is a paucity of comprehensive, multi-factorial prediction models specifically designed for CPZ/SAM. Nomograms, as visual and quantitative tools, can integrate multiple independent risk factors to predict an individual's probability of an event, offering significant practical value in clinical decision-making.[9] This study, therefore, aims to develop and validate such a nomogram, providing a more robust and clinically applicable tool for early risk stratification than single-factor analyses or general alerts.

This study was aimed to screen independent risk factors through multivariate analysis and construct and validate a nomogram model to provide a basis for early clinical intervention. The study adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines,[10] ensures data homogeneity through strict inclusion and exclusion criteria, and uses multiple statistical methods to evaluate model performance, including ROC curve, calibration curve, and DCA, to comprehensively validate the predictive efficacy and clinical practicability of the model.

Materials and Methods

General Data

Hospitalized patients treated with cefoperazone sodium/sulbactam sodium from January 2022 to December 2024 were enrolled. Inclusion criteria: ① aged > 18 years; ② received cefoperazone sodium/sulbactam sodium treatment; ③ complete clinical data; ④ signed informed consent. Exclusion criteria: ① treatment duration with cefoperazone sodium/sulbactam sodium < 2 days; ② severe comorbidities including advanced liver disease, hematological malignancies, sepsis, severe trauma, or disseminated intravascular coagulation; ③ concurrent use of heparin or oral anticoagulants; ④ allergy to related medications. The study was approved by the hospital ethics committee.

Methods

Data Collection

Patient data were collected via the hospital information system and active adverse drug event monitoring. Coagulation disorder was defined as an increase > 25% in prothrombin time (PT), activated partial thromboplastin time (APTT), or thrombin time (TT) compared to baseline values, a threshold consistent with that used in other studies assessing drug-induced coagulopathy to identify clinically relevant changes[11] The Naranjo Adverse Drug Reaction Probability Scale[12] was used for assessment, with scores ≥ 9 indicating "definite", 5–8 "probable", 1–4 "possible", and < 1 "doubtful"; scores ≥ 1 were defined as cefoperazone sodium/sulbactam sodium-related coagulation disorders. Patients were divided into a coagulation disorder group and a control group based on the occurrence of coagulation disorders.

Based on previous studies,[13–16] initial predictive factors potentially associated with coagulation disorders were classified into five categories: ① comorbidities such as malnutrition, hypoalbuminemia, and chronic kidney disease; ② recent surgical history or bleeding events; ③ duration and daily dose of cefoperazone sodium/sulbactam sodium treatment; ④ concomitant use of other antimicrobial agents that may interfere with coagulation, including tigecycline, carbapenems, vancomycin, and linezolid; ⑤ baseline laboratory data from the most recent blood tests within 14 days before cefoperazone sodium/sulbactam sodium administration, including liver function indices [alanine transaminase (ALT), aspartate transaminase (AST), albumin (ALB), total bilirubin (TBil)], serum creatinine (SCr), hemoglobin (Hb), platelet (PLT), and coagulation indices [fibrinogen (FIB), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT)]—a total of 23 indicators. The geriatric nutritional risk index (GNRI) was calculated using height, body weight, and ALB [GNRI = 1.489 × ALB + 41.7 × (body weight/ideal body weight), where ideal body weight = 22 × height² (m^2)], with GNRI ≤ 91.2 defined as malnutrition, hypoalbuminemia defined as ALB < 35 g/L, and chronic kidney disease determined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[17]

Statistical Analysis

Statistical analyses were performed using SPSS 27.0 and R 4.2.1. Normality of continuous data was assessed using the Shapiro–Wilk test. Normally distributed continuous data were presented as mean ± standard deviation and compared using

independent samples *t*-test. Non-normally distributed data were presented as median (interquartile range) and compared using the Mann–Whitney *U*-test. Categorical data were presented as counts (%) and compared using chi-square test or Fisher's exact test. Variables with $P < 0.05$ in univariate analysis were included in a multivariate logistic regression model (forward stepwise method) to identify independent risk factors. A nomogram was constructed based on regression coefficients, with internal validation performed via 1000 bootstrap resamples to assess the stability and optimism-corrected performance of the nomogram, particularly for the AUC and calibration accuracy. Model evaluation included: ① Discriminative ability: receiver operating characteristic (ROC) curve and area under the curve (AUC); ② Calibration: Hosmer-Lemeshow goodness-of-fit test (H-L test) and calibration curve to assess agreement between predicted and observed probabilities; ③ Clinical utility: decision curve analysis (DCA) to calculate net benefit at different threshold probabilities and clinical impact curve to evaluate predictive performance in 1000 patients. Statistical significance was set at $\alpha = 0.05$ (two-tailed).

Results

Univariate Analysis

Initially, 600 patients treated with CPZ/SAM were screened. After applying inclusion and exclusion criteria, a total of 439 patients were included, with 86 cases (19.59%) in the coagulation disorder group and 353 cases in the control group. Details of patient selection and baseline characteristics of included versus excluded patients are provided in Supplementary Table 1. Univariate analysis showed that the coagulation disorder group had significantly higher proportions of malnutrition, chronic kidney disease, recent bleeding history, prolonged CPZ/SAM treatment duration, carbapenem combination, and higher levels of serum creatinine (SCr) and activated partial thromboplastin time (APTT), while albumin (ALB) and hemoglobin (Hb) levels were significantly lower than those in the control group ($P<0.05$). There were no significant differences in age, gender, length of hospital stay, hypoalbuminemia, recent surgery, concomitant use of tigecycline/vancomycin/linezolid, or other laboratory indices (ALT, AST, TBil, PLT, FIB, PT, TT) between the two groups ($P>0.05$, Table 1).

Multivariate Logistic Regression Analysis

Variables with $P<0.05$ in univariate analysis (malnutrition, chronic kidney disease, recent bleeding history, treatment duration, carbapenem combination, SCr, ALB, Hb, APTT) were included in the multivariate model. Forward stepwise selection identified five independent risk factors: malnutrition (OR=2.856, 95% CI:1.823–5.892, $P<0.001$), recent

Table 1 Univariate Analysis of Coagulation Disorders in Patients Treated with CPZ/SAM

Variable	Coagulation Disorder Group (n=86)	Control Group (n=353)	t/χ^2 Value	P value
Age (years)	55.59±22.28	54.78±21.89	0.212	0.832
Gender [n(%)]			0.061	0.805
- Male	49 (56.98)	212 (59.99)		
- Female	37 (43.02)	141 (40.01)		
Length of Hospital Stay (d)	10.62±4.28	11.08±4.95	0.687	0.492
Comorbidities [n(%)]				
- Malnutrition	32 (37.21)	62 (17.56)	7.210	0.007
- Hypoalbuminemia	17 (19.77)	48 (13.60)	0.892	0.345
- Chronic Kidney Disease	16 (18.60)	17 (4.82)	6.750	0.009
Medical History [n(%)]				
- Recent Surgery	20 (23.26)	72 (20.40)	0.175	0.676
- Recent Bleeding History	37 (43.02)	89 (25.21)	6.050	0.014
Medication Regimen				
- Treatment Duration (d)	9.51±3.08	7.09±2.31	5.300	<0.001
- Daily Dose (g)	3.23±0.85	3.14±0.92	0.389	0.697

(*Continued*)

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Table 1 (Continued).

Variable	Coagulation Disorder Group (n=86)	Control Group (n=353)	t/χ^2 Value	P value
Concomitant Medications [n(%)]				
- Tigecycline	6 (6.98)	13 (3.68)	0.301	0.583
- Carbapenems	10 (11.63)	7 (1.98)	6.650	0.009
- Vancomycin	3 (3.49)	17 (4.82)	0.078	0.780
- Linezolid	3 (3.49)	7 (1.98)	0.518	0.472
Laboratory Parameters				
- ALB (g/L)	35.69±5.71	39.08±5.37	3.650	<0.001
- SCr (μmol/L)	88.57±15.59	69.89±14.27	7.500	<0.001
- Hb (g/L)	110.52±15.28	127.76±14.91	6.750	<0.001
- APTT (s)	37.82±5.62	30.09±3.41	10.500	<0.001

Abbreviations: ALB, denotes albumin; TBil, denotes total bilirubin; SCr, denotes serum creatinine; FIB, denotes fibrinogen; PT, denotes prothrombin time; APTT, denotes activated partial thromboplastin time; TT, denotes thrombin time.

bleeding history (OR=1.978, 95% CI:1.293–4.011, P<0.001), prolonged treatment duration (OR=1.142, 95% CI:1.058–3.398, P<0.001), carbapenem combination (OR=4.521, 95% CI:1.887–10.216, P<0.001), and elevated serum creatinine (OR=1.068, 95% CI:1.001–2.689, P=0.026, Table 2).

Nomogram Construction

A nomogram was developed based on the five independent risk factors (Figure 1). Each variable corresponds to a score axis; patients obtain individual scores for each factor, sum the total score, and map it to the "predicted probability axis" to estimate the risk of coagulation disorder. For example, a patient with malnutrition (60 points), recent bleeding history (50 points), 10 days of treatment (40 points), carbapenem combination (80 points), and SCr 100 μmol/L (30 points) has a total score of 260, corresponding to a predicted probability of ~75%.

Model Validation

Discriminative Ability

The ROC curve showed an AUC of 0.845 (95% CI:0.801–0.889), with a sensitivity of 88.37% and specificity of 78.75% (Figure 2A).

Calibration

The Hosmer-Lemeshow test indicated good agreement between predicted and observed probabilities (χ^2=2.312, P=0.891), and the calibration curve showed close fitting between predicted and actual values (Figure 2B).

Table 2 Multivariate Analysis of Risk Factors for CPZ/SAM-Related Coagulation Disorders

Variable	β	SE	Wald χ^2	OR	95% CI	P value
Malnutrition	0.750	0.258	3.490	2.856	1.823–5.892	<0.001
Recent Bleeding History	0.608	0.239	3.290	1.978	1.293–4.011	<0.001
Prolonged Treatment Duration	0.162	0.073	3.060	1.142	1.058–3.398	<0.001
Carbapenem Combination	1.440	0.476	4.400	4.521	1.887–10.216	<0.001
Elevated Serum Creatinine	0.018	0.006	2.030	1.068	1.001–2.689	0.026

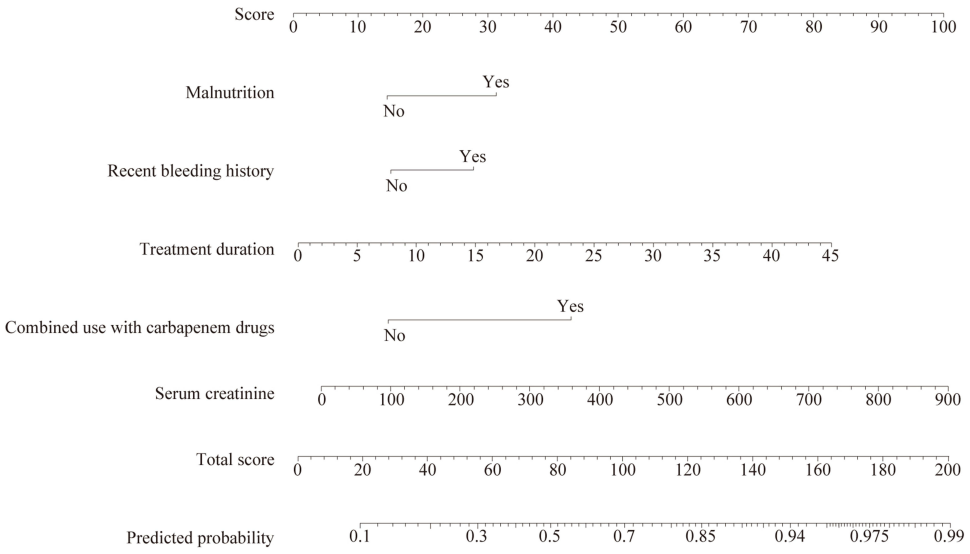

Figure 1 Nomogram for predicting the risk of cefoperazone sodium/sulbactam sodium-related coagulation disorders. Each risk factor corresponds to a score axis. Patients assign scores based on their characteristics (eg, "Malnutrition: Yes" receives the corresponding score), sum the total score, and read the predicted probability of coagulation disorder on the "Predicted Probability" axis.

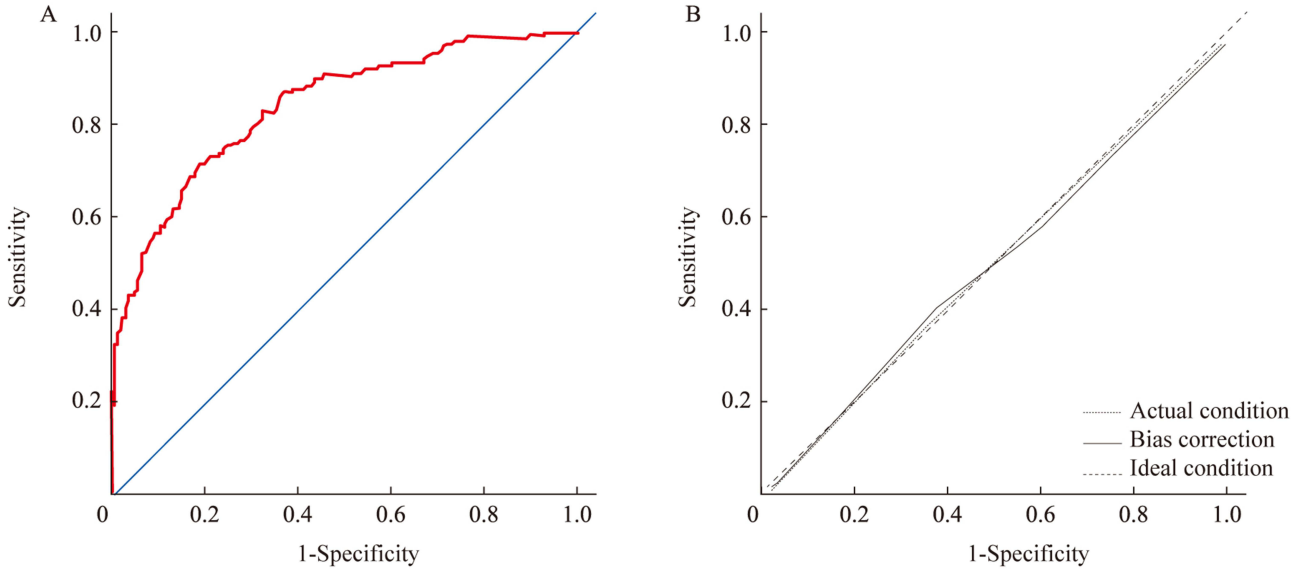

Figure 2 Curves for model predictive performance validation. (**A**) Receiver operating characteristic (ROC) curve, with an area under the curve (AUC) of 0.845, sensitivity of 88.37%, and specificity of 78.75%; (**B**) Calibration curve demonstrating agreement between predicted and observed probabilities, with Hosmer-Lemeshow test result χ^2=2.312, P=0.891.

Clinical Utility

Decision curve analysis (DCA) demonstrated that the nomogram provided moderate net benefit compared to "treat all" or "treat none" strategies across a threshold probability range of 10%-80% (Figure 3A). The clinical impact curve showed high consistency between predicted and actual numbers of coagulation disorders in a 1000-patient cohort (Figure 3B).

Discussion

This study developed a nomogram integrating multidimensional risk factors for predicting CPZ/SAM-related coagulation disorders based on 439 hospitalized patients. The incidence of coagulation disorders was 19.59%, consistent with previous reports (9.2%–20.0%),[18,19] confirming the clinical relevance of this adverse reaction. Five independent risk

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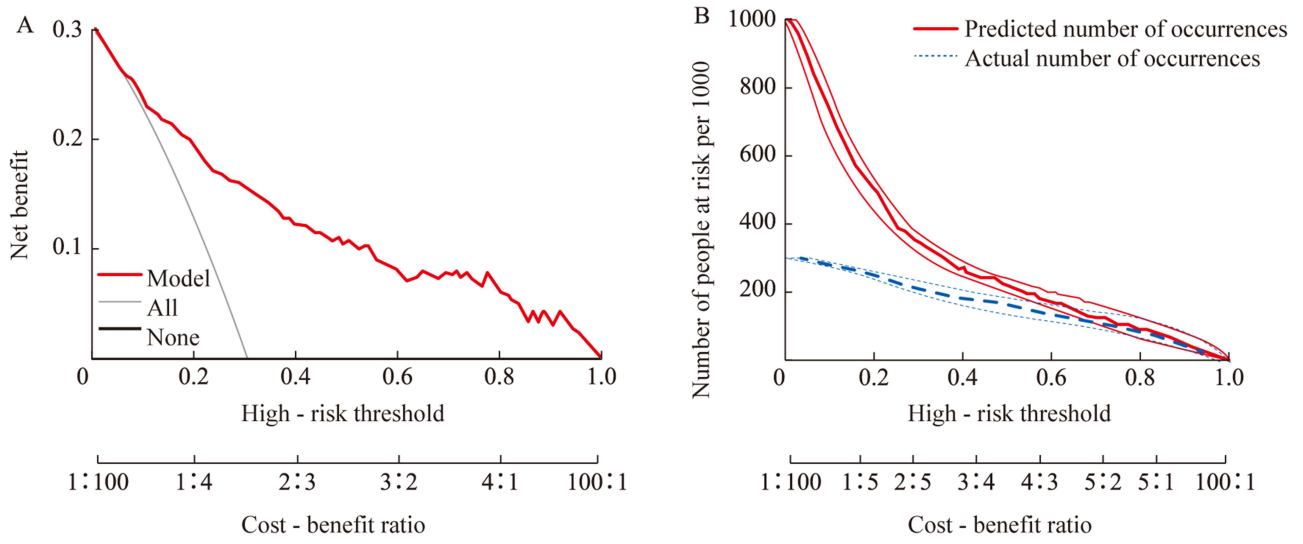

Figure 3 Curves for clinical utility analysis of the model. (**A**) Decision curve analysis (DCA) showing net benefit of the model at different threshold probabilities (gray area indicates threshold ranges where the model's net benefit exceeds "treat all" or "treat none" strategies); (**B**) Clinical impact curve illustrating the agreement between predicted and actual numbers of coagulation disorders in a 1000-patient cohort.

factors were identified: malnutrition, recent bleeding history, prolonged treatment duration, carbapenem combination, and elevated serum creatinine, all closely linked to the pathophysiology of coagulation dysfunction.

The methylthiotetrazole side chain in CPZ/SAM inhibits the synthesis of vitamin K-dependent coagulation factors. Malnourished patients often have insufficient vitamin K reserves or absorption disorders, exacerbating coagulation dysfunction.[20] In this study, malnutrition increased the risk by 2.86-fold (OR=2.856), consistent with Bai et al[21] highlighting the importance of nutritional assessment in identifying high-risk individuals. Recent bleeding history, as an independent risk factor, may indicate underlying coagulation impairment or bleeding tendency, necessitating close monitoring of coagulation indices in such patients.[22]

Prolonged treatment duration was another key risk factor, with a 14.2% increased risk per day of treatment (OR=1.142), consistent with Miao et al[23] who reported a significant risk increase with treatment ≥5 days. Although daily dose was not directly associated with risk, cumulative dose correlates with treatment duration, emphasizing the need to avoid unnecessary prolonged use. Our previous study found that patients with a treatment duration of more than 10 days and a daily dose of more than 6 g were at a high risk of coagulation abnormalities.[24] Carbapenem combination significantly elevated risk (OR=4.521), possibly due to synergistic inhibition of intestinal vitamin K synthesis and exacerbated coagulation impairment from severe infection-related inflammation in patients receiving combination therapy.[25,26] Elevated serum creatinine, reflecting renal dysfunction, may affect drug metabolism and excretion, leading to accumulation and enhanced coagulation inhibition.[27] It is also noteworthy that while chronic kidney disease was significant in univariate analysis, serum creatinine, a more direct measure of renal function, emerged as the independent predictor in the multivariate model, possibly better reflecting the degree of renal impairment relevant to drug accumulation and coagulopathy risk.

The nomogram, with an AUC of 0.845 and excellent calibration, provides a visual tool to quantify risk. Decision curve analysis showed superior net benefit over traditional strategies, indicating good predictive efficacy and clinical utility. Compared with previous single-factor analyses, this multivariable model offers a more comprehensive risk assessment, enabling precise identification of high-risk patients for preventive interventions (eg, vitamin K supplementation or antimicrobial adjustment) to reduce bleeding risk.[21] Recently, Hua et al[11] developed machine learning models to predict coagulation dysfunction associated with various β-lactam antibiotics, including CPZ/SAM, reporting AUCs for CPZ/SAM around 0.768 using approaches like random forest. While machine learning models can capture complex non-linear relationships and potentially offer higher predictive power in certain scenarios, our nomogram based on logistic regression provides a more transparent, interpretable, and easily implementable tool for clinicians at the bedside. The identified risk factors in our study (malnutrition, recent bleeding, treatment duration, carbapenem use, elevated SCr) are readily available clinical parameters,

making the nomogram highly practical. Future research could explore hybrid models or comparative studies to determine the optimal balance between predictive accuracy and clinical interpretability for this specific adverse event.

Limitations include the single-center retrospective design (potential selection bias) and exclusion of patients with severe liver dysfunction, limiting generalizability to specific populations. Furthermore, data on prophylactic vitamin K supplementation, specific types of infections, and detailed bleeding sites were not comprehensively available for all patients, which might influence coagulation status and the model's predictive accuracy. Additionally, unmeasured confounders such as dietary vitamin K intake or variations in hospital protocols for managing mild coagulation changes could have influenced the outcomes. The impact of prophylactic vitamin K use was not analyzed, and future prospective multicenter studies should include variables like vitamin K levels and coagulation factor assays to optimize the model and explore cost-effectiveness of interventions.

Conclusion

In conclusion, the developed nomogram, which integrates five readily accessible clinical risk factors, effectively predicts the risk of CPZ/SAM-related coagulation disorders with good discrimination (AUC 0.845) and calibration. Compared to reliance on single risk factor assessments, this validated multivariable model offers a more precise and individualized quantitative risk estimation, thereby providing a novel and practical tool for antimicrobial stewardship programs to enhance medication safety and guide personalized preventive strategies. Patients with malnutrition, recent bleeding history, prolonged treatment, carbapenem combination, or renal dysfunction require close coagulation monitoring and timely prevention. This model provides a novel tool for antimicrobial stewardship, enhancing medication safety and personalized therapy.

Data Sharing Statement

Data is provided within the manuscript files, further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

The study protocol was approved by The Sixth Hospital of Wuhan (NO.WHSHIRB-K-2025011). The study adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines and performed in accordance with the Helsinki II declaration. Informed consent was obtained from all the study subjects before enrollment.

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Disclosure

The authors declare that they have no competing interests in this work.

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