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Multimodal data-based longitudinal prognostic model for predicting atrial fibrillation recurrence after catheter ablation in patients with patent foramen ovale and paroxysmal atrial fibrillation

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Abstract

Background Clinical studies on atrial fibrillation (AF) recurrence after catheter ablation in patients diagnosed with patent foramen ovale (PFO) and paroxysmal AF (PAF) are scarce. Here, we aimed to develop a nomogram model utilizing multimodal data for the risk stratification of AF recurrence following catheter ablation in individuals diagnosed with PFO and new-onset PAF.

Methods Patients with PFO and PAF who underwent catheter ablation at the Renmin Hospital of Wuhan University from January 2018 to June 2020 were consecutively enrolled. The identification of potential risk factors was conducted using the regression method known as least absolute shrinkage and selection operator. Subsequently, multivariate COX regression analysis was conducted to determine the independent risk factors, after which a nomogram scoring system was developed. The nomogram's performance was assessed via various statistical measures, including receiver operating characteristic curve analysis, calibration curve, and decision curve analysis (DCA).

Results The dataset was partitioned into the development cohort (n = 102) and the validation cohort (n = 43) using a 7:3 ratio. The constructed nomogram included four clinical variables: age, diabetes mellitus, lipoprotein (a), and right ventricular diameter. The area under the curve values of the development and validation cohorts at 1, 2, and 3 years post-catheter ablation were 0.911, 0.812, and 0.786 and 0.842, 0.761, and 0.785, respectively. Additionally, the nomogram demonstrated a significant correlation between the predicted and actual outcomes in the development and validation cohorts, indicating its excellent calibration. Lastly, the DCA findings suggested that the model had notable clinical applicability in predicting the likelihood of AF recurrence within 1, 2, and 3 years after catheter ablation.

†Shoupeng Duan, Xujun Li, Jun Wang, Yuhong Wang and Tianyou Xu have contributed equally to this work.

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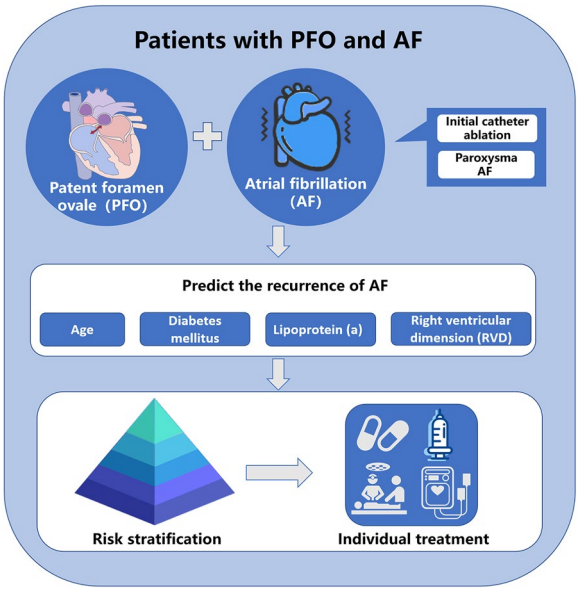
Conclusion The incorporation of multimodal data in a nomogram visualization tool facilitates the concise representation of multimodal data, thereby enhancing the comprehension of the clinical status of patients with PFO and PAF following catheter ablation and providing accurate risk stratification at 1, 2, and 3 years post-treatment.

Trial registration: This trial was registered in the Chinese Clinical Trial Registry.

(ChiCTR2300072320).

Keywords Prediction nomogram, Patent foramen ovale, Recurrent Atrial fibrillation, Catheter ablation

Graphical Abstract



Introduction

Patent foramen ovale (PFO) is a commonly occurring congenital heart disease with a substantially high global prevalence rate [1, 2]. In this condition, the normal closure of the foramen ovale after birth does not occur appropriately in approximately 25% of individuals, potentially leading to abnormal blood circulation [1, 2]. Moreover, the coexistence of PFO and AF is frequently observed in clinical settings [3–5]. PFO, characterized by an incompletely closed or open communication channel between the atria, is often detected alongside AF, which is characterized by irregular and rapid atrial contractions [3–5]. The presence of PFO may also augment the likelihood of AF episodes, whilst potentially leading to paradoxical embolization, wherein blood clots or emboli can traverse from the right to the left atrium through the patent passage of PFO, thereby escalating the risk of ischemic stroke. AF is a prevalent cardiac arrhythmia that significantly affects the health and overall well-being of individuals with this condition [6]. Although catheter ablation is considered an effective therapeutic approach for AF, the persistence of AF recurrence remains a prominent challenge for these patients [7]. Particularly, the optimal treatment strategy for patients with AF co-occurring with PFO remains debated [3–5, 8]. Further, the exact pathophysiological mechanism linking PFO with AF is unclear, with previous clinical evidence suggesting an association between PFO closure and the occurrence or recurrence of AF episodes [3–5, 8].

Notably, AF is a complex and dynamic process with multiple stages that can lead to severe complications, particularly stroke via thrombogenesis [6]. However, the existing literature on catheter ablation in patients with PFO and AF predominantly focuses on the determinants and success rates of the procedure [9, 10]. These studies demonstrate a lack of population specificity and a scarcity of long-term prognostic data. Moreover, there is a significant gap in the thorough examination of the risk of AF recurrence post-catheter ablation. Therefore, the

primary objective of this study is to develop a robust predictive model that integrates various data sources to assess AF recurrence risk in individuals with PFO who underwent catheter ablation.

Methods

Study design and patient population

Patients with PFO complicated with paroxysmal AF (PAF) who were hospitalized in Renmin Hospital of Wuhan University from January 2018 to June 2020 and underwent transesophageal echocardiography (TEE) and initial catheter ablation were enrolled. PAF and PFO were diagnosed according to the common international clinical guidelines [11, 12]. A comprehensive compilation of the study's inclusion and exclusion criteria is provided in the Supplemental Table 1.

This study is part of a registered observational clinical study (ChiCTR2300072320). The study adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with the regulations of our hospital. The study was approved by the Ethics Committee of the Renmin Hospital of Wuhan University in December 2022 and the study period was from December 2022 to December 2024 (No. WDRY2022-K264). Based on the retrospective design of the study, the Institutional Review Board waived the requirement for informed consent of patients for inclusion in the study.

Data collection

The clinical data of the patients that were collected included general information and clinical information, such as gender, age, blood pressure, smoking and drinking status, family history, and past medical and surgical history. Venous blood samples for testing were drawn from the patients after admission and before catheter ablation. All patients underwent laboratory analyses, including routine blood glucose, liver and kidney function, and lipid analysis.

Transesophageal echocardiography

All patients underwent transthoracic echocardiography to obtain their conventional cardiac parameters. Subsequently, TEE was conducted to further confirm PFO diagnosis, as well as to assess the morphology and dimensions of the foramen ovale and the presence of thrombosis in the left atrium and left atrial appendage [13]. All these examinations were performed by experienced sonographers at the Renmin Hospital of Wuhan University.

Percutaneous catheter ablation

In this study, all patients underwent cardiac catheterization to achieve PAF ablation. Before this surgical intervention, the patients underwent comprehensive clinical evaluation and cardiac ultrasound examination to ascertain the suitability and safety of the catheterization procedure. Additionally, the selection of the surgical techniques and procedures was conducted by proficient cardiac electrophysiologists, who carefully considered the patient's medical condition and clinical needs and strictly adhered to the international guidelines and standard operating procedures (Supplemental Methods) [14]. After the catheter ablation procedure, patients received standard anticoagulation therapy and were prescribed antiarrhythmic drugs [14].

Follow-up

The study population was clinically followed up for a median duration of 36 months via outpatient visits or telephone interviews. All enrolled participants underwent a 3-month blanking period following catheter ablation in order to mitigate the potential influence of early arrhythmic events. Subsequently, all participants underwent regular follow-up assessments, which included 24-h Holter monitoring at 3, 6, 9, and 12 months post-ablation. Additionally, participants were required to maintain biannual 12-lead electrocardiograms (ECGs) and undergo 24-h Holter examinations. For those unable to attend outpatient visits, follow-up was conducted through telephone interviews. The primary clinical endpoint was AF recurrence, defined as any documented AF, atrial flutter or atrial tachycardia lasting at least 30 s after the blanking period [15, 16]. Moreover, patients who reported symptoms suspected of AF recurrence were scheduled for additional ECG monitoring to further validate the presence of recurrence.

Construction of prognostic model

We employed a comprehensive range of multimodal data encompassing demographic characteristics, laboratory examination results, and transesophageal echocardiography data. Given the high dimensionality of this dataset, we encountered potential challenges such as overfitting and multicollinearity. Consequently, to identify the most relevant variables for constructing the predictive model, we initially utilized Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis on the multimodal dataset to screen for variables potentially associated with the outcome. Additionally, LASSO regression was employed to identify the indicators significantly associated with AF recurrence, followed by cross-validation to determine the optimal regularization parameters for selecting variables exhibiting the strongest predictive power [17]. To further refine variable selection and account for confounding factors, we conducted backward stepwise Cox regression analyses to identify

independent risk factors associated with the outcome. During this procedure, the final selection of variables was determined based on their statistical significance and their contribution to the Cox regression model.

We then developed a nomogram using the statistically significant predictors. The subsequent evaluation of the scoring system's ability to predict AF recurrence involved the generation of receiver operating characteristic (ROC) curves, which were utilized to assess its accuracy and discriminatory capacity. Additionally, calibration plots were constructed to ascertain the predictive accuracy and calibration of the scoring system by visualizing the relationship between the model-predicted probability of AF recurrence and the observed actual outcomes. Furthermore, decision curve analysis (DCA) was employed to analyze the clinical utility of this prediction system [18]. The nomogram scores of the patients in the development and independent validation cohorts were then calculated, followed by their stratification into high- and low-risk groups based on the median values. Finally, the log-rank test was used to determine any significant differences in the AF recurrence rates between these two groups.

Statistical analysis

Statistical analyses were performed with SPSS version 26 (SPSS Inc., Chicago, IL, USA) and R version 4.2.2 (R Core Team). The baseline clinical data of the included patients underwent a descriptive statistical analysis. In this analysis, the categorical variables were expressed as frequencies and proportions, whereas the distribution of the continuous variables was depicted as medians and interquartile ranges or means and standard deviations. Appropriate hypothesis testing was then conducted to evaluate the distribution of variables in the development and independent validation groups. Fisher's exact or χ^2 tests was utilized for categorical variables, while student's t-test, Mann–Whitney U test, or Kruskal–Wallis test was employed for continuous variables based on the normality and homogeneity of the variance. P-values below 0.05 were considered indicative of statistically significant differences.

Results

Clinical characteristics of the study patients

The baseline characteristics of all patients with PFO and new-onset PAF included in this study are shown in Table 1. A total of 145 patients with PFO and new-onset PAF were retrospectively enrolled. All patients were diagnosed with PFO by "gold standard" TEE. The patients were then divided into a development (n = 102) or validation cohort (n = 43) at a ratio of 7:3.

Among the included patients, the average age was 63 years, with a higher proportion of males (59.3%). During the median follow-up time of 36 months, 44 patients (30.3%) experienced AF recurrence. This incidence rate was similar across the development and validation groups, with 31 (30.4%) and 12 (30.2%) patients exhibiting AF recurrence, respectively.

Potential predictors of recurrent AF and construction of the nomogram

Based on the non-zero coefficients of the LASSO regression model in the development cohort, four variables were identified as potential predictors of AF recurrence: age, diabetes mellitus, lipoprotein (a), and right ventricular diameter (RVD) (Figs. 1 and 2). Further analysis identified age (HR: 1.053, 95% CI 1.006–1.102, $P = 0.025$), diabetes mellitus (HR: 2.607, 95% CI 1.185–5.737, $P = 0.017$), lipoprotein (a) (HR: 1.002, 95% CI 1.001–1.004, $P < 0.001$), and RVD (HR: 1.162, 95% CI 1.010–1.336, $P = 0.035$) as independent risk factors for AF recurrence (Fig. 3). These four independent risk factors were utilized to construct a nomogram for predicting AF recurrence likelihood at 1, 2, and 3 years after catheter ablation in patients with PAF combined with PFO (Fig. 4).

Diagnostic performance of the nomogram

C-index and ROC analysis were employed to assess the discriminatory ability of the constructed nomogram to distinguish patients with PFO accompanied by PAF who were at high risk of recurrent AF after catheter ablation. In the development cohort, the C-index for the nomogram to detect patients at high or low risk for AF recurrence was 0.766 (95% CI 0.684–0.846), while the validation cohort exhibited a C-index of 0.831 (95% CI 0.739–0.923). Subsequently, ROC curve analysis of the nomogram for predicting AF recurrence risk at 1, 2, and 3 years post-ablation demonstrated area under the curve values of 0.911, 0.812, and 0.786 in the development cohort and 0.842, 0.761, and 0.785 in the validation cohort, respectively (Fig. 5A and B).

Calibration plots were further constructed to evaluate the consistency and probability of the nomogram for predicting AF recurrence in the included population. The plots showed a high correlation between the probability of the nomogram predicting AF recurrence and the probability of actually observing AF recurrence in all enrolled patients (Fig. 6A and B). Furthermore, DCA was applied to determine the net benefit of the constructed nomogram. In the development cohort, DCA results revealed a threshold probability of 2–26% for predicting 1-year AF recurrence risk, 1–64% for 2-year AF recurrence risk, and 1–79% for 3-year AF recurrence risk (Fig. 7A–C). In the case of the validation cohort, DCA results exhibited a threshold probability of 2–50% for projecting 1-year

Table 1 Baseline characteristics of patients in the development and validation cohorts

Characteristic of outcome	All cohort (n = 145)	Development cohort (n = 102)	Validation cohort (n = 43)	P
Male, n (%)	86 (59.3%)	56 (54.9%)	30 (69.8%)	0.139
Age (years)	63.0 [56.0; 68.0]	62.5 [55.0; 69.0]	63.0 [60.0; 67.0]	0.547
Hypertension (%)	72 (49.7%)	54 (52.9%)	18 (41.9%)	0.300
Diabetes mellitus (%)	24 (16.6%)	16 (15.7%)	8 (18.6%)	0.851
Current smoking (%)	36 (24.8%)	27 (26.5%)	9 (20.9%)	0.621
Current alcohol consumption (%)	23 (15.9%)	15 (14.7%)	8 (18.6%)	0.735
Family history of hypertension (%)	3 (2.07%)	2 (1.96%)	1 (2.33%)	1.000
Family history of coronary heart disease (%)	2 (1.38%)	1 (0.98%)	1 (2.33%)	0.507
Previous MI (%)	4 (2.76%)	4 (3.92%)	0 (0.00%)	0.319
Previous PCI (%)	5 (3.45%)	5 (4.90%)	0 (0.00%)	0.322
NAFLD (%)	2 (1.38%)	2 (1.96%)	0 (0.00%)	1.000
Previous cerebral infarction (%)	38 (26.2%)	26 (25.5%)	12 (27.9%)	0.924
TIA (%)	1 (0.69%)	1 (0.98%)	0 (0.00%)	1.000
Hemicrania (%)	22 (15.2%)	14 (13.7%)	8 (18.6%)	0.621
Interventional closure of PFO (%)	13 (8.97%)	10 (9.80%)	3 (6.98%)	0.755
Neutrophil count ($\times 10^9$/L)	3.14 [2.58; 4.16]	3.20 [2.55; 4.17]	3.14 [2.62; 3.98]	0.910
Lymphocyte ($\times 10^9$/L)	1.63 [1.27; 2.04]	1.67 [1.29; 2.13]	1.56 [1.21; 1.88]	0.295
NLR	1.96 [1.47; 2.70]	1.97 [1.44; 2.62]	1.95 [1.54; 2.83]	0.519
Platelet count ($\times 10^9$/L)	192 (60.1)	195 (62.0)	184 (55.2)	0.286
PLR	111 [88.8; 145]	112 [87.8; 142]	108 [94.4; 147]	0.678
Mean platelet width	12.7 [11.4; 15.2]	12.7 [11.4; 15.0]	13.0 [11.4; 16.3]	0.588
hs-CRP (mg/L)	0.72 [0.22; 1.72]	0.72 [0.22; 1.87]	0.62 [0.22; 1.40]	0.605
Creatinine (μmol/L)	71.0 [58.0; 84.0]	70.5 [57.0; 84.8]	72.0 [62.5; 82.0]	0.526
eGFR ml/(min1.73 m^2)	90.2 (17.0)	90.6 (18.3)	89.2 (13.8)	0.615
Uric Acid (mmol/L)	380 (107)	377 (104)	388 (114)	0.577
GLU (mmol/L)	4.97 [4.50; 5.79]	4.95 [4.45; 5.57]	5.05 [4.59; 5.86]	0.250
TG (mmol/L)	1.24 [0.96; 1.80]	1.21 [0.96; 1.80]	1.45 [1.00; 1.81]	0.703
TC (mmol/L)	3.97 [3.21; 4.55]	4.02 [3.30; 4.56]	3.76 [3.18; 4.28]	0.180
HDL-C (mmol/L)	1.11 [0.92; 1.26]	1.10 [0.93; 1.23]	1.14 [0.94; 1.33]	0.345
LDL-C (mmol/L)	2.12 (0.75)	2.19 (0.78)	1.97 (0.67)	0.094
Lipoprotein a (g/L)	98.0 [49.9; 248]	118 [58.3; 258]	79.0 [30.0; 191]	0.178
TBil (μmol/L)	13.2 [10.4; 18.0]	13.7 [10.5; 19.2]	11.7 [9.60; 15.9]	0.119
DBil (μmol/L)	4.20 [3.20; 6.10]	4.30 [3.30; 6.30]	4.00 [3.15; 5.05]	0.271
GGT (μ/L)	26.0 [18.0; 43.0]	26.0 [18.0; 43.0]	27.0 [19.5; 36.5]	0.984
Fibrinogen (g/L)	2.50 [2.19; 3.02]	2.46 [2.16; 2.95]	2.55 [2.28; 3.18]	0.193
AAOD (mm)	35.0 [33.0; 37.0]	35.0 [32.2; 37.0]	35.0 [33.0; 37.5]	0.718
MPAD (mm)	23.0 [21.0; 25.0]	23.0 [21.0; 25.0]	23.0 [21.5; 24.5]	0.930
LAD (mm)	42.8 (5.97)	42.3 (6.27)	43.9 (5.10)	0.131
LVDD (mm)	46.0 [43.0; 49.0]	46.0 [43.0; 49.0]	46.0 [43.0; 49.0]	0.927
RAD (mm)	38.0 [35.0; 45.0]	38.0 [34.2; 45.0]	38.0 [36.0; 44.5]	0.852
RVD (mm)	21.0 [20.0; 23.0]	21.0 [20.0;23.0]	21.0 [20.0; 23.0]	0.891
IVSD (mm)	10.0 [9.00; 11.0]	10.0 [9.00; 11.0]	10.0 [9.00; 10.0]	0.786
LVEF (%)	55.0 [52.0; 56.0]	56.0 [52.0; 57.5]	54.0 [53.0; 56.0]	0.673
The width of the PFO (cm)	0.20 [0.20; 0.30]	0.20 [0.20; 0.30]	0.20 [0.20; 0.22]	0.461
Atrial septal aneurysm (%)	5 (3.45%)	3 (2.94%)	2 (4.65%)	0.633
Recurrent atrial fibrillation (%)	44 (30.3%)	31 (30.4%)	13 (30.2%)	1.000

MI: myocardial infarction; PCI: percutaneous coronary intervention; NAFLD: nonalcoholic fatty liver disease; TIA: transient ischemic attacks; PFO: patent foramen ovale; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet -to-lymphocyte ratio; hs-CRP: high-sensitivity C-reactive protein; eGFR: glomerular filtration rate; GLU: glucose; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TBil: total bilirubin; DBil: Direct Bilirubin; GGT: gamma-glutamyl transpeptidase; AAOD: ascending aorta diameter; MPAD: main pulmonary artery diameter; LAD: left atrium diameter; LVDD: left ventricular

Table 1 (continued)

end-diastolic diameter; RAD: right atrium diameter; RVD: right ventricular diameter; IVSD: interventricular septal thickness at diastole; LVEF: left ventricular ejection fraction

Values are given as n (%), mean (SD), or median (IQR)

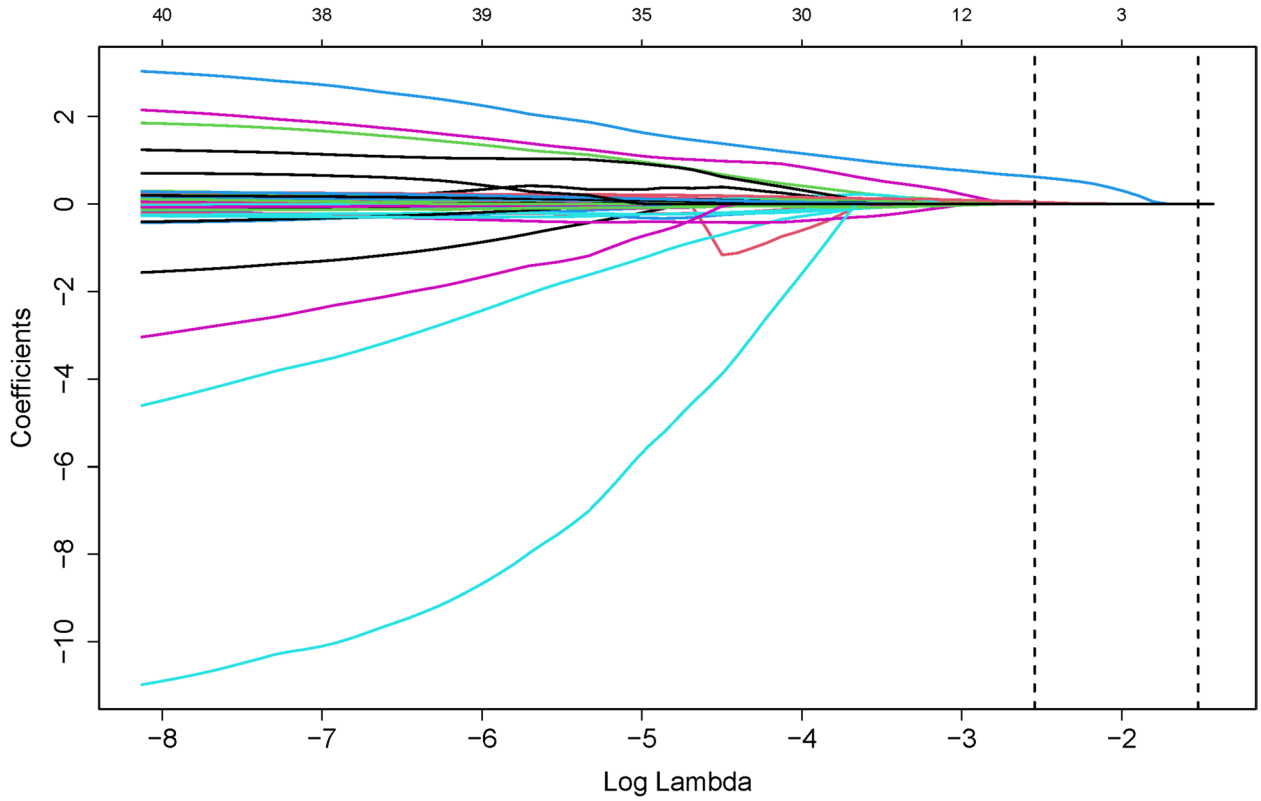


Fig. 1 LASSO regression for selecting potential predictive factors for AF recurrence from 41 candidate variables (refer to Table 1)

AF recurrence risk, 1–96% for 2-year AF recurrence risk, and 1–65% for 3-year risk of AF recurrence (Fig. 7D–F). Therefore, our constructed nomogram showed good performance in the study population based on ROC curve analysis, C-index, calibration curve, and DCA results.

Further, we applied the constructed nomogram to the development and validation cohorts and divided the patients into high- and low-risk groups according to the median risk scores obtained using the nomogram (Supplement Fig. 1A and 1B). The Kaplan–Meier survival curve analysis showed that AF recurrence risk in the high-risk group was higher than that in the low-risk group at the 1-, 2-, and 3-year follow-up periods in the development and validation cohorts ($P < 0.001$).

Discussion

In this study, we constructed a prediction nomogram to forecast AF recurrence risk 1, 2, and 3 years after catheter ablation in patients with PFO and PAF. This model was created by examining multimodal data that indicated four significant indicators: age, diabetes mellitus, lipoprotein (a), and RVD. The performance of the prediction nomogram was subsequently validated using various statistical methods, demonstrating the favorable predictive ability of our constructed nomogram in the development and validation cohorts. Furthermore, the inclusion of variables in our prediction nomogram further enhances its contribution to the risk stratification of patients with PFO and AF following initial catheter ablation and offers novel insight into the clinical management of this specific population.

AF is a prevalent cardiac arrhythmia exhibiting a persistent recurrence risk even after ablation treatment [6]. However, the complex nature of PAF often leads to its incorrect assessment and oversight, causing delayed implementation of appropriate therapeutic interventions and often marked consequences in clinical settings [6]. Thus, an improved risk stratification framework to proficiently identify potential and innovative prognostic determinants for patients with AF

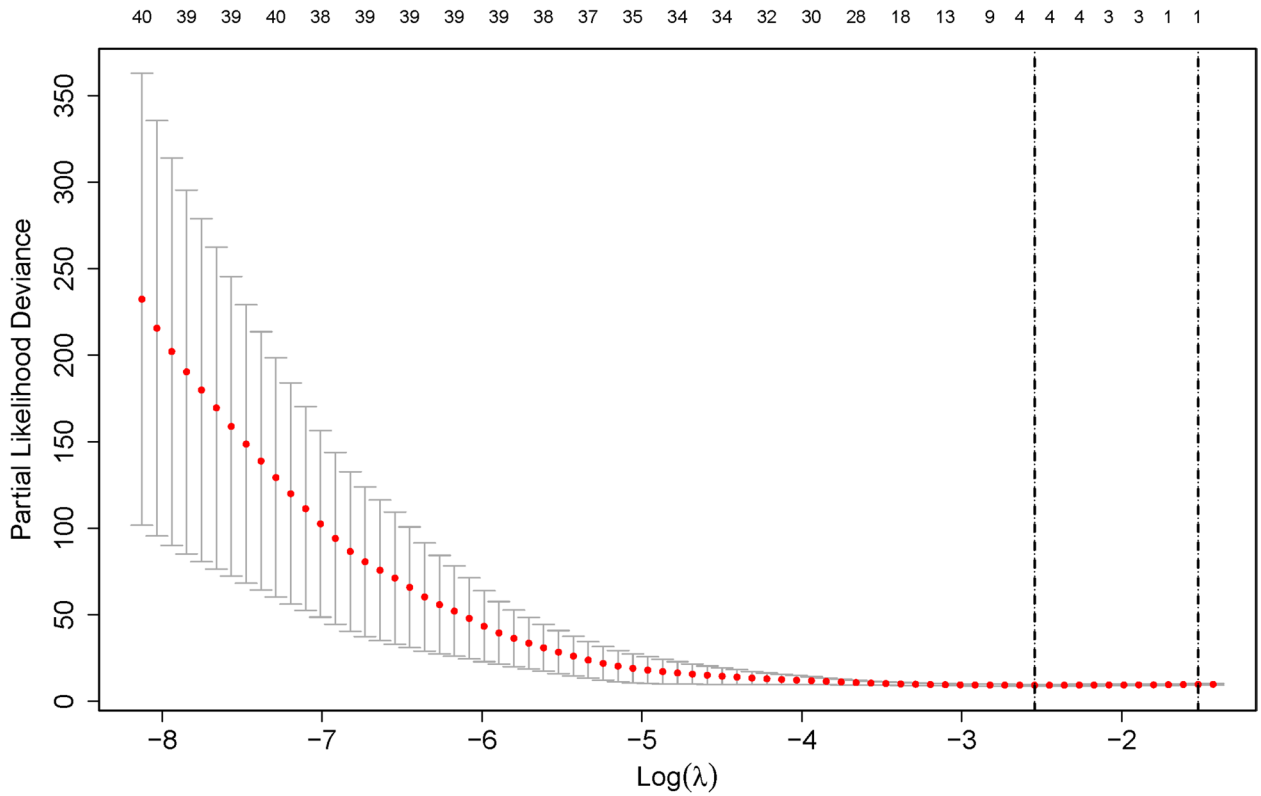


Fig. 2 The tenfold cross-validation evaluation method for determining the optimal λ parameter. The lower abscissa is the λ value in the LASSO regression model, while the upper abscissa represents the corresponding number of non-zero coefficients. Additionally, the vertical axis shows the binomial deviance

who underwent catheter ablation is urgently required [19–22]. Consistent clinical data have suggested that an AF risk scoring tool can help clinicians assess patients' risk for AF recurrence or other adverse events as well as assist them in better managing and understanding the patients' condition for optimal outcomes [23–26]. Currently, numerous scoring systems, such as $CHADS_2$, CHA_2DS_2-VASc, APPLE and CAAP-AF, have been proposed to forecast the diverse risk factors associated with AF [27–29]. These well-established risk assessment instruments have demonstrated varying prognostic efficacy in predicting AF recurrence after catheter ablation [27–29]. Furthermore, other scoring tools are available for clinicians to gain valuable insight into the relationship between PFO and stroke risk or other adverse events [30, 31]. However, despite the substantial patient population and prevalence rate associated with PFO complicated with AF, insufficient clinical data are currently available on the unique characteristics of this population. Therefore, this study aimed to examine the characteristics of individuals presenting with PFO accompanied by AF, considering their distinct clinical attributes and risk factors. Currently, accumulating evidence indicates the suitability of predictive nomograms and scoring systems as visualization tools for cardiovascular disease, enabling individualized risk assessment and clinical decision support [32–37]. Considering the complex condition of PAF combined with PFO, we employed multimodal data screening and created a predictive nomogram to offer a personalized visualization tool for assessing AF recurrence risk in this population. Based on our findings, the nomogram incorporating age, diabetes mellitus, lipoprotein (a), and RVD demonstrated favorable predictive capability in determining AF recurrence risk following catheter ablation in patients with PFO and PAF. Notably, in contrast to existing predictive tools such as the CHADS2 and CHA2DS2-VASc scores [38], which primarily assess stroke risk rather than AF recurrence, our nomogram offers a more targeted approach specifically tailored for this patient population. While these conventional scoring systems provide valuable insights into thromboembolic risk, they inadequately address the complexities associated with AF recurrence, particularly in patients with PFO. Furthermore, our nomogram's incorporation of diverse data types enhances its

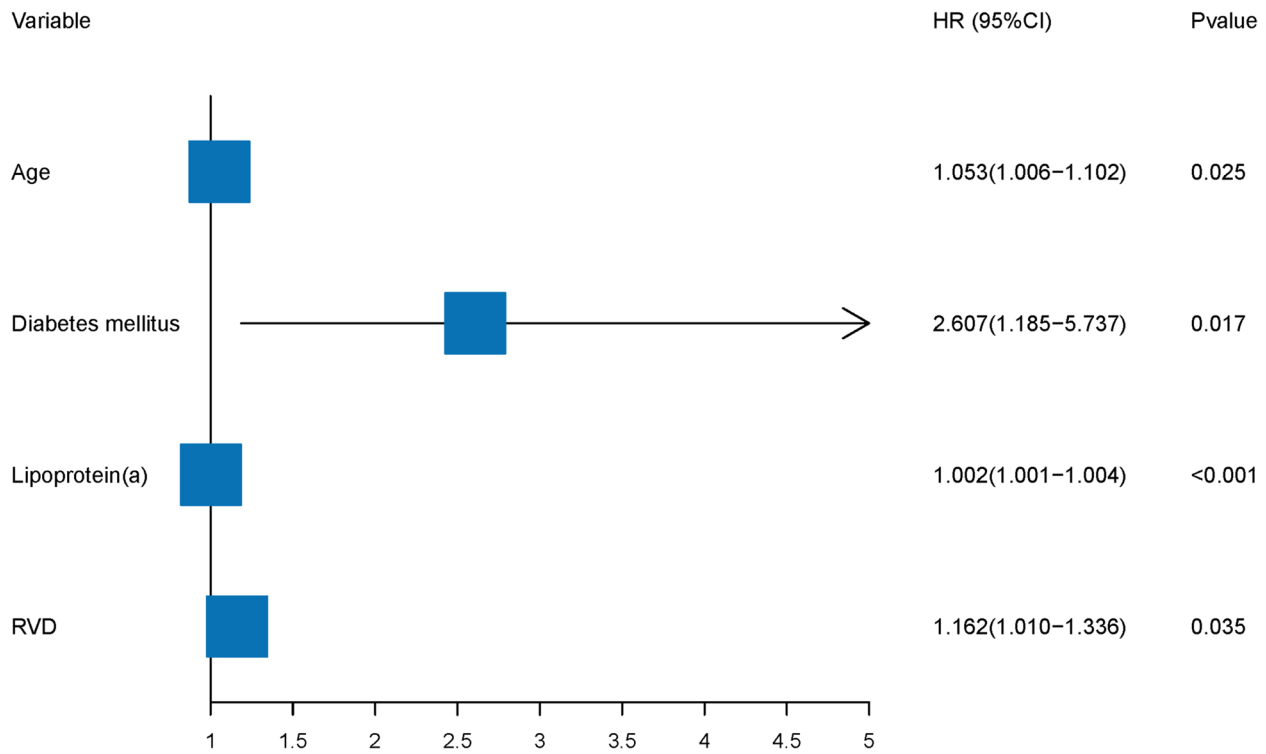


Fig. 3 A forest plot of the hazard ratios (HRs) in the development cohort for the independent prognostic variables identified by multivariate COX regression

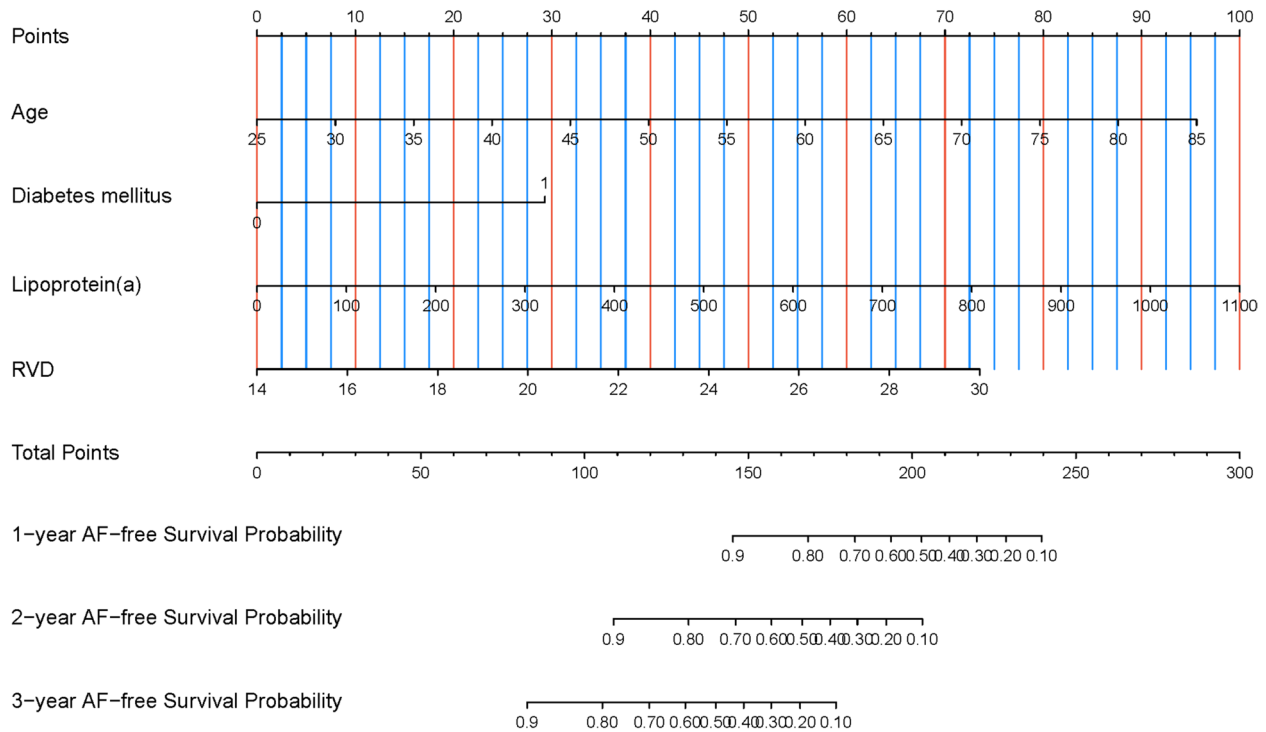


Fig. 4 Nomogram predicting the probability of AF recurrence at 1, 2, and 3 years after catheter ablation in patients with PFO and PAF. The nomogram displays four risk factors (age, diabetes mellitus, lipoprotein (a), and right ventricular diameter [RVD]) along the vertical axis and their corresponding scores on the horizontal axis. The probability of AF recurrence based on the total score can be obtained by vertically connecting the scores of each factor

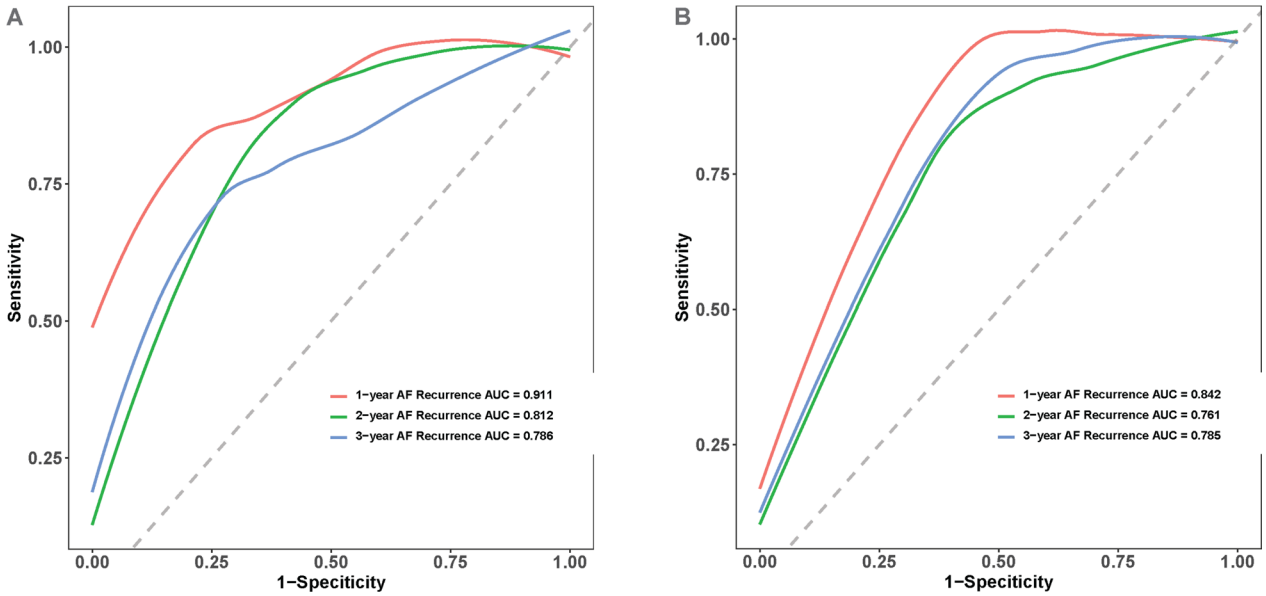


Fig. 5 ROC curve analysis for evaluating the predictive accuracy of the nomogram for AF recurrence in the **A** development and **B** validation cohorts

predictive accuracy and clinical applicability, which is crucial for personalized patient management. Additionally, our model is user-friendly and straightforward while demonstrating substantial predictive accuracy, exhibiting significant potential in clinical applications.

Recent clinical studies have established the possibility of new-onset AF after PFO closure, with age > 60 years and diabetes mellitus as relevant risk factors [4]. These findings suggest a correlation between PFO and AF, wherein the presence of PFO may increase the risk of developing AF [3–5, 8–10]. Our study data also demonstrated that age and diabetes mellitus were significant predictors, aligning with the previous research observations and enhancing the reliability and generalizability of our results. Furthermore, our study elucidated the significance of age and diabetes mellitus in individuals with PFO and AF, underscoring the importance of these risk factors in preventing and managing AF recurrence after catheter ablation. Additionally, lipoprotein (a) is a plasma lipid metabolite linked with an increased risk of atherosclerosis and cardiovascular disease [39, 40]. Previous studies have also demonstrated the association of lipoprotein (a) with AF [41]. Moreover, elevated levels of lipoprotein (a) may reflect the presence of vascular lesions and an increased inflammatory state, which in turn may exacerbate the chances of AF development and recurrence [41]. In this study, we found that lipoprotein (a) might be a significant prognostic factor for AF recurrence after catheter ablation in patients with co-existing PAF and PFO. This finding further substantiates the involvement of lipoprotein (a) in AF etiology and progression. Lastly, our investigation also uncovered that RVD could potentially contribute to the increased likelihood of AF reoccurrence in individuals diagnosed with PAF and PFO. Although some studies have reported the relationship between RVD and AF [42, 43], the precise mechanism underlying this association remains unknown. Therefore, additional investigations are necessitated to validate our findings and enhance the understanding of the role of RVD in risk stratification for AF recurrence in patients with PAF and PFO.

Although a correlation between PFO and AF has been established, the exact processes involved require elucidation. One possible explanation is that PFO presents conditions for thrombus formation, facilitating thrombus entry into the left atrium via the atrial septum [44, 45]. Other research suggests that even though PFO does not cause AF directly, it may involve a site that increases the risk of AF development or recurrence [46, 47]. In line with this concept, PFO has been shown to affect the stability and conductivity of atrial electrical activity by increasing the load and dilatation of the atrium [48]. In patients with PFO, interatrial communication causes right-to-left shunting under certain conditions [49], resulting in increased atrial volume load and hemodynamic changes in the atrial septum. This phenomenon potentially induces atrial dilatation and electrophysiological alterations, ultimately promoting AF development. Therefore, the main aim of this study was to concentrate on a specific group of individuals

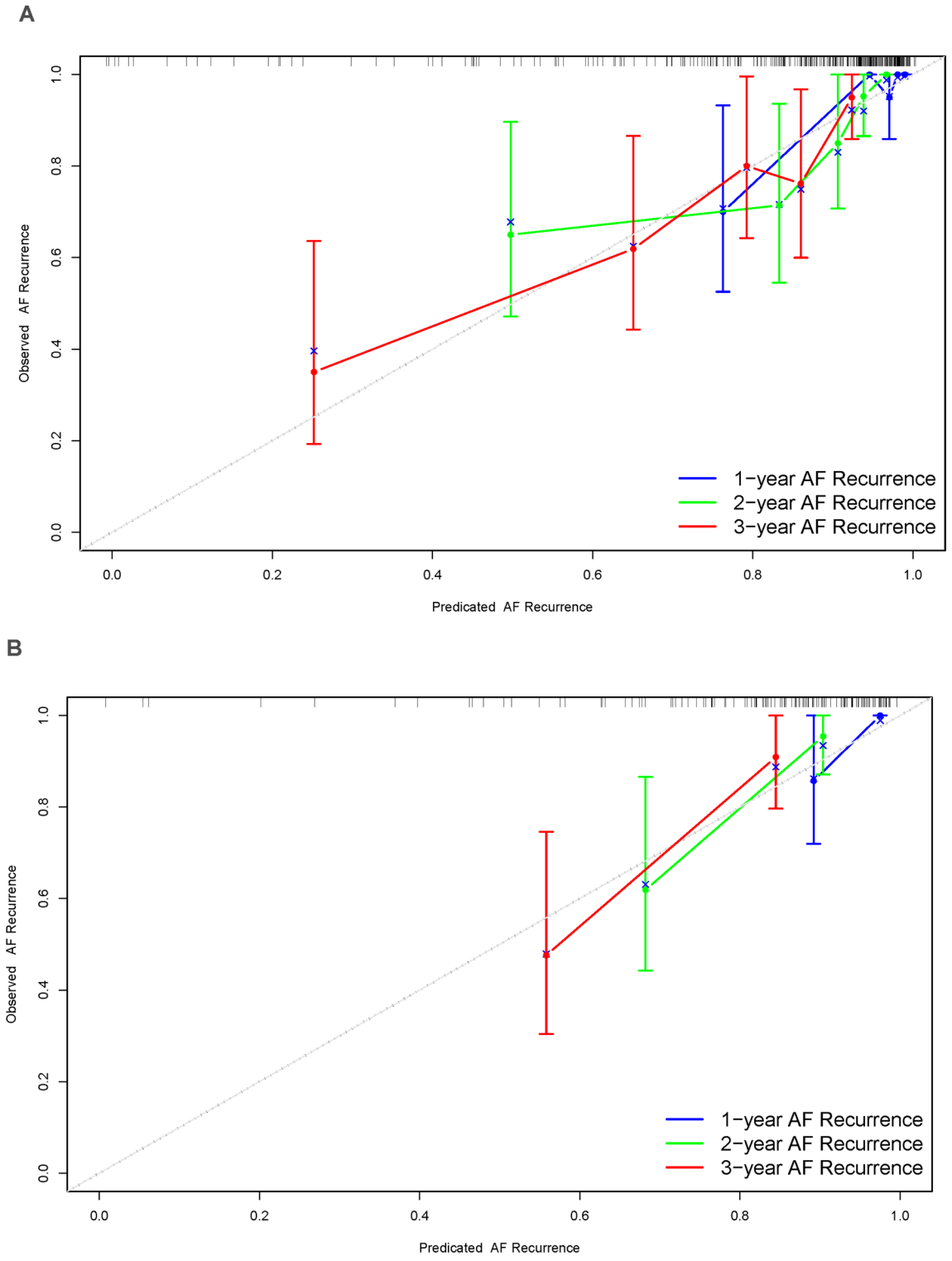


Fig. 6 Calibration curves for 1-, 2- and 3-year AF recurrence predictors in the **A** development and **B** validation cohorts

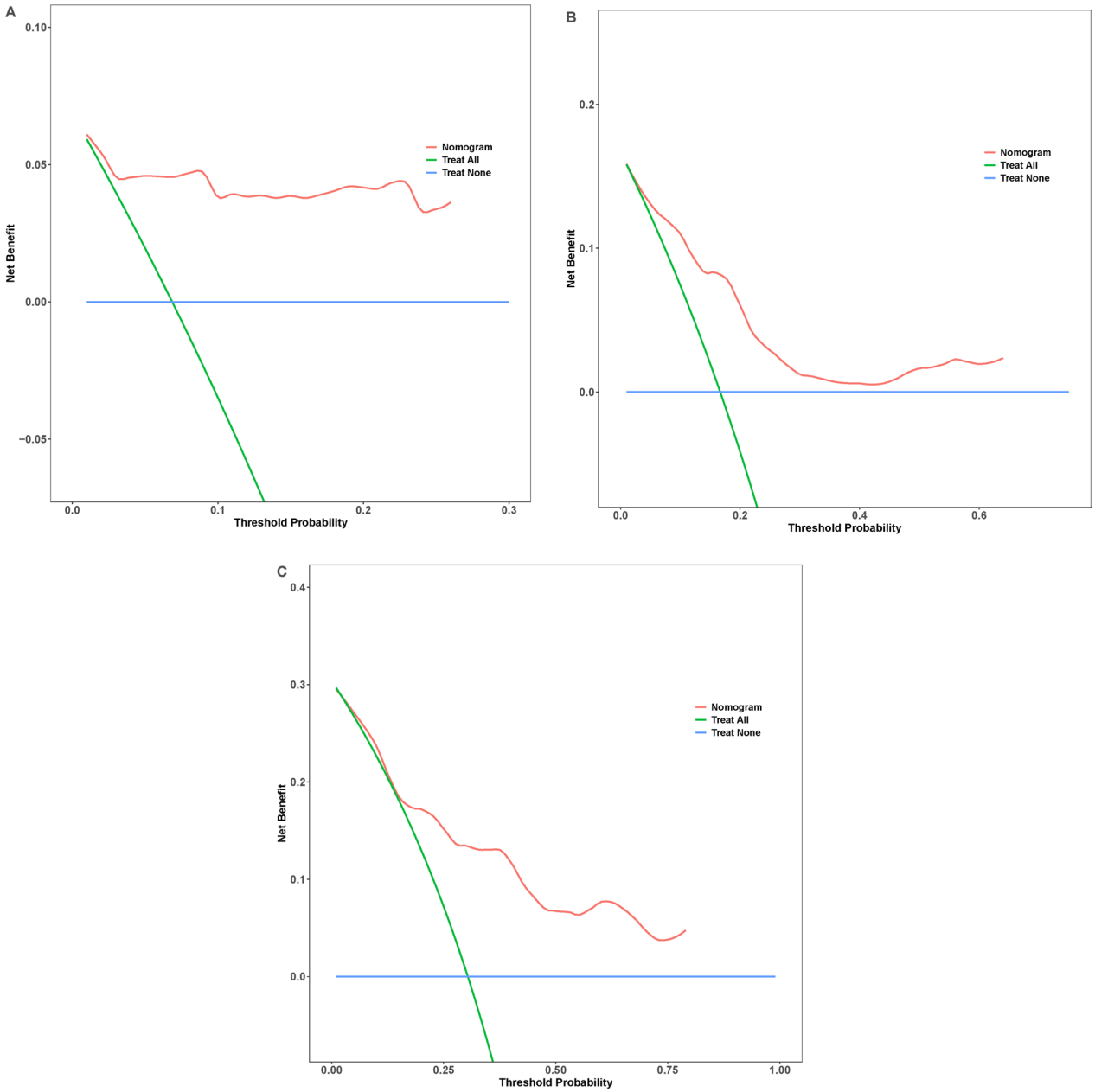


Fig. 7 Decision curve analysis (DCA) for predicting 1-year AF recurrence risk in the **A** development and **D** validation cohorts, 2-year AF recurrence risk in the **B** development and **E** validation cohorts, and 3-year AF recurrence risk in the **C** development and **F** validation cohorts. The DCA evaluates the effectiveness of the nomogram for clinical use, with the horizontal axis representing decisions for different risk thresholds and the vertical axis expressing the net benefit. Additionally, the shape and position of the curves reflect the advantages of the nomogram scoring system at different decision thresholds

who have both PFO and PAF. This particular population has significant clinical relevance due to its heightened susceptibility to AF recurrence after catheter ablation, along with the involvement of complex pathophysiological mechanisms. Correspondingly, the nomogram that we developed by incorporating multimodal data confers improved capabilities for assessing the probability of AF recurrence as well as for formulating appropriate interventions to enhance outcomes and prognosis in this patient population.

This study presents the inaugural predictive nomogram specifically tailored for patients with PFO and PAF undergoing catheter ablation, thereby addressing a significant deficiency in the management of this high-risk

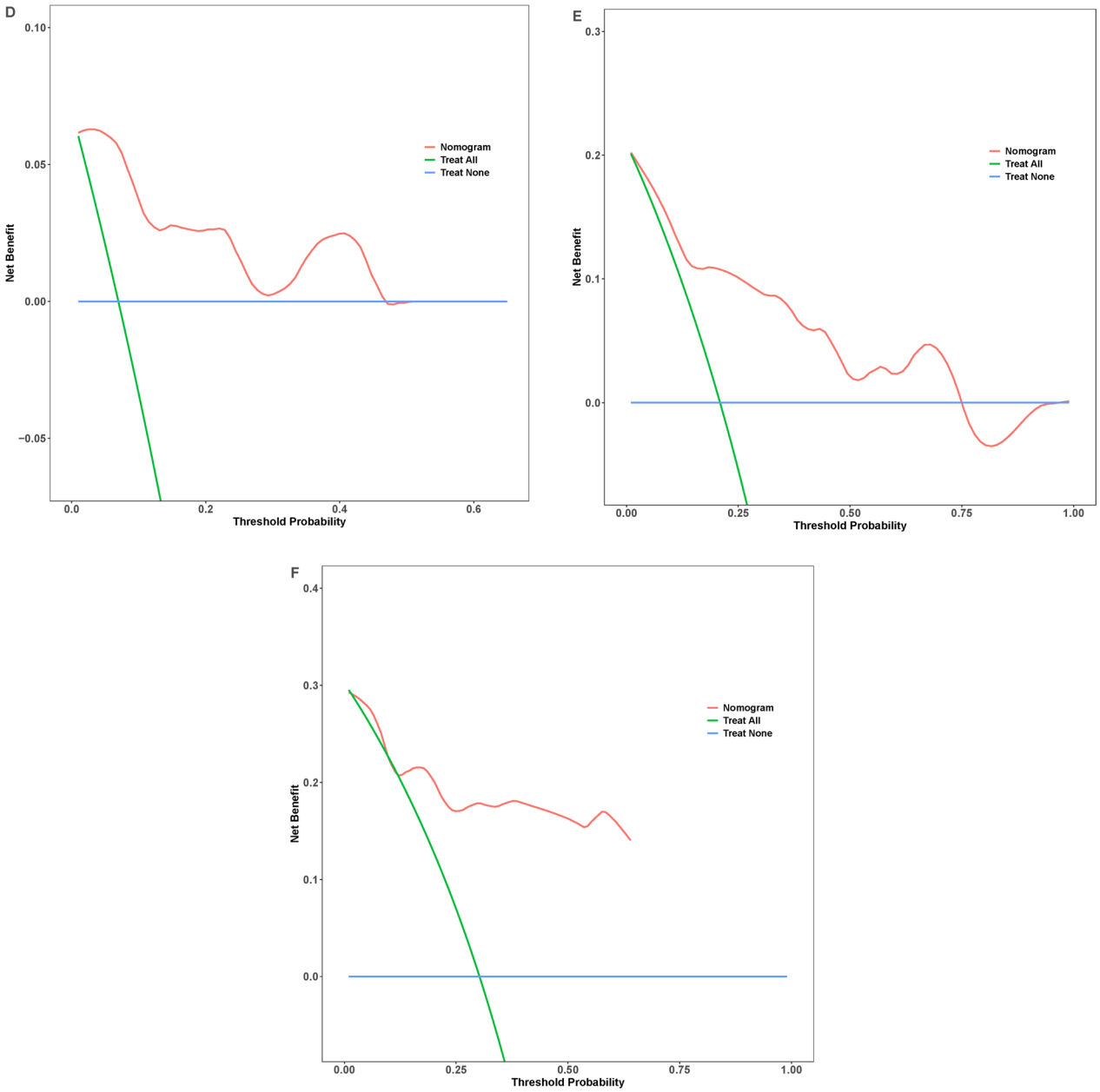


Fig. 7 continued

cohort. The nomogram employs four pivotal variables—patient age, diabetes mellitus, lipoprotein (a), and right ventricular dysfunction—to provide clinicians with an efficient tool for early identification of patients at elevated risk for atrial fibrillation recurrence. Based on the model's risk assessment outcomes, clinicians can effectively implement personalized follow-up and intervention strategies for high-risk patients, thus reducing AF recurrence. This study offers a novel perspective on risk assessment in managing post-catheter ablation patients with PFO and PAF, demonstrating potential clinical applicability.

Study strengths

This study constitutes a pioneering effort in the development of a predictive nomogram specifically designed for patients with PFO and PAF undergoing catheter ablation. It represents the first research initiative to integrate multimodal data-including clinical variables, biomarkers, and imaging parameters-to accurately assess the risk of atrial

fibrillation recurrence within this distinct patient cohort. This work addresses a critical gap in the application of existing scoring tools for this high-risk group. By identifying key predictors, including age, diabetes mellitus, lipoprotein (a), and right ventricular diameter, our model addresses a significant gap in existing risk assessment tools. It provides clinicians with a practical and effective method for stratifying patients according to their individual risk profiles. This innovative approach enhances personalized management strategies and holds considerable potential for improving clinical outcomes in this high-risk population.

Study limitations

Although our study represents significant progress in the scoring system for patients with PFO and PAF, this research has several limitations that should be addressed. First, this study was conducted based on data from a single center with a relatively small sample size and possible selection bias. Therefore, larger samples and multicenter studies are required to validate our findings and improve the reliability and generalizability of this study. Second, we concentrated on a specific patient cohort presenting with PFO and PAF, wherein all participants underwent primary catheter ablation. Thus, these results may not be generalizable to individuals who underwent subsequent catheter ablation. Thirdly, despite adjusting for major confounding variables in our study, we acknowledge that there may exist uncontrolled underlying factors that could potentially influence the recurrence of AF. Fourth, the use of regular outpatient follow-up and telephone interviews may lead to an underestimation of AF recurrence, thus necessitating the future consideration of wearable devices or implantable recorders for a more comprehensive assessment. Finally, although our scoring system demonstrated good performance in predicting AF recurrence risk, further validation is required for its application in clinical practice. Consequently, future prospective studies are necessary to evaluate the accuracy, feasibility, and utility of this scoring system in clinical decision-making and intervention guidance.

Conclusions

Our study is the first to develop a predictive nomogram using the multimodal data of patients with PFO and initial AF catheter ablation, facilitating the accurate prediction of 1-, 2- and 3-year AF recurrence risk in this population. Our study findings provide an important basis for risk assessment and clinical decision-making in patients with co-existing PFO and PAF who underwent initial catheter ablation. Further studies are needed to validate and expand these results, as well as explore the underlying mechanisms and pathophysiological processes of PFO and PAF to enable early diagnosis, personalized treatment, and optimize clinical outcomes in this patient population.

Supplementary Information

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Supplementary Material 1.

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None.

Author contributions
L.Y. and H.J. conceived and performed the study; S.D., X.L., Y.W. and J.W. performed the clinical study and wrote the manuscript; T.X., F.G., Y.W., L.S., Z.L., X.Y., X.S. and H.L. data collection and revision; L.Z. and Y.W. drafting the article or critically revising it for important intellectual content. All authors contributed to the article and approved the submitted version.

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Availability of data and materials
Individual participant data that underlie the results reported in this article, after de-identification can be obtained from the corresponding author upon reasonable request.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Mac Grory B, Ohman EM, Feng W, et al. Advances in the management of cardioembolic stroke associated with patent foramen ovale. BMJ. 2022;9(376): e063161.
2. Kutty S, Sengupta PP, Khandheria BK. Patent foramen ovale: the known and the to be known. J Am Coll Cardiol. 2012;59(19):1665–71.
3. Guedeney P, Laredo M, Zeitouni M, et al. Supraventricular arrhythmia following patent foramen ovale percutaneous closure. JACC Cardiovasc Interv. 2022;15(22):2315–22.
4. Oliva L, Huszti E, Hall R, et al. Incidence of new-onset atrial fibrillation after transcatheter patent foramen ovale closure using 15 years of Ontario administrative health data. Heart Rhythm. 2022;19(9):1414–20.

5. Skibsted CV, Korsholm K, Pedersen L, et al. Long-term risk of atrial fibrillation or flutter after transcatheter patent foramen ovale closure: a nationwide Danish study. Eur Heart J. 2023. https://doi.org/10.1093/eurheartj/ehad305.
6. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129(8):837–47.
7. Alrumayh A, Alobaida M. Catheter ablation superiority over the pharmacological treatments in atrial fibrillation: a dedicated review. Ann Med. 2021;53(1):551–7.
8. Mas JL, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med. 2017;377(11):1011–21.
9. Wang T, Jin X, Lu Y, et al. Impact of patent foramen ovale with left-to-right shunt on atrial fibrillation ablation in young patients. Indian Heart J. 2024;76(4):286–90.
10. Barrio-Lopez MT, Castellanos E, Betancur A, et al. The presence of a large patent foramen ovale reduces acute and chronic success in atrial fibrillation ablation. J Interv Card Electrophysiol. 2022;64(3):705–13.
11. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42(5):373–498.
12. Kavinsky CJ, Szerlip M, Goldsweig AM, et al. SCAI guidelines for the management of patent foramen ovale. J Soc Cardiovasc Angiogr Interv. 2022;1:100039.
13. Silvestry FE, Cohen MS, Armsby LB, et al. Guidelines for the echocardiographic assessment of atrial septal defect and patent foramen ovale: from the American Society of Echocardiography and Society for Cardiac Angiography and Interventions. J Am Soc Echocardiogr. 2015;28(8):910–58.
14. Perry M, Kemmis Betty S, Downes N, et al. Atrial fibrillation: diagnosis and management-summary of NICE guidance. BMJ. 2021;21(373): n1150.
15. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018;20(1):e1–160.
16. Guo F, Wang J, Wu M, et al. Novel insight into neurofilament light chain and rhythm outcomes after catheter ablation of new-onset atrial fibrillation: a prospective cohort study. Heart Rhythm. 2024;S1547–5271(24):03266–71.
17. Zhou T, Wang Y, Xu Y, et al. Multimodal data integration for enhanced longitudinal prediction for cardiac and cerebrovascular events following initial diagnosis of obstructive sleep apnea syndrome. J Glob Health. 2024;17(14):04103.
18. Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16(4):e173–80.
19. Andrade JG, Deyell MW, Macle L, et al. Progression of atrial fibrillation after cryoablation or drug therapy. N Engl J Med. 2023;388(2):105–16.
20. Tzou WS, Marchlinski FE, Zado ES, et al. Long-term outcome after successful catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3(3):237–42.
21. Turagam MK, Neuzil P, Schmidt B, et al. Safety and effectiveness of pulsed field ablation to treat atrial fibrillation: one-year outcomes from the MANIFEST-PF registry. Circulation. 2023;148(1):35–46.
22. Weerasooriya R, Khairy P, Litalien J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol. 2011;57(2):160–6.
23. Kornej J, Hindricks G, Kosiuk J, et al. Comparison of CHADS2, R2CHADS2, and CHA2DS2-VASc scores for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation: the Leipzig Heart Center AF Ablation Registry. Circ Arrhythm Electrophysiol. 2014;7(2):281–7.
24. Kornej J, Schumacher K, Sommer P, et al. Very late arrhythmia recurrences in patients with sinus rhythm within the first year after catheter ablation: the Leipzig Heart Center AF Ablation Registry. Europace. 2019;21(11):1646–52.
25. Artola Arita V, Van De Lande ME, Khalilian Ekrami N, et al. Clinical utility of the 4S-AF scheme in predicting progression of atrial fibrillation: data from the RACE V study. Europace. 2023;25(4):1323–31.
26. Killu AM, Granger CB, Gersh BJ. Risk stratification for stroke in atrial fibrillation: a critique. Eur Heart J. 2019;40(16):1294–302.
27. Letsas KP, Efremidis M, Giannopoulos G, et al. CHADS2 and CHA2DS2-VASc scores as predictors of left atrial ablation outcomes for paroxysmal atrial fibrillation. Europace. 2014;16(2):202–7.
28. Kornej J, Hindricks G, Shoemaker MB, et al. The APPLE score: a novel and simple score for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation. Clin Res Cardiol. 2015;104(10):871–6.
29. Winkle RA, Jarman JW, Mead RH, et al. Predicting atrial fibrillation ablation outcome: the CAAP-AF score. Heart Rhythm. 2016;13(11):2119–25.
30. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology. 2013;81(7):619–25.
31. Kent DM, Saver JL, Ruthazer R, et al. Risk of paradoxical embolism (RoPE)-estimated attributable fraction correlates with the benefit of patent foramen ovale closure: an analysis of 3 trials. Stroke. 2020;51(10):3119–23.
32. Xu Y, Wang J, Zhou Z, et al. Multimodal prognostic model for predicting chronic coronary artery disease in patients without obstructive sleep apnea syndrome. Arch Med Res. 2023;55(1):102926.
33. Wang J, Xu Y, Zhu J, et al. Multimodal data-driven, vertical visualization prediction model for early prediction of atherosclerotic cardiovascular disease in patients with new-onset hypertension. J Hypertens. 2024. https://doi.org/10.1097/HJH.0000000000003798.
34. Ye Z, Xu Y, Tang L, et al. Predicting long-term prognosis after percutaneous coronary intervention in patients with new onset ST-elevation myocardial infarction: development and external validation of a nomogram model. Cardiovasc Diabetol. 2023;22(1):87.
35. Wang J, Wu X, Sun J, et al. Prediction of major adverse cardiovascular events in patients with acute coronary syndrome: development and validation of a non-invasive nomogram model based on autonomic nervous system assessment. Front Cardiovasc Med. 2022;3(9):1053470.
36. Xu Y, Ye Z, Wang B, et al. Novel insights into the predictors of obstructive sleep apnea syndrome in patients with chronic coronary syndrome: development of a predicting model. Oxid Med Cell Longev. 2022;27(2022):5497134.
37. Duan S, Wang J, Yu F, et al. Enrichment of the postdischarge GRACE score with deceleration capacity enhances the prediction accuracy of the long-term prognosis after acute coronary syndrome. Front Cardiovasc Med. 2022;27(9):888753.
38. Aspberg S, Chang Y, Atterman A, et al. Comparison of the ATRIA, CHADS2, and CHA2DS2-VASc stroke risk scores in predicting ischaemic stroke in a large Swedish cohort of patients with atrial fibrillation. Eur Heart J. 2016;37(42):3203–10. https://doi.org/10.1093/eurheartj/ehw077.
39. Li JJ, Ma CS, Zhao D, et al. Lipoprotein(a) and cardiovascular disease in chinese population: a beijing heart society expert scientific statement. JACC Asia. 2022;2(6):653–65.
40. Miksenas H, Januzzi JL Jr, Natarajan P. Lipoprotein(a) and cardiovascular diseases. JAMA. 2021;326(4):352–53. https://doi.org/10.1001/jama.2021.3632. Erratum in: JAMA. 2022;327(1):86.
41. Mohammadi-Shemirani P, Chong M, Narula S, et al. Elevated lipoprotein(a) and risk of atrial fibrillation: an observational and Mendelian randomization study. J Am Coll Cardiol. 2022;79(16):1579–90.
42. Aziz EF, Kukin M, Javed F, et al. Right ventricular dysfunction is a strong predictor of developing atrial fibrillation in acutely decompensated heart failure patients, ACAP-HF data analysis. J Card Fail. 2010;16(10):827–34.
43. Nishimura S, Izumi C, Yamasaki S, et al. Impact of right ventricular function on development of significant tricuspid regurgitation in patients with chronic atrial fibrillation. J Cardiol. 2020;76(5):431–7.
44. Yan C, Li H, Wang C, et al. Frequency and size of in situ thrombus within patent foramen ovale. Stroke. 2023;54(5):1205–13.
45. Yan C, Li H. Preliminary investigation of in situ thrombus within patent foramen ovale in patients with and without stroke. JAMA. 2021;325(20):2116–8.
46. Spence JD, Sposato LA. The intriguing association between patent foramen ovale and atrial fibrillation. Kardiol Pol. 2021;79(7–8):725–7.
47. Krishnamurthy Y, Ben-Ami J, Robbins BT, et al. Incidence and time course of atrial fibrillation following patent foramen ovale closure. Catheter Cardiovasc Interv. 2022;100(2):219–24.
48. Homma S, Messé SR, Rundek T, et al. Patent foramen ovale. Nat Rev Dis Primers. 2016;21(2):15086.
49. Liu K, Wang BZ, Hao Y, et al. The correlation between migraine and patent foramen ovale. Front Neurol. 2020;1(11):543485.