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ORIGINAL RESEARCH

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Nomogram for predicting bleeding events in nonvalvular atrial fibrillation patients receiving rivaroxaban: A retrospective study

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Abstract

Background and Aims: To construct a bleeding events prediction model of nonvalvular atrial fibrillation (NVAF) patients receiving rivaroxaban.

Methods: We conducted a retrospective cohort study in patients with NVAF who received rivaroxaban from June 2017 to March 2019. Demographic information and clinical characteristics were obtained from the electronic medical system. Univariate analysis was used to find the primary predictive factors of bleeding events in patients receiving rivaroxaban. Multiple analysis was conducted to screen the primary independent predictive factors selected from the univariate analysis. Finally, the independent influencing factors were applied to build a prediction model by using R software; then, a nomogram was established according to the selected variables visually, and the sensitivity and specificity of the model was evaluated.

Results: Twelve primary predictive factors were selected by univariate analysis from 46 variables, and multivariate analysis showed that older age, higher prothrombin time (PT) values, history of heart failure and stroke were independent risk factors of bleeding events. The area under curve (AUC) for this novel nomogram model was 0.828 (95% CI: 0.763–0.894). The mean AUC over 10-fold stratified cross-validation was 0.787, and subgroup analysis validation also showed a satisfied AUC. In addition, the decision curve analysis showed that the PT in combination with CHA2DS2-VASc and HASBLED was more practical and accurate for predicting bleeding events than using CHA2DS2-VASc and HASBLED alone.

Conclusions: PT in combination with CHA2DS2-VASc and HASBLED could be considered as a more practical and accurate method for predicting bleeding events in patients taking rivaroxaban.

KEYWORDS

bleeding, nomogram, prothrombin time, rivaroxaban

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1 | INTRODUCTION

Nonvalvular atrial fibrillation (NVAF) is a clinically common arrhythmia characterized by rapid and disordered electrical activity in the atrium. Relevant epidemiological surveys estimate a total population incidence of atrial fibrillation as ranging from 0.4% to 2%.[1] NVAF increases the risk of atrial thrombi, most commonly in the left atrium and the left atrial appendage (LAA), which is the primary source of embolism among NVAF patients.[2] Furthermore, patients with NVAF may have a five-fold increased risk of stroke, reducing their quality of life and increasing the risk of mortality.[3] NVAF-caused stroke can be prevented by anticoagulation by acting on the LAA according to treatment guidelines.[4]

Rivaroxaban is a direct oral anticoagulant (DOAC) that directly inhibits factor Xa. The US Food and Drug Administration approved rivaroxaban to prevent venous thrombosis in adults after elective hip or knee arthroplasty, reduce the risk of deep venous thrombosis (DVT) recurrence and pulmonary embolism after acute DVT, and reduce the risk of stroke and systemic embolism in adult patients with NVAF. The daily dose of rivaroxaban ranges from 10 to 30 mg, according to the indication and the individual's renal function.[5] In May 2015, rivaroxaban was approved in China for adult patients with NVAF, with a recommended daily dose of 20 mg (15 mg for patients with reduced renal function).

In terms of efficacy, rivaroxaban has been shown to be equal to or better than warfarin.[6] It has a rapid onset, fewer potential drug interactions, a wide treatment window, and convenient administration. There is no need to monitor the anticoagulation intensity of rivaroxaban due to its predictable pharmacokinetics and pharmacodynamics.[7] Although routine coagulation tests for rivaroxaban are not required, bleeding events are still the leading cause of adverse reactions and discontinuation of rivaroxaban.[8] To monitor high-risk patients undergoing rivaroxaban therapy, it is essential to identify the risk factors associated with bleeding events related to rivaroxaban.

A meta-analysis indicates that Xa inhibitors were associated with a higher risk of major adverse cardiovascular events and bleeding among heart failure and coronary artery disease or peripheral artery disease.[9] Another study suggests that the use of DOAC is associated with increased gastrointestinal bleeding, especially when used within 0–6 months in Asian patients with NVAF.[10] Previous studies on the relationship between laboratory parameters and rivaroxaban have been conducted. Several studies have shown that rivaroxaban prolongs prothrombin time (PT) in a concentration-dependent manner.[11,12] PT and activated partial thromboplastin time (APTT) can be used to qualitatively assess the presence of rivaroxaban,[13] and rivaroxaban levels can be estimated by establishing a cut-off for PT and international normalized ratio (INR) values.[14] Additionally, monitoring PT and INR can help determine if a patient has taken an overdose of rivaroxaban.[15] Routine coagulation tests could be used to identify concentrations of rivaroxaban beyond the therapeutic range.[14] Other studies have presented an alternative perspective, namely, that the PT of INR is determined by multiple variables. Patients with atrial fibrillation treated with rivaroxaban may have similar clinical outcomes, although they have different INR values[16]; monitoring results depend on detection methods and reagent.[17] The objective of this study was to identify the most practical predictors of bleeding events and developed a bleeding prediction model for NVAF patients who are being treated with rivaroxaban.

2 | MATERIALS AND METHODS

2.1 | Study protocol

A retrospective cohort study was conducted on patients with NVAF who were treated with rivaroxaban from June 2017 to March 2019 at two tertiary hospitals. Demographic information and clinical characteristics were obtained from the electronic medical system. Patients with any of the following were included: (1) over 18 years of age, and (2) treated with rivaroxaban for at least four continuous weeks to ensure a steady state of anticoagulation. Patients with any of the following were excluded: (1) a history of clinically significant bleeding (e.g., gastrointestinal or intracranial hemorrhage) in the past 6 months, (2) a history of high risk of bleeding (e.g., marked reduction of platelets, abnormal coagulation function) in the past 3 months, (3) coagulopathy-related liver disease, (4) moderate or severe liver dysfunction (Child-Pugh classification B or C), (5) renal failure (creatinine clearance CrCl < 15 mL/min), (6) acute bacterial endocarditis, (7) pregnant, (8) treated with HIV protease inhibitors or azole antifungal formulations, excluding fluconazole, and (9) missing data of coagulation parameters.

2.2 | Laboratory testing and clinical follow up

Coagulation parameters were thrombin time, fibrinogen, PT, and APTT. These were measured by the automatic coagulation analyzer. Plasma levels of D-dimers were detected by an enzyme-linked immunosorbent assay. All patients underwent clinical examination and laboratory evaluation of hemoglobin concentration, hematocrit, and liver and kidney function. CrCl was calculated using the Cockroft-Gault formula. CHA2DS2-VASc and HASBLED scores were determined for risk stratification of thromboembolism and bleeding events. Follow-up visits were scheduled at 1, 2, 3, 6, 9, and 12 months after discharge, depending on patient needs.

2.3 | Evaluation and verification of the prediction model

To evaluate the sensitivity and specificity of the model, the area under curve (AUC) of receiver operating characteristic curve was used to estimate the performance of the nomogram prediction model via R software.[18] To verify the transferability of this model, the 10-fold stratified cross-validation and the subgroup analysis (gender and age) were performed. To verify the clinical efficacy of the identified risk

factors in predicting the bleeding risk, decision curve analysis (DCA) was employed by analyzing the net benefit under different risk thresholds in patients taking rivaroxaban.[19] The predictive power of these identified risk factors was then evaluated by Net Reclassification Index (NRI) and Integrated Discrimination Index (IDI).[20]

2.4 | Definition of bleeding events

Major bleeding events were defined as those involving fatal bleeding, bleeding in critical areas or organs (e.g., intracranial, intraarticular, intraspinal, intraocular, retroperitoneal, or overt gastrointestinal bleeding), and bleeding causing transfusion of two or more units of whole blood or red cells or a drop in hemoglobin level ≥20 g/L (1.24 mmol/L).[21,22] Bleeding that did not cause serious consequences was regarded as a minor event. Such events included oozing of the incision site, puncture site, and catheter site, gastrointestinal bleeding, urogenital tract bleeding, subcutaneous hematoma, ecchymosis, purpura, gingival bleeding, hematemesis, hemoptysis, speckles in the sputum, epistaxis, hematochezia, melena, spots on toilet paper, and detected or macroscopic hematuria.

2.5 | Statistical analysis

Means (standard deviation, SD) or medians (interquartile range, IQR) were produced for continuous variables, while counts and percentages were computed for categorical variables. Continuous variables were compared using the two-tailed Student's *t*-test or Wilcoxon signed rank test, and categorical variables were compared using Pearson's chi-square test or Fischer's exact test. The logistic regression analysis was adopted to analyze the characteristic factors and to identify the independent risk factors for bleeding events. The independent predictor variables with statistical p value less than 0.1 in univariate analysis were adopted to multivariate analysis, and finally were used to construct a nomogram model using R software.[23] A p value of <0.05 (two-sided) was considered statistically significant, and confidence intervals (CIs) were calculated at the 95% level. All statistical analyses were conducted using SPSS (version 25) and R software (version 4.0.1).

3 | RESULTS

3.1 | Patient characteristics

A total of 509 NVAF patients were included in the study. The mean age was 67.7 years, and 63.3% were men. The mean follow-up was 282.5 days. The mean CHA2DS2-VASc score[24] was 2.72, and 73.7% (375/509) of the patients had scores ≥2. The mean HASBLED score[25] was 1.98, with 31.6% (161/509) having scores ≥3. Among included patients, 72.9% (371/509) were taking 20 mg of rivaroxaban, and 27.1% (138/509) were prescribed a reduced dose of rivaroxaban (15 mg) adjusted for their renal function. A total of 30.8% (157/509) of patients took antiplatelet drugs (aspirin or clopidogrel). The most common clinical NVAF symptoms were palpitation, fatigue, chest tightness, and decreased exercise tolerance.

3.2 | Bleeding events

Thirty-eight patients (7.5%) had bleeding events during follow-ups: four major bleedings and 34 minor bleedings. No patients died from bleeding. The most common bleeding event was gastrointestinal bleeding (36.8%, 14/38), followed by gingival (23.7%, 9/38), epistaxis (10.5%, 4/38), bloody sputum (10.5%, 4/38), and subcutaneous (7.9%, 3/38) bleedings. One person had hematuria, and one had a conjunctival hemorrhage. Two patients had bleeding events leading to a drop in hemoglobin level of ≥ 20 g/L (1.24 mmol/L). Two patients who were taking aspirin concurrently had major gastrointestinal bleeding events. Table 1 shows the clinical and demographic data for the two groups.

3.3 | Screening for independent predictors of bleeding events

Univariate and multivariate analysis was performed to identify independent predictors of bleeding events in patients taking rivaroxaban (Table 2). Older age (OR 1.12 [95% CI: 1.06–1.19], $p < 0.001$), higher PT values (OR 1.14 [95% CI: 1.02–1.30], $p < 0.001$), history of heart failure (OR 3.47 [95% CI: 1.16–10.18], $p = 0.02$) and stroke (OR 7.23 [95% CI: 1.93–28.54], $p = 0.004$) were independently associated with bleeding events.

3.4 | Nomogram model quantifying the bleeding risk of patients taking rivaroxaban

The total points of each independent predictor was calculated for the final nomogram model (Figure 1A), which ranged from 0 to 100; the corresponding risk rate ranged from 0.1 to 0.9. The higher the total points, the higher the risk of bleeding in patients taking rivaroxaban. The score was nearly 100 points for "Age = 90 years" and 65 points for "PT = 32 s" in this nomogram model. The AUC for this model was 0.828 (95% CI: 0.763–0.894). According to the validation results, the mean AUC over 10-fold stratified cross-validation was 0.787; subgroup analysis validation also showed a satisfied AUC (Figure 1B).

3.5 | PT in combination with the CHA2DS2-VASc and HASBLED for predicting bleeding events

The improved discrimination ability for bleeding events in categorical NRI and IDI were not observed in newly identified independent predictors in our nomogram model. However, the results were

TABLE 1 The clinical and demographic data for the two groups.

Variables	No-bleeding group (*N* = 471)	Bleeding group (*N* = 38)	*p* value	Variables	No-bleeding group (*N* = 471)	Bleeding group (*N* = 38)	*p* value
Age, years; mean (SD)	67.12 (11.88)	74.71 (10.23)	<0.001	TG, mmol/L; medians (IQR)	1.32 (0.93, 2.03)	1.39 (0.87,1.81)	0.68
Age >75, *n* (%)	140 (29.72)	20 (52.63)	0.04	HDL-c, mmol/L; medians (IQR)	1.16 (0.93, 1.41)	1.03 (0.88, 1.20)	0.07
Male, *n* (%)	297 (63.06)	25 (65.79)	0.74	LDL-c, mmol/L; medians (IQR)	1.95 (1.37, 2.59)	2.0 (1.36, 2.66)	0.74
Hypertension, *n* (%)	277 (58.81)	24 (63.16)	0.60	FBG, mmol/L; medians (IQR)	5.4 (4.9, 6.8)	5.3 (4.7, 6.2)	0.40
Hyperlipidemia, *n* (%)	34 (7.22)	1 (2.63)	0.46	HbA1c, %; medians (IQR)	5.9 (5.5, 6.4)	5.9 (5.5, 6.3)	0.67
Diabetes, *n* (%)	86 (18.26)	6 (15.79)	0.70	cTnT, ng/mL; medians (IQR)	0.01 (0.01,0.02)	0.02 (0.01, 0.05)	0.003
Heart failure, *n* (%)	69 (14.65)	12 (31.58)	0.006	CK-MB, ng/mL; medians (IQR)	14 (11, 18)	14 (10,18)	0.61
Peripheral artery disease, *n* (%)	23 (4.88)	2 (5.26)	>0.99	NT-proBNP, pg/mL; medians (IQR)	574.2 (197.85,1291)	1270.5 (709.4, 3103.75)	<0.001
Coronary heart disease, *n* (%)	174 (36.94)	16 (42.11)	0.53	Antiplatelet drug, *n* (%)	141 (29.94)	16 (42.11)	0.12
Previous stroke, *n* (%)	75 (15.92)	13 (34.21)	0.004	ACEI, *n* (%)	103 (21.87)	8 (21.05)	0.90
Smoke, *n* (%)	112 (23.78)	10 (26.32)	0.74	ARB, *n* (%)	192 (40.76)	15 (39.47)	0.87
Alcohol, *n* (%)	71 (15.07)	6 (15.79)	0.91	CCB, *n* (%)	124 (26.33)	12 (31.58)	0.49
RIVA dose, mg; medians (IQR)	15 (10, 20)	10 (10, 16.25)	0.24	Statins, *n* (%)	243 (51.59)	21 (55.26)	0.67
Hematocrit, %; medians (IQR)	41.35 (38.2, 44.18)	39.65 (36.95, 44.58)	0.25	Metformin, *n* (%)	31 (6.58)	2 (5.26)	>0.99
Hemoglobin, g/L; medians (IQR)	137.5 (127,147)	139.5 (126.25, 216)	0.76	Sulfonylureas, *n* (%)	28 (5.94)	0 (0)	0.24
PLT, 100*109/L; medians (IQR)	190 (156,228)	181.5 (144.5, 216)	0.32	Amiodarone, *n* (%)	106 (22.51)	8 (21.05)	0.83
ALT, U/L; mean medians (IQR)	21.5 (13, 30)	17.5 (12.75, 25.25)	0.08	β-blocker, *n* (%)	281 (59.66)	28 (73.68)	0.09
AST, U/L; mean medians (IQR)	21 (17, 27)	19.5 (16, 26.75)	0.56	PPI, *n* (%)	246 (52.23)	21 (55.26)	0.72
SCr, μmol/L; medians (IQR)	80 (69, 93)	88 (77, 108)	0.012	APTT, s; medians (IQR)	27.5 (25.8, 30.0)	27.7 (26.2, 29.75)	0.64
SCr > 115, *n* (%)	39 (8.28)	8 (21.05)	0.008	PT, s; medians (IQR)	11.8 (11.0,12.7)	13.2 (12.3, 14.7)	<0.001
UA, μmol/L; medians (IQR)	360 (293, 433.75)	408 (272.5, 503.5)	0.33	TT, s; medians (IQR)	17.6 (16.9,18.3)	17.3 (16.9, 18.2)	0.22
eGFR, mL/min/1.73 m^2; medians (IQR)	78 (65, 90)	66 (52, 80)	0.002	FIB, ug/mL; medians (IQR)	275 (237.5, 356)	306 (240, 356)	0.13
eGFR < 45, *n* (%)	35 (7.43)	7 (18.42)	0.014	D-D, mg/L; medians (IQR)	0.25 (0.19, 0.66)	0.33 (0.21,0.67)	0.17
TC, mmol/L; medians (IQR)	3.89 (3.18, 4.64)	3.48 (3.08, 4.70)	0.41	INR; medians (IQR)	1.05 (0.99, 1.20)	1.22 (1.05,1.94)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; ARB, angiotensin receptor blockers; AST, aspartate aminotransferase; CCB, calcium channel blockers; CK-MB, creatine kinase-MB; cTnT, cardiac troponin T; D-D, D-dimer; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; FIB, fibrinogen; HbA1c, glycosylated hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; INR, international normalized ratio; LDL-c, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PLT, platelets; PPI, proton pump inhibitor; PT, prothrombin time; RIVA, rivaroxaban; SCr, serum creatinine; TC, total cholesterol; TG, triglycerides; TT, thrombin time; UA, urate.

TABLE 2 Univariate and multivariate analysis of independent predictors of bleeding event.

Characteristics		Univariate		Multivariate		Characteristics		Univariate		Multivariate	
		OR (95% CI)	*p*	OR (95% CI)	*p*			OR (95% CI)	*p*	OR (95% CI)	*p*
Age		1.073 (1.036–1.115)	<0.001	1.12 (1.06–1.19)	<0.001	PT		1.203 (1.101–1.323)	<0.001	1.14 (1.02–1.30)	<0.001
Age75	≥75 versus <75	1.979 (1.019–3.897)	0.04			TT		1 (0.976–1.015)	0.97		
Gender	Male versus Female	0.888 (0.43–1.751)	0.73			FIB		1.001 (0.998–1.005)	0.43		
Smoke	Yes versus No	1.138 (0.512–2.344)	0.73			D-D		0.959 (0.653–1.197)	0.77		
Alcohol	Yes versus No	1.051 (0.385–2.44)	0.91			INR		2.814 (1.48–5.199)	0.001	2.33 (0.85–5.89)	0.08
Hemoglobin		1.004 (0.983–1.026)	0.69			Hypertension	Yes versus no	1.201 (0.613–2.436)	0.6		
PLT		0.998 (0.992–1.004)	0.53			Hyperlipidemia	Yes versus no	0.347 (0.019–1.685)	0.30		
ALT		0.975 (0.945–0.999)	0.08	0.97 (0.92– 1.01)	0.16	Diabetes	Yes versus no	0.839 (0.309–1.937)	0.70		
AST		0.998 (0.974–1.01)	0.78			Stroke	Yes versus no	2.746 (1.31–5.526)	<0.001	7.23 (1.93–28.54)	0.004
SCr		1.019 (1.006–1.031)	0.003	1.01 (0.99–1.02)	0.49	Heart failure	Yes versus no	2.689 (1.256–5.478)	<0.001	3.47 (1.16–10.18)	0.02
UA		1.002 (0.999–1.005)	0.13			PAD	Yes versus no	1.077 (0.169–3.846)	0.92		
eGFR		0.966 (0.946–0.986)	0.001			CHD	Yes versus no	1.077 (0.169–3.846)	0.92		
TC		0.88 (0.621–0.997)	0.46			Statins	Yes versus no	1.154 (0.595–2.269)	0.67		
TG		0.814 (0.53–1.106)	0.28			Antiplatelet	Yes versus no	1.702 (0.855–3.322)	0.12		
HDL-c		0.479 (0.17–1.206)	0.14			PPI	Yes versus no	1.13(0.582–2.222)	0.72		
LDL-c		1.086 (0.737–1.556)	0.66			CCB	Yes versus no	1.288 (0.61–2.578)	0.49		
FBG		0.945 (0.77–1.092)	0.52			ACEI	Yes versus no	0.95 (0.396–2.043)	0.90		
HbA1c		0.933 (0.63–1.193)	0.67			ARB	Yes versus no	0.944 (0.471–1.841)	0.87		
cTnT		0.705 (0.061–1.419)	0.62			Propafenone	Yes versus no	0 (0–567141406.234)	0.98		
CK-MB		1.003 (0.973–1.019)	0.81			Amiodarone	Yes versus no	0.916 (0.382–1.967)	0.83		
NT-proBNP		1 (1–1)	0.02	1.00 (1.00–1.00)	0.33	β-blockers	Yes versus no	1.893 (0.927–4.181)	0.09		
CHA2DS2-VASc		1.279 (1.062–1.538)	0.009	0.42 (0.25–0.47)	0.003	Metformin	Yes versus no	0.787 (0.124–2.749)	0.75		
HASBLED		1.964 (1.465–2.684)	<0.001	1.89 (1.24–2.89)	0.006	Sulfonylureas	Yes versus no	0 (0–7709564860.127)	0.98		
APTT		1.012 (0.933–1.084)	0.76			Anticoagulation	Yes versus no	1.702 (0.855–3.322)	0.12		

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; ARB, angiotensin receptor blockers; AST, aspartate aminotransferase; CCB, calcium channel blockers; CHD, coronary heart disease; CK-MB, creatine kinase-MB; cTnT, cardiac troponin T; D-D, D-dimer; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; FIB, fibrinogen; HbA1c, glycosylated hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; INR, international normalized ratio; LDL-c, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAD, peripheral artery disease; PLT, platelets; PPI, proton pump inhibitor; PT, prothrombin time; SCr, serum creatinine; TC, total cholesterol; TG, triglycerides; TT, thrombin time; UA, urate.

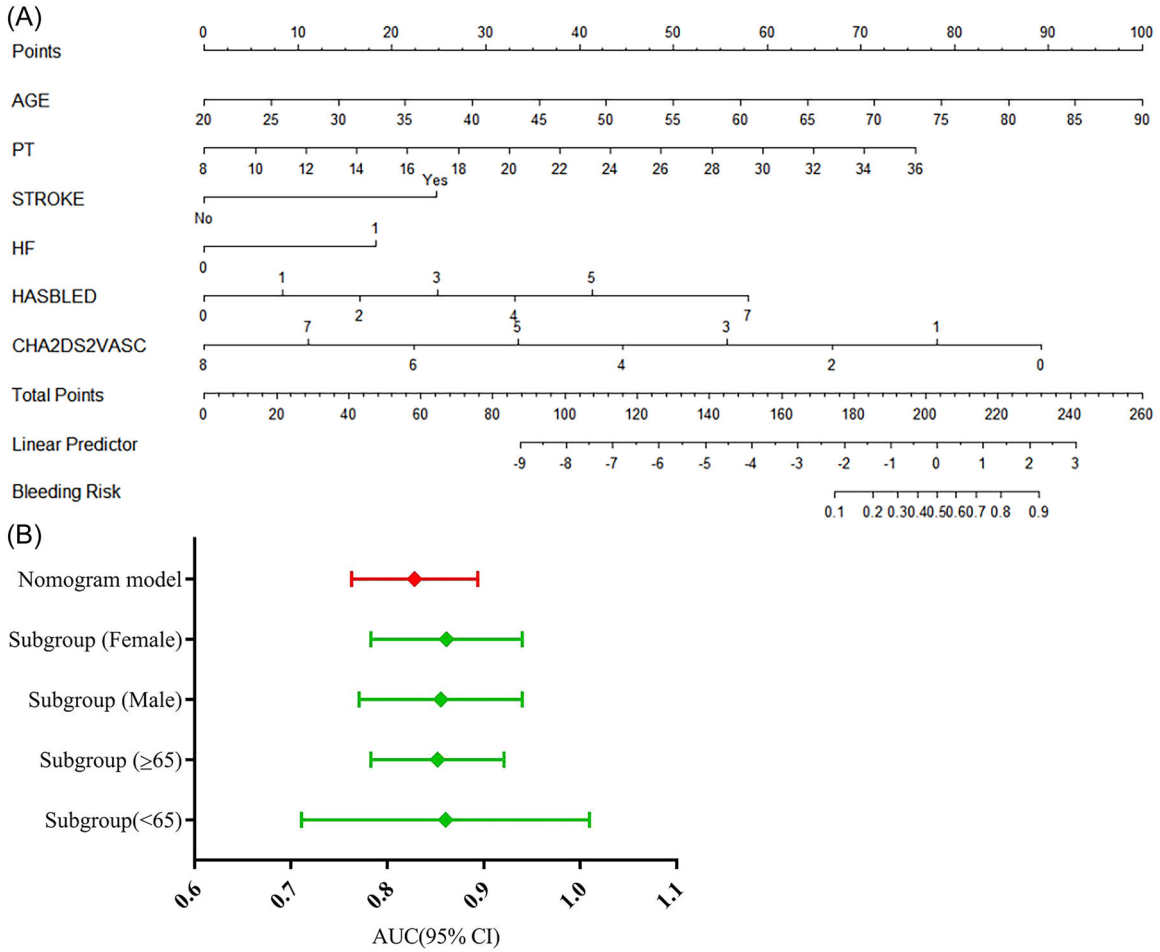

FIGURE 1 (A) Nomogram model quantifying the bleeding risk of patients taking rivaroxaban. The total score (ranging from 0–100) of each factor was calculated; the corresponding risk rate ranged from 0.1 to 0.9. The higher the total score, the higher the risk of bleeding event in patients taking rivaroxaban. (B) The AUC of the nomogram model and subgroups.

greatly improved in PT in combination with CHA2DS2-VASc and HASBLED for predicting bleeding events in patients taking rivaroxaban, with an NRI > 0.20 (95% CI: 0.0678–0.3468) ($p = 0.004$) and IDI > 0.10 (95% CI: 0.0286–0.189) ($p = 0.008$). In addition, the DCA curve showed that PT in combination with CHA2DS2-VASc and HASBLED was more practical and accurate in predicting bleeding events than using CHA2DS2-VASc and HASBLED alone (Figure 2).

4 | DISCUSSION

Rivaroxaban is indicated for stroke and systemic embolism prophylaxis in patients with NVAF. It has additional indications for treatment and prevention of DVT and pulmonary embolism without the need for routine blood monitoring.[26] Compared with VKA, rivaroxaban has the advantage of reducing the incidence of major bleeding and simplifying perioperative management. Nevertheless, patients taking rivaroxaban may experience severe bleeding or require urgent unplanned surgery.[27]

According to our findings, the incidence of bleeding events associated with rivaroxaban in patients with NVAF was 7.5%. Gastrointestinal bleeding was the most common bleeding event, in line with other studies.[28] A study of rivaroxaban ADR based on the FDA adverse event database showed that gastrointestinal bleeding is the most common ADR, accounting for 15.56% of ADR reports in thrombosis prevention. In addition, when rivaroxaban was used to prevent atrial fibrillation and cerebrovascular accident, severe intracranial hemorrhage (ICH) of ADR occurred in 10th position, accounting for 1.05% and 1.22%, respectively.[28] Compared with the general ICH cohort, OAC-ICH patients are older, have larger ICH volumes, more frequent intraventricular hemorrhage (IVH) and, importantly, more frequent hematoma enlargement, all of which are important prognostic factors.[26]

Because routine blood coagulation monitoring tests are usually not applicable to emergencies during rivaroxaban treatment, and due to a lack of specific reversal agents, there is a general concern that bleeding complications during rivaroxaban treatment cannot be adequately controlled and may lead to adverse results.[29] Therefore, it is crucial to predict the risk of bleeding, considering the fatal adverse effects in patients who received rivaroxaban. Our purpose was to frame a risk score model that can be referred in clinical work

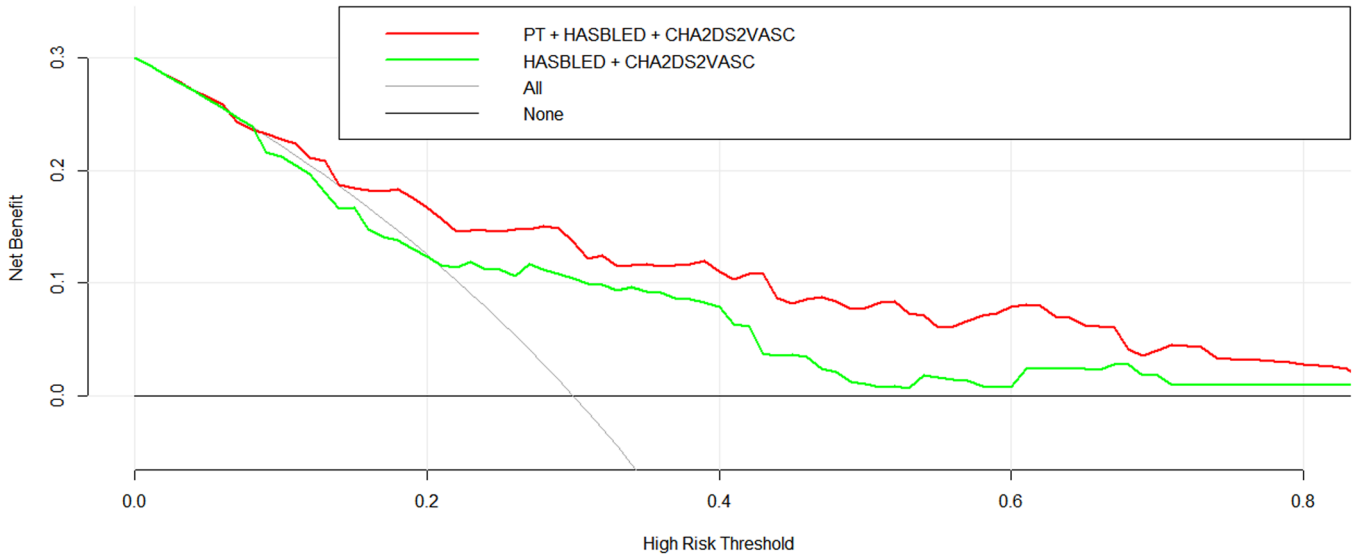

FIGURE 2 The DCA curve validating the clinical efficacy of the PT in combination with CHA2DS2-VASc and HASBLED in predicting the bleeding risk of patients taking rivaroxaban. The *y* axis represents the net benefit. The gray solid line represents that all patients had bleeding. The gray dotted line represents that all patients had no bleeding event. The red and green solid line represents the clinical efficacy of PT in combination with CHA2DS2-VASc and HASBLED, as well as CHA2DS2-VASc and HASBLED alone, for predicting bleeding events.

to predict the risk of bleeding in patients with DOAC. Furthermore, the nomogram model we developed can enable clinicians to identify high-risk bleeding factors early on, allowing for the establishment of an appropriate treatment program and the implementation of targeted measures to prevent mortality.

Advanced age (>75 years) was an independent predictor of bleeding. Age affects the elimination and metabolism of rivaroxaban. According to a previous study, the plasma elimination half-life of rivaroxaban increased more in older adults (11–13 h) compared to young adults (5–9 h).[30] Similarly, compared to the younger subjects, the plasma concentration of rivaroxaban was higher in the elderly subjects. As reported in a phase I study, the AUC of rivaroxaban was 41% higher than that in young subjects.[31] These changes are mainly attributable to the lower renal and nonrenal clearance of rivaroxaban in the elderly, resulting in the lower metabolism of rivaroxaban. Other studies also observed similar phenomena.[32–34] Taken together, these results suggest that although no dosage adjustment of rivaroxaban is required based on age alone, clinicians should closely monitor these patients, especially in the advanced age group (>75 years).

In our study, serum creatinine and eGFR showed significant differences between bleeding and nonbleeding groups. The proportion of patients with serum creatinine (>115 μmol/L) and eGFR (<45 mL/min/1.73 m^2) were greater in bleeding groups than nonbleeding groups. Renal impairment affects rivaroxaban clearance. Approximately one-third of the rivaroxaban dose is excreted unchanged through the kidneys.[35] A previous study demonstrated that decreased renal clearance of rivaroxaban in patients with renal impairment led to increased plasma exposure and pharmacodynamic effects of rivaroxaban.[36] Another study showed that plasma concentrations of rivaroxaban increased, while mean values for AUC were 1.44-fold (mild kidney impairment), 1.52-fold (moderate kidney impairment), and 1.64-fold (severe kidney impairment), higher than in healthy controls.[37]

Our findings revealed that heart failure and previous stroke were comorbidities associated with bleeding. The results are similar to a Swedish Atrial Fibrillation cohort study.[38] A separate Asian study[39] evaluated the effectiveness and safety of four DOACs in patients with NVAF. The study found that significant bleeding persisted in high-risk subgroups, including those with secondary stroke prevention or CHA2DS2-VASc score (including congestive heart failure) ≥ 4.

A systematic review of 50 studies found that rivaroxaban prolonged PT in a concentration-dependent manner.[40] We found that PT and INR exhibited significant differences between the two groups compared to other coagulation tests. The findings suggest that PT and INR are recommended over APTT for detecting factor Xa inhibitors in the absence of anti-Xa assays. Furthermore, ROC curves determined that PT was the most likely predictor of bleeding events in our study. Logistic regression confirmed that PT was an independent predictor of bleeding events. Rivaroxaban concentrations showed a good correlation with PT in a study of 184 samples from 91 patients who took DOACs.[41] A single-center retrospective cohort study of 199 hospitalized patients who received rivaroxaban showed that a PT of ≥30 s was associated with a significantly higher risk of bleeding.[42]

The AUC of ROC was 0.858, indicating that the model had good performance. However, the improved discrimination ability for bleeding events in categorical NRI and IDI were not observed in newly identified independent predictors in our nomogram model. CHA2DS2-VASc and HASBLED contained risk factors other than PT in the model. The DCA curve showed that PT in combination with CHA2DS2-VASc and HASBLED was more practical and accurate in predicting bleeding events.

5 | LIMITATIONS

Our study has several limitations. First, it is a two-center retrospective study with a relatively small sample size; as a retrospective design, selection bias is possible. Second, we performed only internal validation for this model, and external validation is needed to improve its predictive value. Third, our study only observed patients with rivaroxaban and did not take warfarin or other DOACs as the control. Fourth, we did not measure the drug concentration of rivaroxaban which relates to clinical information such as age and renal function, since the drug concentration of rivaroxaban was not routinely measured in our hospital.

6 | CONCLUSIONS

Herein, after reviewing numerous studies and evaluating multiple variables, we demonstrated that older age, higher PT values, history of heart failure and stroke are independent risk factors of bleeding events in NVAF patients with rivaroxaban therapy. With these findings, we established and validated a novel nomogram for the risk of bleeding events. This model suggested that PT, in combination with CHA2DS2-VASc and HASBLED, can help clinicians identify patients with a high risk of bleeding during rivaroxaban therapy; the model showed high accuracy and favorable discrimination for bleeding prediction.

AUTHOR CONTRIBUTIONS

Chang Cao: Conceptualization; methodology; visualization; writing—original draft; writing—review and editing. **Yijiao Xu**: Formal analysis; methodology; software; validation; visualization; writing—original draft. **Weiwen Jiang**: Investigation; resources; validation; visualization; writing—original draft; writing—review and editing. **Shujing Wu**: Data curation; formal analysis; methodology; validation; visualization. **Yun Shen**: Formal analysis; resources; software; writing—review and editing. **Xiaotong Xia**: Investigation; resources; writing—review and editing. **Lumin Wang**: Visualization; writing—original draft. **Huijun Zhang**: Formal analysis; writing—review and editing. **Hongni Jiang**: Formal analysis; software. **Xiaoyu Li**: Conceptualization; project administration; supervision. **Xiaoye Li**: Conceptualization; data curation; methodology; project administration; resources; supervision; writing—original draft. **Yanrong Ye**: Conceptualization; project administration; resources; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. All authors have read and approved the final version of the manuscript (corresponding author or manuscript guarantor) had full access to all of the data in this study and takes completeresponsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Ethics Committee of Fudan University and Zhongshan Hospital, Fudan University.

TRANSPARENCY STATEMENT

The lead author Xiaoyu Li, Xiaoye Li, Yanrong Ye affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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