

Clinical value of predicting lower extremity deep vein thrombosis based on nomogram combined with four-item thrombosis assay in transfused ICU patients

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ABSTRACT

This study aims to develop and evaluate a nomogram incorporating four thrombosis biomarkers—plasmin- α_2 -plasmin inhibitor complex (PIC), tissue-type plasminogen activator-inhibitor complex (t-PAIC), thrombin-antithrombin complex (TAT), and thrombomodulin (TM)—for the prediction of lower extremity deep vein thrombosis (DVT) in critically ill patients receiving blood transfusions. Fifty-six eligible patients, enrolled between February 2020 and February 2022, were prospectively followed for 12 months and subsequently stratified into a DVT group ($n = 44$, incidence 78.57%) and a non-DVT group ($n = 12$). Comparative analysis at baseline revealed significantly elevated plasma levels of PIC, t-PAIC, TAT, and TM in the DVT group ($P < 0.05$). Multivariate logistic regression confirmed the four markers as independent DVT risk factors. The constructed nomogram exhibited favorable calibration, as evidenced by consistent calibration curves and a nonsignificant Hosmer–Lemeshow goodness-of-fit test ($\chi^2 = 0.367$, $P = 0.478$). Receiver operating characteristic (ROC) curve analysis produced an area under the curve (AUC) of 0.787 (95% confidence interval [CI]: 0.643–0.832), with a sensitivity of 86.76% and a specificity of 70.54%. Collectively, these findings indicate that PIC, t-PAIC, TAT, and TM serve as independent predictors of DVT in transfused ICU patients, and that the proposed nomogram offers a robust and clinically applicable tool for individualised risk stratification.

Keywords: plasmin- α_2 -plasmin inhibitor complex, tissue plasminogen activator-inhibitor complex, thrombin-antithrombin complex, thrombomodulin, deep vein thrombosis, nomogram

INTRODUCTION

Lower extremity deep vein thrombosis (DVT) is a prevalent clinical complication, with a higher incidence among critically ill patients receiving blood

transfusions in the intensive care unit (ICU). This condition may lead to severe adverse events, including pulmonary embolism and sepsis, which in turn contribute to increased mortality rates and prolonged hospital stays^[1]. Consequently, accurate

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Received 14 April 2026, Revised 11 June 2026, Accepted 29 June 2026

DVT risk stratification is essential for the timely implementation of targeted prophylactic strategies^[2-3]. Recent studies have increasingly adopted four thrombotic biomarkers, including plasmin- α_2 -plasmin inhibitor complex (PIC), tissue-type plasminogen activator-inhibitor complex (t-PAIC), thrombin-antithrombin complex (TAT), and thrombomodulin (TM), for DVT risk prediction^[4-5]. The nomogram, a visual predictive tool, enables individualized DVT risk assessment by integrating multiple clinical variables to quantify thrombotic susceptibility, thereby supporting precise risk stratification and informed clinical decision-making^[2-3]. The aforementioned four-marker panel reflects critical aspects of coagulation cascade activation and fibrinolytic system homeostasis; indeed, aberrant fluctuations in these markers are associated with disrupted coagulation-fibrinolysis balance and may herald an unfavorable clinical prognosis^[6-7]. Nevertheless, studies regarding the synergistic application of nomogram models with this four-biomarker panel for DVT risk prediction remain limited, and no consistent consensus has yet been established. Accordingly, this study aims to fill this knowledge gap by constructing an integrated predictive framework, thereby providing clinicians with a reliable tool to enhance DVT risk management and improve clinical outcomes in transfused ICU patients.

SUBJECTS AND METHODS

Research subjects

A total of 56 ICU patients who received blood transfusions between February 2020 and February 2022 were enrolled in this study. The cohort comprised patients aged 63 to 77 years, with a mean age of 59.45 ± 8.49 years. This study was approved by the Hospital Ethics Committee (Approval No. YXLL-2024-248), and written informed consent was obtained from all participants or their family members.

Inclusion criteria were as follows: (1) fulfillment of standard clinical indications for blood transfusion during ICU admission; (2) intact consciousness with preserved cognitive and communicative abilities; and (3) provision of written informed consent for study participation.

Exclusion criteria comprised: (1) presence of malignant tumors or limited life expectancy; (2) severe dysfunction of major vital organs; (3) preexisting psychiatric disorders; and (4) inability to cooperate with the study procedures.

Diagnosis of lower extremity DVT

The diagnosis of lower extremity DVT was established in accordance with the *Diagnostic and Efficacy Criteria for Lower Extremity Deep Vein Thrombosis*^[8]. Key clinical features included swelling or severe pain of the affected limb and superficial vein distension, accompanied by a positive Homans' sign (straight leg dorsiflexion test). The final diagnosis was confirmed by venography.

Collection of patient general information

Baseline clinical data were retrospectively retrieved from the electronic medical record (EMR) system, including age, body mass index (BMI), disease duration, smoking status, alcohol consumption, diabetes mellitus, hypertension, renal insufficiency, bladder stones, and chronic prostatitis^[9-10].

Detection of PIC, t-PAIC, TAT, and TM

Venous blood samples were collected from each patient within 2 hours of ICU admission using vacuum-negative-pressure tubes with citrate anticoagulant. The collected blood samples were centrifuged at 4 °C, and the separated plasma samples were preserved at -20 °C for subsequent biochemical detection. Plasma levels of TAT, TM, PIC, and t-PAIC were determined by a fully automated chemiluminescence immunoassay analyzer (Shine i2900, Wondfo Biotech Co., Ltd., Guangzhou, China).

Construction and validation of a nomogram model

Based on the independent predictors identified and their corresponding regression coefficients derived from the multivariable logistic regression analysis, a predictive nomogram model was constructed using the Regression Modeling Strategies (RMS) package in R software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria)^[2]. In this nomogram, the value of each predictor variable was linearly transformed into a point score ranging from 0 to 100. The sum of the individual point scores across all predictor variables yielded a total point score, which was then mapped to the predicted probability of lower extremity DVT^[3]. Internal validation of the model was conducted using the Bootstrap method. Model discrimination was quantified by the concordance index (C-index), and predictive performance was further evaluated using the area under curve (AUC) of the receiver operating characteristic (ROC) curve^[2].

Taking TM as an example, for every 1 U/mL increment in its plasma concentration, the assigned risk score on the nomogram increases by

approximately 20 points. To apply this model for individualized DVT risk estimation, the following stepwise procedure should be followed. First, the patient's specific measurement for each of the four predictor variables is located on its respective axis along the nomogram. A vertical line is then drawn upward from each value to the "Points" axis to obtain the corresponding score for that variable. The scores for all four variables are summed to generate a total point score. Finally, this total score is located on the "Total Points" axis, from which a vertical line is drawn downward to intersect the "Predicted Probability" axis. The value at this intersection represents the patient's individualized predicted probability of developing lower extremity DVT.

Statistical analysis

Statistical analysis was performed using SPSS software (version 27.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$) and were compared between the DVT and non-DVT groups using the independent samples Student's *t*-test. Categorical data were presented as frequencies with constituent ratios

or percentages (%) and were compared using the Pearson's chi-square test (χ^2 test). For all statistical tests, the significance level (α) was set at 0.05, and $P < 0.05$ was considered statistically significant.

RESULTS

Incidence of lower extremity DVT after ICU blood transfusion

Among the 56 enrolled ICU patients receiving blood transfusions, 44 developed lower extremity DVT during the 12-month follow-up period, yielding an overall incidence of 78.57%. These 44 patients with newly diagnosed DVT constituted the DVT group, whereas the remaining 12 patients who did not develop DVT were assigned to the non-DVT group.

Comparison of general data between the DVT and non-DVT groups

Comparative analysis between the two groups revealed that plasma levels of PIC, t-PAIC, TAT, TM, and age were significantly higher in the DVT group than in the non-DVT group, with all differences reaching statistical significance ($P < 0.05$) ([Table 1](#)).

Table 1 Comparison of general data between the DVT and non-DVT groups

General data	DVT group (<i>n</i> = 44)	Non-DVT group (<i>n</i> = 12)	<i>t</i> / χ^2	<i>P</i> -value
Age ($\bar{x} \pm s$, years)	69.02 $\pm$ 8.41	59.08 $\pm$ 7.24	3.729	0.000
BMI ($\bar{x} \pm s$, kg/m ²)	23.01 $\pm$ 0.32	22.98 $\pm$ 0.35	0.282	0.779
Disease duration ($\bar{x} \pm s$, days)	2.17 $\pm$ 0.59	2.23 $\pm$ 0.64	0.307	0.760
Smoking [<i>n</i> (%)]	10 (22.73)	3 (25.00)	0.027	0.869
Alcohol consumption [<i>n</i> (%)]	13 (29.55)	4 (33.33)	0.064	0.800
Diabetes [<i>n</i> (%)]	13 (29.55)	3 (25.00)	0.095	0.757
Hypertension [<i>n</i> (%)]	14 (31.82)	5 (41.67)	0.408	0.523
Renal insufficiency [<i>n</i> (%)]	11 (25.00)	3 (25.00)	0.000	1.000
Bladder stones [<i>n</i> (%)]	10 (22.73)	5 (41.67)	1.725	0.189
Chronic prostatitis [<i>n</i> (%)]	14 (31.82)	5 (41.67)	0.408	0.523
TAT (ng/mL)	2.15 $\pm$ 0.27	1.46 $\pm$ 0.08	8.697	0.000
TM (U/mL)	12.72 $\pm$ 1.51	8.88 $\pm$ 1.49	7.830	0.000
PIC (pg/mL)	0.87 $\pm$ 0.19	0.43 $\pm$ 0.04	7.924	0.000
t-PAIC (ng/mL)	8.67 $\pm$ 0.89	4.73 $\pm$ 0.74	14.042	0.000

DVT: deep vein thrombosis; BMI: body mass index; TAT: thrombin-antithrombin complex; TM: thrombomodulin; PIC: plasmin- α_2 -plasmin inhibitor complex; t-PAIC: tissue-type plasminogen activator-inhibitor complex.

Multivariable stepwise logistic regression analysis of risk factors for lower extremity DVT after ICU blood transfusion

The occurrence of new-onset lower extremity DVT following blood transfusion in ICU patients was designated as the dependent variable (coded as 0 for absence of DVT and 1 for presence of DVT). PIC, t-PAIC, TAT, and TM were included as independent variables into a multivariable stepwise logistic

regression model. The results demonstrated that all four biomarkers—PIC, t-PAIC, TAT, and TM—were independent risk factors for lower-extremity DVT in the study cohort ($P < 0.05$) ([Table 2](#)).

Construction, validation, and efficacy evaluation of the nomogram risk model

Based on the four independent risk factors (PIC, t-PAIC, TAT, and TM) and their corresponding

Table 2 Logistic regression analysis of risk factors for lower extremity DVT after ICU blood transfusion

Variables	β	SE	Wald	P-value	OR	95% CI
PIC	1.256	0.361	12.105	< 0.001	3.511	1.445~8.534
t-PAIC	1.003	0.325	9.524	< 0.001	2.726	1.122~6.626
TAT	1.437	0.526	7.463	< 0.001	4.208	1.731~10.227
TM	1.513	0.427	12.555	< 0.001	4.540	1.868~11.035

DVT: deep vein thrombosis; ICU: intensive care unit; SE: standard error; OR: odds ratio; CI: confidence interval; PIC: plasmin- α_2 -plasmin inhibitor complex; t-PAIC: tissue-type plasminogen activator-inhibitor complex; TAT: thrombin-antithrombin complex; TM: thrombomodulin.

regression coefficients, a nomogram model was constructed to predict the risk of lower extremity

DVT in ICU patients receiving blood transfusions (*Fig. 1*).

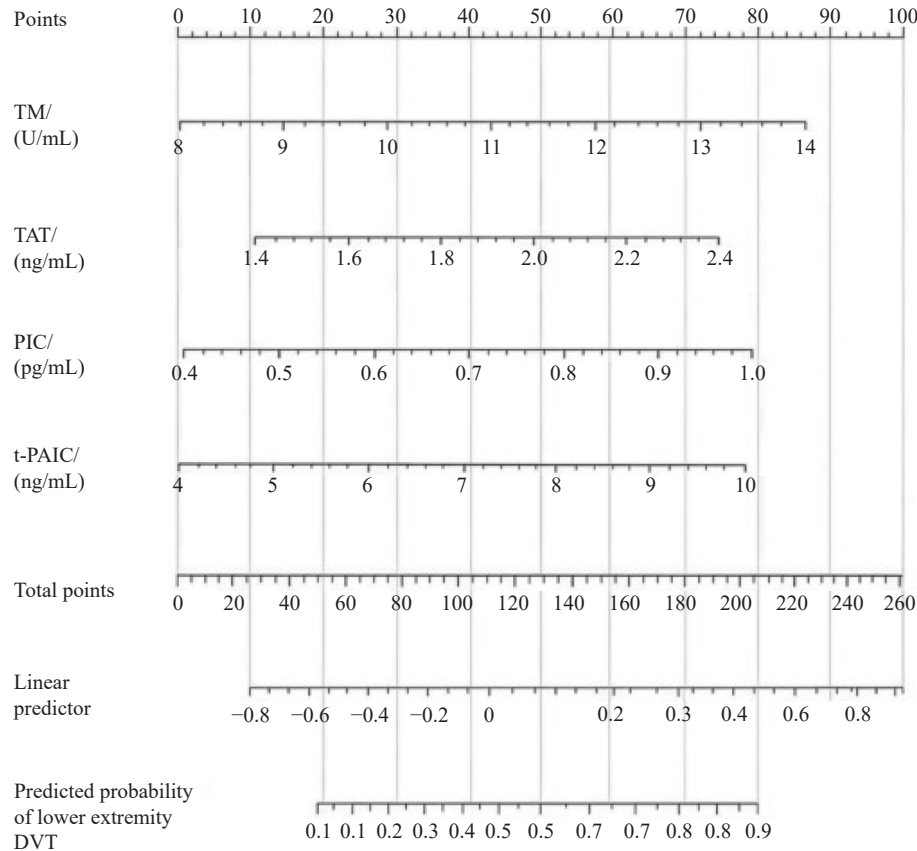


Fig. 1 Nomogram for predicting lower extremity deep vein thrombosis (DVT) risk in transfused intensive care unit (ICU) patients based on four plasma thrombotic biomarkers. TM: thrombomodulin; TAT: thrombin-antithrombin complex; PIC: plasmin- α_2 -plasmin inhibitor complex; t-PAIC: tissue-type plasminogen activator-inhibitor complex.

This study further proposed a rapid scoring nomogram method based on tabular analysis. Specifically, in the rapid scoring table for lower extremity DVT risk in transfused ICU patients, the individual score corresponding to each biomarker measurement was determined according to the measured values (*Table 3*). The individual scores for all four indicators were then summed to obtain a total point score. Based on this total, the corresponding predicted probability of DVT occurrence was derived from the comparison table linking total points to predicted probability of developing lower extremity DVT (*Table 4*). The corresponding clinical preventive

and interventional strategies were formulated according to the risk stratification criteria matching the predicted probability.

A calibration curve was plotted, which exhibited favorable consistency with the ideal reference curve. The Hosmer–Lemeshow goodness-of-fit test yielded a non-significant result ($\chi^2 = 0.367$, $P = 0.478$), confirming satisfactory model calibration (*Fig. 2*).

ROC curve evaluation of the predictive value of the nomogram risk model

Internal validation of the nomogram was performed using the bootstrap resampling method, yielding a C-

Table 3 Rapid scoring nomogram for lower extremity DVT risk in transfused ICU patients

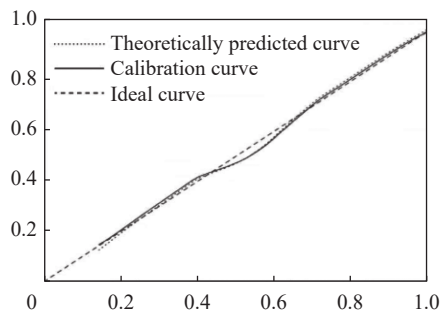
Category	TM		TAT		PIC		t-PAIC	
	Test result (U/mL)	Score	Test result (ng/mL)	Score	Test result (pg/mL)	Score	Test result (ng/mL)	Score
Scores	< 8.0	0	< 1.4	0	< 0.4	0	< 4.0	0
	8.0–8.9	10	1.4–1.5	10	0.4–0.49	10	4.0–4.9	10
	9.0–9.9	20	1.6–1.7	20	0.5–0.59	20	5.0–5.9	20
	10.0–10.9	30	1.8–1.9	30	0.6–0.69	30	6.0–6.9	30
	11.0–11.9	40	2.0–2.1	40	0.7–0.79	40	7.0–7.9	40
	12.0–12.9	50	2.2–2.3	50	0.8–0.89	50	8.0–8.9	50
	13.0–13.9	60	≥ 2.4	60	0.9–0.99	60	9.0–9.9	60
	≥ 14.0	70			≥ 1.0	70	≥ 10.0	70

DVT: deep vein thrombosis; ICU: intensive care unit; TM: thrombomodulin; TAT: thrombin-antithrombin complex; PIC: plasmin- α_2 -plasmin inhibitor complex; t-PAIC: tissue-type plasminogen activator-inhibitor complex.

Table 4 Comparison of total points and predicted probability of lower extremity DVT

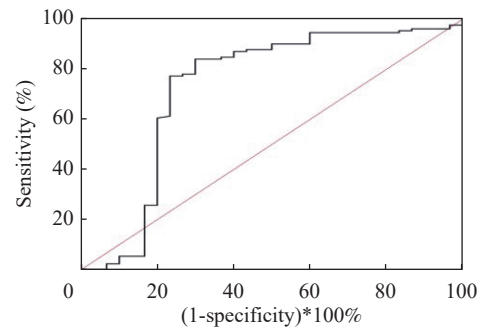
Total points	Predicted probability (%)
0	1.00
50	10.00
100	25.00
150	40.00
200	60.00
250	75.00
300	85.00
350	95.00
400	99.00

Total points: sum the individual scores of the four biomarkers—plasmin- α_2 -plasmin inhibitor complex (PIC), tissue-type plasminogen activator-inhibitor complex (t-PAIC), thrombin-antithrombin complex (TAT), and thrombomodulin (TM)—to obtain the total points. Risk stratification criteria: high risk (predicted deep vein thrombosis [DVT] probability $\geq 70\%$), moderate risk (predicted DVT probability 40%–70%), low risk (predicted DVT probability $< 40\%$).

**Fig. 2** Calibration curve of the nomogram predicting lower extremity deep vein thrombosis (DVT) in transfused intensive care unit (ICU) patients.

index of 0.784 (95% confidence interval [CI]: 0.705–0.876). This value indicates that the nomogram model exhibited good discriminative performance. Subsequently, ROC curve analysis was performed, with the total risk score as the independent variable and the occurrence of new-onset lower extremity DVT as the dependent variable. The model achieved a

sensitivity of 86.76% (95% CI: 75.87%–93.75%), a specificity of 70.54% (95% CI: 64.23%–74.56%), and an AUC of 0.787 (95% CI: 0.643–0.832). Collectively, these statistical metrics corroborated the favorable predictive performance of the nomogram model (Fig. 3).

**Fig. 3** Receiver operating characteristic (ROC) curve of the nomogram for predicting lower extremity deep vein thrombosis (DVT) in transfused intensive care unit (ICU) patients.

DISCUSSION

Lower extremity DVT represents a prevalent and multifactorial complication among ICU patients who received blood transfusions, with the condition typically manifesting within weeks to months following transfusion. In the present 12-month follow-up cohort, the incidence of lower extremity DVT reached 78.57%, which is higher than the 63.9% rate previously reported by Auriti A *et al.* in 2017^[11]. Such discrepancy may be attributable to several factors, including the relatively limited sample size, the advanced age of the enrolled patients, and their overall poorer baseline health status.

Multivariable logistic regression analysis identified PIC, t-PAIC, TAT, and TM as independent risk factors for post-transfusion lower extremity DVT. As a key protein participating in thrombolysis, PIC

suppresses plasminogen activation and consequently impairs thrombus degradation^[4,6]. In critically ill patients following transfusion, elevated circulating PIC concentrations may result from platelet activation, inflammatory cascades, and physiological stress^[12]. T-PAIC is a complex formed by tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1)^[6]. While t-PA primarily facilitates fibrin degradation, PAI-1 exerts an inhibitory effect on t-PA activity. In critically ill transfused patients, elevated t-PAIC levels are mainly attributed to increased PAI-1 expression, which ultimately suppresses endogenous fibrinolytic activity through inactivation of t-PA^[5]. TAT, a complex composed of thrombin and antithrombin III (AT-III), serves as a sensitive biomarker reflecting the activation status of the coagulation system^[7]. In critically ill transfused patients, elevated TAT levels primarily result from excessive coagulation system activation and reduced AT-III consumption^[4]. TM is a membrane-bound glycoprotein that binds to coagulation factor IIa, thereby facilitating protein C activation and suppressing excessive coagulation cascade activity^[13]. In critically ill transfused patients, reduced TM levels are closely associated with aberrant coagulation system activation and persistent inflammatory responses^[12].

Patients with lower extremity DVT typically present with aggravated inflammatory responses and disrupted coagulation homeostasis, both of which contribute to elevated TAT levels. In contrast, circulating TM levels are markedly decreased in DVT cases. As a critical molecule with dual anticoagulant and anti-inflammatory properties, TM maintains coagulation balance. Degradation or functional impairment of TM can trigger excessive activation of the coagulation cascade^[13]. Accordingly, the downregulated TM levels observed in patients with lower extremity DVT may serve as a valuable biomarker for evaluating disease severity and guiding individualized clinical management^[7]. Nevertheless, it is important to recognize that alterations in these biomarkers serve as auxiliary indicators for diagnosis and risk prediction rather than as standalone diagnostic criteria. Accordingly, diminished circulating TM concentrations are frequently observed among patients with lower extremity DVT.

Based on the four independent risk factors identified above, we constructed and validated a nomogram model for predicting post-transfusion lower extremity DVT in ICU patients. The calibration curve exhibited excellent consistency with the ideal curve, and the Hosmer-Lemeshow goodness-of-fit test

revealed a non-significant result, indicating favorable model calibration. Internal bootstrap validation yielded a C-index of 0.784 (95% CI: 0.705–0.876), demonstrating good discriminative ability of the nomogram. ROC curve analysis was performed using the total risk score as the predictive variable and DVT occurrence as the outcome variable. The model achieved a sensitivity of 86.76% (95% CI: 75.87%–93.75%), a specificity of 70.54% (95% CI: 64.23%–74.56%), and an AUC of 0.787 (95% CI: 0.643–0.832), collectively confirming favorable predictive performance. This nomogram model provides a reliable method for risk evaluation of post-transfusion lower extremity DVT in ICU patients.

As an effective predictive tool, the validated model is capable of identifying high-risk individuals susceptible to DVT, thereby facilitating early clinical risk stratification and targeted intervention^[3,14]. The established nomogram demonstrates favorable sensitivity and specificity, indicative of robust predictive performance. Moreover, this predictive tool enables clinicians to formulate individualized preventive regimens and therapeutic strategies^[15]. For patients stratified into the high-risk group by this nomogram, prophylactic anticoagulation or physical thromboprophylaxis should be administered as early as possible to reduce the incidence of DVT. For those at moderate risk, daily re-examination of thrombotic biomarkers combined with intermittent pneumatic compression therapy is recommended. In contrast, low-risk patients may receive routine basic nursing care without intensified anticoagulation or additional preventive interventions, thereby avoiding overtreatment and reducing unnecessary laboratory and imaging examinations^[14].

In conclusion, PIC, t-PAIC, TAT, and TM are independent risk factors for post-transfusion lower extremity DVT in ICU patients. The newly developed nomogram model possesses robust predictive performance and offers a reliable tool for clinical DVT risk stratification in this high risk population.

Author contributions

Conceptualization, Xuehua He and Qiang Zhang; Methodology, Jiajia Qiao; Software, Jiajia Qiao; Validation, Xuehua He and Xiuzhe Wang; Formal Analysis, Xiaojing Yang; Investigation, Xiaojing Yang; Resources, Xiuzhe Wang and Xiaojun Guo; Data Curation, Yuesheng Wu; Writing – Original Draft Preparation, Xuehua He and Jiajia Qiao; Writing – Review & Editing, Qiang Zhang; Visualization, Xiuzhe Wang; Supervision, Qiang

Zhang; Project Administration, Xuehua He; Funding Acquisition, Xuehua He.

Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Hospital Ethics Committee (Approval No. YXLL-2024-248).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Funding

This research was funded by the grant from the Shanxi Provincial Health Commission (Grant No. 2024001).

Declaration of competing interest

The authors declared no conflict of interests.

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