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RESEARCH

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# Nomogram-based prediction of the prognosis in patients with free floating venous thrombus after closed traumatic fracture

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**Abstract**

**Background** Free-floating venous thrombosis (FFVT), a distinct subtype of deep vein thrombosis (DVT), is associated with pulmonary thromboembolism (PTE) and carries a high mortality risk.

**Objective** This study aimed to develop a nomogram to predict the prognosis of FFVT in patients with closed traumatic fractures.

**Materials and methods** A retrospective analysis of clinical and ultrasound data from 326 patients with FFVT post-closed traumatic fractures was conducted. Patients were divided into training ($n=240$, January 2019–June 2023) and validation ($n=86$, June 2023–June 2024) sets. Prognostic risk factors were identified using LASSO and multivariable logistic regression. A nomogram was constructed using R Studio, and its predictive accuracy was validated via calibration curves, receiver operating characteristic (ROC) analysis, and external validation.

**Results** Independent risk factors for FFVT progression to closed thrombus included D-dimer levels, FFVT location, collateral blood flow volume around the thrombus, and thrombus margins ($P<0.05$). The model demonstrated high discriminative ability, with a C-index of 0.945. ROC analysis revealed areas under the curve (AUC) of 0.949 (training set) and 0.924 (validation set). Calibration curves confirmed strong agreement between predicted and observed outcomes.

**Conclusion** The nomogram provides an accurate prognostic tool for FFVT in patients with closed traumatic fractures, aiding clinical decision-making to improve patient outcomes.

**Clinical trial number** Not applicable.

**Keywords** Free floating venous thrombosis, Nomogram, Prediction model, Prognosis, Risk factors

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## Introduction

Deep vein thrombosis (DVT), characterized by blood clot formation in deep veins, frequently affects the lower limbs. Among DVT subtypes, free floating venous thrombosis (FFVT) s presents distinct clinical challenges due to its unique morphological features and prognostic implications. FFVT is defined by a thrombus that remains unattached to the venous wall, exhibiting pendulum-like mobility within the lumen. Such mobility is particularly prominent at major venous junctions, including the superficial/deep femoral vein confluence, iliac vein bifurcation, saphenofemoral junction, and iliocaval junction [1]. FFVT predominantly occurs in the lower limbs and represents a critical complication in patients with traumatic fractures [2]. The unanchored thrombus carries a high risk of embolization, potentially leading to pulmonary thromboembolism (PTE)—a condition associated with mortality rates of 3–5% [3–5]. The insidious onset of FFVT frequently delays diagnosis, with many cases remaining undetected until patients manifest PTE-related symptoms.

The diagnostic accuracy and non-invasive nature of ultrasound examination for venous thrombosis have established it as a cornerstone in the diagnostic and management pathway for thrombotic conditions [6]. It enables comprehensive evaluation of thrombus stability, anticoagulation efficacy, and longitudinal progression [7, 8]. Advancements in imaging techniques have allowed for more precise identification and characterization of FFVT, as highlighted by a study by Cogo et al. that utilized contrast-enhanced ultrasound to improve the visualization of thrombi [9]. However, while DVT diagnosis and treatment are well-studied, prognostic predictors and management protocols for FFVT remain poorly defined. Current clinical practice lacks standardized treatment guidelines for FFVT, resulting in substantial management heterogeneity [1]. Moreover, a systematic review by Kearon et al. evaluated the efficacy of various anticoagulant regimens in the management of venous thromboembolic diseases, suggesting that individualized treatment plans based on the patient's risk profile may be more effective than a one-size-fits-all approach [10]. This underscores the importance of a personalized medicine approach in the management of FFVT.

This study aims to identify independent prognostic factors for FFVT in patients with closed traumatic fractures and construct a predictive nomogram. This tool is designed to guide clinical decision-making, mitigate thrombosis-related complications, and enhance long-term patient outcomes.

## Materials and methods

### Participants

This study retrospectively included 326 patients with FFVT after closed traumatic fractures between January 2019 and June 2024 in our hospital. According to the natural history and ultrasound findings of FFVT, the training set ($n=240$, January 2019–June 2023) comprised 164 patients with thrombus recanalization (Recanalization group) and 76 with thrombus fixation (Fixation group). The validation set ($n=86$, June 2023–June 2024) included 60 recanalization and 26 fixation cases. This study was approved by the medical ethics committee of our hospital (2024MER204).

### Inclusion criteria and exclusion criteria

The inclusion and exclusion criteria were as follows. Inclusion criteria: (1) patients diagnosed with an isolated closed traumatic fracture; (2) patients with FFVT confirmed by ultrasound; (3) patients who underwent routine blood tests, including fasting blood glucose and coagulation tests at admission. Exclusion criteria: (1) patients with a history of venous thrombosis in the lower limbs or other areas; (2) patients with a history of trauma or surgery in the past six months; (3) patients with a history of neoplasms or cardiovascular diseases; (4) patients with incomplete data.

### Data collection

Clinical data, including sex, age, BMI (Body Mass Index), smoking history, drinking history, diabetes, hypertension, hyperlipidemia, fracture causes, time interval from injury to thrombosis, fracture sites, D-dimer, and coagulation indexes (TT, Thrombin Time; PT, Prothrombin Time; APTT, Activated Partial Thromboplastin Time; FIB, Fibrinogen), were collected. Ultrasonic data, including ultrasonic imaging, FFVT sites, perithrombotic blood flow, and thrombus margins, were also collected.

### Ultrasound examination

Within 48 h of admission, patients underwent their first ultrasound examination. Ultrasound examinations were performed using a GE LOGIQ E9 ultrasound device (GE Healthcare, Milwaukee, WI, USA) with 9 MHz linear probes (type 9 L). Patients were required to be in a supine or lateral position, with both legs extended and slightly externally rotated to relax the muscles. The examination process was carried out gently to avoid deformation of the lumen caused by probe pressure, which could prevent thrombus detachment. The scanning range included the external iliac vein, femoral vein, popliteal vein, posterior tibial vein, peroneal vein, and intramuscular veins of the lower leg. The thrombus margins and the blood flow within the lumen were observed. Based on the boundary between the thrombus and the venous wall, FFVT margins were classified as well-defined or ill-defined. In color Doppler imaging, the sampling frame was placed at the head of the thrombus to observe the spontaneous blood flow within the venous lumen. As shown in Fig. 1A, color Doppler imaging showed the collateral blood flow around the thrombus. Depending on whether the collateral flow around the thrombus occupied 50% of the luminal diameter, collateral blood flows were classified as high-flow and low-flow. Based on the location where FFVT occurred, FFVT sites were divided into iliac-femoral vein thrombus, popliteal vein thrombus, and lower leg vein thrombus. All ultrasound examination processes were jointly completed by two ultrasound technicians with over 10 years of experience. Follow-up ultrasound examinations were conducted on the 28th day after discharge (Fig. 1B).

## Statistical analysis

All data were analyzed using SPSS (version 23, SPSS Inc., Chicago, IL, USA) and R software (version 4.1.2, https://www.R-project.org). Before analysis, the normality of the data was assessed. In the study, continuous variables were expressed as Median (Interquartile Range) and compared with the Mann-Whitney U test between two groups. Categorical variables were expressed as numbers (percentages) and compared using the Chi-square test. Univariate analysis was used to identify variables with statistical differences with a P value < 0.05 between two groups. The differential variables serving as independent variables in the training set were employed in the LASSO regression and multivariate logistic regression analysis to determine the independent risk factors affecting the prognosis in patients with FFVT after closed traumatic fractures. The nomogram model was constructed using the "rms" package in R software, and the C-index was calculated. Calibration curves were drawn to compare the predicted and observed outcomes after bias correction. Receiver operating characteristic (ROC) curves were plotted to assess the predictive ability of the model using the data from the training set and the validation set. A P value < 0.05 was defined as statistically significant.

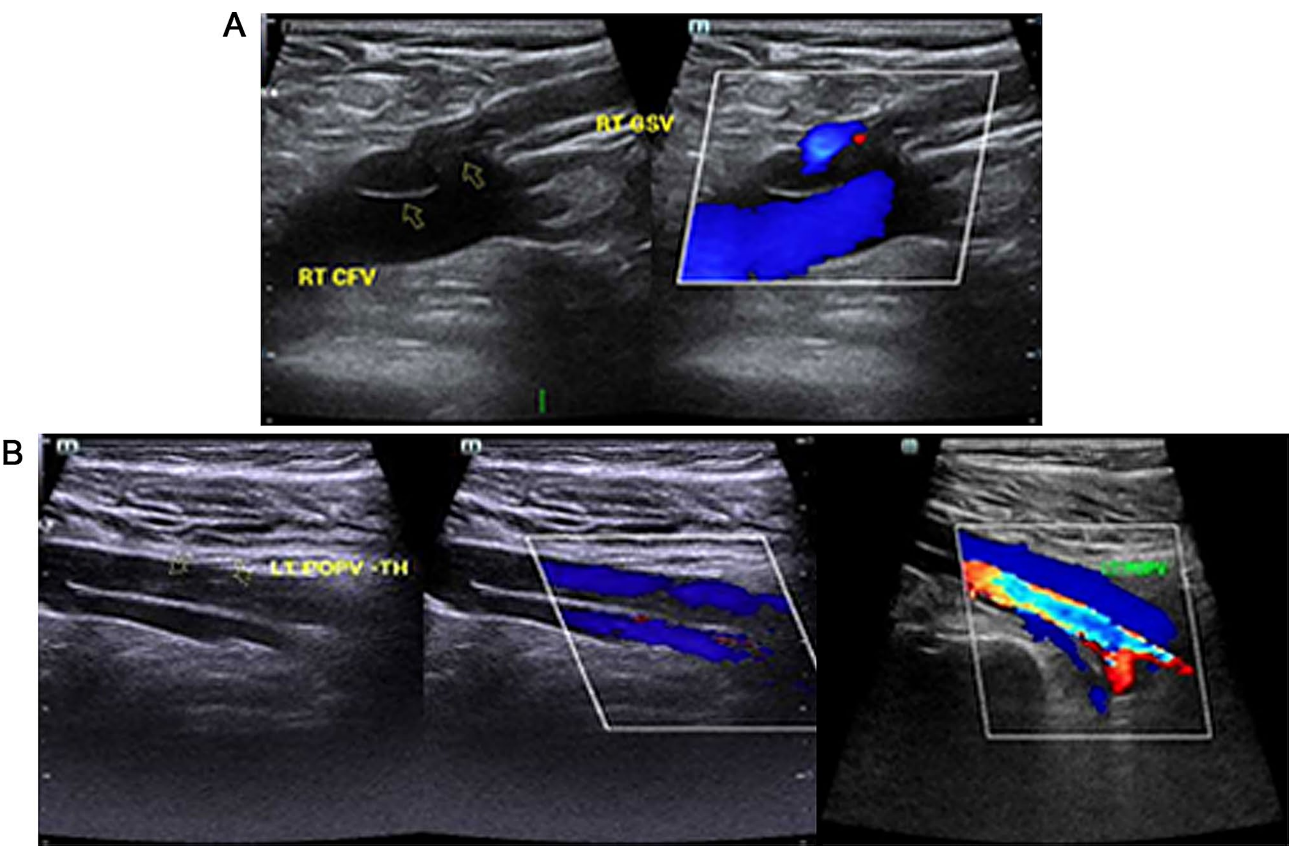


**Fig. 1** Representative ultrasonic imaging. **A**) Color Doppler imaging revealed Free-Floating Venous Thrombus (FFVT) in the right femoral vein, presenting with blood high-flow around the FFVT in iliac-femoral vein. **B**) A male patient developed a FFVT in the right popliteal vein after a traumatic injury by a two-dimensional image and a color Doppler image. On the 28th day after discharge, a follow-up ultrasound showed that the thrombus had dissolved and disappeared

## Results

### Characteristics analysis of patients with FFVT after closed traumatic fractures

A total of 326 patients with FFVT after closed traumatic fractures were included in the study, divided into the training set ($n = 240$) and the validation set ($n = 86$). There were 63 cases of iliac-femoral vein thrombosis, 232 cases of popliteal vein thrombosis, and 31 cases of calf vein thrombosis. No significant differences in clinical characteristics were observed between the training set and the validation set ($P > 0.05$, Supplementary Table 1).

In the training set of 240 patients with FFVT after closed traumatic fractures, there were 42 cases of iliac-femoral vein thrombosis, 179 cases of popliteal vein thrombosis, and 19 cases of calf vein thrombosis. Univariate analysis of clinical characteristics in the training set revealed significant differences in age and plasma D-dimer levels, thrombus location, the collateral blood flow around the thrombus, and the thrombus margins between the Recanalization group ($n = 164$) and the Fixation group ($n = 76$) ($P < 0.05$). No significant differences were observed in gender, BMI, smoking history, drinking history, hypertension, hyperlipidemia, diabetes, laboratory parameters (thrombin time, TT; prothrombin time, PT; activated partial thromboplastin time, APTT; fibrinogen, FIB), fracture causes, fracture sites, and time from injury to thrombosis formation between the two groups (all $P > 0.05$, Table 1).

### Independent risk factors for model

Among the 16 characteristic variables, 5 differential variables identified in the univariate analysis were entered into the LASSO regression analysis to mitigate the influence of confounding factors and multicollinearity. The dynamic process of variable selection is depicted in Fig. 2A, and the process of screening variables through 10-fold cross-validation is shown in Fig. 2B. Ultimately, four variables with nonzero coefficients were selected, including D-dimer, thrombus location, collateral blood flow around the thrombus, and thrombus margins. Multivariable regression analysis demonstrated that D-dimer (OR = 4.732; 95% CI 2.275–9.845; $P < 0.001$), thrombus location (compared to the calf vein, the popliteal vein showed the highest recanalization rate [OR = 0.057; 95% CI 0.016–0.208; $P < 0.001$], followed by iliac-femoral vein [OR = 0.123; 95% CI 0.030–0.507; $P < 0.001$]), low-flow around the thrombus (OR = 40.616; 95% CI 18.089–91.198; $P < 0.001$), and ill-defined thrombus margins (OR = 13.452; 95% CI 6.671–27.126; $P < 0.001$) were independent risk factors for FFVT progressing to a closed thrombus in patients with FFVT after closed traumatic fractures (Table 2).

### Predictive nomogram construction

Based on the results of the multivariable regression analysis, a nomogram model for predicting the prognosis of patients with FFVT after closed traumatic fractures was constructed (Fig. 3). In our nomogram, the amount of collateral blood flow around the thrombus was the greatest contributor to predicting the prognosis of patients with FFVT after closed traumatic fractures (100 points), followed by thrombus margin (58.0 points) and D-dimer (42.5 points). The Bootstrap method was applied for internal verification, and the C-index was calculated using the RMS package. To evaluate the predictive performance of this model, ROC curves were plotted (Fig. 4). The area under the curve (AUC) of 0.949 (95% CI 0.923–0.976) in the training set and 0.924 (95% CI 0.863–0.986) in the validation set indicated the model's strong discrimination and predictive ability. Calibration curves were plotted to assess the calibration and consistency of the model, as shown in Fig. 5. The C-index of 0.943 and the excellent fit between the ideal curve and the calibration curve in both the training and validation sets suggested the model's high discriminative power and predictive ability.

## Discussion

DVT, a common complication in patients with traumatic fractures, has an incidence rates ranging from 9.1 to 11.1% following trauma [11, 12]. As a special type of non-occlusive thrombus, FFVT was reported to occur annually in 0.1% adults [13, 14]. Characterized by attachment to the vessel wall only at its origin and floating in other parts, FFVT is particularly susceptible to detachment, posing a significant risk for Pulmonary Thromboembolism (PTE). As time goes on, endothelial cells, fibroblasts, and myofibroblasts grow from the vessel wall into the interior of the thrombus, forming new granulation tissue. The thrombus is gradually replaced by granulation tissue and tightly adheres to the vessel wall, eventually causing permanent deformity of the venous wall [15]. It was also reported that delayed thrombus resolution after the first DVT episode is associated with the development of post-thrombotic syndrome (PTS) [16, 17]. In this study, we constructed a predictive nomogram model using retrospective clinical and ultrasound imaging data from 240 patients to predict the prognosis of FFVT progressing to a closed thrombus in patients with FFVT after closed traumatic fractures. Our findings demonstrated that D-dimer levels, location of FFVT, flow around the thrombus, and thrombus margin are independent risk factors affecting the prognosis of FFVT. This nomogram model offers a valuable tool for predicting the progression of FFVT and can aid in the clinical management of patients with this condition.

**Table 1** Clinical characteristics analysis in training set

| | Recanalization group ($n=164$) | Fixation group ($n=76$) | $P$ value |
|---|---|---|---|
| **Sex** | | | 0.893 |
| Male | 90(54.9%) | 41(53.9%) | |
| Female | 74(45.1%) | 35(46.1%) | |
| **Age (years)** | 61(16) | 64(21) | 0.037 |
| **BMI (kg/m$^{-2}$)** | 23.3(4.0) | 23.47(4.1) | 0.742 |
| **Smoking history** | | | 0.312 |
| Yes | 22(13.4%) | 14(18.4%) | |
| No | 142(86.6%) | 62(82.6%) | |
| **Drinking history** | | | 0.938 |
| Yes | 20(12.2%) | 9(11.8%) | |
| No | 144(87.8%) | 67(88.2%) | |
| **Diabetes** | | | 0.534 |
| Yes | 23(14.0%) | 13(17.1%) | |
| No | 141(86.0%) | 63(82.9%) | |
| **Hypertension** | | | 0.168 |
| **Yes** | 40(24.4%) | 25(32.9%) | |
| **No** | 124(75.6%) | 51(67.1%) | |
| **Hyperlipidemia** | | | 0.728 |
| Yes | 19(11.6%) | 10(13.2%) | |
| No | 145(88.4%) | 66(86.8%) | |
| **Fracture causes** | | | 0.281 |
| High Fall Injury | 12(7.3%) | 8(10.5%) | |
| Traumatic injury | 122(74.4%) | 61(80.3%) | |
| Traffic accident | 29(17.7%) | 7(9.2%) | |
| Explosion injury | 1(0.6%) | 0(0) | |
| **Time from injury to thrombosis(days)** | 6(6.0) | 5(5.0) | 0.381 |
| **Fracture sites** | | | 0.281 |
| Pelvis | 6(3.7%) | 4(5.3%) | |
| Thigh | 57(34.8%) | 38(50.0%) | |
| Knee | 73(44.5%) | 19(25.0%) | |
| Shank | 9(5.5%) | 5(6.6%) | |
| Ankle | 7(4.3%) | 2(2.6%) | |
| Spine | 7(4.3%) | 7(9.2%) | |
| Upper limb | 5(3.0%) | 1(1.3%) | |
| **D-dimer** | | | <0.001 |
| < 550 μg/L | 73(44.5%) | 16(21.1%) | |
| ≥ 550 μg/L | 91(55.5%) | 60(78.9%) | |
| **Coagulation** | | | |
| **TT (s)** | 14.4(1.7) | 14.3(1.4) | 0.998 |
| **PT (s)** | 11.7(1.0) | 11.8(1.1) | 0.394 |
| **APTT (s)** | 27.6(3.2) | 28.4(3.2) | 0.173 |
| **FIB (g/L)** | 3.11(1.0) | 2.92(1.1) | 0.292 |
| **FFVT locations** | | | <0.001 |
| Calf vein | 3(1.8%) | 16(21.1%) | |
| Popliteal vein | 138(84.2%) | 41(53.9%) | |
| iliac-femoral vein | 23(14.0%) | 19(25.0%) | |
| **Flow around the thrombus** | | | <0.001 |
| High-flow | 134(81.7%) | 6(7.9%) | |
| Low-flow | 30(18.3%) | 70(92.1%) | |
| **Thrombus margins** | | | <0.001 |
| Well-defined margins | 145(88.4%) | 22(28.9%) | |
| Ill-defined margins | 19(11.6%) | 54(71.1%) | |

BMI (Body mass index); FFVT (Free floating venous thrombosis); TT (Thrombin Time); PT (Prothrombin Time); APTT (Activated Partial Thromboplastin Time); FIB (Fibrinogen). Continuous variables were expressed as Median (IQR, Interquartile Range) and Categorical variables were expressed as Numbers (Percentages)

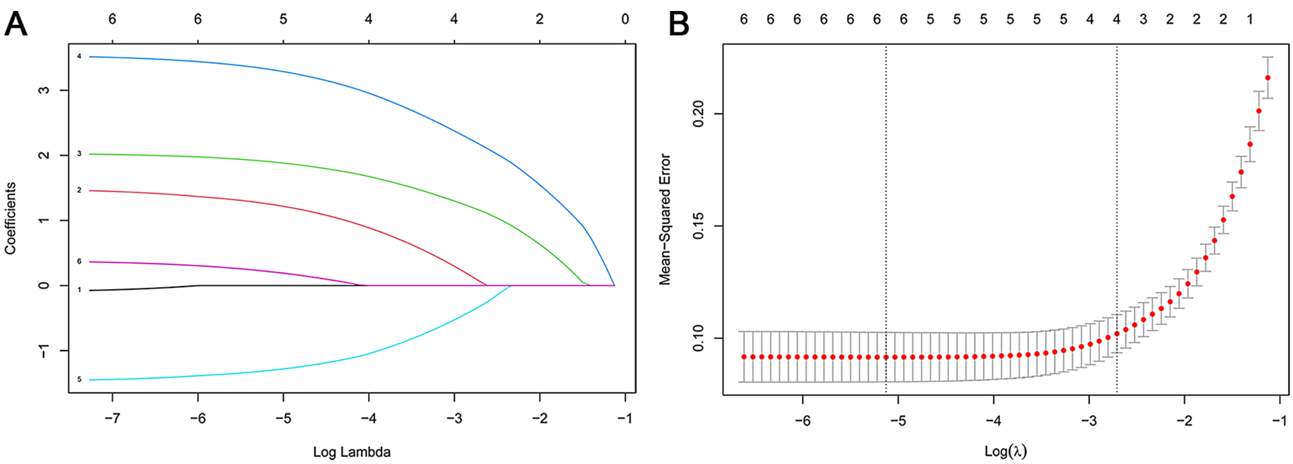


**Fig. 2** Variable selection by the LASSO binary logistic regression model. **A**) LASSO coefficient profile plot was produced for filtering variables; **B**) The optimal penalty coefficient lambda (λ) was generated in LASSO through tenfold cross-validation. The partial likelihood deviation (binomial deviation) curve versus log (λ) was plotted. Dotted vertical lines were drawn based on one standard error criterion

**Table 2** Multivariable regression analysis of the risk factors affecting the prognosis in patients with FFVT after closed traumatic fractures

| Variables | *β* | *Sig* | *Wald* $\chi^2$ | *OR* | *95% CI* | *P value* |
|---|---|---|---|---|---|---|
| Calf vein (ref) | | | | | | |
| Popliteal vein | -2.866 | 0.662 | 18.749 | 0.057 | 0.016–0.208 | <0.001 |
| iliac-femoral vein | -2.096 | 0.723 | 8.401 | 0.123 | 0.030–0.507 | 0.004 |
| D-dimer | 1.544 | 0.374 | 17.297 | 4.732 | 2.275–9.845 | <0.001 |
| Flow around the thrombus | 3.704 | 0.413 | 80.559 | 40.616 | 18.089–91.198 | <0.001 |
| Thrombus margins | 2.599 | 0.358 | 52.755 | 13.452 | 6.671–27.126 | <0.001 |

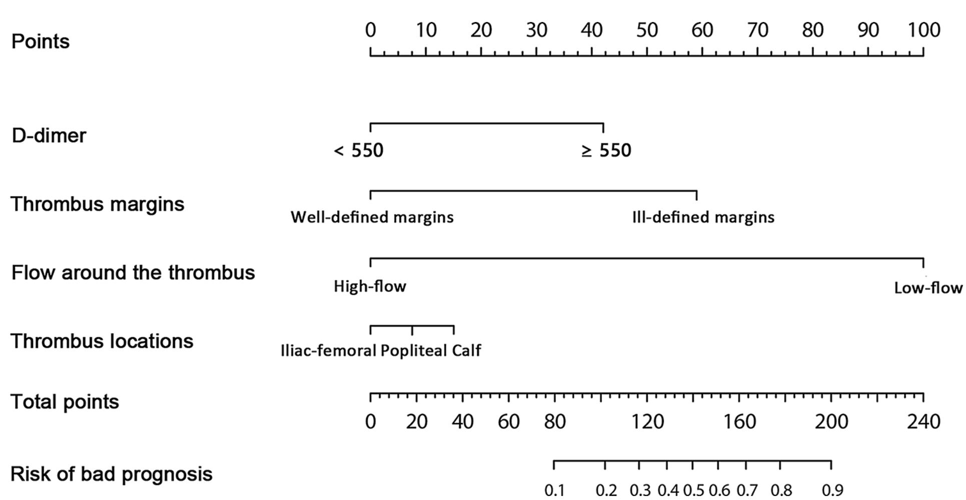


**Fig. 3** Predictive nomogram for the prognosis of patients with FFVT after closed traumatic fracture

D-dimer functions as a marker of coagulation and fibrinolytic activation. It is a fibrin degradation product present in the blood after thrombus formation and can rapidly assess thrombotic activity [18]. Our results showed that preoperative plasma D-dimer levels are an independent risk factor affecting the prognosis of FFVT in trauma patients, which is consistent with previous research [19]. In Huang et al.'s study, D-dimer levels were independently associated with all-cause mortality in patients with dilated cardiomyopathy [19]. A D-dimer level > 2800 μg/L has been identified as an independent risk factor for the stability of lower extremity DVT [7]. Our findings illustrated that increased preoperative D-dimer levels are associated with an increased risk of incomplete thrombus recanalization. Elevated D-dimer levels indicate thrombus residue, difficulty in dissolving,

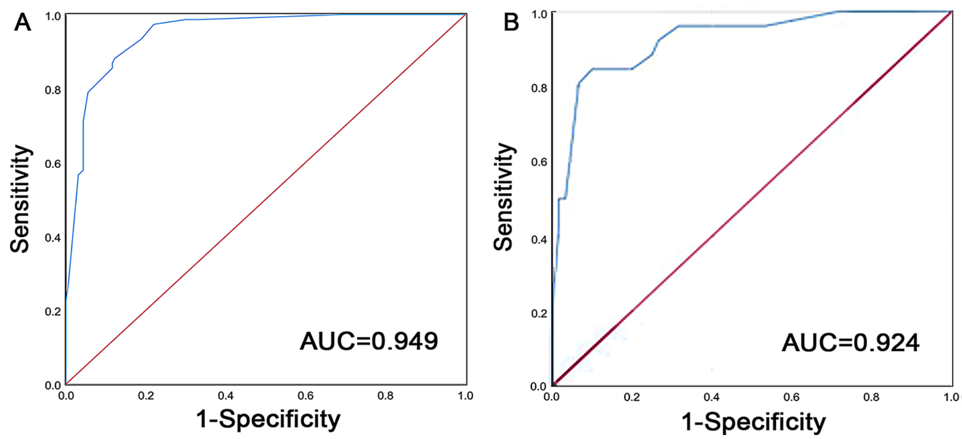


**Fig. 4** Receiver operating characteristic (ROC) curves for the assessment of accuracy of nomogram prediction model. **A**) The training set, **B**) The validation set

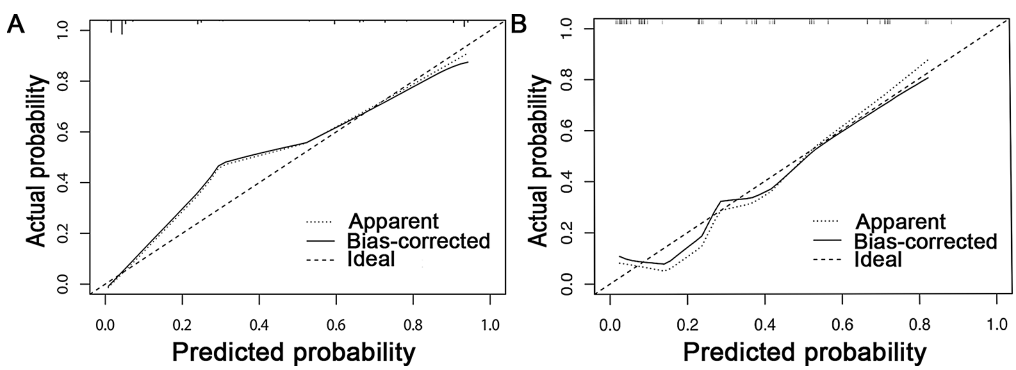


**Fig. 5** The calibration curves for FFVT prognosis risk nomogram in patients with closed traumatic fractures of **A**) the training set and **B**) the validation set. The x-axis represented the nomogram-predicted probability, and y-axis represented the actual probability of a free-floating thrombus failing to resolve and progressing to a closed thrombus

and continuous activation of inflammatory pathways in patients with FFVT identified for the first time after trauma. It was reported that high levels of D-dimer are independently associated with the occurrence of PTS in patients with initially identified DVT [19]. For patients with high preoperative D-dimer levels, it is crucial to strengthen monitoring and take timely and appropriate therapeutic interventions to minimize the risk of FFVT transforming into a closed thrombus and prevent the occurrence of PTS.

The locations of FFVT are crucial for predicting prognosis, which may correlate with its stability and further affect the patient's risk of developing Pulmonary Thromboembolism (PTE). Among the 240 patients with FFVT in our study, the most common site for FFVT was the popliteal vein, accounting for 74.5%, followed by the iliac-femoral vein at 17.5%, and the calf vein at 7.9%. Moreover, 68% (164/240) of patients achieved complete thrombus recanalization after short-term treatment, while 32% (76/240) of patients formed closed thrombi, especially those in the calf vein (84.2%, 16/19). Compared to FFVT in the calf vein, FFVT in the popliteal vein was most prone to recanalization, followed by the iliac-femoral vein. The lower leg has relatively fewer venous valves and slower blood flow velocities, making it more susceptible to thrombus expansion proximally into the main venous vessels, leading to whole-limb venous thrombotic lesions, which recanalize more slowly than segmental obstructions [20, 21]. The thrombus formation range of the calf vein is relatively small, followed by a smaller impact on venous blood reflux and mild triggering of a severe inflammatory response, resulting in less pronounced clinical symptoms, which may be the cause of the easy formation of closed thrombi in the calf veins. The higher recanalization rates of FFVT in the popliteal and iliac-femoral veins suggest that clinicians should consider early retrieval of the inferior vena cava filter after its placement in patients with FFVT to prevent difficulties in filter retrieval. Rauba et al. discovered that the success rate of filter retrieval significantly decreased with increasing implantation time [22].

The characteristics of thrombus margin are equally crucial for predicting prognosis. The thrombus margin may be associated with the freshness and activity of the thrombus, thereby affecting prognosis. In the early stages of FFVT formation, only the thrombus head is attached to the vessel wall, with the body and tail of the thrombus not completely obstructing the lumen. The thrombus is free from the vessel wall and floats within the vascular lumen, surrounded by a considerable amount of bypass flow. The relative surface area between the thrombolytic factors in the blood and the thrombus is large, leading to the formation of fissures and multiple small lumen-like channels within the thrombus, which accelerates thrombus dissolution. Additionally, the thrombus is fresh and not organized, with a mostly clear margin. Over time, the formation and deposition of fibrous collagen increase, causing the thrombus to grow in size and adhere more extensively to the surrounding vessel wall. This is often accompanied by the ingrowth of neovascularization and inflammatory tissue factors, leading to a tight adhesion between the thrombus and the venous wall. The blood flow around the thrombus decreases, and the thrombus margin becomes rough and indistinct. Wu et al. demonstrated that an increase in thrombus weight and volume significantly reduces the recanalization rate of the thrombus [23]. This may explain why thrombi with indistinct margins, larger volumes, and minimal blood flow are more likely to form closed thrombi. Our findings suggested that the amount of collateral blood around the thrombus may reflect the impact of the thrombus on venous return. An increase in collateral blood flow may indicate a greater impact of the thrombus on the venous system, thereby affecting prognosis. Ultrasound examinations can reflect the progression of thrombus formation [24], and ultrasound elasticity can reflect different stages of thrombus formation [25], providing valuable imaging information for clinical thrombus treatment and monitoring processes. Early detection and treatment of post-thrombotic venous wall damage can reduce residual venous obstruction and reshape it into permanent thrombosis.

The nomogram model developed in this study demonstrated a high C-index value (0.945), indicating the model's good discrimination ability. The AUC under the ROC curve was 0.949 in the training set and 0.924 (95% CI 0.863–0.986) in the validation set, respectively, confirming the model's excellent diagnostic performance. Furthermore, the calibration curves in both the training set and the validation set also showed good fitness, suggesting a high predictive capacity of the model. Considering this study was a retrospective study, there may be selection bias and information bias. The limited sample size may affect the stability and universality of the model. Therefore, future studies should aim to validate this model with a larger sample size and through multicenter data to enhance its reliability and applicability.

In summary, this study has successfully identified four key independent risk factors for the prognosis of FFVT in patients with closed fractures, including D-dimer levels, thrombus location, flow around the thrombus, and the clarity of the thrombus margins. A predictive nomogram model, developed based on these risk factors, has shown promising diagnostic efficacy and accuracy. This model has the potential to significantly enhance clinical decision-making by providing a clearer understanding of FFVT outcomes. It can guide healthcare professionals to proactively implement targeted interventions, such as anticoagulant therapy and thrombolytic treatment, thereby improving the quality of life for patients affected by FFVT following closed traumatic fractures.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12880-025-01695-0.

Supplementary Material 1

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Not applicable.

**Author contributions**
Yao Wei provided input into the concept and design of the study. Changxu Guo and Xiaoyu Chen collected and assembled the data. Wei Yao and Yuan Yu wrote and critically revised the article. All authors have read and approved the final version at the time of submission.

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**Data availability**
All data generated or analyzed during this study are included in this enclosed article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the Medical Ethics Committee of Tianjin Hospital (2024MER204). Written informed consent was waived due to the nature of retrospective study.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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