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ORIGINAL RESEARCH

A Nomogram Model Containing Genetic Polymorphisms to Predict Risk of Pulmonary Embolism in Pregnant Women

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Introduction: Pulmonary embolism (PE), the most serious presentation of venous thromboembolism (VTE), is associated with a high rate of mortality and expense. Clinical studies on pregnant women with PE are scarce. The aim of this study was to analyze the clinical impact of fibrinolytic enzyme activation inhibitor-1 (PAI-1) 4G/5G genetic polymorphisms, methylenetetrahydrofolate reductase (MTHFR) rs1801131 (A1298C) and rs1801133 (C677T) genetic polymorphisms, and establish a predictive model for pregnant women.

Material and Methods: Between September 2022 and August 2023, 53 pregnant women with PE were enrolled. Using the propensity score matching method, 106 consecutive pregnant women without VTE were 1:2 matched. The relevant patient data were collected, and the susceptibility genes for PE were detected to determine genetic polymorphisms, and PE susceptibility in pregnant women, as well as to develop predictive models.

Results: Our study showed that 4G/4G homozygous mutations increased the risk of pregnant PE fourfold (OR = 4.46, 95% CI = 1.59–12.50, P = 0.004), whereas the 4G allele mutation increased the risk twofold (OR = 2.33, 95% CI = 1.35–4.04, P = 0.002). A nomogram was established to predict the risk of pregnant women with PE by four predictive features including PAI-1 genetic polymorphisms, international normalized ratio (INR), antithrombin-III (AT-III) activity, and platelet count (PLT). The area under the curve (AUC) of the nomogram was 0.821 (0.744–0.898). The AUC of the internal validation group was 0.822 (0.674–0.971). Decision curve analysis revealed that the nomogram has a higher net benefit in the following threshold: probability interval of ≥15%.

Conclusion: The PAI-1 4G/4G genotype is an independent risk factor for pregnant women with PE; furthermore, the presence of the 4G allele can increase the risk of PE. The study established a nomogram to predict the risk of PE in pregnant women.

Keywords: pulmonary embolism, pregnant women, genetic polymorphisms, PAI-1, nomogram model

Introduction

Venous thromboembolism (VTE) refers to a thrombotic event that occurs in the venous circulatory system, which includes deep vein thrombosis and pulmonary embolism (PE). VTE may result in serious complications such as post-thrombotic syndrome, post-PE syndrome, and even death.[1–3] PE is the most severe presentation of VTE. In 2020, an article published in Lancet suggested that the average annual PE-associated mortality rate is 6.8 per 100,000 per year; furthermore, the rate exponentially increases with age.[4] The main pathophysiological mechanisms underlying thrombosis are hypercoagulable states, blood flow stasis, and vascular endothelial damage (Virchow's triad).[5] Pregnancy could increase the risk of VTE by four to five times by aggravating this pathophysiological state. PE during pregnancy and

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puerperium is associated with high mortality, especially with mortality in hospitals.[6,7] Globally, PE-related deaths during pregnancy account for 3% of all pregnant deaths.[8] Data from the United States have revealed that the in-hospital mortality rate of pregnant women with acute PE is 200 times higher than those without PE.[9] Notably, the risk of PE in pregnant women was significantly higher in the 2019 post-pandemic trend for coronavirus disease.[10,11] However, there are limited clinical studies in China.

According to statistics, 20% to 50% of maternal VTE patients are susceptible to thrombophilia. Genetic polymorphisms play a vital role in PE development and progression, such as PAI-1 4G/5G genetic polymorphisms, and MTHFR genetic polymorphisms.[12] Inherited genetic polymorphisms are not only associated with VTE formation but also highly associated with pregnancy abortion, residual thrombosis and development of post-thrombotic syndrome. However, genetic mutations in patients with PE are highly personalized, with complex ethnic and regional characteristics. There are inconsistencies regarding the role of gene mutations in the diagnosis of pulmonary embolism. Studies on genetic polymorphisms and PE susceptibility in pregnant women are relatively limited.[13] It is not suitable to use computed tomography pulmonary angiography (CTPA) frequently for pregnant women, due to the potential risk of teratogenicity and carcinogenicity. There are several PE risk models specific for pregnant women like pregnancy-adapted YEARS algorithm or pregnancy-adapted Geneva score.[14,15] These models mainly contain some clinical signs and symptoms. However, there is no significant difference between the early symptoms of PE in pregnant women and normal pregnancy reactions, so it is difficult to assess the risk of PE in pregnant women only by clinical symptoms and signs. The diagnosis and treatment of pulmonary embolism has become more challenging based on the atypical clinical symptoms of maternity with pulmonary embolism and worries about the fetal safety. And relevant studies have shown that approximately 17% of VTE-related deaths can be avoided via the early prevention.[16] Therefore, it will be convenient to have a simple and fast risk prediction model to predict the risk of PE.

In our study, we analyzed the association between genetic polymorphisms and PE in Asian pregnant women by recombining PAI-1 and folate metabolism-related genes. We established a predictive model for the early identification of high-risk pregnancies and for administering anticoagulant prophylaxis early to minimize the risk of PE.

Material and Methods

Subjects

A total of 53 pregnant women with PE aged 32.58 ±4.47 years were recruited in this study from September 2022 to August 2023. During the same period, 106 non-VTE pregnant women, aged 31.58 ±4.45 years, were matched according to their age groups (up to 5 years), the receipt of in-vitro fertilization (IVF), and a history of adverse pregnancy and delivery. We categorized the patients into the model group (n = 120) and the internal validation group (n = 39) in a 3:1 ratio. We collected the basic information, relevant laboratory test results, history of previous illnesses, and other clinical information from both the groups and assessed and followed up on the outcome of the treatment of pregnant women with PE. This study was approved by the Ethics Committee of Shanghai Sixth People's Hospital (approval number: 2021–220-(1); clinical trial registration number: ChiCTR2200063325, Chinese Clinical Trial Registry). Our study complied with the Declaration of Helsinki. All participants provided written informed consent.

Inclusion Criteria

The subjects were enrolled based on the following inclusion criteria: 1) age ≥18 years, no history of smoking or drinking, and no family history of VTE; 2) pregnancy or puerperium; 3) no concomitant thrombotic disease before the pregnancy; 4) PE confirmed by CTPA, and the clinical date are complete; 5) provision of signed informed consent by the patient and family members.

Exclusion Criteria

The subjects were excluded from the study based on the following criteria: 1) age <18 years; 2) thrombosis due to secondary factors such as severe cardiovascular, cerebrovascular and hepatic, and renal diseases, malignancy, and fracture; 3) patients who were unable to continue with the clinical trial for any reason.

Experimental Procedure

Sample preparation: A disposable vacuum blood draw tube (purple cap tube) was used to draw 2–3 mL of the peripheral venous blood at the immediate moment of admission from the 2 groups of subjects and anticoagulated with EDTA.

Testing procedure: The sample (200 μL) was mixed in a 1.5-mL centrifuge tube, to which 1.2 mL of 1 X NH4Cl pre-treatment solution was added, and the tube was turned up and down 10 times and then left for 5 min at room temperature before the color of the liquid in the tube changed to a clear red. The tube was then centrifuged at 3000 rpm (or 500–700 xg) for 5 min, the upper layer of clear red liquid was discarded, and 1 mL of 1 X NH4Cl was added to thoroughly resuspend the leukocytes settled at the bottom of the tube. After centrifugation at 3000 rpm (or 500–700 xg) for 5 min, the upper layer of the liquid was discarded, and 30–50 μL of nucleic acid purification reagent (Yaojinbao, Beijing Huaxia Times Gene Technology Co., Ltd., China) was added to the tube and mixed by repeated blowing. The tube was placed at room temperature for 30 min and shaken and mixed twice during this period. Then, 4 μL of the prepared sample was added to the Sequencing Reaction Universal Kit for testing the gene (Beijing Huaxia Times Gene Technology Co., Ltd.), followed by mixing thoroughly and testing with a micro-fluorescence detector (Fluotec 48E, Tianlong Technology).

Statistical Analysis

All data were documented, calculated, and analyzed by using the SPSS 26.0, R Project (version 4.2.0), R Studio (Open-Source Edition), and GraphPad Prism 8.0 software. Clinical data from the case and control groups were compared, and the results were analyzed by *t*-test or Mann–Whitney *U*-test for quantitative data, and presented as the mean ± standard deviation or median ± quartiles, and by $\chi 2$ test or Fisher's exact test for categorical data, described as frequencies (percentages). The $\chi 2$ test was applied to determine whether the genotype frequencies at each locus were in the Hardy–Weinberg Equilibrium. Binary logistic regression was performed to analyze the independent risk factors for pregnant women with PE and the association of genetic polymorphisms with PE in different genetic models. The rms package of R software was applied to plot the receiver operating characteristic curve (ROC) and calibration curve, as well as to perform the decision curve analysis (DCA) and internal validation. The efficacy of the two models was compared by the DeLong test. The degree of association was expressed as the dominance ratio (OR) and its 95% confidence interval (95% CI), and the test level was usually considered as 0.05, with $P < 0.05$ (two-sided) indicating a statistically significant difference.

Results

Baseline Characteristics

The baseline characteristics of the case and control groups are presented in Table 1. All baseline clinical differences were not statistically significant ($P > 0.05$). Statistically significant differences were observed between the groups in terms of international normalized ratio (INR), fibrinogen degradation product (FDP), prothrombin time (PT), and antithrombin-III (AT-III) activity. Moreover, no statistically significant differences were observed between the groups in terms of the D-dimer level and platelet count (PLT).

Analysis of the Association Between Genetic Polymorphisms and Pregnant Women with PE

Genotype Determination and Hardy-Weinberg Equilibrium Test

We sequenced for three genetic loci, namely, rs1801133 and rs1801131 of the MTHFR gene and the PAI-1 4G/5G gene. The genotype distribution in both the groups is presented in Table 2. The Hardy–Weinberg equilibrium test was performed for the genotype distribution of the three loci in the control group. The test revealed that MTHFR C677T does not conform to the Hardy–Weinberg equilibrium ($\chi 2 = 9.896$, $P = 0.01$), whereas PAI-1 4G/5G and MTHFR A1298C conform to the Hardy–Weinberg equilibrium ($\chi 2 = 0.71$, $P = 0.700$ and $\chi 2 = 0.71$, $P = 0.700$, respectively); the samples were representative.

Table 1 The Clinical Baseline Characteristics of the Case and Control Groups

Variables	Model group		
	Case (n=40)	Control (n=80)	P value
Age, Mean (SEM)	32.73 ± 0.79	32.04 ± 0.49	0.443
Pre-pregnancy BMI, Mean (SEM)	24.93±0.56	25.92±0.33	0.110
Gestational age, Median (IQR)	39 (39,39)	39 (38,40)	0.941
Receipt of IVF, n (%)			1
No	37 (92.5)	73 (91.3)	
Yes	3 (7.5)	7 (8.8)	
Adverse pregnancy and delivery history, n (%)			0.768
No	29 (72.5)	60 (75.0)	
Yes	11 (27.5)	20 (25.0)	
Delivery mode, n (%)			0.673
Natural birth	29 (72.5)	55 (68.8)	
Caesarean birth	11 (27.5)	25 (31.3)	
Parity, n (%)			0.673
Primipara	29 (72.5)	55 (68.8)	
Multipara	11 (27.5)	25 (31.3)	
Massive hemorrhage, n (%)			0.215
No	38 (95.0)	69 (86.3)	
Yes	2 (5.0)	11 (13.8)	
Balloon compression, n (%)			0.664
No	39 (97.5)	76 (95.0)	
Yes	1 (2.5)	4 (5.0)	
Hypertension, n (%)			0.438
No	36 (90.0)	76 (95.0)	
Yes	4 (10.0)	4 (5.0)	
Diabetes, n (%)			0.308
No	35 (87.5)	64 (80.0)	
Yes	5 (12.5)	16 (20)	
SLE, n (%)			1
No	39 (97.5)	79 (98.8)	
Yes	1 (2.5)	1 (1.3)	
INR, Median (IQR)	0.98 (0.95,1.04)	0.96 (0.91,1.00)	0.005
PT, s, Median (IQR)	11.3 (10.9,11.9)	11.1 (10.5,11.5)	0.005
D-dimer, mg/L, Median (IQR)	2.42 (1.58,4.05)	1.93 (1.35,3.36)	0.224
FDP, mg/L, Median (IQR)	8.10 (5.43,11.85)	5.70 (4.13,9.38)	0.047
AT-III, %, Median (IQR)	77.45 (68.05,84.35)	83.00 (77.33,94.08)	<0.001
Hb, g/L, Median (IQR)	110 (102,125)	115 (110,124)	0.145
PLT, $\times 10^9$/L, Median (IQR)	207 (174,261)	198 (146,248)	0.068

Notes: BMI Body Mass Index, IVF In-vitro fertilization, SLE Systemic Lupus Erythematosus, INR International normalized ratio, PT Prothrombin time, FDP Fibrin degradation product, AT-III Antithrombin III activity, Hb Hemoglobin, PLT Platelet counts, SEM Standard Error of Mean, IQR Interquartile range, Massive hemorrhage defined as bleeding greater than 800 mL.

Analysis of the Association Between Genetic Polymorphisms and Pregnant Women with PE

To explore the association between genetic polymorphisms and pregnant women with PE, univariate logistic regression analysis was performed. It revealed that only the PAI-1 genetic polymorphisms were associated with pregnant women with PE. When compared with the 5G allele, the frequency of the 4G allele was significantly higher in controls (OR = 2.33, 95% CI = 1.35–4.04, P = 0.002). When compared with the 5G/5G genotype, the 4G/4G genotype was significantly correlated with pregnant women with PE (OR = 4.46, 95% CI = 1.59–12.50, P = 0.004); however, the 5G/4G genotype did not exhibit a statistically significant difference (OR = 1.39, 95% CI = 0.55–3.49, P = 0.485), as demonstrated in Table 3. To further analyze the interaction between the PAI-1 genetic polymorphisms and pregnant women with PE, the following three different genetic

Table 2 Genotype Distribution of Case and Control Groups

Variables	Model group		
	Case (n=40)	Control (n=80)	P value
PAI-1, n (%)			0.010
4G/4G	15 (37.5)	11 (13.8)	
5G/4G	14 (35.0)	33 (41.3)	
5G/5G	11 (27.5)	36 (45.0)	
MTHFR C677T, n (%)			0.121
TT	15 (37.5)	34 (42.5)	
CT	18 (45.0)	22 (27.5)	
CC	7 (17.5)	24 (30.0)	
MTHFR A1298C, n (%)			0.781
CC	0 (0)	1 (1.3)	
AC	10 (25.0)	23 (28.7)	
AA	30 (75.0)	56 (70.0)	

Notes: PAI-1 fibrinolytic enzyme activation inhibitor-1, MTHFR methylenetetrahydrofolate reductase.

models were used: dominant, recessive, and additive. Statistically significant differences were observed in the recessive (4G/4G vs 5G/4G + 5G/5G) and additive (4G/4G vs 5G/4G vs 5G/5G) models (OR = 3.76, 95 CI% = 1.53–9.28, P = 0.004 and OR = 2.07, 95% CI = 1.23–3.49, P = 0.006, respectively). However, as demonstrated in Table 3, there was no correlation between genetic polymorphisms and pregnant women with PE in the dominant model (OR = 2.16, 95% CI = 0.95–4.91, P = 0.067).

Analysis of the Relevance of Laboratory Data to Pregnant Women with PE

To explore the correlation between pregnant women with PE and laboratory indicators, we conducted a univariate logistic regression analysis of INR, PT, D-dimer, FDP, AT-III activity, Hb, and PLT at the immediate moment of admission. The results revealed associations among INR, AT-III activity, and PLT with PE (OR = 1.12, 95% CI = 1.04–1.21, P = 0.002;

Table 3 Analysis of the Association of PAI-1 Gene Polymorphisms with Maternal PE Patients

Model	Model group			
	Case, n	Control, n	P value	OR (95% CI)
Allele				
4G	44	55	0.002	2.333 (1.349–4.037)
5G	36	105	1	
Genotype				
4G/4G	15	11	0.004	4.463 (1.593–12.503)
5G/4G	14	33	0.485	1.388 (0.553–3.485)
5G/5G	11	36	1	
Dominant model				
4G/4G+5G/4G	29	44	0.067	2.157 (0.948–4.907)
5G/5G	11	36	1	
Recessive model				
4G/4G	15	11	0.004	3.764 (1.526–9.281)
5G/5G+5G/4G	25	69	1	
Additive model				
4G/4G	15	11	0.006	2.071 (1.230–3.487)
5G/4G	14	33		
5G/5G	11	36		

OR = 0.92, 95% CI = 0.88–0.96, P < 0.001; OR = 1.01, 95% CI = 1.00–1.01, P = 0.047). No significant correlations were observed with the other laboratory indicators, as depicted in Table 4.

Clinical Predictive Model

Construction of a predictive model based on genetic polymorphisms and evaluation of the model's predictive efficacy

We combined the univariate logistic regression analysis (P < 0.05) of the independent variables in a multivariate logistic regression analysis, revealing that the PAI-1 genetic polymorphisms, INR, AT-III activity, and PLT were significantly associated with pregnant women with PE. These genetic polymorphisms and laboratory indicators were integrated into a nomogram for predicting the risk of PE in pregnant women. The points on each variable axis were summed to obtain the total score prediction. The corresponding predicted probabilities are shown on the bottom axis in Figure 1. The nomogram was evaluated, and the calibration curve indicated that the actual predicted values aligned well with the nomogram predictions, thus providing a good fit. The area under the ROC curve (AUC) was 0.821 (0.744–0.898), with the optimal cutoff value of 84.776. At this threshold, the sensitivity was 0.769, and specificity was 0.808, indicating an excellent identification capability of the model. We employed DCA to assess the benefit of the model to patients, and the findings revealed that the nomogram exhibited a significantly greater net benefit in the probability interval with a threshold of ≥15%. Internal validation of the nomogram yielded an AUC of 0.822 (0.674–0.971), suggesting an identification ability. On employing a bootstrap method for internal validation, which was repeated 1000 times with the original data, a mean absolute error of 0.043 was obtained. This finding confirmed that the prediction model closely approximated the ideal model (Figure 2).

Analysis of Caprini Scale for Predictive Efficacy and Comparison of Two Predictive Models

The Caprini scale was developed and modified by Caprini in 2010, and its validity and feasibility in assessing the risk of VTE were widely validated in multiple disciplines.[17] The ROC curve was plotted with the Caprini score at the immediate moment of admission as the test variable and the risk of PE in pregnant women as the outcome variable. The results indicated that the AUC of the model and validation groups were 0.809 (0.730–0.888) and 0.741 (0.557–0.926), respectively. In the model group, we noted a higher risk of PE at a score of >4.5 by obtaining the optimal cutoff value, with the sensitivity of 0.500 and specificity of 0.988, as shown in Figure 2. Table 5 shows the comparison of the two predictive models with a DeLong test, indicating that no statistically significant difference was obtained in terms of efficacy between the nomogram model and Caprini score in both the model and validation groups (P = 0.838, P = 0.506). The analysis revealed that the nomogram model had a higher Youden index when compared to the Caprini score (0.538 vs 0.488, 0.577 vs 0.538). Furthermore, the nomogram model was superior to the Caprini score system in terms of sensitivity (0.800 vs 0.500, 0.769 vs 0.538), while the Caprini score system was superior to the nomogram model in terms of specificity (0.988 vs 0.738, 1 vs 0.808).

Table 4 Analysis of the Relevance of Laboratory Indicators with Maternal PE Patients

Variables	Model group			
	Case	Control	*P* value	OR (95% CI)
INR, Median (IQR)	0.99 (0.95, 1.04)	0.96 (0.91, 1.00)	0.002	1.121 (1.043–1.205)
PT, s, Median (IQR)	11.5 (10.95, 11.90)	11 (10.48, 11.5)	0.458	1.011 (0.983–1.039)
D-dimer, mg/L, Median (IQR)	2.40 (1.73, 4.10)	1.91 (1.37, 3.48)	0.745	0.988 (0.921–1.061)
FDP, mg/L, Median (IQR)	8.10 (6.05, 12.00)	5.80 (4.30, 9.48)	0.610	0.995 (0.974–1.015)
AT-III, %, Median (IQR)	79.30 (70.55, 84.55)	83.45 (77.85, 91.25)	<0.001	0.917 (0.878–0.958)
Hb, g/L, Median (IQR)	110 (101, 125)	115 (109, 124)	0.220	0.983 (0.956–1.010)
PLT, $\times 10^9$/L, Median (IQR)	204 (172, 266)	198 (153, 240)	0.047	1.006 (1.000–1.011)

Notes: INR International normalized ratio, PT Prothrombin time, FDP Fibrin degradation product, AT-III Antithrombin III activity, Hb Hemoglobin, PLT Platelet counts, IQR Interquartile range.

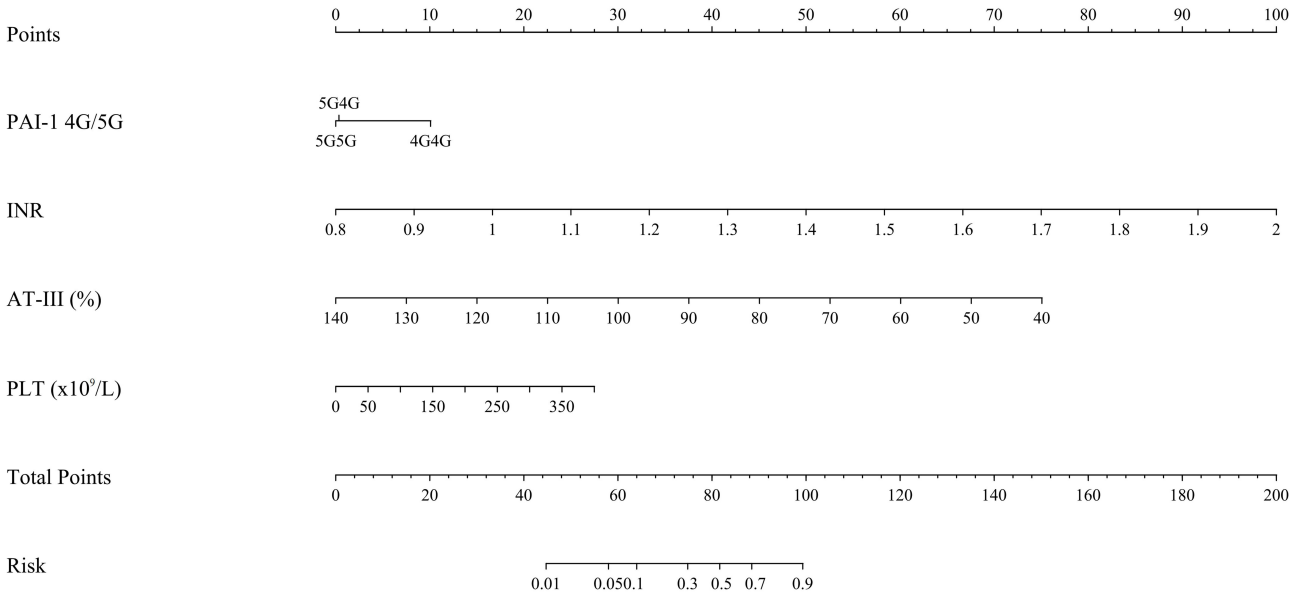

Figure 1 Nomogram predicting PE in pregnant patients. (PAI-1 fibrinolytic enzyme activation inhibitor-1, INR International normalized ratio, AT-III Antithrombin III, PLT Platelet counts.).

Discussions

Genome-wide association studies have consistently demonstrated a high association between gene mutations and the risk of VTE, along with adverse pregnancy outcomes, such as miscarriage and infertility.[18–20] PAI-1 genetic polymorphisms have been directly linked to the PAI-1 expression, where the 4G allele is capable of upregulating the PAI-1 gene expression, consequently elevating the PAI-1 levels in the plasma.[12] PAI-1 plays a pivotal role in maintaining the dynamic balance of the coagulation-fibrinolytic system, majorly inhibiting tissue-type and urokinase-type fibrinogen activators. Elevated PAI-1 levels disrupt fibrinogen activation, which triggers excessive fibrin accumulation in the vasculature, thereby promoting thrombosis.[21] Our findings indicated that 4G/4G homozygous mutations significantly increased the risk of PE fourfold, whereas the 4G allele mutation increased the risk twofold in pregnant women. Further exploration of genetic polymorphisms and their association with PE involved the application of three different genetic models, which revealed a significant correlation between PAI-1 gene mutations and PE under both recessive and additive models. These findings align with those of Zhang et al,[22] indicating the importance of monitoring the PE risk among 4G/4G homozygotes. However, our study did not establish a significant correlation between the 5G/4G genotype and PE in pregnant women. We believe that this discrepancy may have arised from the presence of both a transcriptional activator and a repressor loci near the 5G allele, whereas only transcriptional activator loci were observed near the 4G allele, which induced an insignificant correlation between PE and the 5G/4G genotype. In contrast, Wang et al reported that the PAI-1 genetic polymorphisms were not associated with PE.[23] This inconsistency may be attributed to variations in the dietary and lifestyle habits among the populations. Our study targeted pregnant women, whereas Wang et al's study was of the general population, which was mainly older males. And the sample size of Wang's study was small, leading to discrepancy of results.

Two common polymorphisms in the MTHFR gene may be associated with hyperhomocysteinemia, and the mechanisms underlying hyperhomocysteinemia have been reported to affect the vascular endothelium and blood system.[24,25] Neither of the two genetic polymorphisms in the MTHFR gene demonstrated any significant relevance to PE in our study, which corroborates the conclusions reported by Gao et al.[13,26] In contrast, a meta-analysis suggested that both the MTHFR polymorphisms may be potential biomarkers for PE.[27] We hypothesized that this discrepancy possibly stems from MTHFR mutant purity only binding to vitamin B when vitamin B levels are low, which consequently increases the Hey levels and the risk of thrombosis. Our study focused on a specific population of pregnant women who predominantly initiated vitamin B and folic acid supplementation early in pregnancy, thereby maintaining a normalized serum Hey

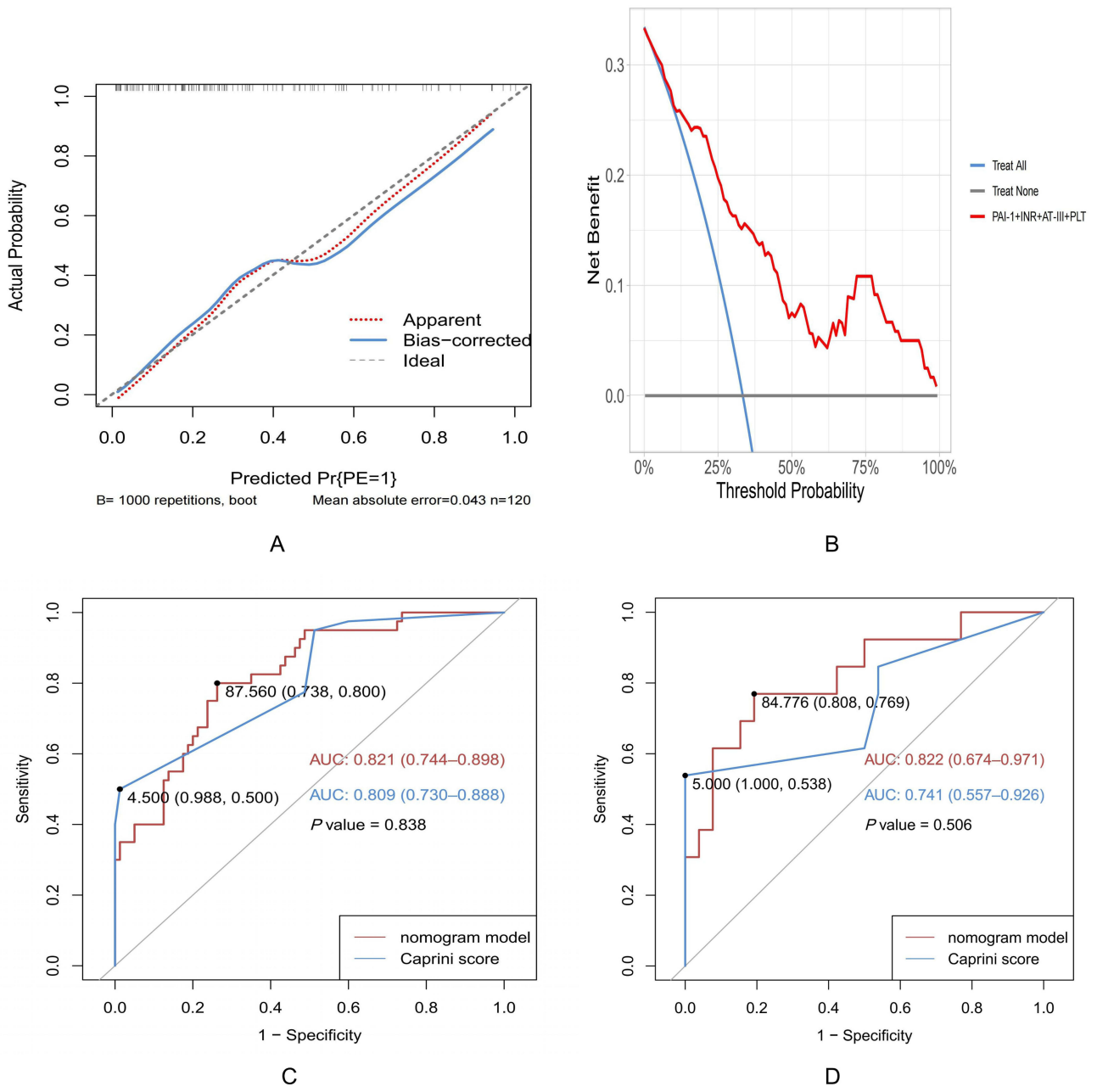

Figure 2 (**A**) Calibration plot of the Nomogram for the probability of PE in pregnant patients. (**B**) DCA of the Nomogram of PE in pregnant patients. (**C**) ROC of PE in pregnant patients (model group). (**D**) ROC of PE in pregnant patients (validation group).

levels.[28] The thrombosis risk increased only when the Hey concentrations exceeded 2.43 mg/L (>18 μmol/L).[29] Furthermore, the MTHFR C677T genotype frequency in our study did not meet the Hardy–Weinberg equilibrium test, which warrants further evaluations with expanded sample size.

Numerous studies have highlighted the predictive potential of laboratory indicators for thrombotic events, such as white blood cell count, PLT, D-dimer, and AT-III activity.[30] Our findings indicated the significance of INR, AT-III activity, and PLT in relation to pregnant women with PE. D-dimer and FDP, markers of hypercoagulability, and secondary hyperfibrinolysis, did not exhibit a significant correlation, which is inconsistent with the findings reported by Basile Mouhat et al[31,32] This variance may be attributed to the fact that our study focused on pregnant women and that the state of pregnancy and childbirth naturally leads to an increase in the D-dimer and FDP levels, which is particularly evident from the mid-gestation stage onward.[33,34] As INR is more stable than PT in assessing coagulability, it is

Table 5 Comparison of Nomogram Modeling and Caprini Score

Predictive models	Nomogram model	Caprini score	*P* value
Model group			
AUC	0.821 (0.744–0.898)	0.809 (0.730–0.888)	0.838
Youden index	0.538	0.488	
Sensitivity	0.800	0.500	
Specificity	0.738	0.988	
Validation group			
AUC	0.822 (0.674–0.971)	0.741 (0.557–0.926)	0.506
Youden index	0.577	0.538	
Sensitivity	0.769	0.538	
Specificity	0.808	1	

Notes: AUC area under-The-curve.

commonly used to monitor the effect of anticoagulation therapy, but there are few studies analyzing the relationship with thromboembolism. Usually, elevated INR values may increase the risk of bleeding in patients. When clotting ability is inhibited, blood may not clot effectively, which can lead to bleeding. However, an increase of INR leads to the increase of PE risk in our study. This may be due to the fact that the blood is too diluted and the inhibition of clot formation is weakened, which can lead to blood clots. The patient's genetics, underlying medical conditions, medication use, and other factors may affect the INR value to a variable degree.[35] AT-III is a serine protease inhibitor that exerts its anticoagulant activity primarily by acting on thrombin and factor Xa, accounting for approximately 70% of the total activity of the anticoagulation system. The low circulating antithrombin activity of AT-III was associated with low heparin efficacy.[36] In this study, we found that low AT-III levels significantly increased the risk of PE in pregnant women, which is consistent with the results of Masayuki Okuno et al.[37] Notably, low plasma AT-III levels have been associated with acute liver failure, cardiovascular disease, and even all-cause mortality in hospital.[38] Therefore, AT-III levels should be closely monitored clinically, and antithrombin replacement therapy could reduce thrombotic complications and all-cause mortality.[39,40]

Previous studies have relied on various risk-scoring tools to assess the PE risk in hospitalized patients such as Caprini score, Padua score,[41–43] Leiden mutations in the coagulation factor V gene (FVL) and mutations in the prothrombin G20210A gene (PGM) which are the main scoring items on these scales are rare in Asia. The lack of several risk factors specific to pregnant women led to inaccuracy when scoring.[44,45] Several PE risk models specific for pregnant women like pregnancy-adapted YEARS algorithm or pregnancy-adapted Geneva score, mainly contain some clinical signs and symptoms or laboratory indicators such as D-dimers. However, there is no significant difference between the early symptoms of PE in pregnant women and normal pregnancy reactions, mainly with tachycardia, chest discomfort, dyspnea and other symptoms, so it is difficult to assess the risk of PE in pregnant women only by clinical symptoms and signs. Therefore, it is essential to establish a simple and fast risk prediction model for pregnant women to predict the risk of PE, as it can reduce the adverse outcomes. In our study, we constructed a novel nomogram by PAI-1 genetic polymorphisms, INR, AT-III, and PLT for the rapid prediction of PE risk. We evaluated its validity based on parameters such as AUC, DCA, and accuracy, which all showed favorable results. We used the Caprini score to assess the predictive efficacy of PE in pregnant women and compared the nomogram model with the Caprini score. The results suggested no statistically significant difference in terms of the efficacy. However, compared to the Caprini score, the nomogram model showed a higher Youden index, suggesting that the total ability of this model to screen true patients versus non-patients was better. The nomogram model was superior to the Caprini score scale in terms of sensitivity both in the model and validation groups. Although the Caprini score system outperforms the nomogram model in terms of specificity, the higher sensitivity is more suitable for clinical needs when underdiagnosis of a disease can cause serious consequences and early prevention is beneficial to patients. In summary, constructing a thrombosis risk prediction model for pregnant women in China is important, and our prediction model could serve as a valuable reference for early intervention strategies.

Limitations

Our study has certain limitations. First, it is important to acknowledge that this is a single-center case–control study of a relatively small sample size. The low prevalence of pregnant women with PE requires consideration when expanding the sample size, which may extend the study duration. Second, we did not measure the folic acid and Hey levels to investigate whether folic acid and B vitamin supplementation can mask the association between MTHFR genetic polymorphisms and pregnant women with PE. Accordingly, we intend to explore these aspects more comprehensively in the future. Finally, our prediction model lacks external validation, and we have continued to collect data to construct an external validation set, thereby validating the predictive capabilities of this risk assessment model.

Conclusions

In conclusion, our study highlights the crucial role of genetic polymorphisms in pregnant women with PE. We identified PAI-1 4G/4G genotype as an independent risk factor for PE, with 4G allele mutations significantly increasing the PE risk. In addition, INR, AT-III, and PLT emerged as significant factors associated with pregnant women with PE. Our innovative approach combined PAI-1 genetic polymorphisms with INR, AT-III, and PLT to establish a prediction model capable of rapidly assessing the risk of pregnant women with PE. Our prediction model could serve as a valuable reference for early intervention strategies.

The Ethics Ratify

This study was approved by the Ethics Committee of Shanghai Sixth People's Hospital, with ethical approval number: 2021-220-(1). Clinical trial registration number is ChiCTR2200063325, Chinese Clinical Trial Registry.

Data Sharing Statement

The data that support the findings of the study are available on request from the corresponding author. Requests to access these datasets should be directed to breeze-huang@hotmail.com.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Huiqin Sun and Lu Zhou are co-first authors for this study. The authors report no conflicts of interest in this work.

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