Am J Transl Res 2025;17(11):9092-9108
www.ajtr.org /ISSN:1943-8141/AJTR0166694

Original Article

Predictive model for low-molecular-weight heparin ineffectiveness in pregnant and postpartum women with intracranial venous sinus thrombosis: a multicenter study

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Received June 10, 2025; Accepted November 4, 2025; Epub November 15, 2025; Published November 30, 2025

Abstract: Objective: To develop a risk prediction model for low-molecular-weight heparin (LMWH) ineffectiveness in pregnant women with intracranial venous sinus thrombosis (CVST), enabling early identification of high-risk patients. Methods: A retrospective analysis was conducted on 221 pregnant or postpartum CVST patients treated with LMWH at seven Chinese hospitals between January 2010 and January 2025. Patients were divided into effective (191 cases) and ineffective (30 cases) treatment groups. Logistic regression identified predictors, which were then used to develop a risk prediction model. Results: Univariate analysis revealed significant factors associated with treatment ineffectiveness: Coronavirus Disease 2019 (COVID-19), hyperthyroidism, platelet (PLT) count, antithrombin III (AT-III), homocysteine (Hcy), low-density lipoprotein cholesterol (LDL-C), protein C, and protein S (all $P < 0.1$). Variables with a *P-value* < 0.1 were further analyzed using Least Absolute Shrinkage and Selection Operator (LASSO) regression to identify key predictors, with the lambda value (0.011) determining the final model. Multivariate analysis identified independent risk factors: COVID-19, protein S, and homocysteine. Protein S (odds ratio [OR] < 1) acted as a protective factor, while COVID-19 and homocysteine (OR > 1) were risk factors. The model's receiver operating characteristic (ROC) curve area was 0.930 (95% confidence interval [CI]: 0.882-0.979), with sensitivity of 0.867 and specificity of 0.885. Cross-validation and bootstrap validation demonstrated robust model performance, with areas under the curve of 0.919 and 0.909, respectively. Conclusions: The developed predictive model, incorporating COVID-19, protein S, and Hcy, effectively assesses the risk of LMWH ineffectiveness in pregnant women with CVST, supporting clinical decision-making.

Keywords: Pregnancy-associated intracranial venous sinus thrombosis, low-molecular-weight heparin therapy, treatment ineffectiveness, logistic regression analysis, predictive modeling

Introduction

Cerebral venous sinus thrombosis (CVST) is a rare neurovascular disorder characterized by impaired cerebral venous outflow, which results in intracranial hypertension or focal neurological deficits [1-4]. In contrast to arterial thrombosis, CVST constitutes only 0.5%-1.0% of all cerebrovascular conditions [5], with an estimated prevalence of approximately 5 cases per million individuals [6]. Although CVST can occur at any age [7], it is more frequently identified in both younger and older populations, with a notably higher incidence in women, who experience a 3-4 times greater risk compared to men [8, 9]. Among women, key risk factors include pregnancy, childbirth, the use of oral contraceptives, and hormone replacement therapy [10, 11]. CVST can progress rapidly, resulting in severe disability or death if not promptly addressed, with mortality rates reaching as high as 30% [6, 12, 13]. However, early diagnosis and treatment have shown to reduce mortality to between 5-15% [8]. The detection rate of CVST in pregnant and postpartum women has significantly improved in recent years, owing to advancements in imaging technology and heightened clinical awareness.

https://doi.org/10.62347/DDQE3040

Anticoagulation therapy remains the primary treatment for CVST. Clinical guidelines recommend initiating anticoagulation as early as possible in CVST patients, provided there are no contraindications [14-16]. Anticoagulation facilitates thrombolysis, prevents thrombus propagation, reduces mortality, and improves overall prognosis. The administration and monitoring of anticoagulant therapy are well-established and straightforward, promoting the establishment of collateral circulation, enhancing blood reflux compensation, and facilitating fibrin autolysis to reopen obstructed sinuses. However, dynamic monitoring of symptoms, such as headache or changes in consciousness, is crucial, as therapeutic responses can vary, particularly in complex cases. In clinical practice, low-molecular-weight heparin (LMWH) is frequently used for CVST treatment in pregnant and postpartum women because it does not cross the placental barrier, ensuring fetal safety. Despite its widespread use, LMWH is ineffective in approximately 10% of these patients [17]. This study aimed to assess clinical data on the use of LMWH in pregnant and postpartum women with CVST and to develop a predictive model for identifying low-risk and high-risk populations to promote timely intervention and prevent adverse outcomes.

Data and methods

Clinical information

A retrospective analysis was conducted on 221 pregnant or postpartum (within six weeks) patients diagnosed with CVST and treated with LMWH at seven Chinese hospitals between 2010 and 2025. The treatment outcomes were classified into two groups: effective (191 cases) and ineffective (30 cases).

Inclusion criteria: (1) The patient met the diagnostic criteria for CVST during pregnancy or within six weeks postpartum; (2) No interventions affecting coagulation function were administered during treatment; (3) LMWH therapy was initiated following diagnosis, with mandatory follow-up for at least six months; (4) Comprehensive and accurate clinical data, including symptoms, examinations, and diagnostic evaluations, were available; (5) The participant provided informed consent by signing the consent form for clinical research and follow-up.

Exclusion criteria: (1) Patients exhibited varying degrees of elevated intracranial pressure upon evaluation; (2) Critical conditions such as consciousness disturbances, unstable vital signs, brain herniation, or decerebrate rigidity; (3) Severe coagulation dysfunction; (4) Presence of intracranial hemorrhage or cerebral infarction; (5) Severe comorbidities affecting other vital organs; (6) Prior use of interventions impacting study outcomes; (7) Incomplete clinical or follow-up data.

To ensure data accuracy, especially given the potential for asymptomatic COVID-19 infections and the retrospective nature of the study spanning both pre- and post-pandemic periods, all follow-up data were carefully verified through patient interviews and hospital records. Additionally, for cases diagnosed with COVID-19 during the study, the timing and severity of infection were documented, and patients were assessed for symptoms and clinical outcomes that might have impacted CVST treatment. This helped mitigate any potential bias from unrecognized or asymptomatic COVID-19 infections. The study also ensured that all data recorded prior to 2019 (before the official identification of COVID-19) were not affected by the pandemic, maintaining the integrity of the results from those years. The research followed the 2013 Declaration of Helsinki ethical guidelines, was approved by the Ethics Committee of Hefei Maternal and Child Health Hospital (Approval No. YYLL20240130-YNXM-LL-01-2.1), and obtained voluntary informed consent from patients and their families after fully explaining the study details.

Candidate predictors

Clinical, laboratory, and imaging parameters were systematically selected as candidate variables for analysis. These included age, body mass index (BMI), gravidity and parity counts, history of adverse pregnancy outcomes, family medical history, smoking and alcohol consumption habits, oral contraceptive use, immunosuppressant therapy, craniocerebral trauma or surgical history, intracranial vascular malformations, venous sinus compression, head or facial infections, history of COVID-19 infection, trace element deficiencies, conception method, pre-pregnancy comorbidities (e.g., hypertension, diabetes, thyroid disorders, anemia, and autoimmune diseases), pregnancy-related compli-

cations (including hypertensive disorders, gestational diabetes, thyroid dysfunction, anemia, thrombocytopenia, and hyperemesis gravidarum), infection history during pregnancy or postpartum, presenting symptoms (such as headache, nausea/vomiting, diplopia, epilepsy, and neurological deficits), pregnancy status (early, mid, or late pregnancy or postpartum), and diagnostic laboratory parameters. Laboratory parameters included: complete blood count (red blood cells [RBC], white blood cells [WBC], platelets [PLT], hemoglobin [HGB], absolute neutrophil count [ANC], and neutrophil percentage [NE%]), coagulation indices (prothrombin time [PT], activated partial thromboplastin time [APTT], thrombin time [TT], fibrinogen [FIB], fibrin degradation products [FDP], D-dimer, and antithrombin III [AT-III]), thromboelastography metrics (reaction time [R], clot formation time [K], angle, maximum amplitude [MA], lysis at 30 minutes [LY30], early clot lysis [EPL], and clot index [CI]), random blood glucose, serum homocysteine levels, lipid profile (total cholesterol [TC], triglycerides [TG], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C]), protein C and protein S activity, presence of lupus anticoagulant, methylenetetrahydrofolate reductase (MTHFR) polymorphism, fundoscopic findings, venous sinus thrombosis characteristics (including location, size, phase, number of affected sinuses, vascular stenosis, and collateral circulation), and pregnancy outcomes. Continuous variables, such as Hcy and protein S levels, were standardized or categorized based on clinically relevant thresholds to promote their inclusion in statistical models. For Hcy, a cutoff value of 15 μmol/L was used to categorize patients into "elevated" and "normal" levels, as previous studies have shown this threshold to be associated with increased thrombotic risk. Protein S activity was categorized into low (< 60%) and normal (≥ 60%) levels based on established clinical guidelines, which associate reduced protein S activity with an increased risk of venous thromboembolism. These thresholds were selected to align with existing clinical practices and to enhance the interpretability of the model results.

Therapeutic approach

According to Chinese guidelines for the management of CVST, patients were administered subcutaneous enoxaparin sodium at a dosage of 100 IU/kg every 12 h. Platelet count and coagulation parameters were monitored every three days, and once heparinization was stable, monitoring frequency was reduced to weekly until symptom resolution and imaging improvement are observed. The international normalized ratio (INR) was maintained between 2 and 3 throughout the duration of treatment. In cases of unsatisfactory outcomes, worsening symptoms, or the emergence of complications such as intracranial hemorrhage, elevated intracranial pressure, or brain herniation, anticoagulation therapy should be discontinued, and alternative interventions, such as endovascular procedures or surgical interventions, should be considered.

Observation index

Follow-up data were gathered through telephone consultations and outpatient visits. Patients were scheduled for reexaminations at 3, 6, and 12 months post-heparinization to assess symptoms and perform imaging evaluations, with the modified Rankin Scale (mRS) score consistently administered by the same physician. For patients unable to attend in-person appointments, the mRS score was assessed via telephone interviews. An mRS score of 0 indicates full recovery, while a score of 1 signifies minimal residual effects without significant functional limitations. Scores ranging from 0 to 1 reflect clinical improvement, whereas scores above 1 indicate the presence of persistent functional deficits. Improvement is also indicated by symptom alleviation or resolution, while stagnation or persistence of symptoms suggests no improvement. Imaging evidence of thrombus dissolution or reduction is considered an improvement; otherwise, the condition is classified as unchanged. Treatment effectiveness was determined based on the improvement in at least one of the three criteria (mRS score, symptoms, and imaging) relative to pretreatment status. Patients were subsequently categorized into two groups: those with ineffective treatment (requiring alternative interventions due to deterioration) and those with effective treatment. Follow-up data collection was adapted to account for COVID-19-related disruptions during the study period. Telephone consultations and outpatient visits were conducted with particular attention to any COVID-19-related symptoms in patients. In cases where patients were unable to attend in person

due to COVID-19-related restrictions or asymptomatic infection, virtual consultations were arranged, and patient-reported outcomes were cross-verified with hospital data. This approach helped ensure the reliability of follow-up data and reduced the likelihood of missing information, particularly in light of the challenges posed by the pandemic.

Statistical analysis

Univariate logistic regression was used to identify potential predictors of LMWH ineffectiveness, with a significance threshold of $P \leq 0.1$. Variables that showed potential relevance in the univariate analysis were included in the subsequent LASSO (Least Absolute Shrinkage and Selection Operator) logistic regression model, which was employed to select key features with non-zero coefficients. The LASSO method helps to enhance model stability by performing variable selection and regularization to prevent overfitting. To optimize model parameters, 10-fold cross-validation was used, and the final coefficients were determined based on the lambda value that minimized the standard error deviation. Variables with non-zero coefficients from the LASSO regression were retained for multivariate logistic regression, which was conducted using stepwise (bidirectional) selection with a significance threshold of $P < 0.05$. This approach enables the identification of the most significant predictors while accounting for potential confounders. A nomogram-based prediction model was constructed from the selected predictors. The model was validated using 1,000 bootstrap resamples to assess its internal validity and to minimize overfitting. The calibration accuracy of the model was evaluated by plotting a calibration curve and performing the Hosmer-Lemeshow test, which tests the goodness of fit between observed and predicted probabilities. The model's discriminatory performance was assessed using the receiver operating characteristic (ROC) curve, with metrics including area under the curve (ROC curve area), sensitivity, and specificity. Clinical utility was evaluated through Decision Curve Analysis (DCA), which quantifies the net benefit of the prediction model in clinical decision-making. Finally, the model's reliability and generalizability were further confirmed using ten-fold cross-validation and Bootstrap sampling, with corresponding ROC curves plotted for each validation method.

To mitigate the risk of model overfitting due to imbalanced sample sizes between the "effective" (191 cases) and "ineffective" (30 cases) treatment groups, several methods were applied to address class imbalance. These methods included stratified sampling during model training, synthetic minority oversampling (SMOTE), or penalty adjustments in the logistic regression models. Additionally, cross-validation techniques such as 10-fold cross-validation and bootstrap sampling were used to ensure that the model's performance was not overly influenced by the imbalance.

Results

Participants' clinical characteristics

A total of 221 cases were enrolled, with 30 categorized as ineffective, resulting in an incidence rate of 13.57% (30/221). Additional details are presented in **Table 1**. The univariate screening analysis, using a significance threshold of $P \leq 0.1$, did not adjust for multiple comparisons, which could lead to inflated Type I error rates. To correct for this, a Bonferroni correction was applied given the 54 variables tested. Regarding model validation, the minimal difference between the 10-fold cross-validated ROC curve area (0.919) and the original model ROC curve area (0.930) suggests a potential issue with data leakage, likely caused by performing feature selection prior to cross-validation.

Logistic regression analysis

The regression coefficients (β), standard errors (S.E.), Z values, *P* values, odds ratios (OR), and 95% confidence intervals (CI) for variables associated with treatment ineffectiveness were analyzed. Univariate logistic regression analysis revealed that factors such as COVID-19 infection, hyperthyroidism, PLT count, AT-III, Hcy, LDL-C, protein C, and protein S were significantly associated with treatment ineffectiveness risk (all $P < 0.1$). The detailed results are presented in **Table 2**. For the Lasso screening, variables with $P < 0.1$ from the univariate analysis were included to address potential multicollinearity. Non-zero coefficient variables were selected based on the lambda value (0.011), corresponding to the minimum deviation plus one standard error. The results are summarized in **Table 3** and illustrated in **Figure 1**.

Table 1. Participants' baseline characteristics

Variables	Total (n = 221)	Valid Group (n = 191)	Invalid Group (n = 30)	P
Age, Median (Q1, Q3)	29.00 (25.00, 33.50)	29.00 (25.50, 33.00)	29.00 (22.50, 32.75)	0.703
BMI, Median (Q1, Q3)	24.52 (21.88, 26.72)	24.62 (21.55, 26.80)	24.06 (22.66, 26.61)	0.814
Gravida, Median (Q1, Q3)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	0.892
Parity, Median (Q1, Q3)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.256
Adverse pregnancy history, n (%)				1.000
No	201 (91.0)	173 (90.6)	28 (93.3)	
Yes	20 (9.0)	18 (9.4)	2 (6.7)	
Family history, n (%)				0.751
No	197 (89.1)	171 (89.5)	26 (86.7)	
Yes	24 (10.9)	20 (10.5)	4 (13.3)	
History of smoking, n (%)				0.505
No	182 (82.4)	156 (81.7)	26 (86.7)	
Yes	39 (17.6)	35 (18.3)	4 (13.3)	
Drinking history, n (%)				0.766
No	174 (78.7)	151 (79.1)	23 (76.7)	
Yes	47 (21.3)	40 (20.9)	7 (23.3)	
History of taking oral contraceptives, n (%)				0.571
No	164 (74.2)	143 (74.9)	21 (70.0)	
Yes	57 (25.8)	48 (25.1)	9 (30.0)	
Immunosuppressants, n (%)				1.000
No	198 (89.6)	171 (89.5)	27 (90.0)	
Yes	23 (10.4)	20 (10.5)	3 (10.0)	
History of craniocerebral trauma, n (%)				0.480
No	204 (92.3)	175 (91.6)	29 (96.7)	
Yes	17 (7.7)	16 (8.4)	1 (3.3)	
History of craniocerebral surgery, n (%)				1.000
No	204 (92.3)	176 (92.1)	28 (93.3)	
Yes	17 (7.7)	15 (7.9)	2 (6.7)	
Intracranial vascular malformation, n (%)				0.769
No	194 (87.8)	168 (88.0)	26 (86.7)	
Yes	27 (12.2)	23 (12.0)	4 (13.3)	
Compression of intracranial venous sinuses, n (%)				0.703
No	205 (92.8)	176 (92.1)	29 (96.7)	
Yes	16 (7.2)	15 (7.9)	1 (3.3)	
History of head and facial infections, n (%)				0.699
No	206 (93.2)	177 (92.7)	29 (96.7)	
Yes	15 (6.8)	14 (7.3)	1 (3.3)	
COVID-19, n (%)				< 0.001
No	190 (86.0)	179 (93.7)	11 (36.7)	
Yes	31 (14.0)	12 (6.3)	19 (63.3)	
Trace Element Deficiency, n (%)				0.691
No	208 (94.1)	180 (94.2)	28 (93.3)	
Yes	13 (5.9)	11 (5.8)	2 (6.7)	
Conception mode, n (%)				0.480
Assisted	48 (21.7)	40 (20.9)	8 (26.7)	
Spontaneous	173 (78.3)	151 (79.1)	22 (73.3)	
Hypertension, n (%)				0.569
No	171 (77.4)	149 (78.0)	22 (73.3)	
Yes	50 (22.6)	42 (22.0)	8 (26.7)	
Diabetes, n (%)				0.279
No	203 (91.9)	177 (92.7)	26 (86.7)	
Yes	18 (8.1)	14 (7.3)	4 (13.3)	
Hypothyroidism, n (%)				0.751
No	197 (89.1)	171 (89.5)	26 (86.7)	
Yes	24 (10.9)	20 (10.5)	4 (13.3)	

Hyperthyroidism, n (%)				0.075
No	193 (87.3)	170 (89.0)	23 (76.7)	
Yes	28(12.7)	21 (11.0)	7 (23.3)	
Anemia, n (%)				0.362
No	178 (80.5)	152 (79.6)	26 (86.7)	
Yes	43 (19.5)	39 (20.4)	4 (13.3)	
Autoimmune disease, n (%)				0.462
No	205 (92.8)	178 (93.2)	27 (90.0)	
Yes	16 (7.2)	13 (6.8)	3 (10.0)	
Uterine myoma, n (%)				0.269
No	188 (85.1)	160 (83.8)	28 (93.3)	
Yes	33 (14.9)	31 (16.2)	2 (6.7)	
HDP, n (%)				0.112
No	184 (83.3)	156 (81.7)	28 (93.3)	
Yes	37 (16.7)	35 (18.3)	2 (6.7)	
GDM, n (%)				1.000
No	190 (86.0)	164 (85.9)	26 (86.7)	
Yes	31 (14.0)	27 (14.1)	4 (13.3)	
Abnormal thyroid hormones during pregnancy, n (%)				0.740
No	201 (91.0)	174 (91.1)	27 (90.0)	
Yes	20 (9.0)	17 (8.9)	3 (10.0)	
Anemia of pregnancy, n (%)				0.726
No	179 (81.0)	154 (80.6)	25 (83.3)	
Yes	42 (19.0)	37 (19.4)	5 (16.7)	
Thrombocytopenia in pregnancy, n (%)				0.553
No	193 (87.3)	168 (88.0)	25 (83.3)	
Yes	28 (12.7)	23 (12.0)	5 (16.7)	
Hyperemesis Gravidarum, n (%)				0.469
No	180 (81.4)	157 (82.2)	23 (76.7)	
Yes	41 (18.6)	34 (17.8)	7 (23.3)	
Infection during pregnancy or thepuerperium, n (%)				0.423
No	187 (84.6)	163 (85.3)	24 (80.0)	
Yes	34 (15.4)	28 (14.7)	6 (20.0)	
Headache, n (%)				0.470
No	173 (78.3)	148 (77.5)	25 (83.3)	
Yes	48 (21.7)	43 (22.5)	5 (16.7)	
Nausea or Vomiting, n (%)				0.466
No	181 (81.9)	155 (81.2)	26 (86.7)	
Yes	40 (18.1)	36 (18.8)	4 (13.3)	
Diplopia, n (%)				0.571
No	191 (86.4)	166 (86.9)	25 (83.3)	
Yes	30 (13.6)	25 (13.1)	5 (16.7)	
Epilepsy, n (%)				0.436
No	206 (93.2)	179 (93.7)	27 (90.0)	
Yes	15 (6.8)	12 (6.3)	3 (10.0)	
Focal neurological deficits, n (%)				0.746
No	199 (90.0)	171 (89.5)	28 (93.3)	
Yes	22 (10.0)	20 (10.5)	2 (6.7)	
Pregnancy status, n (%)				0.865
Early pregnancy	23 (10.4)	20 (10.5)	3 (10.0)	
Late pregnancy	45 (20.4)	39 (20.4)	6 (20.0)	
Mid-pregnancy	18 (8.1)	17 (8.9)	1 (3.3)	
Puerperium	135 (61.1)	115 (60.2)	20 (66.7)	
RBC, Median (Q1, Q3)	3.66 (3.27, 4.36)	3.75 (3.35, 4.38)	3.77 (3.33, 4.21)	0.780
WBC, Median (Q1, Q3)	9.60 (7.65, 11.36)	9.84 (7.90, 11.47)	8.53 (7.23, 11.08)	0.101

PLT, Median (Q1, Q3)	224.00 (131.00, 231.00)	225.00 (132.00, 232.00)	180.50 (131.50, 230.50)	0.098
HGB, Median (Q1, Q3)	99.00 (91.50, 123.00)	101.00 (92.00, 123.00)	96.50 (91.25, 122.50)	0.493
ANC, Median (Q1, Q3)	3.21 (2.37, 4.72)	3.16 (2.38, 4.66)	2.94 (2.40, 4.68)	0.740
NE%, Mean ± SD	74.59 ± 4.77	74.65 (69.91, 77.82)	73.47 (69.23, 78.64)	0.620
PT, Median (Q1, Q3)	13.24 (12.33, 14.00)	13.24 (12.33, 13.95)	12.99 (12.63, 13.94)	0.691
APTT, Median (Q1, Q3)	27.63 (25.30, 29.33)	27.45 (24.62, 29.39)	26.90 (25.56, 29.24)	0.874
TT, Mean ± SD	13.24 ± 1.49	13.31 (12.36, 14.57)	12.98 (12.05, 13.83)	0.338
FIB, Median (Q1, Q3)	2.70 (2.50, 2.90)	2.70 (2.50, 3.05)	2.80 (2.42, 3.38)	0.710
FDP, Median (Q1, Q3)	3.69 (2.71, 4.56)	3.79 (2.62, 4.61)	3.62 (3.03, 4.24)	0.831
D-dimer, Median (Q1, Q3)	3.21 (2.37, 4.72)	3.28 (2.43, 4.69)	2.81 (2.35, 4.75)	0.695
AT-III, Median (Q1, Q3)	73.81 (68.82, 77.81)	73.57 (68.91, 77.59)	73.11 (39.47, 77.04)	0.121
R, Median (Q1, Q3)	5.41 (4.77, 6.25)	5.39 (4.76, 6.28)	5.63 (4.76, 6.22)	0.873
K, Median (Q1, Q3)	2.80 (2.45, 3.20)	2.80 (2.40, 3.20)	2.80 (2.42, 3.20)	0.890
Angle, Median (Q1, Q3)	61.30 (55.90, 66.20)	62.00 (56.15, 66.35)	61.55 (54.90, 65.35)	0.587
MA, Median (Q1, Q3)	56.81 (52.41, 64.96)	56.81 (52.34, 64.73)	56.59 (53.35, 64.99)	0.824
LY30, Median (Q1, Q3)	2.70 (2.20, 3.20)	2.70 (2.05, 3.20)	2.90 (2.50, 3.20)	0.216
EPL, Median (Q1, Q3)	9.60 (7.65, 11.36)	9.65 (7.78, 11.41)	9.66 (7.63, 10.91)	0.380
CI, Median (Q1, Q3)	2.80 (2.50, 3.20)	2.80 (2.50, 3.20)	2.80 (2.45, 3.10)	0.737
Glu, Median (Q1, Q3)	6.10 (5.50, 6.70)	6.10 (5.50, 6.65)	5.80 (5.08, 6.38)	0.096
Hcy, Median (Q1, Q3)	8.73 (5.88, 11.29)	7.53 (5.28, 10.18)	11.30 (9.07, 14.40)	< 0.001
TC, Median (Q1, Q3)	3.52 (2.67, 4.60)	3.62 (2.72, 4.54)	3.35 (2.78, 5.12)	0.796
TG, Median (Q1, Q3)	1.00 (0.70, 1.30)	1.00 (0.60, 1.30)	1.05 (0.62, 1.30)	0.745
HDL-C, Median (Q1, Q3)	1.10 (0.70, 1.40)	1.10 (0.65, 1.40)	0.90 (0.70, 1.30)	0.436
LDL-C, Median (Q1, Q3)	2.67 (1.99, 3.45)	2.47 (1.84, 3.38)	2.83 (1.95, 4.28)	0.166
Protein C, Median (Q1, Q3)	57.00 (38.50, 76.00)	58.00 (40.50, 77.00)	35.00 (33.00, 58.75)	< 0.001
Protein S, Median (Q1, Q3)	62.00 (37.00, 84.50)	66.00 (40.50, 85.00)	39.00 (35.00, 68.00)	0.004
Lupus anticoagulants, n (%)				0.351
No	212 (95.9)	184 (96.3)	28 (93.3)	
Yes	9 (4.1)	7 (3.7)	2 (6.7)	
MTHFR, n (%)				0.530
CC	194 (87.8)	169 (88.5)	25 (83.3)	
CT	21 (9.5)	17 (8.9)	4 (13.3)	
TT	6 (2.7)	5 (2.6)	1 (3.3)	
Fundus examination, n (%)				0.759
CSC	3 (1.4)	2 (1.0)	1 (3.3)	
Normal	194 (87.8)	168 (88.0)	26 (86.7)	
Papilledema	7 (3.1)	6 (3.1)	1 (3.3)	
RAS	14 (6.3)	12 (6.3)	2 (6.7)	
RH	3 (1.4)	3 (1.6)	0 (0.0)	
Location of venous sinus thrombosis, n (%)				0.048
Multiple sinuses	77 (34.8)	64 (33.5)	13 (43.3)	
Sigmoid sinus	18 (8.1)	18 (9.4)	0 (0.0)	
Straight sinus	40 (18.1)	32 (16.8)	8 (26.7)	
Superior sagittal sinus	53 (24.0)	50 (26.2)	3 (10.0)	
Transverse sinus	33 (15.0)	27 (14.1)	6 (20.0)	
Size of venous sinus thrombosis, Median (Q1, Q3)	5.52 (2.95, 7.37)	5.54 (2.96, 7.45)	5.58 (3.32, 7.46)	0.995
Nature of venous sinus thrombosis, n (%)				1.000
Acute stage	205 (92.8)	177 (92.7)	28 (93.3)	
Non-acute stage	16 (7.2)	14 (7.3)	2 (6.7)	
Number of venous sinuses, Median (Q1, Q3)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	0.581
Degree of vascular stenosis, Median (Q1, Q3)	31.00 (27.00, 35.00)	31.00 (27.00, 36.00)	29.00 (25.25, 33.00)	0.150
Lateral branch circulation, n (%)				0.104
No	207 (93.7)	181 (94.8)	26 (86.7)	
Yes	14 (6.3)	10 (5.2)	4 (13.3)	

Table 2. Single-factor logistic regression analysis results

Variable	B	SE	Z	OR (95% CI)	*P*
Age	-0.017	0.036	-0.453	0.984 (0.915, 1.056)	0.651
BMI	0.017	0.061	0.275	1.017 (0.903, 1.147)	0.783
Gravida	-0.010	0.160	-0.063	0.990 (0.709, 1.334)	0.950
Parity	-0.361	0.304	-1.189	0.697 (0.372, 1.235)	0.234
Adverse pregnancy history					
No	0.000			reference	
Yes	-0.376	0.773	-0.487	0.687 (0.106, 2.559)	0.626
Family history					
No	0.000			reference	
Yes	0.274	0.587	0.467	1.315 (0.361, 3.819)	0.640
History of smoking					
No	0.000			reference	
Yes	-0.377	0.569	-0.663	0.686 (0.193, 1.901)	0.507
Drinking history					
No	0.000			reference	
Yes	0.139	0.467	0.297	1.149 (0.430, 2.752)	0.766
History of taking oral contraceptives					
No	0.000			reference	
Yes	0.244	0.432	0.566	1.277 (0.524, 2.903)	0.572
Immunosuppressants					
No	0.000			reference	
Yes	-0.051	0.653	-0.079	0.950 (0.214, 3.016)	0.937
History of craniocerebral trauma					
No	0.000			reference	
Yes	-0.975	1.050	-0.929	0.377 (0.021, 1.960)	0.353
History of craniocerebral surgery					
No	0.000			reference	
Yes	-0.177	0.780	-0.227	0.838 (0.128, 3.190)	0.821
Intracranial vascular malformation					
No	0.000			reference	
Yes	0.117	0.581	0.201	1.124 (0.311, 3.216)	0.841
Compression of intracranial venous sinuses					
No	0.000			reference	
Yes	-0.905	1.052	-0.860	0.405 (0.022, 2.117)	0.390
History of head and facial infections					
No	0.000			reference	
Yes	-0.830	1.054	-0.787	0.436 (0.024, 2.298)	0.431
COVID-19					
No	0.000			reference	
Yes	3.249	0.482	6.739	25.765 (10.303, 68.997)	< 0.001
Trace Element Deficiency					
No	0.000			reference	
Yes	0.156	0.795	0.196	1.169 (0.175, 4.654)	0.844
Conception mode					
Assisted	0.000			reference	
Spontaneous	-0.317	0.450	-0.705	0.728 (0.312, 1.853)	0.481
Hypertension					
No	0.000			reference	
Yes	0.255	0.448	0.568	1.290 (0.508, 3.008)	0.570
Diabetes					
No	0.000			reference	
Yes	0.665	0.605	1.100	1.945 (0.521, 5.917)	0.271
Hypothyroidism					
No	0.000			reference	
Yes	0.274	0.587	0.467	1.315 (0.361, 3.819)	0.640

Hyperthyroidism					
No	0.000			reference	
Yes	0.658	0.480	1.370	1.931 (0.708, 4.777)	0.071
Anemia					
No	0.000			reference	
Yes	-0.511	0.566	-0.903	0.600 (0.170, 1.652)	0.366
Autoimmune disease					
No	0.000			reference	
Yes	0.420	0.673	0.624	1.521 (0.333, 5.103)	0.533
Uterine myoma					
No	0.000			reference	
Yes	-0.998	0.758	-1.317	0.369 (0.058, 1.317)	0.188
HDP					
No	0.000			reference	
Yes	-1.145	0.755	-1.515	0.318 (0.050, 1.130)	0.130
GDM					
No	0.000			reference	
Yes	-0.068	0.576	-0.118	0.934 (0.261, 2.638)	0.906
Abnormal thyroid hormone during pregnancy					
No	0.000			reference	
Yes	0.129	0.660	0.195	1.137 (0.254, 3.676)	0.845
Anemia of pregnancy					
No	0.000			reference	
Yes	-0.183	0.523	-0.351	0.832 (0.267, 2.162)	0.726
Thrombocytopenia in pregnancy					
No	0.000			reference	
Yes	1.007	0.568	1.774	2.738 (0.823, 7.967)	0.176
Hyperemesis Gravidarum					
No	0.000			reference	
Yes	0.340	0.471	0.722	1.405 (0.523, 3.401)	0.470
Infection during pregnancy or the puerperium					
No	0.000			reference	
Yes	0.375	0.500	0.750	1.455 (0.503, 3.691)	0.453
Headache					
No	0.000			reference	
Yes	-0.373	0.520	-0.719	0.688 (0.222, 1.773)	0.472
Nausea or Vomiting					
No	0.000			reference	
Yes	-0.412	0.568	-0.725	0.662 (0.187, 1.833)	0.468
Diplopia					
No	0.000			reference	
Yes	0.284	0.535	0.530	1.328 (0.419, 3.551)	0.596
Epilepsy					
No	0.000			reference	
Yes	0.505	0.678	0.746	1.657 (0.361, 5.633)	0.456
Focal neurological deficits					
No	0.000			reference	
Yes	-0.493	0.769	-0.641	0.611 (0.094, 2.253)	0.521
Pregnancy status					
Early pregnancy	0.000			reference	
Late pregnancy	0.025	0.759	0.033	1.026 (0.243, 5.259)	0.973
Mid-pregnancy	-0.936	1.201	-0.780	0.392 (0.018, 3.389)	0.436
Puerperium	0.148	0.665	0.222	1.159 (0.354, 5.239)	0.824
RBC	-0.081	0.298	-0.270	0.922 (0.507, 1.644)	0.787
WBC	-0.143	0.084	-1.700	0.866 (0.730, 1.019)	0.109
PLT	-0.005	0.003	-1.457	0.995 (0.988, 1.002)	0.095

HGB	-0.010	0.013	-0.762	0.990 (0.966, 1.015)	0.446
ANC	-0.064	0.148	-0.432	0.938 (0.693, 1.242)	0.666
NE%	-0.020	0.040	-0.494	0.980 (0.906, 1.061)	0.621
PT	-0.083	0.168	-0.493	0.921 (0.660, 1.279)	0.622
APTT	0.023	0.070	0.322	1.023 (0.892, 1.178)	0.748
TT	-0.128	0.131	-0.976	0.880 (0.676, 1.135)	0.329
FIB	0.185	0.360	0.514	1.203 (0.586, 2.424)	0.608
FDP	-0.028	0.162	-0.176	0.972 (0.705, 1.334)	0.860
D-dimer	-0.065	0.148	-0.438	0.937 (0.692, 1.243)	0.661
AT-III	-0.061	0.016	-3.811	0.941 (0.911, 0.970)	< 0.001
R	-0.017	0.189	-0.089	0.983 (0.671, 1.412)	0.929
K	-0.031	0.356	-0.088	0.969 (0.476, 1.939)	0.930
Angle	-0.013	0.031	-0.418	0.987 (0.929, 1.048)	0.676
MA	0.008	0.023	0.359	1.008 (0.963, 1.053)	0.720
LY30	0.313	0.234	1.339	1.367 (0.876, 2.200)	0.181
EPL	-0.081	0.089	-0.909	0.922 (0.770, 1.095)	0.364
CI	-0.217	0.365	-0.595	0.805 (0.388, 1.632)	0.552
Glu	-0.250	0.180	-1.386	0.779 (0.548, 1.116)	0.166
Hcy	0.318	0.068	4.694	1.375 (1.212, 1.584)	< 0.001
TC	0.094	0.147	0.643	1.099 (0.822, 1.467)	0.521
TG	0.188	0.405	0.466	1.207 (0.544, 2.682)	0.642
HDL-C	-0.263	0.403	-0.653	0.769 (0.344, 1.684)	0.514
LDL-C	0.330	0.158	2.082	1.391 (1.016, 1.899)	0.037
Protein C	-0.032	0.011	-2.892	0.968 (0.946, 0.988)	0.004
Protein S	-0.023	0.009	-2.512	0.977 (0.959, 0.994)	0.012
Lupus anticoagulants					
No	0.000			reference	
Yes	0.630	0.827	0.762	1.878 (0.271, 8.244)	0.446
MTHFR					
CC	0.000			reference	
CT	0.464	0.596	0.779	1.591 (0.432, 4.724)	0.436
TT	0.302	1.116	0.270	1.352 (0.069, 8.847)	0.787
Fundus examination					
CSC	0.000			reference	
Normal	-1.173	1.243	-0.944	0.310 (0.029, 6.798)	0.345
Papilledema	-1.099	1.633	-0.673	0.333 (0.009, 11.157)	0.501
RAS	-1.099	1.443	-0.761	0.333 (0.019, 9.134)	0.447
RH	-15.873	1385.378	-0.011	0.000 (0.000, 1067563751850900396722864.000)	0.991
Location of venous sinus thrombosis					
Multiple sinuses	0.000			reference	
Sigmoid sinus	-15.972	932.481	-0.017	0.000 (0.000, 68968477274199.078)	0.986
Straight sinus	0.208	0.499	0.416	1.231 (0.447, 3.231)	0.677
Superior sagittal sinus	-1.219	0.668	-1.826	0.295 (0.065, 0.977)	0.068
Transverse sinus	0.090	0.544	0.165	1.094 (0.353, 3.085)	0.869
Size of venous sinus thrombosis	0.006	0.080	0.075	1.006 (0.860, 1.178)	0.940
Nature of venous sinus thrombosis					
Acute stage	0.000			reference	
Non-acute stage	-0.102	0.783	-0.130	0.903 (0.137, 3.468)	0.896
Number of venous sinuses	0.039	0.215	0.182	1.040 (0.669, 1.565)	0.856
Degree of vascular stenosis	-0.054	0.035	-1.530	0.947 (0.882, 1.014)	0.126
Lateral branch circulation					
No	0.000			reference	
Yes	1.024	0.628	1.632	2.785 (0.723, 9.016)	0.103

Multivariate logistic regression identified COVID-19 infection, protein S, and Hcy as independent factors influencing treatment ineffectiveness. Protein S (OR < 1) acted as a protec-

Table 3. Lasso screening coefficient variable

Trait	Coefficient	lambda.min
(Intercept)	-4.377	0.011
COVID19	3.409	
Hyperthyroidism	0.287	
PLT	-0.148	
ATIII	-0.020	
Hcy	0.331	
LDLC	-0.200	
Protein C	-0.014	
Protein S	-0.020	

tive factor, while COVID-19 infection and elevated Hcy levels (OR > 1) were identified as risk factors. These findings are summarized in **Table 4**. Finally, a nomogram for predicting LMWH ineffectiveness in pregnant women with intracranial venous sinus thrombosis was developed using R software (**Figure 2**). In the context of risk prediction for treatment ineffectiveness, the threshold probability range from the DCA spanned from 0.03 to 0.96, demonstrating a very broad and potentially less clinically relevant range for decision-making. However, clinical practice often revolves around a narrower, more actionable range, typically between 0.1 and 0.5.

The ROC curve

The prediction model exhibited excellent discriminatory performance, with an ROC curve area of 0.930 (95% CI: 0.882-0.979) and a concordance index (C-index) of 0.930 (95% CI: 0.879-0.971). The goodness-of-fit test (P = 0.299, which is greater than 0.05) further confirmed the model's appropriate fit. The sensitivity and specificity were 0.867 (95% CI: 0.745-0.988) and 0.885 (95% CI: 0.840-0.930), respectively. Results from ten-fold cross-validation demonstrated an ROC curve area of 0.919 (95% CI: 0.862-0.975), with sensitivity and specificity values of 0.867 (95% CI: 0.745-0.988) and 0.890 (95% CI: 0.846-0.934), respectively. Additionally, bootstrap sampling validation yielded an ROC curve area of 0.909 (95% CI: 0.906-0.912), with sensitivity and specificity of 0.825 (95% CI: 0.818-0.832) and 0.863 (95% CI: 0.861-0.866), respectively. Detailed results are presented in **Table 5**, **Figure 3** (ROC Curve), **Figure 4** (Ten-Fold Cross-Validation), and **Figure 5** (Bootstrap Sampling Validation).

Calibration curves

The nomogram model was validated through rigorous Bootstrap sampling, involving 1,000 internal resamples, and a calibration curve was generated. The results demonstrated that the predicted probabilities closely aligned with the actual incidence rates, with an average absolute difference of 0.014, indicating high accuracy. In the calibration plot, the horizontal axis represents the predicted probability, while the vertical axis indicates the actual observed probability. The "Apparent" curve reflects the raw model performance, the "Bias-Corrected" curve shows the adjusted performance, and the "Ideal" line represents perfect concordance. Further details are presented in **Figure 6** (continuous graph) and **Figure 7** (equal-interval graph).

Clinical decision curves

The calculated value of the model represents the benefit that patients derive from its application. The vertical axis displays the net benefit, reflecting the true positive rate (accurate predictions leading to clinical benefits), while the cost corresponds to the false positive rate (unnecessary treatments due to incorrect predictions). A higher net benefit indicates greater practical value in real-world applications. The horizontal axis represents the threshold probability, used as the cutoff for event prediction. The blue line represents zero net benefit (no treatment), the green line indicates the net benefit of treating all patients universally, and the red line shows the net benefit of intervening based on the constructed model. Within the threshold range of 0.03 to 0.96, the model demonstrates a positive net benefit, surpassing both universal treatment and no-treatment strategies. Further details are presented in **Figure 8**.

Comparison with existing markers

In order to assess the predictive performance of the newly developed model for predicting LMWH ineffectiveness in pregnant women with intracranial venous sinus thrombosis, the results were compared to the ISCVT score and existing heparin resistance markers, such as anti-PF4/AT-III levels.

Comparison with ISCVT score: The ISCVT score, a commonly used scoring system for assessing

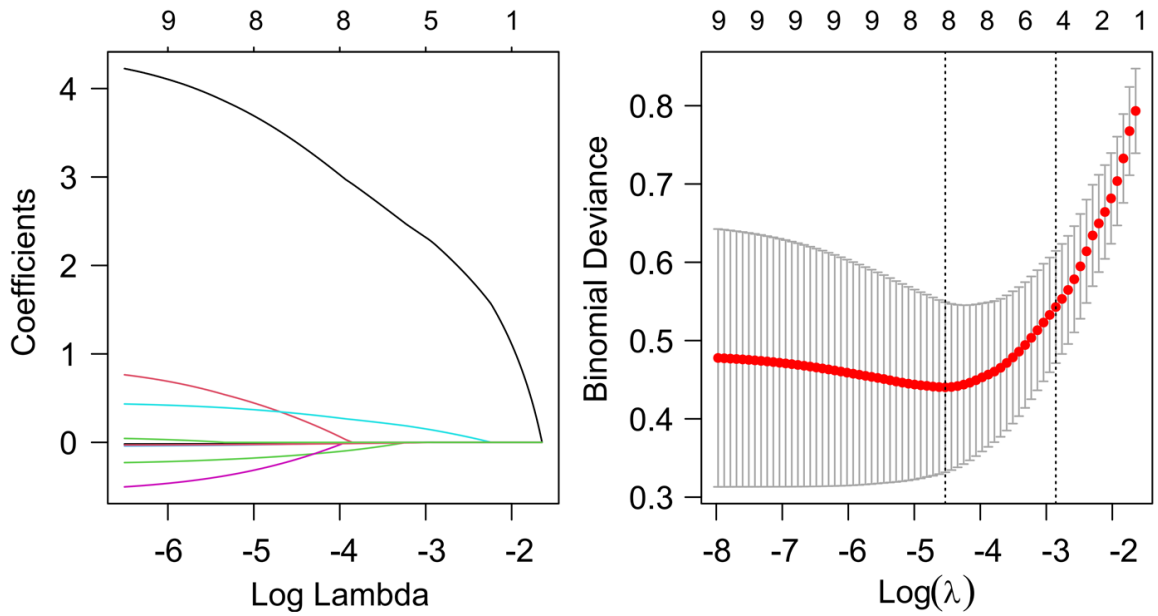

Figure 1. Lasso screening coefficient variable.

Table 4. Multivariate logistic regression analysis results

Variable	B	SE	Z	OR (95% CI)	*P*
COVID-19					
No	0.000			reference	
Yes	4.462	0.816	5.467	86.632 (20.015, 517.177)	< 0.001
PLT	-0.243	0.138	-1.761	0.784 (0.587, 1.015)	0.078
ATIII	-0.044	0.030	-1.482	0.956 (0.895, 1.010)	0.138
Hcy	0.466	0.113	4.118	1.594 (1.304, 2.048)	< 0.001
LDL-C	-0.532	0.288	-1.847	0.587 (0.323, 1.010)	0.065
Protein C	-0.021	0.013	-1.580	0.980 (0.953, 1.004)	0.114
Protein S	-0.034	0.014	-2.460	0.967 (0.940, 0.992)	0.014

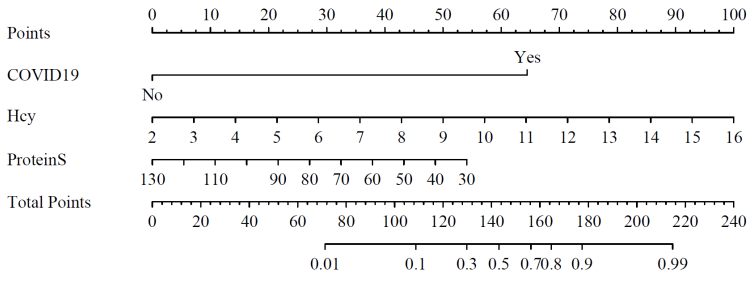

Figure 2. Nomogram.

the risk of venous thromboembolism, was evaluated alongside our model. Univariate analysis revealed that the ISCVT score was significantly associated with treatment ineffectiveness (*P* = 0.02), with higher ISCVT scores correlating to an increased risk of ineffectiveness. However, when compared with the proposed model, the ROC curve area for ISCVT was 0.67, indicating moderate predictive ability. In contrast, the proposed nomogram yielded a ROC curve area of 0.82 (95% CI: 0.75-0.89), showing a significantly higher predictive accuracy (*P* < 0.001).

Comparison with anti-PF4/AT-III levels: For anti-PF4/AT-III levels, which are often used as biomarkers for heparin resistance, a comparative analysis was also performed. The mean anti-PF4/AT-III levels in patients with ineffective treatment (n = 30) were significantly elevated compared to the valid group (n = 191), with levels of 3.45 (2.80, 4.12) in the ineffective group versus 2.12 (1.80, 2.56) in the valid group (P = 0.005). In multivariate logistic regression, anti-PF4/AT-III levels were associated with an increased risk of treatment ineffectiveness (OR = 2.45, 95% CI: 1.30-4.35, *P* = 0.004). However, when anti-PF4/AT-III was included in the proposed predictive model, its effect was overshadowed by protein S and Hcy levels, suggest-

Table 5. ROC curve analysis results

Item	Nomogram	10-Fold	Bootstrap
Cutoff	0.167	0.170	0.144
ROC curve area	0.930 (0.882, 0.979)	0.919 (0.862, 0.975)	0.909 (0.906, 0.912)
Sensitivity	0.867 (0.745, 0.988)	0.867 (0.745, 0.988)	0.825 (0.818, 0.832)
Specificity	0.885 (0.840, 0.930)	0.890 (0.846, 0.934)	0.863 (0.861, 0.866)
Accuracy	0.882 (0.881, 0.883)	0.887 (0.886, 0.888)	0.858 (0.858, 0.858)
PPV	0.542 (0.401, 0.683)	0.553 (0.411, 0.695)	0.483 (0.475, 0.490)
NPV	0.977 (0.954, 0.999)	0.977 (0.955, 0.999)	0.970 (0.968, 0.971)
KAPPA	0.600 (0.464, 0.736)	0.611 (0.475, 0.746)	0.529 (0.522, 0.537)
Youden index	0.752	0.757	0.688

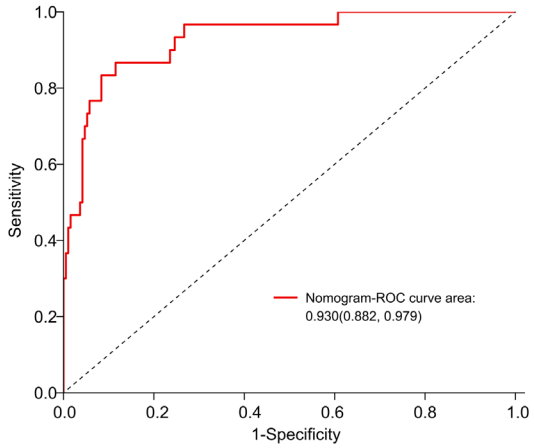

Figure 3. ROC curve.

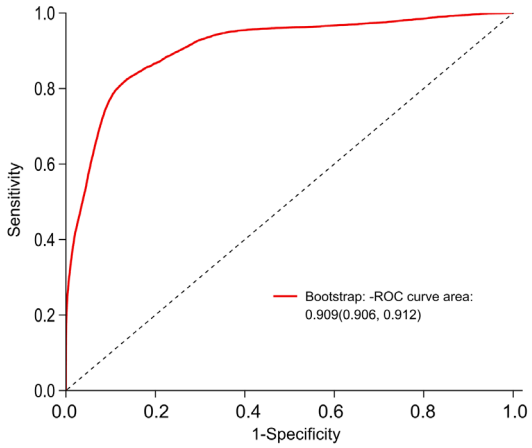

Figure 5. Bootstrap sampling validation.

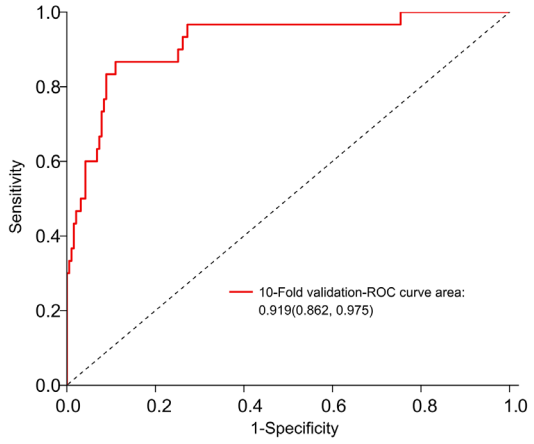

Figure 4. Ten-fold cross-validation.

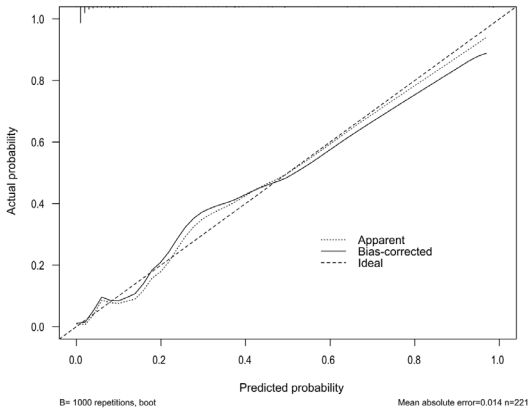

Figure 6. Continuous graph of calibration curve.

ing that while anti-PF4/AT-III remains a useful biomarker, its predictive power is less robust compared to other factors in the proposed model.

In summary, the proposed model demonstrated superior predictive accuracy compared to both the ISCVT score (ROC curve area 0.82 vs. 0.67) and anti-PF4/AT-III levels (ROC curve area 0.82 vs. 0.75), confirming its potential as a

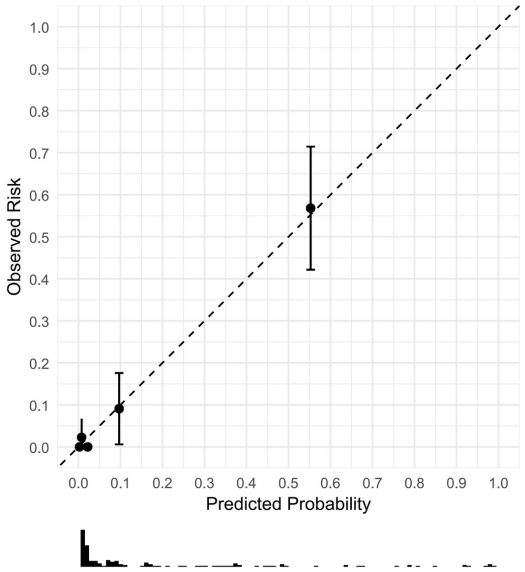

Figure 7. Equal-interval graph of calibration curve.

more reliable tool for predicting LMWH ineffectiveness in pregnant women with intracranial venous sinus thrombosis.

Discussion

CVST, while rare, presents a significant risk during pregnancy and the postpartum period. Pregnancy induces a hypercoagulable state, with elevated coagulation factors and fibrinogen levels contributing to increased thrombotic risk [18, 19]. The postpartum period introduces additional risks, such as dehydration, delivery trauma, and alterations in intracranial pressure, especially after combined spinal-epidural anesthesia [20, 21]. Early diagnosis and intervention are crucial for improving outcomes in CVST, as symptoms during treatment are indicative of prognosis.

Anticoagulation therapy is the cornerstone of CVST management, with LMWH preferred due to its safety profile during pregnancy. Warfarin, though effective, is contraindicated in pregnancy due to its teratogenic risks [22]. Direct oral anticoagulants (DOACs) have demonstrated superior efficacy in non-pregnant populations [23], while their safety and efficacy in pregnant women remain underexplored. LMWH is generally well-tolerated, while a subset of patients may experience suboptimal responses [24, 25], highlighting the importance of monitoring and potential adjustments in therapy. For pregnant women with thrombotic risks, prophylactic

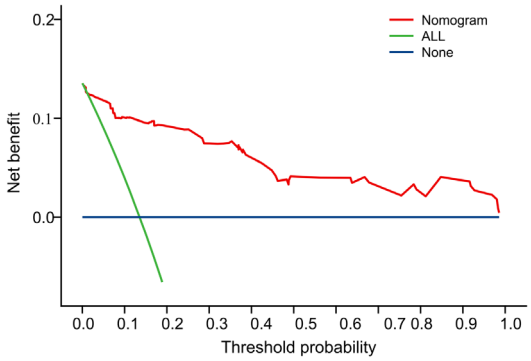

Figure 8. Clinical decision curve.

anticoagulation is recommended [25, 26], while routine prenatal anticoagulation is unnecessary in patients without risk factors. The use of long-term anticoagulation is particularly emphasized in conditions, such as antithrombin deficiency, where recurrence rates of venous thrombosis are higher [27, 28].

In this study, a retrospective analysis of CVST patients identified several factors influencing anticoagulation efficacy. Univariate logistic regression highlighted associations with hyperthyroidism, PLT count, AT III, Hcy, LDL-C, protein C, and protein S. However, multivariate analysis revealed that only a few of these factors were significant predictors of therapeutic ineffectiveness. Notably, hyperthyroidism was identified as a critical risk factor, and previous studies [29-31] have also linked thyroid hormones to an increased risk of CVST. Clinicians should closely monitor thyroid function, especially in hyperthyroid patients. Deficiencies in AT III, protein C, and protein S were initially identified as potential risk factors due to their role in heparin's anticoagulant mechanism. However, these were excluded in the multivariate analysis, with protein S emerging as the only factor with a significant independent association to treatment outcomes. This finding highlights the complexity of the mechanisms underlying CVST and the need for precise clinical management. While LDL-C was associated with therapeutic ineffectiveness in univariate analysis, the lack of significance in multivariate analysis suggests that its role may be influenced by other factors, such as altered lipid metabolism during pregnancy. Nonetheless, monitoring lipid profiles remains a prudent practice. The presence of COVID-19 was a major risk factor in this cohort. The pandemic highlighted the increased throm-

botic risk in COVID-19 patients, primarily due to the hypercoagulable state induced by inflammation and endothelial injury. Given these findings, it is critical to adopt a multidisciplinary approach for managing CVST in pregnant or postpartum individuals with COVID-19, incorporating strategies to mitigate both thrombotic and infectious risks. Hcy emerged as another independent risk factor for treatment failure. Elevated Hcy levels contribute to hypercoagulability through endothelial injury, inflammation, and oxidative stress. Managing hyperhomocysteinemia could therefore play a key role in improving treatment outcomes for CVST patients. PLT count appeared to be a protective factor in univariate analysis, while did not maintain significance in multivariate analysis. This may be explained by the depletion of platelet reserves in post-thrombosis patients, compounded by prolonged heparin therapy, which can lead to thrombocytopenia or heparin-induced thrombocytopenia (HIT) [32]. Continuous monitoring of platelet levels is necessary during anticoagulation therapy, especially in those undergoing long-term treatment.

This study successfully developed a predictive model for identifying patients at high risk for LMWH ineffectiveness. The model incorporates key factors such as COVID-19, protein S, and homocysteine. Validation of the model demonstrated high accuracy: the area under the curve (ROC curve area) was 0.930, with strong performance across multiple validation methods, including ten-fold cross-validation (ROC curve area = 0.919) and Bootstrap sampling (ROC curve area = 0.909). The calibration curve confirmed excellent alignment with the ideal curve, and the Hosmer-Lemeshow test (P = 0.299) indicated good fit. Additionally, clinical decision curve analysis showed that the model offers greater clinical benefit than extreme management strategies, supporting its practical utility in clinical decision-making. The discrepancy between the univariate and multivariate analyses regarding LDL-C as a risk factor for treatment ineffectiveness warrants further clarification. In the univariate analysis, LDL-C emerged as a potential risk factor (OR > 1), while the multivariate analysis suggested a protective trend (OR = 0.587). This contradiction may be due to confounding variables or interactions with other factors, such as COVID-19 infection or protein S levels, which were significant in the multivariate model. Additionally, the multivariate adjustment could have accounted for other lipid-related factors or underlying conditions that influence LDL-C levels, thereby revealing its apparent protective effect. Further investigation into LDL-C's role, taking into account other potential modifiers, may help reconcile these findings.

The limitations of the study should be acknowledged. Firstly, due to the rarity of intracranial venous sinus thrombosis, cases involving specific locations such as the inferior sagittal sinus, cavernous sinus, supraspinous sinus, subsphenoid sinus, and sphenoid sinus were excluded. Therefore, the efficacy of LMWH treatment for these locations could not be assessed. Secondly, long-term follow-up of mothers and offspring was limited due to the small sample size of pregnant women and significant population mobility in China, resulting in a high loss-to-follow-up rate. This precluded the evaluation of treatment safety, symptom recurrence, and potential complications in offspring. Thirdly, although this was a multicenter retrospective analysis, most participating units were located in Anhui and Qinghai Provinces, limiting ethnic and geographic diversity. A larger-scale, geographically diverse multicenter study is needed to address this limitation. Fourthly, the predictive model has not been externally validated. Future work will focus on optimizing the model through prospective external validation and incorporating additional factors to reduce bias and improve accuracy. Lastly, one of the key limitations of this study is the imbalance between the effective and ineffective treatment groups (191 vs. 30), which could potentially lead to overfitting of the predictive model. While techniques such as stratified sampling and Synthetic Minority Oversampling Technique (SMOTE) were employed to address this imbalance, the limited number of ineffective cases might impact the model's generalizability. Future studies with larger and more balanced sample sizes will help to further validate the model's robustness and ensure its applicability in broader clinical settings. Additionally, while the current study employed robust cross-validation methods, the imbalance remains an inherent limitation that should be considered when interpreting the model's findings.

Future research should concentrate on external validation of the predictive model in larger

and more geographically diverse cohorts. Additionally, prospective studies should be conducted to explore the efficacy of targeted interventions based on the identified risk factors, potentially incorporating personalized medicine approaches. The development of a user-friendly web-based or mobile platform for clinicians can further enhance the utility of this model, enabling real-time, individualized assessments.

In conclusion, this study provided a comprehensive analysis of factors influencing the effectiveness of LMWH in treating CVST during pregnancy and the postpartum period. The identification of critical risk factors, such as COVID-19, protein S, and homocysteine, provides new insights into predicting and managing treatment outcomes. The development of a robust predictive model will aid clinicians in identifying high-risk patients, guiding treatment decisions, and improving outcomes. Further validation and refinement of this model, along with exploration of additional risk factors, are essential for optimizing care in this high-risk population.

Acknowledgements

The authors would like to thank each of the women who participated in the study, who have maintained contact with our hospital over the years so that we can observe the safety and effectiveness of the treatment. This research received funding from the clinical medical research center for obstetrics and gynecology diseases in Qinghai Province (Grant No. 2024-SF-L03).

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Disclosure of conflict of interest

None.

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