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ORIGINAL RESEARCH

Correlation Between PhenoAgeAccel and Clinical Outcomes in Atrial Fibrillation Patients Undergoing Radiofrequency Catheter Ablation

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Purpose: To investigate the relationship between phenotypic age (PhenoAge) and accelerated phenotypic age (PhenoAgeAccel) and recurrence of atrial fibrillation (AF) in patients after radiofrequency catheter ablation (RFCA).

Patients and Methods: Preoperative PhenoAge and PhenoAgeAccel were determined in AF patients undergoing RFCA. We used logistic regression models and subgroup analysis to study the relationship between PhenoAge and PhenoAgeAccel and the risk of AF recurrence. As for revealing the value of PhenoAgeAccel in predicting AF recurrence, the ROC curve analysis was performed. To further detect the enhancement role of in PhenoAgeAccel in the APPLE score and a model of established risk factors in predicting AF recurrence, C-statistics, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) was conducted.

Results: A total of 322 patients with AF who underwent RFCA in our hospital were included in the present study. The mean follow-up period was 21 months. The frequency of AF recurrence increased gradually as the PhenoAgeAccel index rose. The optimal cut-off value of the PhenoAgeAccel index was −0.338. Patients with PhenoAgeAccel ≥ -0.338 had a significantly greater likelihood of experiencing recurrent AF than those with PhenoAgeAccel <-0.338 (OR 3.989, 95% CI 2.006–7.933, $p < 0.001$). The association was also reflected in each subgroup. Incorporating the PhenoAgeAccel into the APPLE score and the existing model of established risk factors for recurrence may result in enhancements to the C-statistics, NRI and IDI ($p<0.05$), respectively.

Conclusion: PhenoAgeAccel was positively and independently associated with AF recurrence following RFCA.

Keywords: atrial fibrillation, radiofrequency catheter ablation, recurrence, phenotypic age, accelerated phenotypic age

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a worldwide prevalence of 37.5 million cases (0.51% of the population), increasing by 33% over the last two decades.[1] Radiofrequency ablation (RFCA) for atrial fibrillation is highly beneficial and effective for most symptomatic patients. However, the recurrence rate of AF after RFCA is reported to be 20–50% from different centers.[2,3] The substantial cost and high recurrence rate continue to discourage many individuals.[4,5] Simple, inexpensive, and efficient prediction methods are needed to forecast the risk of recurrence following RFCA for AF, thereby enhancing health outcomes and reducing healthcare costs.

Atrial fibrillation incidence increases with age, from 0.1% to 9% in adults under 55 to those over 80 years.[6] The underlying mechanisms include electrical, structural, and Ca^{2+} handling remodeling, as well as mitochondrial dysfunction, telomere attrition, cellular senescence, macro-autophagy dysfunction, and gut dysbiosis,[7–10] all crucial for maintaining normal rhythm after RFCA. However, some studies show no significant age differences in recurrence rates after RFCA.[11,12]

The underlying reason may be that chronological age (CA) could not accurately reflect functional and health status or predict disease prognosis. New age metrics need to represent the body's state more accurately. Morgan E. Levine et al[13] developed a new formula for calculating age using ten variables, including CA, for the phenotypic age predictor, showing superior prediction to DNA methylation measures.

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Phenotypic age (PhenoAge) or PhenoAgeAccel (PhenoAge minus CA) is correlated with heightened risk of various adverse outcomes, like stroke severity and disability,[14] cardiovascular disease (CAD), cancer depression and mortality,[15,16] even after accounting for CA. CAD has been independently associated with AF,[17,18] while complete revascularization during AF ablation significantly reduces recurrence rates, highlighting ischemia correction's importance for rhythm control.[19] PhenoAge, more indicative of body condition, differs from CA and can be influenced by external factors, offering potential intervention avenues. Identifying PhenoAgeAccel individuals is crucial for enabling timely interventions and delaying disease onset.

Current research indicates the relationship between PhenoAge or PhenoAgeAccel and AF recurrence after RFCA is not fully understood. This study aims to assess the relationship between PhenoAge, PhenoAgeAccel and clinical outcomes following RFCA in AF patients in order to provide a theoretical basis for future clinical strategies for these individuals.

Materials and Methods

Study Population

Figure 1 presents the flow chart for this study, a critical component visualizing the research process. This retrospective analysis utilized the comprehensive Electronic Medical Record system of patients admitted to the inpatient Department of Cardiology at the Affiliated Hospital of Xuzhou Medical University. The study focused on a specific timeframe, from September 2018 to September 2021. The sample population comprised 398 patients undergoing their first radiofrequency ablation treatment. Inclusion criteria were non-valvular AF and first-time radiofrequency catheter ablation. Exclusion criteria excluded individuals with severe hepatic or renal dysfunction, any form of organic heart disease, recent blood transfusions or other surgeries, preoperative infections, comorbid hematologic or rheumatic immune system diseases, and a history of tumors.

Radiofrequency Ablation Operation Method

To effectively manage persistent atrial fibrillation, a multi-faceted approach was employed. Firstly, a precise three-dimensional reconstruction of the left atrium and pulmonary veins was completed using the electroanatomic mapping system, CARTO 3 model. Once completed, circumferential pulmonary vein isolation was performed in every patient. Additional ablation procedures were undertaken if required, targeting key areas such as the left atrial apex, posterior line, anterior line, and mitral isthmus. In some cases, patients underwent direct current cardioversion if atrial fibrillation

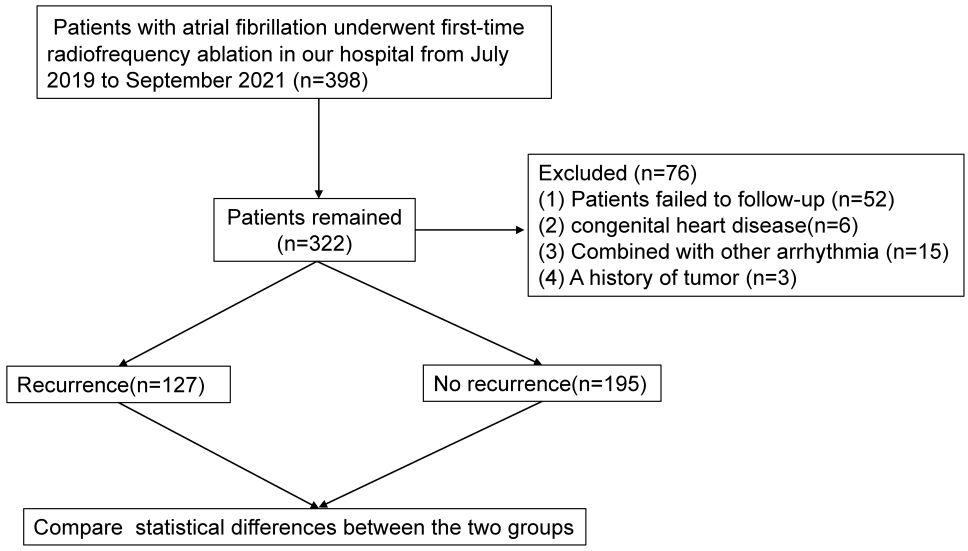

Figure 1 Flow chart of our study.

persisted despite initial ablation procedures. All patients were prescribed two medications post-operation: amiodarone and rivaroxaban for 3 months.

Data Collection

The baseline and clinical characteristics were carefully extracted from the medical record system by a team of trained physicians, who were blinded to the study's objective to minimize potential bias. In addition to this, patient demographics and a comprehensive list of clinical characteristics were meticulously recorded, ensuring a detailed and thorough examination of the collected data. General information included age, sex, body mass index, duration of AF, type of AF, smoking history, hypertension history, diabetes history, coronary artery disease history, APPLE score, and CHA2DS2-VASc score. Blood markers were recorded including white blood cell count, lymphocyte count, monocyte count, platelet count, mean (red) cell volume, red cell distribution width (RDW), alkaline phosphatase, hemoglobin level, hypersensitive C-reactive protein (hs-CRP) level, fasting plasma glucose level, serum creatinine level (SCr), triglyceride level, total cholesterol level (TC), low-density lipoprotein-C level (LDL-C), and high-density lipoprotein-C level (HDL-C). Imaging data included cardiac ultrasound, 12-lead electrocardiogram, and 24-hour Holter monitoring were collected. PhenoAge and PhenoAgeAccel were calculated separately using specific methods as following.

Measurement of PhenoAge and PhenoAgeAccel

Our research adopted the comprehensive PhenoAge definition from Morgan E. Levine et al[13] enabling calculations of both PhenoAge and its acceleration, PhenoAgeAccel. Ten aging-related variables were involved, each contributing uniquely to the aging process, aiming to provide a detailed and nuanced understanding of aging and its acceleration.

$$\text{Phenotypic age} = 141.50 + \frac{Ln[-0.00553 * Ln(\exp(\frac{-1.51714 * \exp(xb)}{0.0076927}))]}{0.09165}$$

Where xb=−19.907–0.0336*Albumin+0.0095*Creatinine+0.1953*Glucose+0.0954*LnCRP-0.0120*Lymphocyte Percent +0.0268* Mean (red) Cell Volume+0.3306*Red Cell Distribution Width+0.00188*Alkaline Phosphatase+0.0554*White Blood Cell Count+0.0804*Chronological Age.

While, PhenoAgeAccel=PhenoAge-Chronological Age (years).

Follow-up

Upon completion of RFCA, patients were prescribed two medications: oral anticoagulants and amiodarone, which they took for 3 months. Throughout this period, patients underwent comprehensive clinical assessments and vital sign monitoring, including 12-lead electrocardiograms (ECGs) to evaluate heart electrical activity, along with 24-hour Holter monitoring to gain a detailed understanding of cardiac health. If AF symptoms arose, additional ECGs or Holter ECGs were performed to assess the underlying cause. After six months, patients transited to regular follow-ups, which include clinical symptom evaluation, drug administration, and electrocardiograms, either in the outpatient clinic or through remote telephone consultations with healthcare providers.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median with interquartile range, while categorical variables were presented as counts and percentages (%). All participants were divided into two groups based on the follow-up results. Univariable and multivariable logistic regression analysis was performed to identify determinants of recurrence in AF patients undergoing first RFCA. Three models were constructed to adjust for confounding variables and examine the relationship between the PhenoAgeAccel index and the recurrence of AF. In Model 1, adjustments were made for sex and BMI. For Model 2, additional adjustments were included on top of Model 1, specifically for hypertension, diabetes, smoking, AF duration, AF type, and CHA_2DS_2-VASc score. As for Model 3, further adjustments were incorporated beyond Model 2, which encompassed left atrial diameter, left ventricular ejection fraction, low-density lipoprotein-C, and total cholesterol. The receiver operating characteristic (ROC) curve analysis was used to evaluate the area under the curve (AUC) and determine the optimal cut-off value. We assessed whether patients with less than or

greater than (or equal to) the cut-off point of the PhenoAgeAccel index in the three multivariate models. Additionally, the C-statistic was computed and compared using De-Long's test to assess whether incorporating the PhenoAgeAccel index into the APPLE score and a model of established risk factors would enhance its predictive values. Additionally, the enhanced predictive capability of the PhenoAgeAccel index was assessed through the computation of the net reclassification improvement (NRI) as well as the integrated discrimination improvement (IDI). All statistical analyses were conducted using R, Version 4.2.3 (https://cran.r-project.org), and two-sided *P*-value < 0.05 was considered to indicate a statistically significant difference.

Results

Baseline Characteristics

Our comprehensive study evaluated 322 participants. The median follow-up time post-RFCA was 21 months. The study population had a mean age of 63 years. 195 participants (60.6% of the total) were male. In terms of co-morbid conditions, 25.5% had coronary artery disease (CAD), 41.9% hypertension, 35.1% diabetes, and 23.9% were active smokers. A thorough analysis of the data revealed statistically significant differences between the recurrence group and non-recurrent groups in BMI, hypertension, AF type, CHA2DS2-VASc score, APPLE score, LAD, LVEF ($p<0.05$) (Table 1). Significant differences were also observed in total cholesterol, LDL-C, white cell count, albumin, lymphocyte percentage, RDW, PhenoAge and PhenoAgeAccel ($p<0.05$) (Table 1), providing insights into potential risk factors and underlying pathophysiology associated with AF.

Table 1 Baseline Characteristics of the Study Population

	Total	**No recurrence**	**Recurrence**	***P***
	N=*322*	**N=*195***	**N=*127***	
Age(y)	63 (54, 68)	63 (54, 68)	62 (55, 68)	0.884
Gender				0.711
Female (n, %)	127 (39.4)	79 (40.5)	48 (37.8)	
Male (n, %)	195 (60.6)	116 (59.5)	79 (62.2)	
Height(m)	1.66 (1.60, 1.72)	1.67 (1.60, 1.72)	1.65 (1.60, 1.72)	0.744
Weight(m)	70 (62, 80)	70 (62, 76)	72 (63, 80)	0.076
BMI (kg/m2)	25.5 (2.98)	25.2 (2.93)	26.1 (2.97)	0.007
AF duration (month)	48 (24, 60)	36 (24, 60)	48 (33, 72)	0.189
CAD (n, %)				0.826
No	240 (74.5)	144 (73.8)	96 (75.6)	
Yes	82 (25.5)	51 (26.2)	31 (24.4)	
Hypertension (n, %)				0.018
No	187 (58.1)	124 (63.6)	63 (49.6)	
Yes	135 (41.9)	71 (36.4)	64 (50.4)	
Diabetes (n, %)				0.156
No	209 (64.9)	133 (68.2)	76 (59.8)	
Yes	113 (35.1)	62 (31.8)	51 (40.2)	

(*Continued*)

Table 1 (Continued).

	Total	**No recurrence**	**Recurrence**	***P***
	N=*322*	**N=*195***	**N=*127***	
AF Type				<0.001
Paroxysmal (n, %)	131 (40.7)	99 (50.8)	32 (25.2)	
Persistent (n, %)	191 (59.3)	96 (49.2)	95 (74.8)	
Smoking (n, %)				0.763
No	245 (76.1)	150 (76.9)	95 (74.8)	
Yes	77 (23.9%)	45 (23.1)	32 (25.2)	
CHA_2DS_2-VASc score	2.19 (1.55)	2.03 (1.49)	2.43 (1.61)	0.023
APPLE score	1.67 (1.12)	1.39 (1.02)	2.11 (1.14)	<0.001
LAD (mm)	42.1 (6.09)	40.7 (5.13)	44.3 (6.80)	<0.001
LVEF (%)	57 (51, 59)	57 (54, 60)	55 (48, 59)	<0.001
eGFR (mL/min*1.73m^{-2})	102 (87, 117)	102 (87, 117)	102 (86, 117)	0.724
Scr (umol/L)	66 (56, 77)	65 (56, 77)	70 (57, 78)	0.216
Hemoglobin (g/L)	147 (139, 155)	147 (140, 156)	147 (138, 154)	0.255
TC (mmol/L)	4.12 (3.39, 4.82)	4.29 (3.53, 4.88)	3.84 (3.25, 4.66)	0.010
TG (mmol/L)	1.19 (0.86, 1.84)	1.15 (0.86, 1.84)	1.24 (0.86, 1.83)	0.778
HDL-C (mmol/L)	1.10 (0.93, 1.30)	1.11 (0.94, 1.40)	1.09 (0.92, 1.25)	0.159
LDL-C (mmol/L)	2.30 (1.68, 2.91)	2.42 (1.75, 2.98)	2.10 (1.67, 2.74)	0.020
Albumin (g/L)	43.5 (40.9, 45.8)	43.8 (41.2, 45.9)	42.7 (40.1, 45.4)	0.021
Glucose (mmol/L)	5.34 (4.88, 6.15)	5.30 (4.85, 6.03)	5.42 (4.97, 6.33)	0.055
WBC (*10^9/L)	5.70 (4.73, 6.70)	5.50 (4.70, 6.50)	5.90 (5.00, 6.95)	0.044
hsCRP (mg/L)	2.0 (0.8, 7.2)	1.6 (0.8, 6.6)	2.2 (1.0, 9.3)	0.170
Lymphocyte percentage (%)	29 (22, 34)	32 (25, 36)	25 (20, 32)	<0.001
Mean Cell Volume(fl)	92.7 (90.2, 96.6)	92.8 (90.2, 96.8)	92.6 (90.4, 96.3)	0.598
Red cell distribution width (%)	12.8 (12.4, 13.3)	12.7 (12.4, 13.2)	12.90 (12.7, 13.40)	0.002
ALP (U/L)	72 (60, 85)	71 (61, 85)	75 (60, 84)	0.703
PhenoAge (y)	57 (47, 65)	56 (47, 62)	59 (50, 67)	0.016
PhenoAgeAccel(y)	−6 (−10, −2)	−7 (−11, −3)	−4 (−7, 2)	<0.001

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; MCV, Mean Cell Volume; ALP, alkaline phosphatase; WBC, white cell count; RDW, red cell distribution width; TC, total cholesterol; TG, Triglyceride; HDL-C, high-density lipoprotein-C; LDL-C, low-density lipoprotein-C; hs-CRP, high sensitivity-C reactive protein; SCr, serum creatinine; LAD, left anterior; LVEF, left ventricular ejection fraction.

Association of the PhenoAgeAccel Index and the Risk of AF Recurrence in Logistic Analysis

The univariate logistic regression analysis indicated that several factors, including PhenoAge, PhenoAgeAccel, BMI, hypertension, AF type, CHA2DS2-VASc score, APPLE score, LAD, LVEF, total cholesterol, LDL-C, white cell count,

albumin, lymphocyte percentage, and RDW, were significantly associated with the recurrence of AF after RFCA, with a *p*-value of less than 0.05. Multivariable logistic regression models identified PhenoAgeAccel (OR 1.116 95% CI 1.056–1.179, *p*=0.001), LAD (OR 1.055 95% CI 1.003–1.108, *p*=0.036), LVEF (OR 0.950 95% CI 0.910–0.992, *p*=0.019), and AF type as independent risk factors of AF recurrence after RFCA. Specifically, PhenoAgeAccel index had an OR of 1.116, 95% CI of 1.056–1.179 (*p*= 0.001), indicating that for every 1 unit increase in PhenoAgeAccel, the odds of AF recurrence after RFCA increased by 11.6% (Figure 2), showing an outstanding relationship with AF recurrence.

As shown in Table 2, patients with PhenoAgeAccel levels above the cut-off of −0.338 had higher rates of AF recurrence compared to those with lower levels (82/258 vs 45/64, *p*<0.001). This association was consistent across all three models. In the fully adjusted model 3, the risk of recurrent AF was significantly higher in patients with PhenoAgeAccel levels above −0.038 compared to those below the cut-off (OR 3.989, 95% CI 2.006–7.933, *p*<0.001).

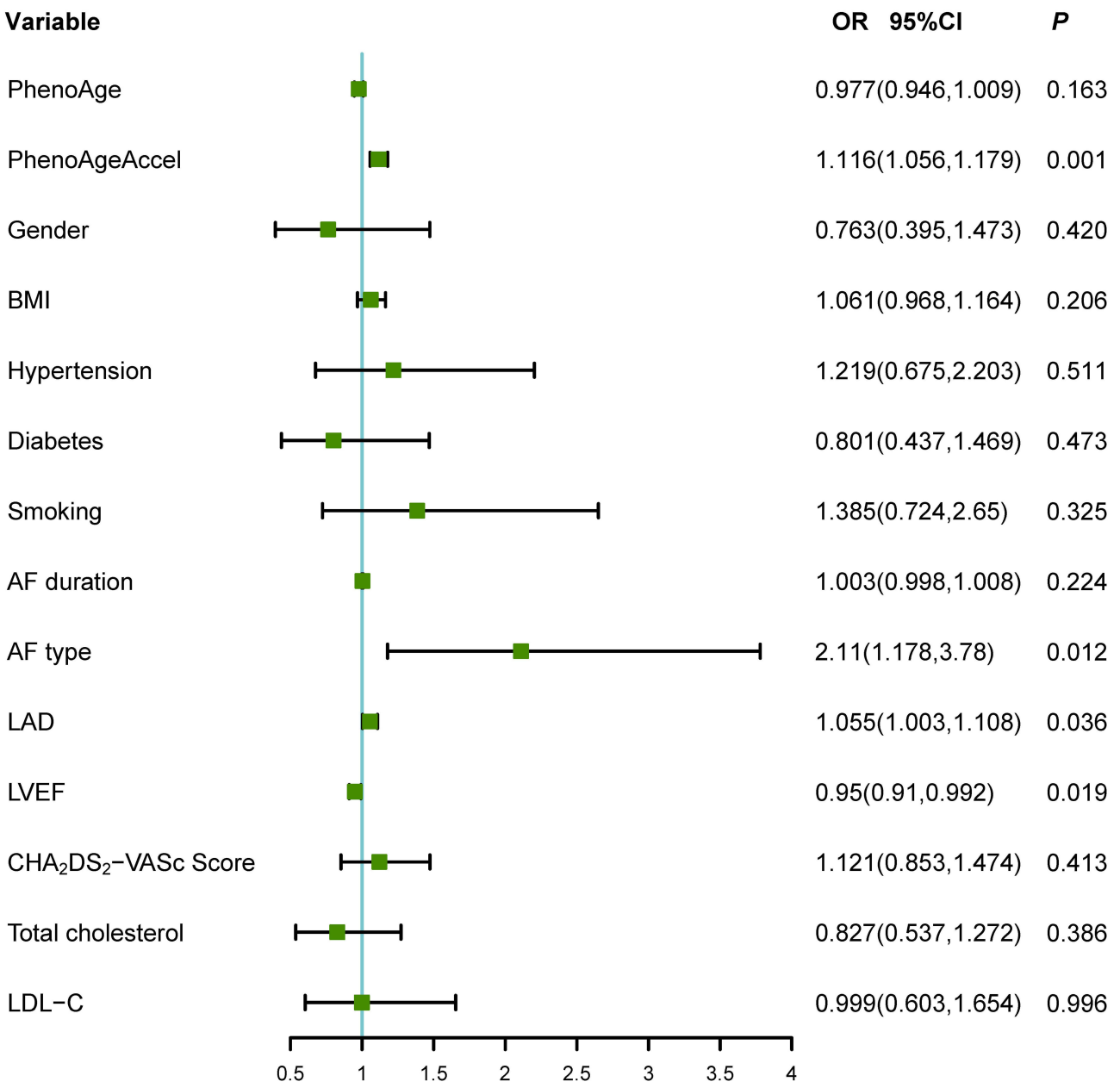

Figure 2 Forest plot of the multivariable logistic regression analysis model in patients with AF undergoing RFCA.

Table 2 Association of PhenoAgeAccel with AF Recurrence Following RFCA in Multivariable Logistic Regression Models

Variable	PhenoAgeAccel		*P*-value
	<-0.338	**≥-0.338**	
Events/patients	82/258	45/64	
Incidence (%)	31.7%	70.3%	
Model 1	1.00 (Ref)	5.598 (3.017,10.387)	<0.001
Model 2	1.00 (Ref)	5.034 (2.604,9.735)	<0.001
Model 3	1.00 (Ref)	3.989 (2.006,7.933)	<0.001

Notes: Model 1: adjusted for sex, and BMI. Model 2: adjusted for sex, BMI, hypertension, diabetes, smoking status, AF duration, AF type, CHA_2DS_2-VASc score. Model 3: adjusted for sex, BMI, hypertension, diabetes, smoking status, AF duration, AF type, CHA_2DS_2-VASc score, LAD, LVEF, LDL-C, TC.
Abbreviations: AF, atrial fibrillation; RFCA, Radiofrequency catheter ablation; confidence interval; BMI, body mass index; LAD, left anterior; LVEF, left ventricular ejection fraction; LDL-C, low-density lipoprotein-C; TC, total cholesterol; OR, odds ratio; CI, confidence interval.

Subgroup Analysis for the Associations of PhenoAgeAccel with the Risk of AF Recurrence

As illustrated in Figure 3, a thorough analysis was conducted to assess the independent relationship between PhenoAgeAccel. This study was carried out across various subgroups, including gender, age, AF history, and underlying medical conditions, to ensure a comprehensive understanding. The consistent observation of a positive correlation between the PhenoAgeAccel index and the risk of AF recurrence within each subgroup was noted. This indicates that a higher PhenoAgeAccel index was associated with an increased likelihood of AF recurrence, suggesting that it could serve as a valuable predictor.

Incremental Effects of the PhenoAgeAccel Index on the Predictive Value of AF Recurrence

Figure 4A of our study showed that the PhenoAgeAccel had a moderate predictive value for AF recurrence with an AUC of 0.664 (95% CI: 0.604−0.724, $p<0.001$). The optimal cut-off value was −0.338. Table 3 and Figure 4B showed that integrating the PhenoAgeAccel into the existing model of risk factors, APPLE, could lead to a statistically significant increase in the C-statistics (0.719(0.661,0.776) vs 0.677 (0.619,0.735), $p=0.024$), NRI (0.259 (0.039–0.481), $p=0.021$), and IDI 0.052 (0.027–0.077), $p<0.001$), suggesting that the PhenoAgeAccel adds incremental prognostic value and discriminatory power to the APPLE model.

Moreover, Table 3 and Figure 4C of our study showcased that integrating the PhenoAgeAccel into a model based on established risk factors, including AF type, left atrial dilatation (LAD), and left ventricular ejection fraction (LVEF), could result in a statistically significant rise in the C-statistics (0.748 (95% CI: 0.694–0.802) vs 0.711(95% CI: 0.653–0.768), $p=0.027$), NRI (0.349(0.128–0.596), $p=0.002$), and IDI (0.051(0.026–0.076), $p<0.001$), indicating that the PhenoAgeAccel adds significant prognostic value when combined with the established risk factors.

Discussion

This study demonstrates that the assessment of PhenoAgeAccel can serve as a simple, direct risk indicator for predicting the recurrence of AF after catheter ablation. To our knowledge, no previous study has examined the potential application of PhenoAge and PhenoAgeAccel in the context of AF recurrence after catheter ablation.

With the aging of global populations, the incidence and prevalence of atrial fibrillation (AF) are rising following the high survival rate with chronic diseases.[20] Although chronological age (which is the time that has passed since birth) is a useful measure for evaluating an individual's aging process, the speed of aging varies among people of the same

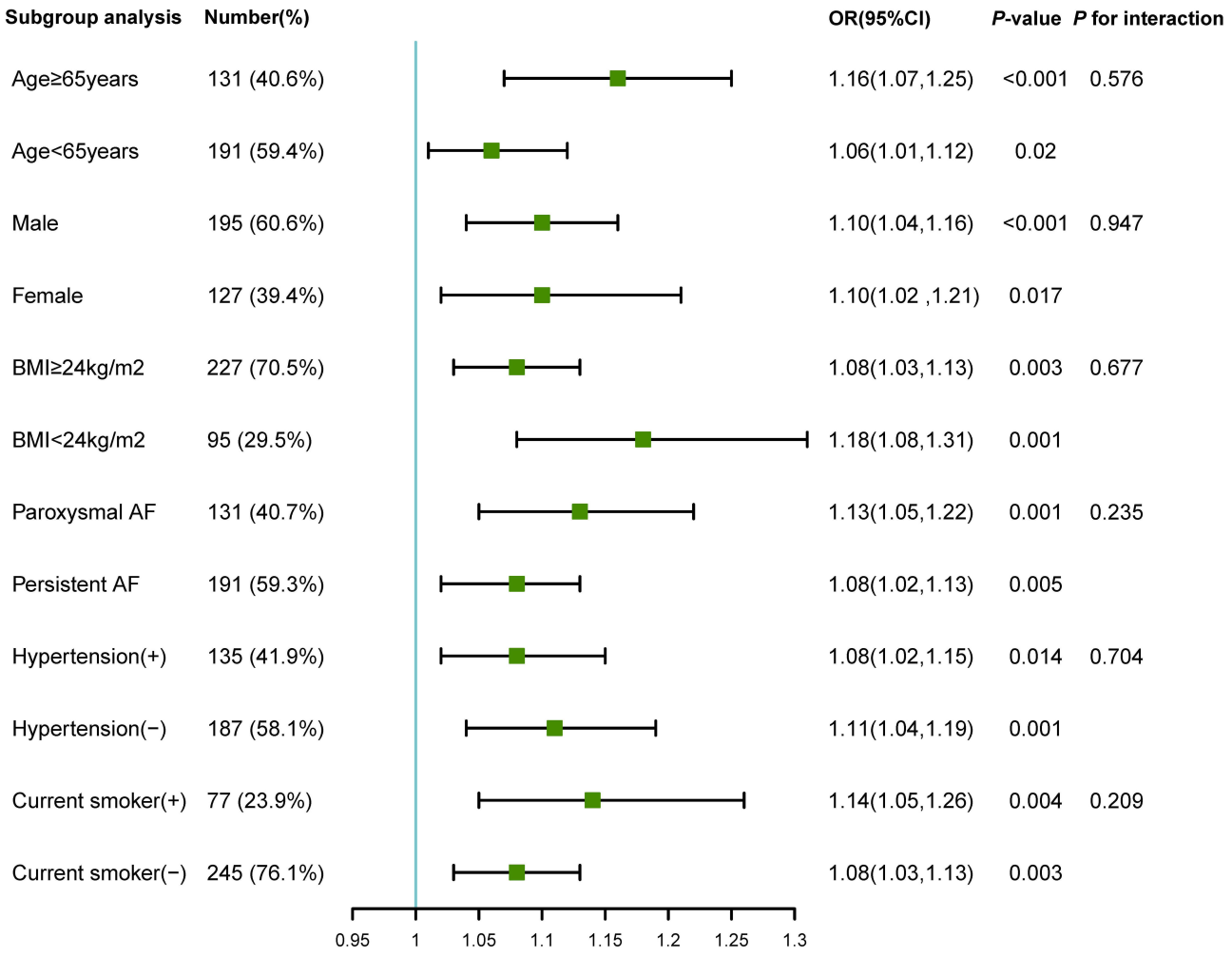

Figure 3 Forest plot investigating the association between the PhenoAgeAccel index and the prevalence of AF recurrence in different subgroups.

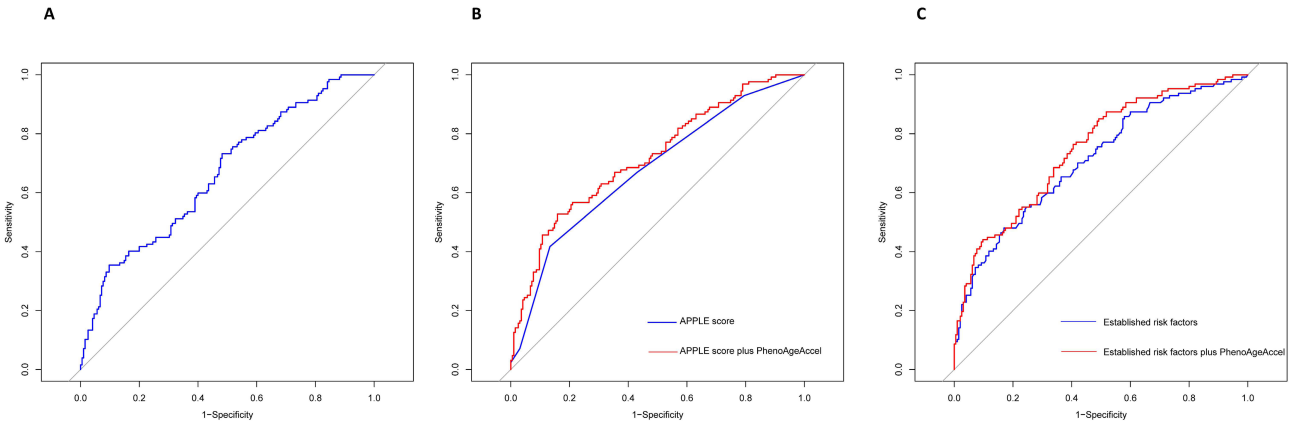

Figure 4 Receiver operating characteristic curve analysis of the PhenoAgeAccel index to predict AF recurrence (**A**) and comparison of the C-statistics when PhenoAgeAccel added to the APPLE score (**B**) and a model including established risk factors risk factors (**C**).

Table 3 Evaluate the Predictive Power of Models for AF Recurrence After RFCA

Models	C-statistic	*P*-value	*P* for comparison	NRI	*P*-value	IDI	*P*-value
APPLE score	0.677 (0.619,0.735)	<0.001		Ref		Ref	
APPLE score plus PhenoAgeAccel index	0.719 (0.661,0.776)	<0.001	0.024	0.259 (0.039–0.481)	*0.021*	0.0523 (0.027–0.077)	<0.001
Established risk factors	0.711 (0.653–0.768)	<0.001		Ref		Ref	
Established risk factors plus PhenoAgeAccel index	0.748 (0.694–0.802)	<0.001	0.027	0.349 (0.128–0.596)	0.002	0.051 (0.026–0.076)	<0.001

Abbreviations: AF, atrial fibrillation; RFCA, Radiofrequency catheter ablation; NRI, net reclassification improvement; IDI, integrated discrimination improvement.The APPLE score is calculated by adding each one point for the following criteria (<65 years, persistent AF, impaired estimated glomerular filtration rate <60 mL/min/1.73m2, left atrial diameter ≥43mm, left ventricular ejection fraction <50%).

chronological age, making it unable to swiftly mirror alterations in diverse biological systems. In contrast, biological age offers a more accurate reflection of differences in individual health status and can explain variation in the aging process.[21] Furthermore, considering the potentially reversible nature of biomarkers that measure biological age, they may serve as partially modifiable risk factors in disease treatment strategies.

To date, no universally accepted gold standard has been established for calculating biological age through clinical biomarkers, and discrepancies may occur across different methodologies. Traditional methods include DNA methylation, telomere length, etc., which require higher costs.[22–24] Studies combined blood chemistry data to construct a new way to represent biological age and showed this method was even superior to DNA methylation measures in predicting healthy lifespan.[13] Phenotypic age and the Klemera-Double method are commonly used clinical indicators to detect physiological changes earlier and at lower cost. Allostatic load and homeostatic dysregulation can also indicate the body's aging state.[25] Among them, PhenoAge demonstrated greater improvement and advantage in predictive disease models, such as stroke, coronary artery disease, and chronic kidney disease.[26] Considering AF is an age-related disease with characteristics of high stroke and heart failure risk,[20,27] the PhenoAge algorithm may be more suitable for constructing the biological age of the AF population.

In the present study, PhenoAge and PhenoAgeAccel showed significantly correlation with AF recurrence by the univariate logistic regression, while PhenoAgeAccel and PhenoAgeAccel index were independent risk factors predicting the AF recurrence after RFCA in multivariable logistic regression models. Patients with levels of PhenoAgeAccel above the cut-off −0.338 had higher rates of AF recurrence than those with PhenoAgeAccel levels below −0.338, which was further verified in different subgroup analyses.

In addition, when PhenoAgeAccel was added to the APPLE score, an established classic risk score for recurrence in clinical, the increase in discrimination was statistically significant. Furthermore, adding the PhenoAgeAccel to the model of established risk factors consisting of AF type, LAD, and LVEF could also lead to an increase in C-statistics. Thus, PhenoAgeAccel was independently and positively associated with recurrence after RFCA in AF patients. With the help of PhenoAge, we aim to translate the complex mechanism of atrial fibrillation recurrence into a simple, easy-to-understand digital language, providing decision-making references for non-medical professionals. In the future, patients' understanding of the recurrence rate following atrial fibrillation radiofrequency ablation surgery has evolved from simply consulting doctors to actively exploring methods to reduce recurrence.

At present, there is no consensus on the exact role of PhenoAgeAccel in elucidating the underlying mechanisms of aging and the outcomes of atrial fibrillation after radiofrequency ablation. We speculate on possible mechanisms as follows.

First, PhenoAgeAccel was computed based on blood biomarkers, including LDL-C, white cell count, albumin, lymphocyte percentage, RDW indicators, and CRP, which had a connective relationship with inflammation, playing important roles in electrical remodeling, structural remodeling and other processes,[28] ultimately affecting AF

recurrence.[29,30] In our previous study, we developed a nomogram model that included a systemic inflammation score to predict the probability of recurrence after RFCA, confirming the contributory effect of inflammation on recurrence following RFCA.[31] Other studies have also shown that the inflammatory cascade plays a pivotal role in the clinical outcomes of AF and in predicting AF recurrence post-cryo-balloon ablation.[32–34]

Additionally, patients with accelerated PhenoAge may experience increased cardiovascular vulnerability,[35,36] limiting their cardiovascular and recovery capacity. Structural changes can lead to ventricular stiffness, impaired stress resistance and so on,[37,38] thus being more likely to result in AF recurrence and adverse outcomes.

In the realm of medical research, there is a growing body of evidence underscoring the potential of multi-domain lifestyle interventions. Numerous studies suggest these interventions may not only slow aging but also prevent chronic diseases.[39] Future studies should, in particular, intensively investigate the specific effects of different lifestyle changes, as well as explore the feasibility and efficacy of alternative interventions. The ultimate aim of such studies should be to determine if these lifestyle interventions, particularly those that target PhenoAgeAccel, a critical aging marker, can significantly improve the prognosis and overall health outcomes of individuals, particularly focusing on patients suffering from atrial fibrillation.

Our study had some limitations. Initially, the absence of a universally accepted 'gold standard' for measuring biological aging should be acknowledged, despite the availability of various validated methods and indicators. Secondly, the retrospective case-control nature of this study restricts its ability to establish causal relationships and limits the assessment to a snapshot of associations at a single moment. However, it can provide important clues and hypotheses for the study of causality, and lay the foundation for further prospective or experimental research. Thirdly, single-center retrospective analysis have inherent limitations in generalizability due to institutional selection bias. The PhenoAgeAccel threshold requires multicenter prospective studies with diverse cohorts and additional biomarkers for clinical translation.

In summary, our investigation employed retrospective data to explore the correlation between PhenoAge, PhenoAgeAccel, and the recurrence rates of atrial fibrillation post radiofrequency catheter ablation. PhenoAgeAccel, as a biomarker, may effectively predict recurrence in patients with atrial fibrillation undergoing RFCA, beyond the scope of conventional assessment. PhenoAgeAccel, assessed through blood biomarkers and physical measurements, offers the potential to delay aging processes or pinpoint high-risk groups for preventive measures. Therefore, further research on PhenoAgeAccel is warranted to explore its full potential in this field and necessitate further validation across diverse populations.

Conclusion

This study demonstrates PhenoAgeAccel was positively and independently associated with AF recurrence following RFCA. Furthermore, our present study suggests that PhenoAgeAccel could improve the predictive value of the APPLE score, a well-established clinical risk score for recurrence, resulting in statistically significant discrimination improvement.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. Due to the study being a retrospective analysis, the review committee waived the requirement for written informed consent. Confidential patient information was removed from the entire data set prior to analysis.

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Disclosure

The authors report no conflicts of interest in this work.

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