BMC Infectious Diseases

RESEARCH Open Access

Development and validation of a risk prediction model for tigecycline-induced hypofibrinogenemia in septic patients: a retrospective cohort study

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Abstract

Background Tigecycline is widely used in China to treat multidrug-resistant bacterial infections, with hypofibrinogenemia being the most common adverse effect due to its impact on coagulation. Although a predictive model for tigecycline-induced hypofibrinogenemia has been developed, it lacks external validation. This study aims to construct a predictive model for the risk of tigecycline-induced hypofibrinogenemia in sepsis patients.

Methods This retrospective cohort study analyzed data from sepsis patients treated with tigecycline in the intensive care unit (ICU) of the People's Hospital of Inner Mongolia Autonomous Region between January 2018 and June 2024. Risk factors for tigecycline-induced hypofibrinogenemia were identified through univariate and multivariate logistic regression analyses. A nomogram prediction model was developed and externally validated using the MIMIC-IV database.

Results A total of 465 patients participated, with 411 in the training set and 54 in the external validation set. Independent risk factors for hypofibrinogenemia included age (OR: 1.02, $p=0.009$), duration of tigecycline treatment (OR: 1.33, $p<0.001$), baseline fibrinogen level (OR: 0.65, $p<0.001$), baseline platelet count (OR: 0.99, $p=0.025$), and the presence of tumors (OR: 2.17, $p=0.021$). The model demonstrated an AUC of 0.85 (95% CI: 0.81–0.89) in the training cohort and 0.83 (95% CI: 0.71–0.95) in the validation cohort. Calibration curves for both cohorts showed strong agreement between predicted and observed hypofibrinogenemia. Decision curve analysis (DCA) indicated good clinical applicability of the model.

Conclusion The developed predictive model effectively predicts the risk of tigecycline-induced hypofibrinogenemia in sepsis patients, providing valuable information for clinical decision-making.

Keywords Tigecycline, Fibrinogen, Nomogram

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Introduction

Tigecycline, a broad-spectrum glycylcycline antibiotic structurally related to tetracyclines, inhibits bacterial protein synthesis by binding to the 30 S ribosomal subunit, thus preventing bacterial growth and reproduction. It is indicated for treating complicated intra-abdominal infections, complicated skin and soft tissue infections, and community-acquired pneumonia [1]. Tigecycline exhibits potent activity against Gram-positive cocci, Gram-negative bacilli, and anaerobes, particularly multidrug-resistant pathogens such as methicillin-resistant Staphylococcus aureus, penicillin-resistant Streptococcus pneumoniae, vancomycin-resistant Enterococcus faecium, and multidrug-resistant Acinetobacter baumannii [2, 3].

Despite tigecycline's proven clinical efficacy, its use is associated with adverse effects, including gastrointestinal disturbances, liver dysfunction, and coagulopathy [4]. Cefoperazone/sulbactam sodium, commonly used broad-spectrum antibiotics, carry the risk of coagulation dysfunction. A real-world study demonstrated that cefoperazone/sulbactam sodium may prolong APTT and PT, but it does not significantly affect fibrinogen levels [5]. Tigecycline, on the other hand, exhibits more complex effects on coagulation. Clinical studies [6, 7] have reported coagulation abnormalities in some tigecycline-treated patients, particularly prolonged activated partial thromboplastin time (APTT), prothrombin time (PT), and reduced fibrinogen levels. Notably, several studies [8–10] have highlighted that hypofibrinogenemia is a common manifestation of coagulation dysfunction in these patients.When combined with cefoperazone/sulbactam sodium, tigecycline may independently induce hypofibrinogenemia, although cefoperazone/sulbactam sodium does not significantly increase the incidence of hypofibrinogenemia [8]. A study by You J et al. [11] found that the incidence of tigecycline-induced hypofibrinogenemia in critically ill Chinese ICU patients could reach 59.9%. Sepsis, often accompanied by multiple organ dysfunction, exacerbates the risk of hypofibrinogenemia, which may worsen disease progression, lead to hemorrhagic complications, prolong hospitalization, increase costs, and adversely affect prognosis. Clinicians should closely monitor this risk, particularly in sepsis patients.

Recent studies [8, 9, 11, 12]have identified several risk factors for tigecycline-induced hypofibrinogenemia, including dosage, therapy duration, patient age, baseline fibrinogen levels, and renal failure.however, these findings remain controversial [13–15]. Previous researches [16, 17]to develop predictive models for hypofibrinogenemia risk during tigecycline therapy have been limited by a lack of external validation. Thus, effectively assessing the risk of hypofibrinogenemia in septic patients receiving tigecycline remains a critical challenge. This study aims to develop a risk prediction model for tigecycline-induced hypofibrinogenemia in septic patients, using a retrospective cohort and external validation via the MIMIC-IV database, to enable early identification and intervention for high-risk patients.

Materials and methods

Study design and setting

We developed and validated a nomogram for predicting hypofibrinogenemia in septic patients treated with tigecycline through a retrospective study. Data were collected from patients who received tigecycline between January 2018 and June 2024 at the Intensive Care Unit (ICU) of Inner Mongolia Autonomous Region People's Hospital and from the MIMIC-IV 2.2 database. Eligible patients were aged ≥ 18 years, treated with tigecycline for ≥ 3 days, diagnosed with sepsis (Sepsis 3.0) [18], and had a fibrinogen (FIB) level ≥ 2.0 g/L within 48 h prior to tigecycline initiation. Exclusion criteria included diagnoses of hematological disorders (e.g., leukemia, myelodysplastic syndrome, multiple myeloma, lymphoma) or use of drugs affecting fibrinogen (e.g., human fibrinogen, venom thrombin, pituitrin, alteplase) and incomplete case data. Under normal conditions, fibrinogen levels in human plasma have a half-life of 3–5 days at 2–4 g/L, and hypofibrinogenemia is defined as fibrinogen < 2 g/L. A fibrinogen level < 2 g/L after tigecycline treatment was defined as tigecycline-induced hypofibrinogenemia [19]. The study adhered to the TRIPOD guidelines, and approval was obtained from the Medical Ethics Committee of Inner Mongolia Autonomous Region People's Hospital. Due to the retrospective design, patient consent was waived.

Data collection

Clinical data for the training set were obtained from the electronic medical records of the People's Hospital of Inner Mongolia Autonomous Region. Data from the MIMIC-IV 2.2 database were extracted using structured query language and cleaned with STATA 15.0, serving as the external validation dataset. Clinicopathological data collected for patients treated with tigecycline included sex, age, comorbidities, infection site, and duration of tigecycline therapy(refers to the time from the initiation of tigecycline treatment to the onset of hypofibrinogenemia). Laboratory data included baseline fibrinogen (FIB), total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), Creatinine(CREA), white blood cell count, prothrombin time (PT), activated partial thromboplastin time (APTT), platelet count, and treatment regimen(High-dose tigecycline was defined as 100 mg every 12 h, and standard-dose as 50 mg every 12 h, with an initial loading dose).

The case group was defined as patients with FIB < 2.0 g/L following tigecycline treatment, while the control group consisted of patients who met the inclusion/exclusion criteria but did not develop hypofibrinogenemia. Evaluation of adverse reactions was performed by two senior pharmacists according to the 2005 guidelines of the National Adverse Reaction Monitoring Center [20]. In case of discrepancies, a third senior pharmacist was consulted. A "positive," "likely," or "possible" evaluation indicated tigecycline-induced hypofibrinogenemia.

Nomogram construction

The data extracted from Inner Mongolia Autonomous Region People's Hospital was used as the training set to construct the model.Univariate regression analysis was first performed, and variables with $p < 0.05$ were included in the subsequent multivariable logistic regression analysis. Significant predictors from this analysis were selected as candidate variables for model construction. Logistic regression was used to estimate the odds ratio (OR) for each candidate variable. A nomogram was then created for a more intuitive representation of the results.

Validation of nomograms

The data extracted from the MIMIC-IV 2.2 database was used as the validation set. employing the external validation method.The accuracy of the nomogram predictions was assessed using the concordance index (C-index). A C-index between 0.50 and 0.70 indicates low accuracy, 0.71 to 0.90 suggests moderate accuracy, and a value greater than 0.90 reflects high accuracy. Calibration curves were employed to compare the predicted and actual outcomes. When the HosmerLemeshow goodness-of-fit test $P > 0.05$, the model has good good agreement.Additionally, decision curve analysis (DCA) was used to evaluate the clinical utility of the model.

Statistical analysis

Data were analyzed using R version 4.3.2 and STATA 15.0 (Stata Corporation, College Station, TX, USA). Normally distributed data are presented as mean ± standard deviation (SD), with comparisons between groups made using independent sample t-tests. Non-normally distributed data are presented as median (interquartile range, IQR), with between-group comparisons performed using nonparametric tests. Categorical variables are expressed as counts (percentages), with the chi-squared test or Fisher's exact test used for analysis. The receiver operating characteristic (ROC) curve was generated using 1,000 bootstrap resamples, and the area under the curve (AUC) was calculated with 95% confidence intervals (CI). All tests were two-tailed, with $p < 0.05$ considered statistically significant.

Results

Patient characteristics

A total of 411 patients were included in the training cohort and 54 in the validation cohort from the MIMIC-IV 2.2 database (Fig. 1). Among them, 170 patients were diagnosed with tigecycline-induced hypofibrinogenemia, yielding an incidence of 41.36%. Of these, 67.06% (114/170) were male, with a median age of 82.0 years (IQR 70.0,90.0) and a median treatment duration of 8.0 days (IQR 5.0,13.0). No significant differences were observed between the two groups in terms of gender, treatment dose, comorbidities, and site of infection (Table 1).

Risk factors for hypofibrinogenemia

Univariate logistic regression analysis was used to screen the risk predictors. There were significant differences in age(OR:1.03, $p < 0.001$),duration(OR:1.28, $p < 0.001$), APTT(OR:1.02, $p = 0.039$),baseline fibrinogen level(OR:0.66,$p < 0.001$),baseline platelet count(OR:0.99,$p = 0.037$),Combined with tumor disease(OR:1.82 $p = 0.025$).The above variables were further included in the multivariable logistic regression analysis. In the multivariable analysis, age(OR:1.02, $p = 0.009$), treatment duration of tigecycline(OR:1.33, $p < 0.001$), baseline fibrinogen level(OR:0.65, $p < 0.001$), baseline platelet count(OR:0.99,$p = 0.025$), and Combined with tumor(OR:2.17,$p = 0.021$) were independent risk factors for hypofibrinogenemia.(Table 2).

Establishment of tigecycline-induced hypofibrinogenemia prediction model and nomogram

Based on multivariable logistic regression analysis, the following variables were included in the prediction model: age (OR: 1.02, $p = 0.009$), duration of treatment (OR: 1.33, $p < 0.001$), fibrinogen level (OR: 0.65, $p < 0.001$), platelet count (OR: 0.99, $p = 0.025$), and combined with tumor (OR: 2.17, $p = 0.021$). Using these factors, we developed a nomogram (Fig. 2). The nomogram indicated that age, treatment duration, and tumor were positively correlated with the score, suggesting that older age, longer treatment duration, and the presence of tumor increase the risk of tigecycline-induced hypofibrinogenemia. Conversely, lower baseline fibrinogen levels and platelet counts were negatively correlated with the score, implying that patients with lower values of these markers are at higher risk for developing hypofibrinogenemia. The cumulative score from these five factors predicts the likelihood of tigecycline-induced hypofibrinogenemia (Fig. 2).In addition, Fig. 3 explains the value of each feature's contribution to the prediction of hypofibrinogenemia, with yellow and dark red representing risk and protective factors, respectively. The length of the graph helps to visualize the degree of influence on the

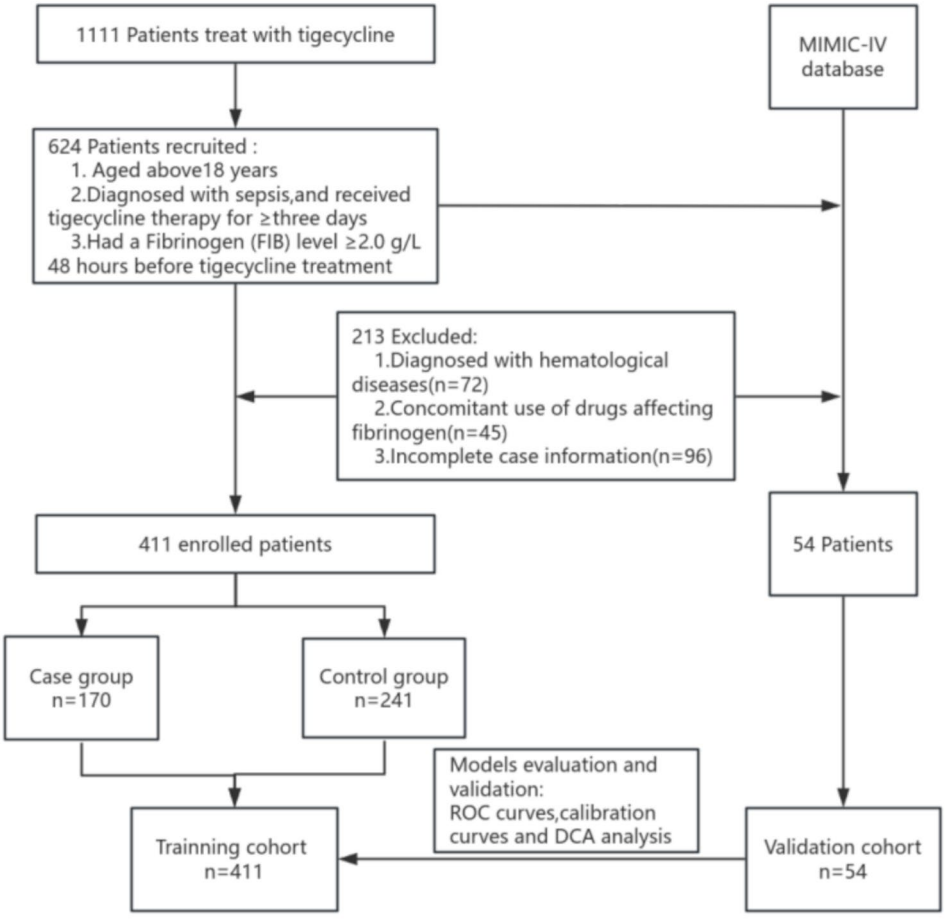

Fig. 1 Flowchart of patients included in this study

prediction; the longer the graph, the greater the influence and the more important the feature(Fig. 3).

Performance assessment and validation of the nomogram

We assessed the nomogram's performance in predicting tigecycline-induced hypofibrinogenemia in both the training and validation cohorts. The model achieved an AUC of 0.85 (95% CI: 0.81–0.89) in the training cohort and 0.83 (95% CI: 0.71–0.95) in the validation cohort (Fig. 4), both exceeding 0.7, indicating good discrimination.Additionally, calibration curves for both cohorts showed a strong agreement between predicted and observed hypofibrinogenemia. The Hosmer-Lemeshow test yielded *p*-values of 0.238 and 0.145 for the training and validation cohorts, respectively, further supporting model concordance ($P > 0.05$) (Fig. 5). The DCA demonstrated the model's clinical utility, with high accuracy across a 5–90% probability range (Fig. 6).

Treatment of Tigecycline-induced hypofibrinogenemia

There is no specific treatment for tigecycline-induced coagulopathy, but the condition can be reversed by discontinuing tigecycline. In cases of severe bleeding, fresh frozen plasma, cryoprecipitate, or human fibrinogen may be administered. In this study, 71.8% (122/170) of patients with tigecycline-induced hypofibrinogenemia discontinued the drug. Of these, 69.7% (85/122) had normalized fibrinogen levels after withdrawal, while 17.2% (21/122) had incomplete test data. Additionally, 13.1% (16/122) of patients received frozen plasma or human fibrinogen supplementation to prevent further bleeding.

Discussion

In this study, we identified risk factors for tigecycline-induced hypofibrinogenemia in septic patients, developed a clinical prediction model, and validated it using data from the MIMIC-IV database. Key risk factors included the presence of tumor, age, tigecycline duration, and baseline fibrinogen and platelet counts.GUO [17] developed a predictive model for tigecycline-induced hypofibrinogenemia in the general population in China, revealing that tigecycline combined with voriconazole increases the risk of hypofibrinogenemia. and tigecycline-induced hypofibrinogenaemia is more likely to

Table 1 Baseline characteristics of the study population

Characteristics	Total (*n* = 411)	Case group (*n* = 170)	Control group (*n* = 241)	*P*-value
Age(years), M (Q_1, Q_3)	79.00 (67.00, 87.00)	82.00 (70.00, 90.00)	77.00 (66.00, 85.00)	**< 0.001**
Male, *n*(%)	296 (72.02)	114 (67.06)	182 (75.52)	0.060
Duration(days), M (Q_1, Q_3)	8.00 (5.00, 13.00)	12.00 (9.00, 15.00)	6.00 (4.00, 9.00)	**< 0.001**
Therapeutic regimen, *n*(%)				0.090
Standard-dose tigecycline	301 (73.24)	117 (68.82)	184 (76.35)	
High-dose tigecycline	110 (26.76)	53 (31.18)	57 (23.65)	
ALT(U/L), M (Q_1, Q_3)	30.80 (14.87, 61.08)	28.00 (12.61, 50.50)	31.00 (17.58, 66.20)	0.100
AST(U/L), M (Q_1, Q_3)	36.00 (24.00, 63.12)	33.06 (22.45, 60.70)	38.42 (25.90, 64.67)	0.184
TBIL(μmol/L), M (Q_1, Q_3)	12.70 (7.70, 21.30)	13.75 (9.34, 23.00)	11.70 (6.99, 20.10)	**0.027**
CREA(μmol/L), M (Q_1, Q_3)	82.27 (53.78, 162.25)	83.75 (52.00, 170.28)	81.90 (55.10, 150.20)	0.846
APTT(s), M (Q_1, Q_3)	32.50 (28.95, 37.60)	33.35 (29.48, 41.12)	32.10 (28.90, 36.80)	**0.036**
PT(s), M (Q_1, Q_3)	14.30 (12.80, 16.30)	14.15 (12.62, 16.10)	14.40 (13.00, 16.30)	0.501
Baseline Fibrinogen(g/L), M (Q_1, Q_3)	4.06 (3.46, 4.84)	3.83 (3.15, 4.48)	4.28 (3.63, 5.34)	**< 0.001**
PLT×10^9/L, M (Q_1, Q_3)	171.00 (96.50, 252.00)	141.50 (84.50, 242.75)	189.00 (107.00, 257.00)	**0.016**
WBC×10^9/L, *n*(%)				0.818
<4	24 (5.84)	10 (5.88)	14 (5.81)	
4–10	123 (29.93)	48 (28.24)	75 (31.12)	
≥ 10	264 (64.23)	112 (65.88)	152 (63.07)	
Concomitant disease, *n*(%)				
COPD	93 (22.63)	41 (24.12)	52 (21.58)	0.544
Hypertension	186 (45.26)	75 (44.12)	111 (46.06)	0.697
Diabetes	105 (25.55)	46 (27.06)	59 (24.48)	0.555
Coronary heart disease	210 (51.09)	94 (55.29)	116 (48.13)	0.153
Tumour	69 (16.79)	37 (21.76)	32 (13.28)	**0.023**
Autoimmune disease	29 (7.06)	13 (7.65)	16 (6.64)	0.694
Cerebrovascular disease	189 (45.99)	80 (47.06)	109 (45.23)	0.714
Types of infection, *n*(%)				
Pulmonary	343 (83.45)	142 (83.53)	201 (83.40)	0.973
Blood	36 (8.76)	12 (7.06)	24 (9.96)	0.306
Urinary tract	105 (25.55)	47 (27.65)	58 (24.07)	0.412

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, Total bilirubin; CREA, Creatinine; COPD, chronic obstructive pulmonary disease; WBC, white blood cell.

occur in patients with malignant haematologic diseases. Although the model was internally validated using the Bootstrap method, external validation is lacking, and the model's generalizability requires further confirmation. HU [8] identified risk factors for tigecycline-associated hypofibrinogenemia in critically ill patients, including intra-abdominal infection, fibrinogen levels at the initiation of tigecycline, maintenance dose, and treatment duration. However, despite identifying these risk factors, the study did not develop a predictive model for clinical decision-making.

Fibrinogen, a protein synthesized by the liver, is a key component of the coagulation-fibrinolytic system. Upon exposure to external stimuli, coagulation factors activate the conversion of fibrinogen to fibrin, which forms thrombi to stop bleeding and repair damaged blood vessels. Normal fibrinogen levels range from 2 to 4 g/L [21]. Guo et al. [17]identified hematologic malignancies as an independent risk factor for tigecycline-induced hypofibrinogenemia, and other studies [22]have shown that acute leukemia can also lead to hypofibrinogenemia. To avoid the influence of hematologic disorders, this study excluded patients with malignant hematologic diseases, found that patients with combined tumors were more likely to develop hypofibrinogenemia.All enrolled patients with concurrent malignancies presented with solid tumors, predominantly lung cancer(80%).Patients with malignant tumors often experience severe depletion and malnutrition, which can impair liver function and reduce fibrinogen synthesis, increasing the risk of hypofibrinogenemia. Tigecycline, with a protein binding rate of 71–89%, can bind to plasma proteins, including fibrinogen, leading to fibrinogen depletion [23]. The antitumor process of the organism is a systemic inflammatory reaction, and in patients with malignant tumors the inflammation is controlled after the use of tigecycline; on the one hand, the inhibition of inflammatory factors by tigecycline may hinder the synthesis of FIB, and on the other hand, tigecycline has not yet been metabolized in time, and it may be bound to the proteins in the plasma,

Table 2 Results of the univariate and multivariable regression analysis of tigecycline-induced hypofibrinogenemia

Variable	Univariate analysis		Multivariatable analysis	
	OR(95%CI)	*P*-value	OR(95%CI)	*P*-value
Age	1.03 (1.01 ~ 1.04)	**< 0.001**	1.02 (1.01 ~ 1.04)	**0.009**
Male	1.52 (0.98 ~ 2.34)	0.061		
Duration	1.28 (1.22 ~ 1.36)	**< 0.001**	1.33 (1.25 ~ 1.41)	**< 0.001**
Therapeutic regimen	1.46 (0.94 ~ 2.27)	0.090		
ALT	1.00 (1.00 ~ 1.00)	0.386		
AST	1.00 (1.00 ~ 1.00)	0.213		
TBIL	1.01 (1.00 ~ 1.02)	0.134		
CREA	1.00 (1.00 ~ 1.00)	0.643		
APTT	1.02 (1.01 ~ 1.04)	**0.039**	1.02 (1.00 ~ 1.05)	0.060
PT	0.99 (0.96 ~ 1.03)	0.690		
Baseline Fibrinogen	0.66 (0.56 ~ 0.78)	**< 0.001**	0.65 (0.53 ~ 0.80)	**< 0.001**
PLT×10^9/L	0.99 (0.99 ~ 0.99)	**0.037**	0.99 (0.99 ~ 0.99)	**0.025**
WBC×10^9/L	—	0.809		
Concomitant disease				
COPD	1.16 (0.72 ~ 1.84)	0.544		
Hypertension	0.92 (0.62 ~ 1.37)	0.697		
Diabetes	1.14 (0.73 ~ 1.79)	0.555		
Coronary heart disease	1.33 (0.90 ~ 1.98)	0.153		
Tumour	1.82 (1.08 ~ 3.06)	**0.025**	2.17 (1.12 ~ 4.18)	**0.021**
Autoimmune disease	1.16 (0.54 ~ 2.49)	0.695		
Cerebrovascular disease	1.08 (0.73 ~ 1.60)	0.714		
Types of infection				
Pulmonary	1.01 (0.59 ~ 1.71)	0.973		
Blood	0.69 (0.33 ~ 1.41)	0.308		
Urinary tract	1.21 (0.77 ~ 1.89)	0.413		

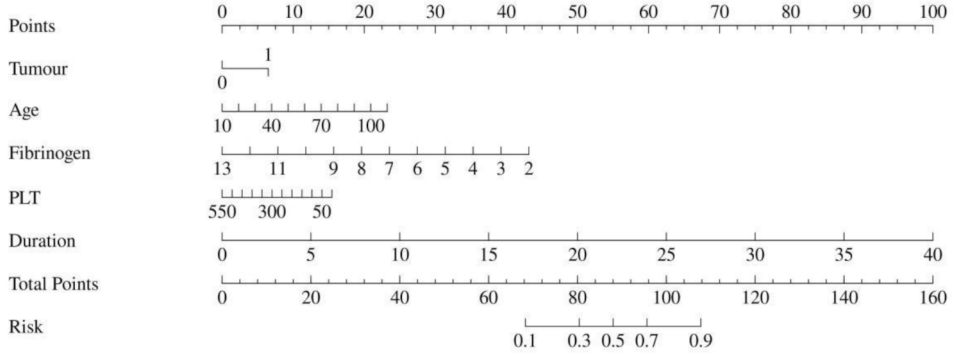

Fig. 2 Nomogram with risk factors for tigecycline-induced hypofibrinogenemia

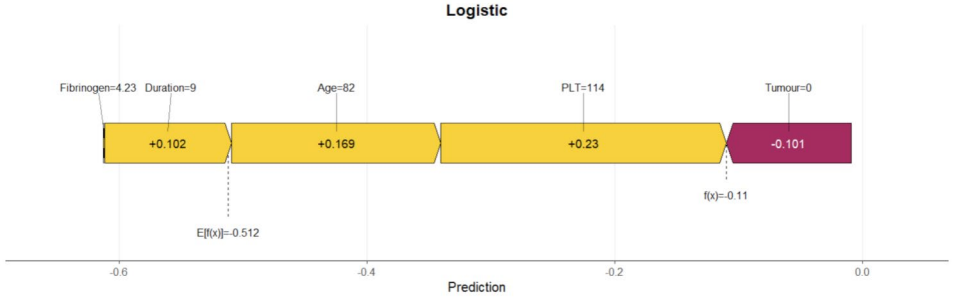

Fig. 3 Contribution of predictive features to the prediction of tigecycline-induced hypofibrinogenemia

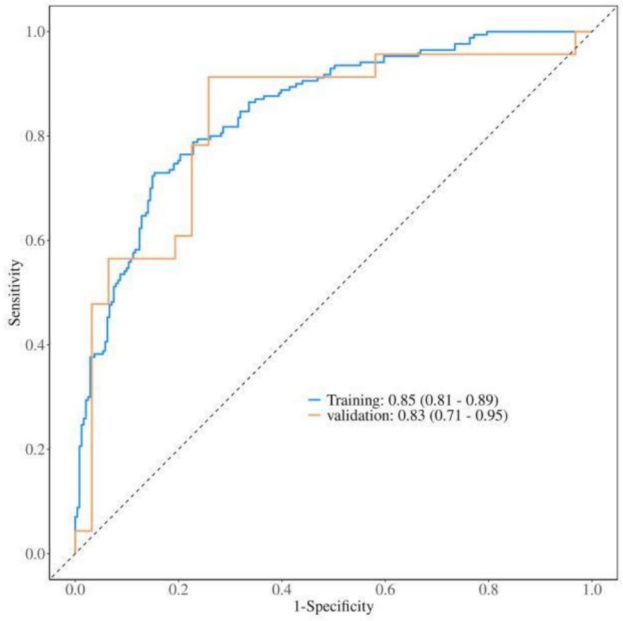

Fig. 4 The ROC curves of the nomogram for tigecycline-induced hypofibrinogenemia in training and validation group
ROC, receiver operating characteristic

resulting in the phenomenon of depletion of FIB, This depletion is typically reversed after discontinuation of the drug [24].

In our study, age emerged as a significant risk factor, with the median age in the hypofibrinogenemia group being 82.0 (70.0, 90.0) years. This aligns with Liu et al.'s [25]finding that an age ≥ 82 years in elderly patients is a threshold for developing hypofibrinogenemia. Lipophilic antimicrobial drugs, such as tigecycline, have an increased volume of distribution in elderly patients, leading to prolonged drug retention. Additionally, age-related declines in liver and kidney function may reduce fibrinogen synthesis [26]. Therefore, close monitoring of fibrinogen levels is recommended when tigecycline is used in patients over 82 years of age with severe infections.

Several studies have correlated the relationship between tigecycline-induced hypofibrinogenemia, treatment duration, and baseline FIB levels [27, 28]. Research indicates that prolonged tigecycline therapy is associated with a greater reduction in plasma FIB levels and longer recovery times [29]. Zhang et al. [10]7 found that patients treated with tigecycline for ≥ 14 days were at an increased risk of hypofibrinogenemia. Our study revealed that the median onset of hypofibrinogenemia was 12.00 (9.00, 15.00) days, with treatment duration serving as an independent predictor. Logistic regression analysis showed a 33% increase in the risk of hypofibrinogenemia for each additional day of treatment. This finding underscores the elevated risk of hypofibrinogenemia with prolonged tigecycline use.The result can guide clinicians to achieve a better balance between treatment and adverse reactions. Clinicians should regularly assess the appropriateness of the treatment duration based on the patient's response to avoid unnecessary prolonged therapy.

According to Hu et al. [8]and Xu et al. [30]baseline fibrinogen levels significantly influence the incidence of hypofibrinogenemia during tigecycline treatment. Our findings align with the author's earlier findings [12, 31], showing that lower baseline fibrinogen is positively correlated with the extent of fibrinogen decline. Logistic regression analysis in our study indicated a 35% increased risk of hypofibrinogenemia for each unit decrease in baseline fibrinogen. Hu et al. [32] reported that baseline fibrinogen levels < 3.6 g/L predict the development of hypofibrinogenemia, while Leng et al. [9]identified fibrinogen < 4 g/L as an independent risk factor for

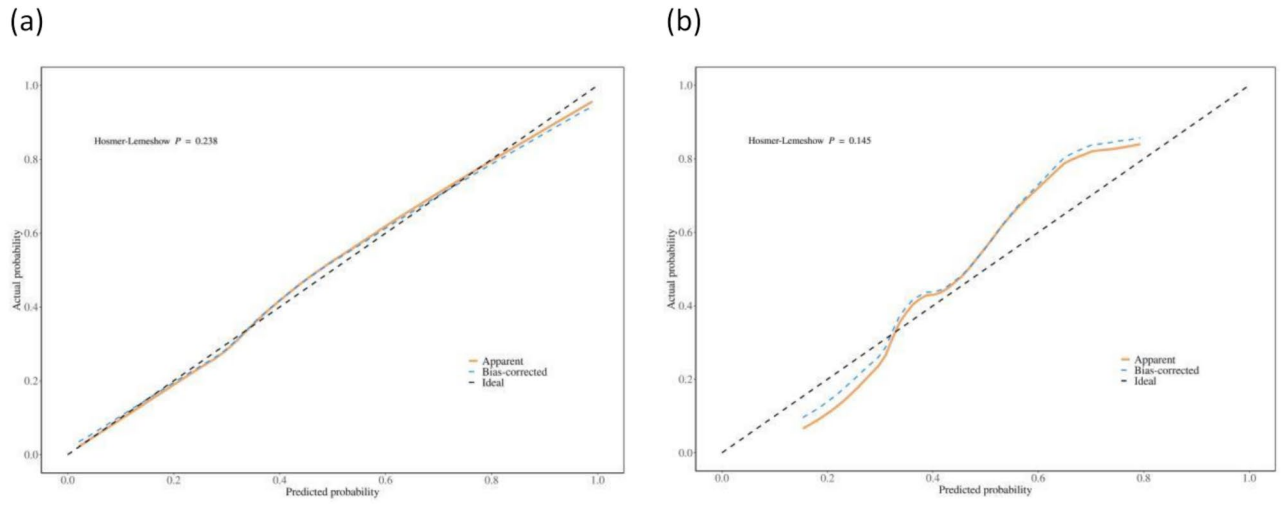

Fig. 5 The calibration curves in the training group (**a**) and validation group (**b**)

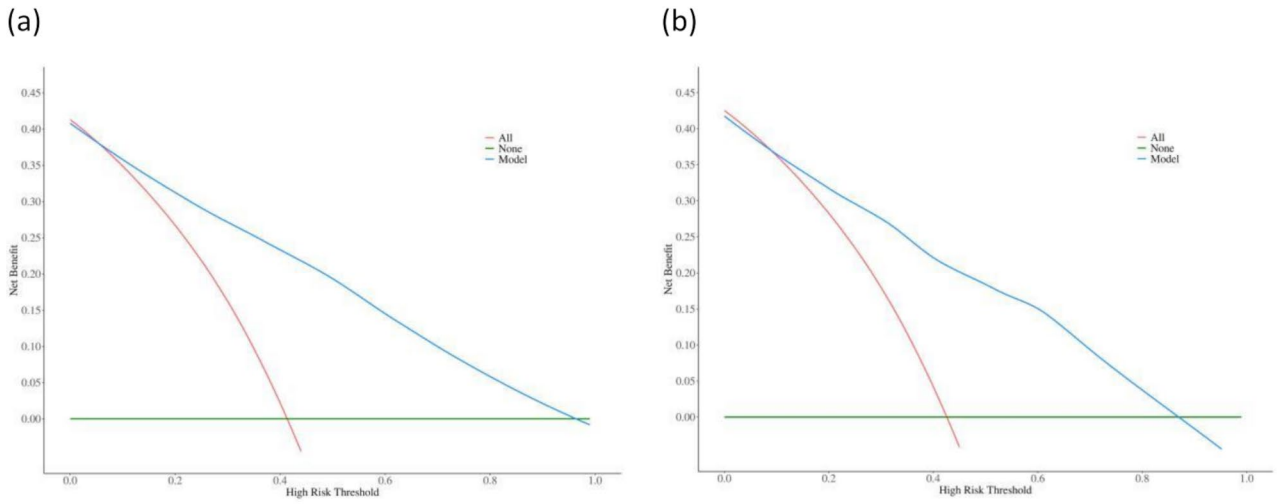

Fig. 6 The DCA in the training group and validation group
DCA, decision curve analysis

this condition.It has been clinically reported that some patients using tigecycline have abnormalities in blood components such as platelets, which in turn cause abnormalities in coagulation and increase the likelihood of hemorrhage [33]. A variety of cytokines can trigger platelet production by megakaryocytes in the bone marrow, including cytokines such as IL-3, IL-6, IL-9, and IL-11.33 Tigecycline inhibits IL-6 and gamma-interferon, with the strongest effects at concentrations < 25 mg/L, leading to platelet downregulation [34]. Tigecycline's metabolism in the liver and kidneys may be influenced by the hepatic and renal function of septic patients, potentially affecting its pharmacokinetics [35]. Since fibrinogen is synthesized in the liver and thrombopoietin in both the liver and kidneys, baseline fibrinogen and platelet levels reflect hepatic and renal function, which can be compromised in septic patients, exacerbating the risk of hypofibrinogenemia with tigecycline use.In our study, baseline fibrinogen and platelet levels were independent predictors of hypofibrinogenemia, and liver and renal function did not significantly affect the results. Some studies suggest that tigecycline, similar to tetracycline antibiotics, may bind to ribosomal sites in liver cells, inhibiting the synthesis of fibrinogen and other coagulation factors, without causing apparent molecular-level liver or renal dysfunction [36, 37]. Thus, assessing baseline coagulation markers is critical before initiating tigecycline therapy.

The training set is used to build the model, allowing it to adjust its parameters and weights to improve prediction accuracy on the input data. However, focusing solely on the training set's performance may lead to overfitting. Notably, no external validation of the tigecycline-induced hypofibrinogenemia prediction model has been reported. This study is the first to incorporate the MIMIC database for external validation, enhancing model stability and extrapolation. However, it has certain limitations. First, it is a retrospective cohort study, introducing potential bias in data acquisition. Second, the external validation using the MIMIC database has limitations, as it primarily includes ICU patient data from the Beth Israel Deaconess Medical Center (BIDMC) in Boston, which may differ from the Chinese population. Additionally, variations in clinical variable detection methods across countries may affect the model's accuracy.

Conclusion

The nomogram developed in this study demonstrates good predictive performance for tigecycline-induced hypofibrinogenemia in septic patients and provides meaningful reference for clinical practice.

Abbreviations

ICU	Intensive care unit
APTT	Activated partial thromboplastin time
PT	Prothrombin time
FIB	Fibrinogen
TBIL	Total bilirubin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CREA	Creatinine
COPD	Chronic obstructive pulmonary disease
WBC	White blood cell
C-index	Concordance index
DCA	Decision curve analysis
ROC	Receiver operating characteristic
AUC	Area under the curve

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11019-w.

Supplementary Material 1

Acknowledgements
We thank all the researchers who have dedicated their time to this research.

Author contributions
HLM conducted the investigation, performed data curation, and wrote the original draft. ZTG contributed to data curation and software development. SJ was responsible for the extraction and download of the MIMIC data. LNC was responsible for data curation, reviewing and editing, and supervision. GLSR contributed to conceptualization, methodology, reviewing and editing, supervision, and formal analysis. All authors reviewed and approved the manuscript.

Funding
Science and Technology Program of the Joint Fund of Scientific Research for the Public Hospitals of Inner Mongolia Academy of Medical Sciences(Project No. 2024GLLH0021).

Data availability
Data is provided within the manuscript or supplementary information files. The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study strictly adhered to the ethical principles outlined in the Declaration of Helsinki for human medical research and was approved by the Ethics Committee of Inner Mongolia People's Hospital(approval number: 202500668 L). The need for patient consent was waived by the Ethics Committee of the Inner Mongolia People's Hospital, as this study is a retrospective analysis involving only existing medical records and data, without direct intervention with individuals or collection of new information. 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.

Competing interests
The authors declare no competing interests.

Received: 18 February 2025 / Accepted: 21 April 2025
Published online: 08 May 2025

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