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Research article

Construction and validation of a perioperative concomitant lower extremity deep vein thrombosis line graph model in patients with aneurysmal subarachnoid hemorrhage

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A R T I C L E I N F O

Keywords:
aSAH
Deep venous thrombosis
Nomogram

A B S T R A C T

Background: To develop and validate a nomogram for predicting the probability of deep venous thrombosis (DVT) in patients with aneurysmal subarachnoid hemorrhage (aSAH) during the perioperative period, using clinical features and readily available biochemical parameters.
Methods: The least absolute shrinkage and selection operator (LASSO) regression technique was employed for data dimensionality reduction and selection of predictive factors. A multivariable logistic regression analysis was conducted to establish a predictive model and nomogram for post-aSAH DVT. The discriminative ability of the model was determined by calculating the area under the curve (AUC).
Results: A total of 358 aSAH patients were included in the study, with an overall incidence of DVT of 20.9%. LASSO regression identified four variables, including age, modified Fisher grade, total length of hospital stay, and anticoagulation therapy, as highly predictive factors for post-aSAH DVT. The patients were randomly divided into a modeling group and a validation group in a 6:4 ratio to construct the nomogram. The AUCs of the modeling and validation groups were 0.8511 (95% CI, 0.7922–0.9099) and 0.8633 (95% CI, 0.7968–0.9298), respectively.
Conclusions: The developed nomogram exhibits good accuracy, discriminative ability, and clinical utility in predicting DVT, aiding clinicians in identifying high-risk individuals and implementing appropriate preventive and treatment measures.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) caused by intracranial aneurysm rupture is a life-threatening disease [1]. Surgical intervention such as clipping and coiling is the standard method of handling this disease, effectively preventing rerupture, bleeding and reducing nerve damage, and the management of complications around the surgical period has also attracted much attention [2].

Deep vein thrombosis (DVT) of the lower extremities is a common complication following subarachnoid hemorrhage [3]. Its pathogenesis is well understood, and scores are now available to predict its occurrence; for example, the Caprini score can assess the risk of DVT based on patient age, BMI, and medical history [4]. However, the accuracy and precision of DVT prediction still need to be improved, and clinicians still endeavor to carry out DVT risk assessment based on clinical indicators, especially for DVT prediction in the perioperative period of neurosurgical aSAH. DVT has been reported to occur in 18% of aSAH patients within the first 2 weeks [5].

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Table 1
Demographic and clinical characteristics of study participants.

Characteristic	DVT = 0 (n = 283)	DVT = 1 (n = 75)	p
Gender, n (%)			0.201
Male	92 (33)	18 (24)	
Female	191 (67)	57 (76)	
AGE, Median (Q1,Q3)	55 (49, 63)	61 (54, 68)	<0.001
Total length of stay, Median (Q1,Q3)	16.4 (12.9, 22.45)	24.7 (19.9, 32.3)	<0.001
Onset time, Median (Q1,Q3)	0 (0, 2)	1 (0, 3)	0.107
Smoke, n (%)			0.024
No	203 (72)	64 (85)	
Yes	80 (28)	11 (15)	
Drink, n (%)			0.609
No	228 (81)	63 (84)	
Yes	55 (19)	12 (16)	
Hypertension, n (%)			0.096
No	183 (65)	40 (53)	
Yes	100 (35)	35 (47)	
Coronary heart disease, n (%)			0.564
No	269 (95)	70 (93)	
Yes	14 (5)	5 (7)	
Diabetes, n (%)			0.705
No	275 (97)	72 (96)	
Yes	8 (3)	3 (4)	
GCS, n (%)			0.072
5	1 (0)	1 (1)	
8	3 (1)	2 (3)	
9	2 (1)	2 (3)	
10	6 (2)	4 (5)	
11	1 (0)	2 (3)	
12	10 (4)	4 (5)	
13	60 (21)	12 (16)	
14	147 (52)	38 (51)	
15	53 (19)	10 (13)	
WFNS, n (%)			0.01
1	56 (20)	13 (17)	
2	204 (72)	46 (61)	
3	0 (0)	1 (1)	
4	22 (8)	14 (19)	
5	1 (0)	1 (1)	
mFISHER, n (%)			<0.001
1	75 (27)	7 (9)	
2	129 (46)	27 (36)	
3	56 (20)	20 (27)	
4	23 (8)	21 (28)	
HH, n (%)			0.002
1	56 (20)	8 (11)	
2	195 (69)	46 (61)	
3	30 (11)	19 (25)	
4	2 (1)	2 (3)	
ICH, n (%)			0.004
No	251 (89)	56 (75)	
Yes	32 (11)	19 (25)	
Hospital-acquired pneumonia, n (%)			<0.001
No	123 (43)	16 (21)	
Yes	160 (57)	59 (79)	
CONSCIOUS, n (%)			0.427
No	40 (14)	14 (19)	
Yes	243 (86)	61 (81)	
PICC, n (%)			0.006
No	265 (94)	62 (83)	
Yes	18 (6)	13 (17)	
Lower limb muscle strength≥3, n (%)			0.013
No	7 (2)	7 (9)	
Yes	276 (98)	68 (91)	
MALIGNANTT, n (%)			0.691
No	275 (97)	74 (99)	
Yes	8 (3)	1 (1)	
transfuse blood, n (%)			0.645
No	213 (75)	59 (79)	
Yes	70 (25)	16 (21)	

(*continued on next page*)

Table 1 (*continued*)

Characteristic	DVT = 0 (n = 283)	DVT = 1 (n = 75)	p
surgery, n (%)			<0.001
Clipping	50 (18)	33 (44)	
coiling	233 (82)	42 (56)	
anticoagulation, n (%)			<0.001
No	99 (35)	51 (68)	
Yes	184 (65)	24 (32)	
barotherapy, n (%)			0.068
No	108 (38)	38 (51)	
Yes	175 (62)	37 (49)	
ICUstay, Median (Q1,Q3)	2 (1, 5)	7 (2, 11)	<0.001
Admission WBC, Median (Q1,Q3)	10.27 (8.16, 13.32)	10.92 (8.65, 13.94)	0.116
Admission RBC, Median (Q1,Q3)	4.32 (4.04, 4.65)	4.27 (4.02, 4.63)	0.588
Admission HB, Median (Q1,Q3)	132 (123, 142)	130 (123.5, 139)	0.575
Admission ALB, Median (Q1,Q3)	41 (39, 45)	42 (39, 44)	0.985
Admission LDH, Median (Q1,Q3)	412 (350, 502)	455 (412.5, 534.5)	0.001
Admission FDP, Median (Q1,Q3)	3.6 (1.95, 6)	5.5 (3.2, 8.35)	<0.001
Admission D-dimer, Median (Q1,Q3)	1.25 (0.64, 2.23)	2 (1.01, 2.98)	0.003
Post-operative WBC, Median (Q1,Q3)	10.06 (8.06, 13)	12.12 (9.55, 15.36)	<0.001
Post-operative RBC, Mean ± SD	4.01 ± 0.58	3.78 ± 0.59	0.003
Post-operative HB, Mean ± SD	122.27 ± 18.69	115.11 ± 16.23	0.001
Post-operative ALB, Median (Q1,Q3)	36 (33, 39)	33 (32, 36)	<0.001
Post-operative LDH, Median (Q1,Q3)	393 (324, 490.5)	513 (437.5, 584.5)	<0.001
Post-operative FDP, Median (Q1,Q3)	3.9 (2.4, 6.5)	10.6 (6.15, 17.25)	<0.001
Post-operative D-dimer, Median (Q1,Q3)	1.2 (0.78, 2.07)	3.3 (1.93, 6.86)	<0.001

Typically, DVT may occur as early as the day after aSAH, with the highest incidence between 5 and 9 days [6]. Due to the complexity of the pathomechanisms of DVT, a single-factor analysis may not provide a comprehensive understanding of the onset and progression of DVT [7]. Therefore, combining multifactorial research methods to establish a more accurate DVT prediction model can better guide the clinic.

A nomogram is a graphical model that combines multiple risk factors to achieve accurate predictions, and it has been widely utilized as a predictive tool in various diseases [8]. To our knowledge, there is currently no reported nomogram specifically designed for predicting lower extremity deep vein thrombosis (LEDVT) in patients with aSAH using population data. Hence, the objective of this study was to identify independent clinical predictors of LEDVT following aSAH and subsequently develop and validate nomograms that can assist in predicting the prognosis of LEDVT in clinical practice.

2. Materials and methods

2.1. Method

This study was a single-center retrospective study.

2.2. Data collection

This study retrospectively collected clinical data from 358 patients with aneurysmal subarachnoid hemorrhage who were admitted to the Department of Neurosurgery of the First Affiliated Hospital of Chongqing Medical University and underwent surgical treatment from January 2019 to December 2021. The patients were categorized into two groups: the LEDVT (lower extremity deep vein thrombosis) group and the non-LEDVT group, based on the presence or absence of lower limb deep vein thrombosis. The inclusion criteria were as follows: (1) meeting the diagnostic criteria for subarachnoid hemorrhage, confirmed by imaging, with symptom onset within 72 h; (2) meeting the diagnostic criteria for deep vein thrombosis, doppler ultrasound was performed within admission and two weeks after surgery, but some patients did not have postoperative ultrasound examination due to rapid recovery and other reasons. The exclusion criteria were as follows: (1) patients with a history of DVT or lower extremity ultrasound findings indicative of old thrombosis; (2) patients in the active stage of concomitant malignancy; (3) patients with various hematologic diseases; (4) patients with recent significant trauma; (5) patients with severe cardiopulmonary, hepatic, or renal diseases. (6) The SARS-Cov-2 PCR results were all negative.

Clinical data, including admission and follow-up information, were collected and recorded for all patients who met the inclusion criteria. The collected data encompassed various aspects, as follows: (1) General information such as the patient's name, age, sex, height, weight, and other relevant details. (2) Current medical history obtained through patient questioning. (3) Past and personal history, including any comorbidities such as hypertension, diabetes, coronary artery disease, among others. (4) Surgical status, indicating whether the patient underwent interventional endovascular treatment or open cranial clamping. (5) Assessment of the patient's disease severity, including evaluation of the Glasgow Coma Scale (GCS), modified Fisher score, World Federation of Neurological Surgeons (WFNS) grade, and Hunt-Hess classification. (6) Laboratory tests conducted after admission.

2.3. Statistical methods

To determine independent predictors of LEDVT in patients with aSAH, unpaired *t*-test or Wilcoxon rank sum test, Pearson chi-square test or Fisher exact test (as appropriate) was used for group comparisons between the LEDVT and non-LEDVT groups. The least absolute shrinkage and selection operator (LASSO) regression technique was used for the selection of data dimensions and predictors. A prediction model and nomogram for LEDVT after aSAH was developed using multivariate logistic regression analysis. The discriminative power of the model was determined by calculating the area under the curve (AUC). Overall, AUC >0.70 was considered to have a good discriminatory power. Decision curve analysis was performed to determine the clinical usefulness of the nomogram by quantifying the net benefit at different threshold probabilities in the validation dataset. All statistical tests were two-sided and p-values <0.05 were considered significant. All statistical analyses were performed using R statistical software (R3.5.1), and the nomogram was constructed using the "rms" package.

3. Results

Among the study participants, 20.9% (75/358) were diagnosed with LEDVT. Table 1 presents the demographic and clinical characteristics of the participants. From the 63 variables initially collected, a total of four variables were selected based on non-zero coefficients obtained from LASSO regression analysis (Fig. 1). These variables included age, modified Fisher classification, total length of stay, and the administration of anticoagulation.

To construct a prediction model for LEDVT, multivariate logistic regression analysis was performed using the four selected variables derived from the LASSO regression technique (Fig. 1(a) and(b)). The study participants were randomly divided into modeling and validation groups in a 6:4 ratio. The nomogram (Fig. 2) was developed based on the modeling group and exhibited favorable predictive performance in both the modeling and validation cohorts, with an AUC of 0.8511 (95% CI, 0.7922–0.9099) and 0.8633 (95% CI, 0.7968–0.9298) respectively (Fig. 3(a) and(b)). Additionally, calibration plots demonstrated good agreement between the predicted probabilities generated by the nomogram and the actual probabilities (Fig. 4). The decision curve analysis of the nomogram is depicted in Fig. 5. These findings confirm the clinical applicability of the nomogram in predicting LEDVT and support the notion that utilizing the nomogram for LEDVT prediction is more advantageous compared to treating all patients or implementing no treatment protocols.

4. Discussion

In this study, a nomogram was created to predict LEDVT after aSAH. the nomogram included 4 variables, including age, modified Fisher classification, total length of stay, and whether anticoagulation was administered. The nomogram has good discriminatory power, correction ability, and clinical application.

First, age is widely recognized as being strongly associated with lower extremity deep vein thrombosis. The likelihood of an adverse outcome after aneurysmal subarachnoid hemorrhage is significantly higher as the patient's overall health tends to deteriorate with age, especially in the presence of other common medical conditions such as hypertension and diabetes mellitus, and the superimposition of multiple risk factors makes the risk of DVT even more pronounced in older patients [9]. Studies have also noted that 65 years of age is an independent risk factor for the development of DVT [10,11]. Secondly, age-related endothelial dysfunction and changes in platelet function may lead to an increased risk of venous thromboembolism in the elderly. With age, the endothelium is more damaged, gradually ages and becomes roughened, which makes blood vessels more susceptible to thrombus formation [12].

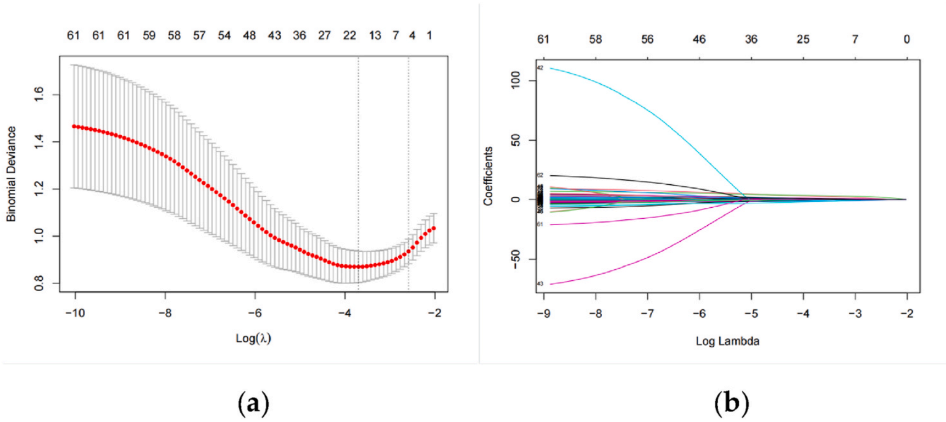


Fig. 1. Predictor selection using the LASSO regression analysis with twentyfold cross-validation. (a) Tuning parameter (lambda) selection of deviance in the LASSO regression based on the minimum criteria (left dotted line) and the 1-SE criteria (right dotted line). (b) A coefficient profile plot was created against the log (lambda) sequence. In the present study, predictor's selection was according to the MIN criteria (left dotted line), where 5 nonzero coefficients were selected. LASSO, least absolute shrinkage and selection operator; SE, standard error.

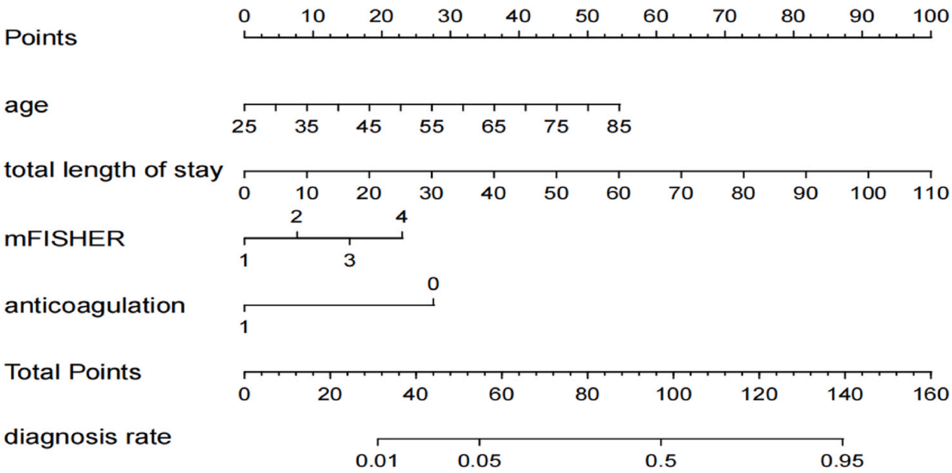
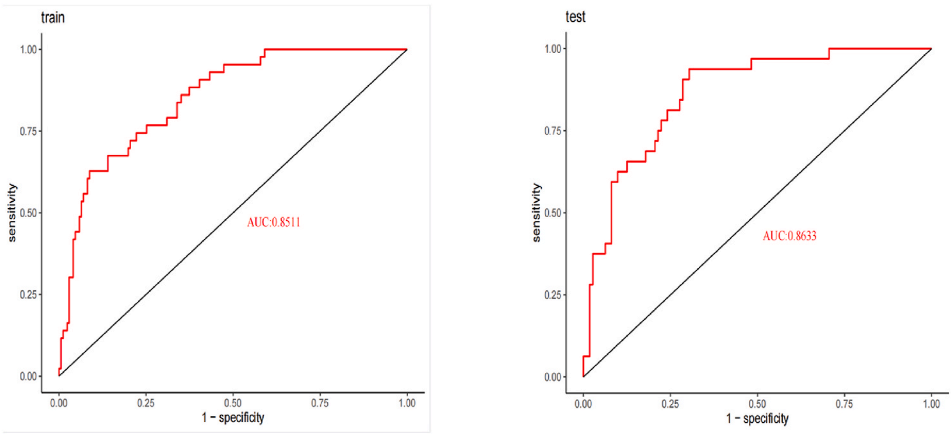


Fig. 2. Illustrates the nomogram which has been developed for predicting lower extremity deep vein thrombosis (LEDVT) in patients. To utilize the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to ascertain the number of points received for every value of the variable. The total points received by the patient are subsequently located on the axis for total points, and a line is drawn downward to the risk axes to determine the risk of LEDVT.



(a) (b)

Fig. 3. ROC curve of the nomogram for predicting LEDVT in patients with SAH. **(a)** ROC curve in the training set; **(b)** ROC curve in the test set. LEDVT: Lower extremity deep vein thrombosis; AUC: Area under the ROC curve; aSAH: Aneurysmal subarachnoid hemorrhage; ROC: Receiver operating characteristic.

Third, aging is accompanied by elevated levels of several plasma components in the blood, such as fibrinogen, coagulation factors (F) VII, FVIII, D-dimer, and homocysteine. Although the clinical significance of such elevations for the risk of VTE is unclear, common genetic risk factors in patients with VTE, such as factor V Leiden and the prothrombin 20210 A mutation, do not appear to vary significantly in proportion between age groups [13]. In addition, it has been suggested that hyperfunction of coagulation factors after subarachnoid hemorrhage may lead to the formation of DVT [14], further increasing the risk of DVT in the elderly.

The Modified Fisher Grade is often used to predict the prognosis of patients with SAH. The Modified Fisher classification is divided into 5 grades, with higher grades implying a greater accumulation of blood around the ventricles, representing a more severe subarachnoid hemorrhage, which to some extent reflects the degree of cerebral arterial vasospasm [15]. Cerebral arterial spasm can lead to insufficient blood supply to the brain, which can cause complications such as ischemia and subsequently lead to prolonged hospitalization. Related studies have shown that prolonged hospitalization is an independent risk factor for deep vein thrombosis in the lower extremities after subarachnoid hemorrhage [5], and prolonged hospitalization is often in turn the result of a variety of factors, such as postoperative pulmonary infection. In our cohort, the rate of postoperative lung infection in the LEDVT group was 59/75, suggesting that this group of patients could benefit from having chest CT.

Neurosurgical clamping and endovascular intervention are commonly used to treat intracranial aneurysms. Interventional treatments are less invasive and result in faster postoperative recovery, whereas clamping treatments require craniotomy, are more traumatic, and require longer hospitalization for recovery [16,17]. The interventional procedures often require endovascular stent

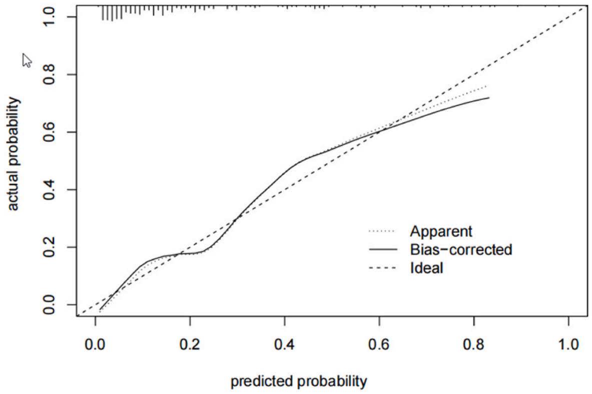


Fig. 4. Calibration curve of the nomogram.

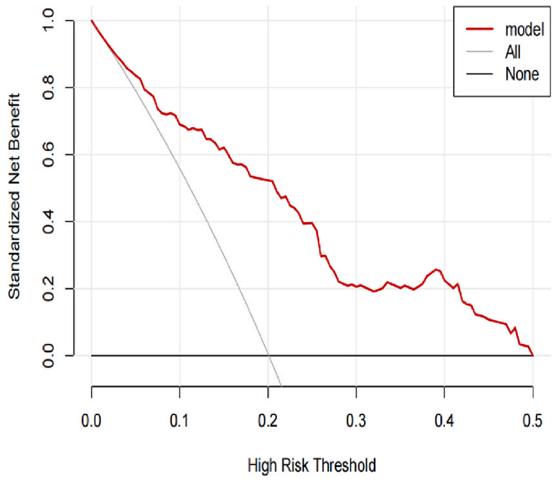


Fig. 5. DCA for the nomogram. A horizontal line indicates that all samples are negative and not treated, with a net benefit of zero. An oblique line indicates that all samples are positive. The net benefit is a backslash with a negative slope. DCA: Decision curve analysis.

implantation, coil tamponade, and other operations, all of which may damage cerebrovascular endothelial cells and platelets, making them more prone to aggregation and coagulation to form thrombi. Therefore, it is often necessary to minimize thrombus formation and reduce the risk of arterial embolism and rebleeding through the use of anticoagulants, and heparin anticoagulation is often used in the treatment of LEDVT [18]. In our patients, the attending surgeon decided whether or not to use anticoagulants postoperatively based on the intraoperative situation and the condition of the patient, and only 24 patients who developed LEDVT did not use anticoagulants (32%), and our results suggest that the use of anticoagulants may reduce the risk of DVT, and that the non-use of anticoagulants is a risk factor for LEDVT, and that, in a placebo-controlled trial, after aneurysm surgery subcutaneous enoxaparin 40 mg/d was performed, the results showed that the risk of intracranial hemorrhage was slightly increased in the enoxaparin group, and the difference between its prognosis and that of the patients in the placebo group was not statistically significant ($P = 0.062$) [19]. Additional studies have indicated that heparin use in aSAH is not only safe but also effective in addressing many of the pathologic mechanisms triggered by aSAH [20,21], but this needs to be validated by prospective studies with larger cohorts.

A nomogram is a graph based on multiple regression analysis in which multiple predictors are integrated simultaneously and then plotted on the same plane with scaled line segments. We integrated the 4 selected independent risk factors into a visual nomogram model that showed good variability in both the modeling cohort 0.8511 (95% CI, 0.7922–0.9099) and the validation cohort 0.8633 (0.7968–0.9298). It is worth mentioning that several studies have used time-competitive risk models to quantify the cumulative incidence of venous thromboembolism after aneurysmal subarachnoid hemorrhage [22]. We can cite a low-risk case: age: 50 years, modified FISHER classification: grade 2, length of hospitalization: 16 days, use of anticoagulants. We chose a case that was relatively young, had a low FISHER classification, a short hospitalization and was on anticoagulants. The model calculated a risk probability of 0.026, indicating that this patient had a relatively low risk of postoperative LEDVT. High-risk case: age: 70 years, modified FISHER classification: grade 4, length of hospitalization: 40 days, no anticoagulants used. We chose a case that was relatively old, had a high FISHER classification, had a long hospitalization and was not on anticoagulants. The model calculated a risk probability of 0.894, indicating that this patient had a relatively high risk of postoperative LEDVT. We would then be in a better position to take measures to prevent the occurrence of LEDVT.

5. Limitations

Our study has several limitations that should be acknowledged. Firstly, the study population consisted solely of patients with aneurysmal subarachnoid hemorrhage from a single center, which raises the need for external validation and generalizability of the proposed nomogram to a larger and more diverse population. Further studies involving multiple centers or a broader patient cohort would enhance the robustness of the nomogram's predictive ability. Secondly, not all patients underwent routine screening for deep vein thromboembolism, which could lead to an underestimation of the true incidence of asymptomatic venous thromboembolism. Asymptomatic cases could potentially go undetected, thereby influencing the reported incidence rates. Future studies implementing systematic and standardized screening protocols for deep vein thromboembolism would provide a more comprehensive understanding of its occurrence in this patient population.

6. Conclusions

In conclusion, our study successfully developed a nomogram utilizing clinical features and readily available biochemical parameters to predict the probability of lower extremity deep vein thrombosis (LEDVT) in patients with aneurysmal subarachnoid hemorrhage during the perioperative period. The nomogram demonstrated favorable predictive accuracy, discriminatory ability, and clinical utility, thereby enabling clinicians to identify individuals at high risk of developing DVT and implement appropriate prevention and control measures. However, it is important to acknowledge the limitations of this study, and future research should focus on validating and refining the nomogram under multicenter settings with larger sample sizes.

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Institutional review board statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (K2023-226). In accordance with national legislation and institutional requirements, written informed consent for participation was not required for this study.

Informed consent statement

Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Disclaimer/publisher's note

The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s).

CRediT authorship contribution statement

Daiqi Xu: Writing – review & editing, Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Han Xiong:** Resources, Data curation. **Shizhen Cui:** Writing – review & editing, Methodology, Data curation. **Jiahe Tan:** Writing – review & editing, Visualization, Validation, Project administration. **Yinrui Ma:** Investigation, Data curation. **Zhaohui He:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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