The relationship between right atrial wall inflammation and poor prognosis of atrial fibrillation based on ^{18}F-FDG positron emission tomography/computed tomography

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Background: Atrial fibrillation (AF) has been identified to increase stroke risk, even after oral anticoagulants (OACs), and the recurrence rate is high after radiofrequency catheter ablation (RFCA). Inflammation is an essential factor in the occurrence and persistence of AF. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is an established molecular imaging modality to detect local inflammation. We aimed to investigate the relationship between atrial inflammatory activity and poor prognosis of AF based on ^{18}F-FDG PET/CT.

Methods: A total of 204 AF patients including 75 with paroxysmal AF (ParAF) and 129 with persistent AF (PerAF) who underwent PET/CT before treatment were enrolled in this prospective cohort study. Clinical data, electrocardiograph (ECG), echocardiography, and cardiac ^{18}F-FDG uptake were collected. Follow-up information was obtained from patient clinical case notes or telephone reviews, with the starting point being the time of PET/CT scan. The follow-up deadline was either the date of AF recurrence after RFCA, new-onset stroke, or May 2023. Cox proportional hazards regression models were used to identify predictors of poor prognosis and hazard ratios (HRs) with 95% confidence intervals (CIs) was calculated.

Results: Median follow-up time was 29 months [interquartile range (IQR), 22–36 months]. Poor prognosis occurred in 52 patients (25.5%), including 34 new-onset stroke patients and 18 recrudescence after RFCA. The poor prognosis group had higher congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (TIA) or thromboembolism (doubled), vascular disease, age 65–74 years, sex category (female) (CHA2DS2-VASc) score [3.0 (IQR, 1.0–3.75) *vs.* 2.0 (IQR, 1.0–3.0),

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P=0.01], right atrial (RA) wall maximum standardized uptake value (SUV_{max}) (4.13±1.82 *vs.* 3.74±1.58, P=0.04), higher percentage of PerAF [39 (75.0%) *vs.* 90 (59.2%), P=0.04], left atrial (LA) enlargement [45 (86.5%) *vs.* 104 (68.4%), P=0.01], and RA wall positive FDG uptake [40 (76.9%) *vs.* 79 (52.0%), P=0.002] compared with the non-poor prognosis group. Univariate and multivariate Cox proportional hazard regression analysis concluded that only CHA2DS2-VASc score (HR, 1.29; 95% CI: 1.06–1.57; P=0.01) and RA wall positive FDG uptake (HR, 2.68; 95% CI: 1.10–6.50; P=0.03) were significantly associated with poor prognosis.

Conclusions: RA wall FDG positive uptake based on PET/CT is tightly related to AF recurrence after RFCA or new-onset stroke after antiarrhythmic and anticoagulation treatment.

Keywords: Atrial fibrillation (AF); positron emission tomography/computed tomography (PET/CT); inflammation; stroke; recurrence

Introduction

Atrial fibrillation (AF) is a prevalent form of cardiac arrhythmia that affects a significant number of individuals, with over 33 million people worldwide living with AF (1). Radiofrequency catheter ablation (RFCA) is an effective therapeutic option for the treatment of AF. However, after RFCA, approximately 20–40% of AF patients may still experience recurrence (2). Besides, AF has been identified to increase stroke risk (3) and the majority of AF patients are now treated with oral anticoagulants (OAC) to prevent stroke (4). However, several studies have pointed out the low adherence to OAC treatment, and that AF patients treated with OAC still had stroke risks, which remain non-negligible (5). Recent studies have identified inflammation as a new pathological feature of the atria in individuals with AF (6). Pathological biopsy is the gold standard for assessing inflammation, but it is invasive and cannot be used for dynamic evaluation. The limited specificity of plasma inflammatory markers poses challenges in accurately detecting localized cardiac inflammation (7). The lack of a precise, non-invasive atrial walls assessment method has hindered our understanding of the clinical implications associated with inflammation.

Positron emission tomography/computed tomography (PET/CT) utilizing ^{18}F-fluorodeoxyglucose (FDG) has proven to be a useful molecular imaging technique in characterizing metabolic activity and inflammatory processes. The level of ^{18}F-FDG uptake, as quantitatively assessed by the maximum standardized uptake value (SUV_{max}), could serve as an indicator for evaluating tissue inflammation (8). Recently, PET/CT has been employed to investigate the level of FDG inflammatory activity in the atria of AF patients (9). Sinigaglia *et al.* conducted a retrospective single center study consisting of 128 matched patients who underwent PET/CT and concluded that right atrium (RA) FDG uptake was an independent risk factor that increased stroke risk, which may be related to inflammation in the RA tissue and endocardial cells (10). Our prior investigation determined that the uptake of RA FDG in PET/CT exhibited significant association with stroke risk, potentially surpassing the predictive accuracy of the congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (TIA) or thromboembolism (doubled), vascular disease, age 65–74 years, sex category (female) (CHA2DS2-VASc) score (11). Watanabe *et al.* demonstrated that among the 15 AF patients who experienced relapse following RFCA, ten individuals (66.7%) exhibited positive FDG uptake, whereas none of the 6 patients without recurrence showed evidence of FDG uptake (12). However, Xie *et al.* found that none of the FDG parameters were predictive of AF recurrence after RFCA (13).

Therefore, the objective of this study was to investigate the correlation between atrial wall FDG uptake and the prognosis of AF, regardless of whether patients underwent RFCA or not. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1129/rc).

Methods

Study population

In this study, patients included were from the clinical trial (trial registration: Chinese Clinical Trial Registry: ChiCTR2000038288). Patients admitted to the Cardiology Department of the Third Affiliated Hospital of Soochow University due to AF were continuously included [AF was diagnosed by cardiologist according to medical history and 12-lead electrocardiograph (ECG)] and underwent high-fat and low-carbohydrate diet and prolonged fast (HFLC + Fast) PET/CT examination. According to the guidelines (14), paroxysmal AF (ParAF) is characterized by a duration of less than 7 days, during which spontaneous conversion to sinus rhythm can occur. On the other hand, PerAF refers to a duration exceeding 7 days and often necessitates electrical or drug intervention for conversion. Diagnosis was established through a diagnostic report, followed by a comparison with the study date to determine the duration of the disease. The exclusion criteria were as follows: (I) individuals having previously undergone ablation for AF; (II) patients who tested positive for coronavirus disease of 2019 (COVID-19); (III) patients diagnosed with thyroid disease; (IV) patients with a known or established diagnosis of sarcoidosis, pulmonary hypertension, or coronary artery disease (CAD), which could affect FDG uptake in the atrium; (V) patients diagnosed with any form of rheumatologic disease. Finally, 204 AF patients were enrolled. The flow chart is shown in *Figure 1*. The investigation conformed with the principles outlined in the Declaration of Helsinki (as revised in 2013). This prospective cohort study was approved by Ethics Committee of the Third Affiliated Hospital of Soochow University ([2020] No. 34). All participants provided written informed consent.

^{18}F-FDG PET/CT imaging

^{18}F-FDG PET/CT images were acquired utilizing a Siemens Biograph mCT [64] PET/CT scanner (Siemens Medical Solutions, Knoxville, TN, USA). The ^{18}F-FDG was supplied by Nanjing Jiangyuan Andy Cozhenge Research and Development Co., Ltd. (Nanjing, China), with a radiochemical purity exceeding 95%. Prior to imaging, participants were required to adhere to the following preparatory measures: (I) consumption of a high-fat, low-carbohydrate diet for two meals; (II) fasting for a duration

exceeding 12 hours. To ensure compliance with dietary restrictions, patients were provided with a comprehensive list of permissible and prohibited food items, as well as a questionnaire to confirm adherence.

Prior to the examination, measurements of height, weight, and fasting blood glucose (FBG) were obtained. In the event that FBG levels exceeded 7.0 mmol/L, patients were rescheduled for further evaluation. A dose of 3.7 MBq/kg of ^{18}F-FDG was administered intravenously. Following a period of 60 minutes of rest in a serene and comfortable setting, the patient assumed a supine position and maintained stable respiration. A 64-slice spiral CT scan was conducted utilizing a tube current of 35 mA, a tube voltage of 120 kV, and a collimation of either 0.6 or 1.2 mm, contingent upon the selected range. The scan time, pitch, and bed advance speed were automatically determined based on the length of the scan. Subsequently, a PET 3D acquisition was performed following the CT scan, involving the acquisition of one bed with a duration of 10 minutes per bed, with the heart positioned at the center of the field of view. Following reconstruction, transaxial, coronal, and sagittal planes were employed to obtain the CT, PET, and fused PET/CT images.

^{18}F-FDG PET/CT imaging analysis

The PET, CT, and fused PET/CT images were subjected to visual and quantitative analysis using post-processing workstations, specifically employing the TrueD software (Siemens, Erlangen, Germany). This analysis was conducted twice by two observers, identified as P.W. and W.Y., to assess the intra- and inter-observer reproducibility. Both observers were unaware of the patients' medical records to minimize potential bias. In cases where there were discrepancies in the visual analysis, a third experienced physician was consulted for additional input. For quantitative analysis, the final result was determined as the average of the measured data provided by the two physicians.

In visual analysis, a 4-point grading system was used in atrial ^{18}F-FDG uptake: grade 0, atrial ^{18}F-FDG uptake was lower than the adjacent blood pool (background); grade 1, atrial ^{18}F-FDG uptake was similar to the background; grade 2, atrial ^{18}F-FDG uptake was slightly higher than the background; grade 3, atrial ^{18}F-FDG uptake was evidently higher than the background (15). Grade 2–3 atrial ^{18}F-FDG uptake was defined as positive FDG uptake. Besides, as the structure between the atrial appendage and the atrium

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│ Patients with AF underwent 18F-FDG    │
│ PET/CT                                 │
│ (n=238)                                │
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                    │
                    │         ┌─────────────────────────────────────────────┐
                    ├────────▶│ 34 patients were excluded:                   │
                    │         │ • Complicated with other cardiac diseases    │
                    │         │   (n=14)                                     │
                    │         │ • Connective tissue disease, acute or chronic│
                    │         │   inflammatory diseases (n=12)               │
                    │         │ • Poor image quality (n=3)                   │
                    │         │ • Previous RFCA and other cardiac surgery    │
                    │         │   (n=5)                                      │
                    │         └─────────────────────────────────────────────┘
                    ▼
┌──────────────────────────────────────┐
│ Finally enrolled patients with AF     │
│ (n=204)                                │
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Patients underwent RFCA (n=55)

Patients without RFCA (n=149)

All patients follow-up >12 months
Poor prognosis: new onset stroke for patients without RFCA or recurrence for patients underwent RFCA

Patients with poor prognosis (n=52)

Patients without poor prognosis (n=152)

RA wall positive uptake (n=40)

No RA wall positive uptake (n=12)

RA wall positive uptake (n=79)
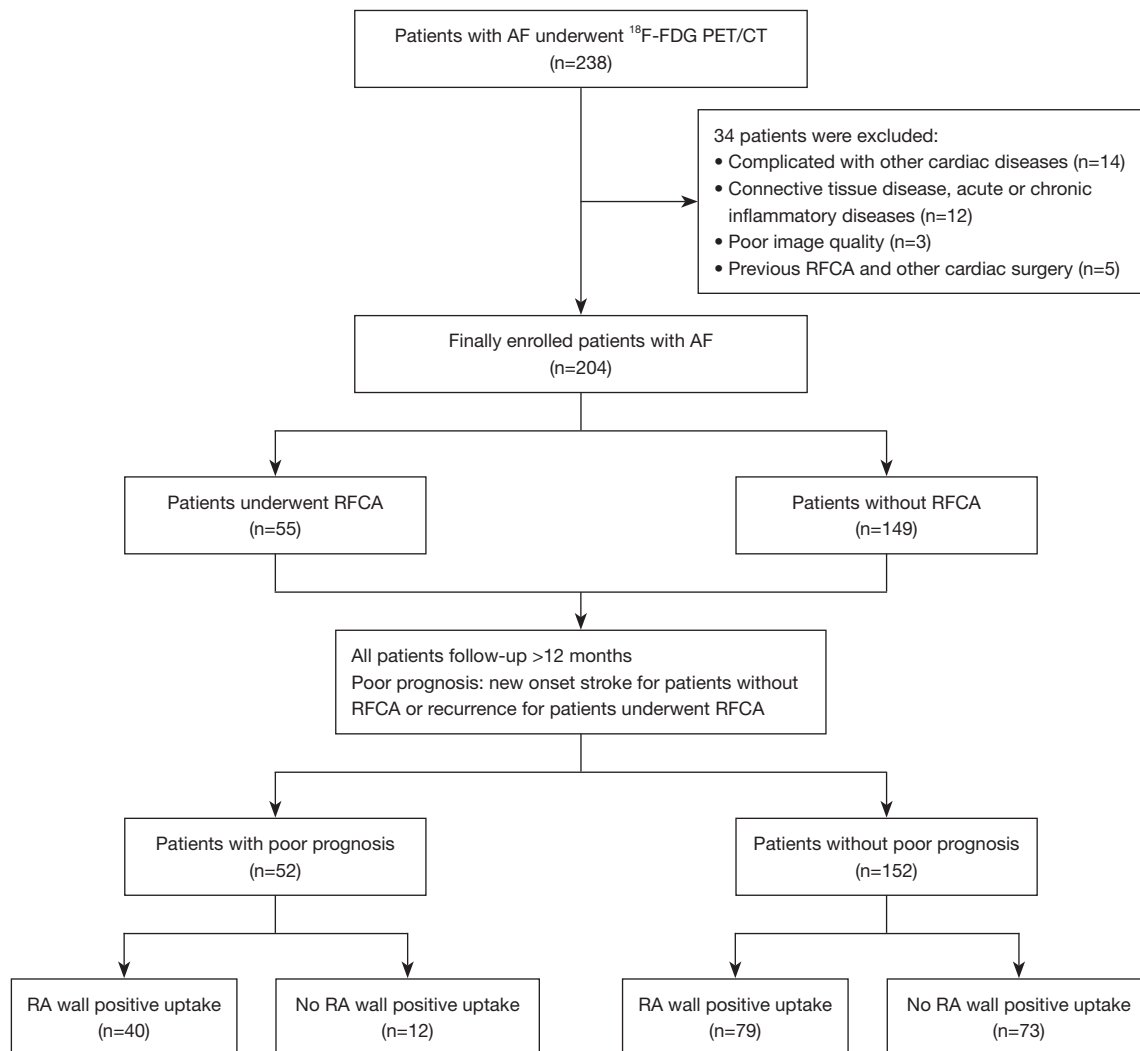
No RA wall positive uptake (n=73)

Figure 1 Flow chart of the population selection in this study. ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; RFCA, radiofrequency catheter ablation; AF, atrial fibrillation; RA, right atrial.

was difficult to distinguish by visual inspection, these two anatomical structures were treated as a unified entity during the analysis of their respective FDG activities.

In cardiac FDG uptake quantitative analysis, the FDG SUV_{max} was selected to represent the activity of different cardiac parts. If the FDG uptake was negative, three circular regions of interest (ROIs) with a diameter of 5 mm were placed on the wall of the atrium or other parts through the fused PET/CT images. To obtain the background value of ^{18}F-FDG uptake, a circular ROI with a diameter of 5 mm was placed on the left atrial (LA) and RA cavity, then the mean SUV (SUV_{mean}) was recorded. Thereafter, a target-to-background ratio (TBR) was calculated.

Echocardiography

Echocardiographic images were obtained using a Philips EPIQ 7C color Doppler ultrasound system (Philips Medical Systems, Andover, MA, USA) with an X5-1 probe at a frequency of 1–5 MHz. All echocardiographic images were acquired in accordance with the guidelines of the American Society of Echocardiography (16).

The patient was placed in the left lateral decubitus position, kept breathing calmly, the electrocardiogram was synchronously recorded to obtain the heart rate and determine the phase, and the average value of 3–5 consecutive cardiac cycles was recorded. The LA diameter

(LAD) and RA diameter (RAD) were measured in the long-axis view of the left ventricle of the sternum; LA volume (LAV) was obtained from apical 4-chamber and 2-chamber views and left ventricular ejection fraction (LVEF) was detected by biplane Simpson method.

Hematological test

After admission, plasma markers were measured for all patients in fasting state, including triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), white blood cell (WBC) count, hemoglobin (Hb), neutrophil, lymphocyte, and C-reactive protein (CRP).

CHA2DS2-VASc score

According to current guidelines, CHA2DS2-VASc is the well-recognized score for stratification of stroke risk in AF patients. The CHA2DS2-VASc score was calculated by incorporating congestive heart failure, hypertension, age ≥75 years (double weight), diabetes, stroke (double weight), vascular disease, age 65–74 years and sex category (female) (17).

Follow-up

Follow-up data were obtained by reviewing medical records and scripted telephone interviews, with the starting point being the time of PET/CT scan. All endpoints were determined by consensus between two blinded reviewers and the follow-up deadline was either the date of recurrence, new-onset stroke, or May 2023. For patients who underwent RFCA, the endpoint event was recurrence of AF defined as AF documented on ECG or lasting longer than 30 seconds on Holter or portable ECG. For patients who did not undergo RFCA but accepted antiarrhythmic and anticoagulation treatment, the endpoint event was new-onset stroke including TIA and thromboembolism confirmed by clinicians through patient symptoms and imaging examinations [CT or magnetic resonance imaging (MRI)].

Statistical analysis

The software SPSS 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism (Version 8; GraphPad Software, San Diego, CA, USA) were used to perform the statistical analysis. The Kolmogorov-Smirnoff test was used to assess the normality of the distribution of continuous variables. Continuous variables were presented as mean ± standard deviation (SD) or median (25th–75th percentile), and compared using Student's t-test or Mann-Whitney U test. Categorical variables were presented as percentages and compared using chi-square test or Fisher's exact test. To explore the influencing factors of positive atrial FDG uptake, a binary logistic regression model was used. The Kaplan-Meier (KM) method was employed to analyze the event-free survival rate over time, and the differences between survival curves were assessed using the log-rank test. Cox proportional hazards regression models were used to identify predictors of poor prognosis and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Intra- and inter-observer reproducibility of FDG uptake measurement were assessed using the intraclass correlation coefficient (ICC). All tests were two-sided, and $P<0.05$ was considered to indicate statistical significance.

Results

Patient characteristics

A total of 204 AF inpatients (mean age: 67.14±9.59 years, male: 65.2%) were included in this analysis, and the detailed characteristics are summarized in *Table 1*. The number of patients undergoing RFCA was 55, whereas 149 patients had been prescribed antiarrhythmic and anticoagulation treatment; 129 patients (63.2%) were PerAF and 75 (36.8%) patients were ParAF. Poor prognosis occurred in 52 patients (25.5%), including 34 stroke patients and 18 recrudescence after RFCA. The poor prognosis group had higher CHA2DS2-VASc score [3.0 (1.0–3.75) *vs.* 2.0 (1.0–3.0)], RA wall SUV$_{max}$ (4.13±1.82 *vs.* 3.74±1.58), higher percentage of PerAF [39 (75.0%) *vs.* 90 (59.2%)], LA enlargement [45 (86.5%) *vs.* 104 (68.4%)], and RA wall positive FDG uptake [40 (76.9%) *vs.* 79 (52.0%)] compared with the non-poor prognosis group (all P<0.05).

Atrial FDG uptake and related factors

A total of 119 AF patients (58.3%) had positive RA wall FDG accumulation. Compared with patients who had RA wall FDG negative uptake, patients with RA wall FDG positive uptake had higher age (69.27±8.02 *vs.* 64.16±10.80 years), course of AF [14.0 (4.0–40.0) *vs.* 12.0 (2.0–31.0)], TG [1.49 (1.06–1.96) *vs.* 1.22 (0.94–1.49)],

Table 1 Baseline characteristics of the study cohort (n=204)

Parameters	Overall (n=204)	Poor prognosis (n=52)	Without poor prognosis (n=152)	P value
Demographic parameters				
Age (years), mean ± SD	67.14±9.59	68.00±8.84	66.85±9.84	0.63
Male, n (%)	133 (65.20)	32 (61.5)	101 (66.4)	0.52
BMI (kg/m^2), mean ± SD	24.18±3.61	25.12±3.55	23.85±3.58	0.98
Smoking, n (%)	72 (35.3)	18 (34.6)	54 (35.5)	0.91
Drinking, n (%)	39 (19.1)	8 (15.4)	31 (20.4)	0.43
Course of AF (months), median (IQR)	12.0 (3.0–39.5)	12.5 (4.0–48.8)	12.0 (2.0–36.0)	0.33
Hypertension, n (%)	113 (55.4)	29 (55.8)	84 (55.3)	0.74
Diabetes, n (%)	26 (12.7)	8 (15.4)	18 (11.8)	0.51
Hyperlipidemia, n (%)	56 (27.5)	13 (25.0)	43 (28.3)	0.65
Persistent AF, n (%)	129 (63.2)	39 (75.0)	90 (59.2)	0.04*
CHA2DS2-VASc score, median (IQR)	2.0 (1.0–3.0)	3.0 (1.0–3.75)	2.0 (1.0–3.0)	0.01*
Hematological parameters				
Glu (mmol/L), mean ± SD	5.75±1.30	5.69±1.24	5.77±1.33	0.38
TG (mmol/L), median (IQR)	1.30 (0.99–1.72)	1.25 (0.90–1.65)	1.32 (1.02–1.77)	0.36
TC (mmol/L), mean ± SD	4.32±0.89	4.30±0.92	4.33±0.88	0.36
HDL (mmol/L), mean ± SD	1.31±0.54	1.32±0.57	1.30±0.54	0.20
LDL (mmol/L), mean ± SD	2.33±0.84	2.32±0.86	2.33±0.84	0.20
WBC (10^9/L), median (IQR)	5.73 (4.87–6.87)	6.11 (5.14–6.85)	5.61 (4.64–6.99)	0.22
Hb (g/L), mean ± SD	133.60±20.94	134.81±19.32	133.19±21.51	0.73
Neutrophil (10^9/L), median (IQR)	3.45 (2.87–4.38)	3.57 (3.06–4.37)	3.43 (2.78–4.39)	0.34
Lymphocyte (10^9/L), median (IQR)	1.51 (1.19–1.97)	1.63 (1.22–2.13)	1.50 (1.16–1.93)	0.47
CRP (mg/L), median (IQR)	3.90 (3.40–5.00)	3.90 (3.25–5.23)	3.80 (3.40–4.96)	0.93
ECG parameters				
Heart rate (beats/minute), mean ± SD	83.61±21.07	87.35±22.35	82.34±20.54	0.77
Echo parameters				
LA enlargement, n (%)	149 (73.0)	45 (86.5)	104 (68.4)	0.01*
LVEF (%), mean ± SD	60.40±5.43	60.15±4.44	60.49±5.74	0.34
RA enlargement, n (%)	98 (48.0)	30 (57.7)	68 (44.7)	0.11
Drugs				
Beta blockers, n (%)	82 (40.2)	24 (46.2)	58 (38.2)	0.64
Statin, n (%)	37 (18.1)	11 (21.2)	26 (17.1)	0.51
Anticoagulants				0.08
Dabigatran, n (%)	72 (35.3)	21 (40.4)	51 (33.6)	
Rivaroxaban, n (%)	98 (48.0)	23 (44.2)	75 (49.3)	
Warfarin, n (%)	34 (16.7)	8 (15.4)	26 (17.1)	

Table 1 (*continued*)

Table 1 (*continued*)

Parameters	Overall (n=204)	Poor prognosis (n=52)	Without poor prognosis (n=152)	P value
LA wall positive FDG uptake, n (%)	43 (21.1)	14 (26.9)	29 (19.1)	0.23
RA wall positive FDG uptake, n (%)	119 (58.3)	40 (76.9)	79 (52.0)	0.002*
LA wall SUV_{max}, mean ± SD	2.96±1.27	3.11±1.24	2.91±1.28	0.09
RA wall SUV_{max}, mean ± SD	3.84±1.65	4.13±1.82	3.74±1.58	0.04*
Spleen SUV_{max}, median (IQR)	2.90 (2.59–3.04)	2.94 (2.55–3.02)	2.86 (2.41–3.02)	0.51
Marrow SUV_{max}, median (IQR)	3.32 (2.86–3.78)	3.36 (3.07–3.90)	3.21 (2.86–3.61)	0.42
LA TBR, median (IQR)	1.21 (1.04–1.65)	1.28 (1.23–1.45)	1.19 (1.12–1.38)	0.27
RA TBR, median (IQR)	1.40 (1.28–2.03)	1.46 (1.30–1.71)	1.38 (1.21–2.01)	0.41
EAT volume (cm^3), mean ± SD	134.94±30.78	130.01±27.95	137.11±32.63	0.43
EAT SUV_{max}, mean ± SD	1.45±0.36	1.49±0.39	1.44±0.36	0.37

*, P<0.05. SD, standard deviation; BMI, body mass index; IQR, interquartile range; AF, atrial fibrillation; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (TIA) or thromboembolism (doubled), vascular disease, age 65–74 years, sex category (female); Glu, blood glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WBC, white blood cell count; Hb, hemoglobin; CRP, C-reactive protein; ECG, electrocardiograph; LA, left atrial; LVEF, left ventricular ejection fraction; RA, right atrial; FDG, fluorodeoxyglucose; SUV_{max}, maximum standardized uptake value; TBR, target-to-background ratio; EAT, epicardial adipose tissue.

heart rate (87.02±23.43 *vs.* 78.85±16.21 beats/minute), LA wall SUV_{max} (3.31±1.46 *vs.* 2.48±0.70), RA wall SUV_{max} (4.71±1.58 *vs.* 2.63±0.70), epicardial adipose tissue (EAT) SUV_{max} (1.50±0.40 *vs.* 1.38±0.30), lower LVEF (62.08±5.70 *vs.* 59.20±4.91), higher percentage of PerAF [108 (90.8%) *vs.* 21 (24.7%)], and poor prognosis [40 (33.6%) *vs.* 12 (14.1%)] (all P<0.05) (*Table 2*).

Atrial FDG uptake and poor prognosis

Median follow-up time was 29 months (interquartile range, 22–36 months). In KM survival curve analysis, the event-free survival rate of patients with positive RA wall FDG uptake was significantly lower than that of patients with negative RA wall FDG uptake, and there was a significant difference between the curves based on log-rank (P=0.009) (*Figure 2*). In univariate Cox proportional hazard regression analysis, CHA2DS2-VASc score (HR, 1.32; 95% CI: 1.09–1.59), LA enlargement (HR, 2.16; 95% CI: 1.00–4.82), and RA wall positive FDG uptake (HR, 2.31; 95% CI: 1.21–4.42) were associated with poor prognosis (all P<0.05). In multivariate Cox proportional hazards regression, only CHA2DS2-VASc score (HR, 1.29; 95% CI: 1.06–1.57) and RA wall positive FDG uptake (HR, 2.68; 95% CI: 1.10–6.50) were significantly associated with poor prognosis

(*Table 3*). *Table 4* presents the reproducibility of PET/CT parameters (LA wall SUV_{max}, RA wall SUV_{max}, EAT SUV_{max}, EAT volume). Both intra- and inter-observer comparisons showed excellent reproducibility in all the measurements (all ICC >0.8). *Figure 3* displays the case example.

Discussion

The main findings were as follows: (I) AF patients with poor prognosis had higher CHA2DS2-VASc score, RA wall SUV_{max}, higher percentage of PerAF, LA enlargement, and RA wall positive FDG uptake compared with non-poor prognosis group; (II) compared with patients who had RA wall FDG negative uptake, patients with RA wall FDG positive uptake had higher age, course of AF, TG, heart rate, LA wall SUV_{max}, RA wall SUV_{max}, and EAT SUV_{max}, lower LVEF, higher percentage of PerAF, and poor prognosis; (III) multivariate Cox proportional hazards regression concluded that CHA2DS2-VASc score and RA wall positive FDG uptake were significantly associated with poor prognosis.

AF is a prevalent cardiac arrhythmia associated with an increased risk of morbidity in stroke. The benefits of anticoagulation therapy to reduce stroke risk in patients with AF are well established, which has been emphasized

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Table 2 Influencing factors of RA wall FDG positive uptake in AF patients

Parameters	RA wall FDG negative uptake (n=85)	RA wall FDG positive uptake (n=119)	P value
Demographic parameters			
Age (years), mean ± SD	64.16±10.80	69.27±8.02	0.006*
Male, n (%)	55 (64.7)	78 (65.5)	0.90
BMI (kg/m²), mean ± SD	23.83±3.42	24.42±3.73	0.25
Smoking, n (%)	27 (31.8)	45 (37.8)	0.37
Drinking, n (%)	8 (9.4)	31 (26.1)	0.43
Course of AF (months), median (IQR)	12.0 (2.0–31.0)	14.0 (4.0–40.0)	0.02*
Hypertension, n (%)	43 (50.6)	70 (58.8)	0.19
Diabetes, n (%)	9 (10.6)	17 (14.3)	0.44
Hyperlipidemia, n (%)	28 (32.9)	28 (23.5)	0.91
Persistent AF, n (%)	21 (24.7)	108 (90.8)	<0.001*
CHA2DS2-VASc score, median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.20
Poor prognosis, n (%)	12 (14.1)	40 (33.6)	0.002*
Hematological parameters			
Glu (mmol/L), mean ± SD	5.67±1.26	5.79±1.34	0.50
TG (mmol/L), median (IQR)	1.22 (0.94–1.49)	1.49 (1.06–1.96)	0.001*
TC (mmol/L), mean ± SD	4.48±0.92	4.21±0.86	0.64
HDL (mmol/L), mean ± SD	1.34±0.59	1.24±0.46	0.19
LDL (mmol/L), mean ± SD	2.50±0.84	2.21±0.83	0.16
WBC (10⁹/L), median (IQR)	5.78 (4.87–7.02)	5.61 (4.67–6.65)	0.38
Hb (g/L), mean ± SD	132.74±21.78	134.21±20.39	0.62
Neutrophil (10⁹/L), median (IQR)	3.62 (2.87–4.62)	3.37 (2.84–4.29)	0.21
Lymphocyte (10⁹/L), median (IQR)	1.58 (1.15–2.05)	1.49 (1.19–1.93)	0.87
CRP (mg/L), median (IQR)	3.62 (3.20–4.80)	4.00 (3.50–5.40)	0.09
ECG parameters			
Heart rate (beats/minute), mean ± SD	78.85±16.21	87.02±23.43	0.001*
Echo parameters			
LA enlargement, n (%)	43 (50.6)	106 (89.1)	<0.001*
LVEF (%), mean ± SD	62.08±5.70	59.20±4.91	<0.001*
RA enlargement, n (%)	18 (21.2)	80 (67.2)	<0.001*

Table 2 (*continued*)

Table 2 (*continued*)

Parameters	RA wall FDG negative uptake (n=85)	RA wall FDG positive uptake (n=119)	P value
^{18}F-FDG PET/CT parameters			
LA wall positive FDG uptake, n (%)	3 (3.5)	40 (33.6)	<0.001*
LA wall SUV$_{max}$, mean ± SD	2.48±0.70	3.31±1.46	<0.001*
RA wall SUVmax, mean ± SD	2.63±0.70	4.71±1.58	<0.001*
EAT SUV$_{max}$, mean ± SD	1.38±0.30	1.50±0.40	0.017*

*, P<0.05. RA, right atrial; FDG, fluorodeoxyglucose; AF, atrial fibrillation; SD, standard deviation; BMI, body mass index; IQR, interquartile range; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (TIA) or thromboembolism (doubled), vascular disease, age 65–74 years, sex category (female); Glu, blood glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WBC, white blood cell count; Hb, hemoglobin; CRP, C-reactive protein; ECG, electrocardiograph; LA, left atrial; LVEF, left ventricular ejection fraction; RA, right atrial; ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; SUV$_{max}$, maximum standardized uptake value; EAT, epicardial adipose tissue.
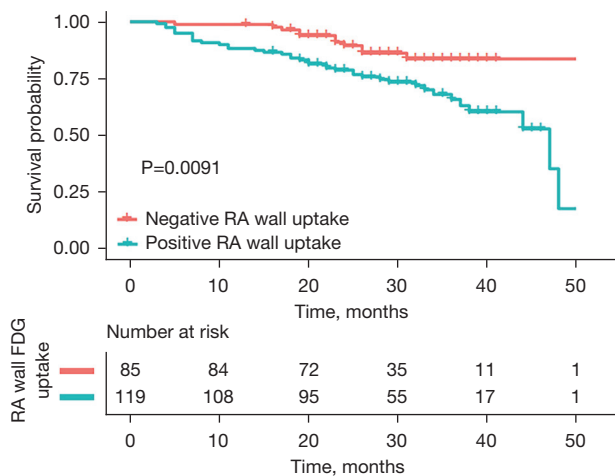
Figure 2 Kaplan-Meier survival curves for patients with positive and negative RA wall FDG uptake. RA, right atrial; FDG, fluorodeoxyglucose.

in the management of all patients unless they are at low-risk (17). However, anticoagulation therapy alone does not completely eliminate the risk of stroke but rather decreases the likelihood. Consequently, a certain percentage of AF individuals may still experience a stroke despite receiving appropriate anticoagulation treatment (18). RFCA demonstrates efficacy in treating AF and exhibits superior ability to reinstate sinus rhythm when compared to pharmaceutical interventions (19). However, the recurrence rate among patients with AF who underwent RFCA has been reported to range from 30% to 60% (20), and the relatively high recurrence rates following RFCA poses a significant challenge (21). Therefore, it is very important to identify the predictors of AF recurrence after RFCA or new-onset stroke after antiarrhythmic and anticoagulation treatment, which will help to guide clinical practice.

Inflammation is an essential factor in the occurrence

Table 3 Univariable and multivariable cox proportional hazard regression analyses for predicting poor prognosis

Parameters	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Persistent AF	1.51 (0.8–2.85)	0.18	1.90 (0.77–4.66)	0.16
CHA2DS2-VASc score	1.32 (1.09–1.59)	0.005	1.29 (1.06–1.57)	0.01*
LA enlargement (%)	2.16 (1.00–4.82)	0.05	1.72 (0.69–4.29)	0.24
RA wall positive FDG uptake (%)	2.31 (1.21–4.42)	0.01	2.68 (1.10–6.50)	0.03*

*, P<0.05. AF, atrial fibrillation; RA right atrial; LA, left atrial; FDG, fluorodeoxyglucose; HR, hazard ratio; CI, confidence interval; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (TIA) or thromboembolism (doubled), vascular disease, age 65–74 years, sex category (female).

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Table 4 Intra- and inter-observer reproducibility

Parameter	Intra-observer		Inter-observer	
	ICC (95% CI)	P value	ICC (95% CI)	P value
LA wall SUV$_{max}$	0.91 (0.86–0.98)	<0.001	0.92 (0.90–0.99)	<0.001
RA wall SUV$_{max}$	0.94 (0.92–0.99)	<0.001	0.94 (0.91–0.99)	<0.001
EAT SUV$_{max}$	0.95 (0.93–0.98)	<0.001	0.96 (0.95–0.99)	<0.001
V-EAT	0.92 (0.90–0.96)	<0.001	0.91 (0.89–0.94)	<0.001

LA, left atrial; SUV$_{max}$, maximum standardized uptake value; RA right atrial; EAT, epicardial adipose tissue; V-EAT, EAT volume; ICC, intraclass correlation coefficient; CI, confidence interval.
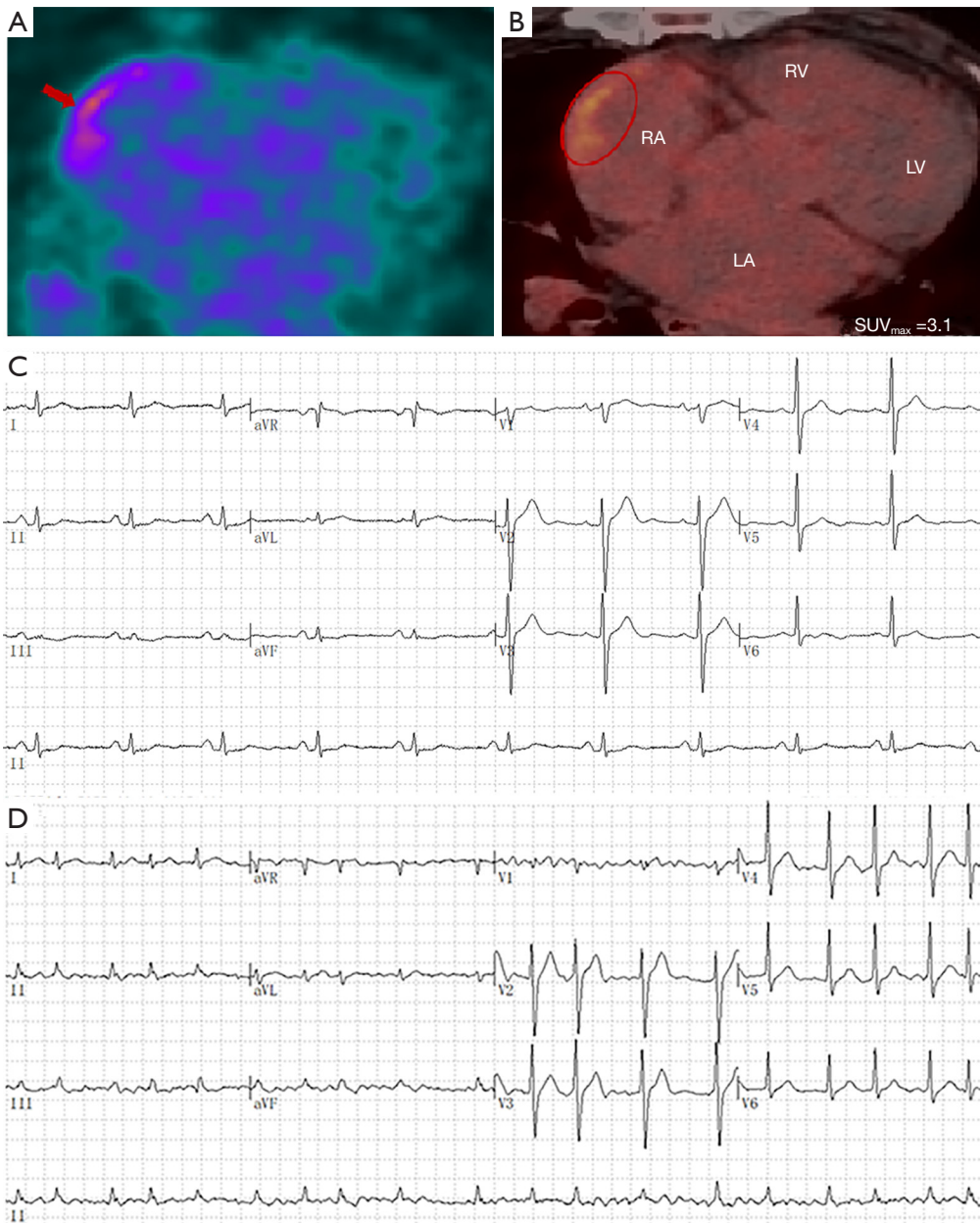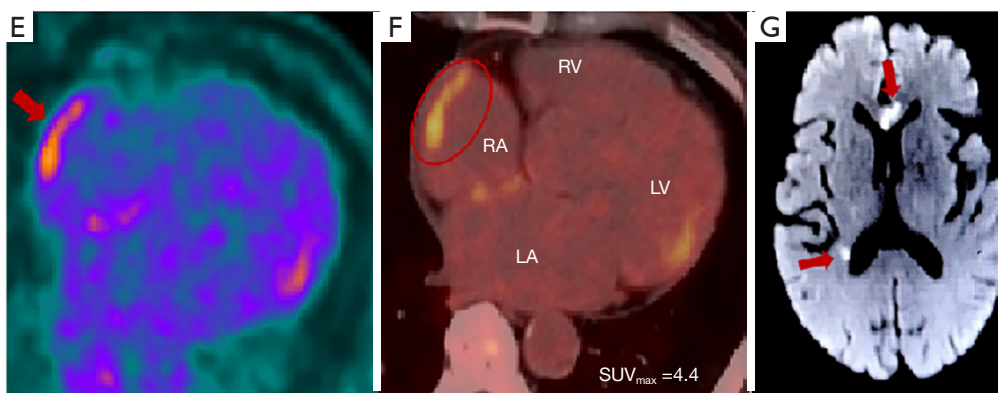
Figure 3 Case example. Case examples during the follow-up (AF recurrence after RFCA and new-onset stroke after antiarrhythmic and anticoagulation treatment). A 75-year-old woman with ParAF underwent PET/CT (HFLC + Fast) prior to RFCA and had AF recurrence after 12 months: (A) PET image (red arrow: RA wall positive uptake); (B) PET/CT image, red oval circle outlines the RA wall FDG uptake (SUV$_{max}$ =3.1); (C) electrocardiogram, postoperative sinus rhythm of RFCA; (D) electrocardiogram, AF recurred 12 months after RFCA. A 57-year-old man with PerAF underwent PET/CT (HFLC + Fast), then accepted antiarrhythmic and anticoagulation treatment, and had new onset stroke after 8 months of the follow-up: (E) PET image (red arrow: RA wall positive uptake); (F) PET/CT image, the red oval circle outlines the RA wall FDG uptake (SUV$_{max}$ =4.4); (G) DWI image (red arrow: acute ischemic stroke in the genu of the corpus callosum and adjacent to the posterior horn of the lateral ventricle). RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; SUV$_{max}$, maximum standardized uptake value; AF, atrial fibrillation; RFCA, radiofrequency catheter ablation; ParAF, paroxysmal AF; PET/CT, positron emission tomography/computed tomography; HFLC + Fast, high-fat and low-carbohydrate diet and prolonged fast; FDG, fluorodeoxyglucose; DWI, diffusion-weighted imaging.

and persistence of AF. Higher levels of inflammation have been associated with an increased risk of AF recurrence after RFCA and a higher risk of stroke (22). There is a limited availability of practicable methods for evaluating cardiac inflammation, with the exception of invasive biopsies. Although inflammatory biomarkers have been proposed as potential correlates of atrial electrical and structural remodeling, the reliability of plasma biomarkers in reflecting local cardiac inflammatory status remains uncertain due to their susceptibility to various confounding factors (23). Recently, the use of ^{18}F-FDG PET imaging has garnered significant interest due to its capability in detecting a wide range of inflammatory diseases (24). FDG PET may be useful for early detection inflammation, SUV$_{max}$ of ^{18}F-FDG PET reflects glucose metabolism of the tissue, and positive FDG uptake has been observed in inflammatory tissues. Besides, a previous study showed that under fasting conditions, during FDG imaging, physiological uptake in the myocardium was significantly suppressed, atrial FDG uptake was rarely observed in healthy participants, and the increased atrial FDG uptake in AF is indicative of inflammation (25).

Univariate and multivariate Cox proportional hazards regression analyses concluded that CHA2DS2-VASc score and RA wall positive FDG uptake were significantly associated with AF recurrence after RFCA or new-onset stroke after antiarrhythmic and anticoagulation treatment, suggesting that this pattern may be regarded as a risk marker of poor prognosis, which emphasized the need to treat these risk factors, if modifiable, beyond antithrombotic therapy and RFCA. The CHA2DS2-VASc is a well acknowledged risk score for stroke in AF, but is also associated with AF recurrence prediction (26). Although the CHA2DS2-VASc scoring may excel in identifying patients with a genuinely low risk, it lacks sufficient discriminatory power to accurately assess elderly patients who are truly at high risk (27). Watanabe *et al.* concluded that atrial FDG uptake was observed in two-thirds of patients with recurrence following various AF treatments, whereas no significant FDG uptake was detected in patients without recurrence, suggesting that regression of inflammation in the atria was presumed to be the cause of the disappearance of FDG uptake in the latter patients. Besides, pathological biopsies of the atria in AF patients showed infiltration of many CD68-positive macrophages and CD3- or CD20-positive lymphocytes, within areas that exhibited FDG uptake (12).

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Our previous study found that RA FDG uptake is an independent risk factor for stroke in multivariate Cox analysis and the median time of stroke was significantly shortened in high RA SUV_{max} group (11). Sinigaglia *et al.* found that RA DFG uptake may be associated with an increased prevalence of cardioembolic stroke (10). Previous study has shown that there is a significant decrease in RA FDG activity after RFCA compared to baseline scans, indicating that atrial FDG uptake can be reversed once AF is terminated (28). Our study assessed the association between RA FDG uptake and adverse prognosis, irrespective of whether the patients underwent RFCA. Revealing the presence of inflammation in AF patients may facilitate the development of tailored anti-inflammatory strategies for the treatment and prevention of unfavorable prognosis.

In the present study, enhanced FDG uptake of AF patients localized mainly in the RA, as described in previous retrospective studies (29,30). The reason that right-atrial wall FDG uptake was statistically significant rather than left-atrial FDG uptake may be as follows. Firstly, AF patients display differential degrees of fibrosis between the left and the right atria, with the LA experiencing a more profound degree of fibrosis. This severe fibrosis is concomitant with apoptosis and eventual mortality of atrial cells, which may subsequently reduce glucose uptake in the LA. Besides, it could be a process of diffuse atrial remodeling related to the AF condition, which can also affect the RA, as structural and electrical remodeling is not limited to the LA. Another possibility could be related to an increased workload on the right side of the heart due to underlying conditions such as pulmonary hypertension, myocardial ischemia, or heart failure. Patients with RA wall FDG positive uptake had higher age, course of AF, TG, heart rate, LA wall SUV_{max}, RA wall SUV_{max}, and EAT SUV_{max}, lower LVEF, higher percentage of PerAF, and poor prognosis than patients with RA wall FDG negative uptake. Similarly, Xie *et al.* also explored the factors relevant to the atrial FDG uptake in AF patients and found that female gender, persistent AF, and EAT activity independently predicted the increased activity in atria (29). EAT was the source of inflammatory mediators and it was reported that inflammatory activity of EAT reflected by SUV is higher in patients with AF than that in controls (15). The strong correlation between RA FDG uptake and EAT uptake further substantiates the assertion that RA FDG uptake represents an inflammatory response.

This study had several limitations. Firstly, histological samples from the atrium were not obtainable for analysis in this study. Secondly, patients did not undergo additional PET/CT examination after treatment; a well-designed prospective and longitudinal study will further clarify the clinical value of atrial FDG imaging and prognosis. Lastly, the thin atrial walls make SUV measurement more influenced by partial volume effects, whereas partial volume correction is not applicable because atrial FDG uptake is invisible in many cases.

Conclusions

RA wall FDG positive uptake based on PET/CT could identify atrial inflammation, which is tightly related to AF recurrence after RFCA or new-onset stroke after antiarrhythmic and anticoagulation treatment.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1129/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1129/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The investigation conformed with the principles outlined in the Declaration of Helsinki (as revised in 2013). This prospective cohort

study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University ([2020] No. 34). All participants provided written informed consent.

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References

1. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114:e257-354.
2. Jaïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clémenty J, Haïssaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulation 2008;118:2498-505.
3. Choi KH, Seo WK, Park MS, Kim JT, Chung JW, Bang OY, Kim GM, Song TJ, Kim BJ, Heo SH, Jung JM, Oh KM, Kim CK, Yu S, Park KY, Kim JM, Park JH, Choi JC, Hwang YH, Kim YJ. Effect of Statin Therapy on Outcomes of Patients With Acute Ischemic Stroke and Atrial Fibrillation. J Am Heart Assoc 2019;8:e013941.
4. Jame S, Barnes G. Stroke and thromboembolism prevention in atrial fibrillation. Heart 2020;106:10-7.
5. Gabet A, Chatignoux E, Grave C, Vallée A, Tuppin P, Béjot Y, Olié V. Stroke Incidence and Death in Atrial Fibrillation Patients Newly Treated with Direct Oral Anticoagulants. Clin Epidemiol 2021;13:131-40.
6. Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. Circ J 2015;79:495-502.
7. Kimura T, Takatsuki S, Inagawa K, Katsumata Y,

Nishiyama T, Nishiyama N, Fukumoto K, Aizawa Y, Tanimoto Y, Tanimoto K, Fukuda K. Serum inflammation markers predicting successful initial catheter ablation for atrial fibrillation. Heart Lung Circ 2014;23:636-43.
8. Irmler IM, Opfermann T, Gebhardt P, Gajda M, Bräuer R, Saluz HP, Kamradt T. In vivo molecular imaging of experimental joint inflammation by combined (18)F-FDG positron emission tomography and computed tomography. Arthritis Res Ther 2010;12:R203.
9. Lawal I, Sathekge M. F-18 FDG PET/CT imaging of cardiac and vascular inflammation and infection. Br Med Bull 2016;120:55-74.
10. Sinigaglia M, Mahida B, Piekarski E, Chequer R, Mikail N, Benali K, Hyafil F, Le Guludec D, Rouzet F. FDG atrial uptake is associated with an increased prevalence of stroke in patients with atrial fibrillation. Eur J Nucl Med Mol Imaging 2019;46:1268-75.
11. Wang B, Xu Y, Wan P, Shao S, Zhang F, Shao X, Wang J, Wang Y. Right Atrial Fluorodeoxyglucose Uptake Is a Risk Factor for Stroke and Improves Prediction of Stroke Above the CHA(2)DS(2)-VASc Score in Patients With Atrial Fibrillation. Front Cardiovasc Med 2022;9:862000.
12. Watanabe E, Miyagawa M, Uetani T, Kinoshita M, Kitazawa R, Kurata M, Ishimura H, Matsuda T, Tanabe Y, Kido T, Kido T, Kurata A, Mochizuki T. Positron emission tomography/computed tomography detection of increased (18)F-fluorodeoxyglucose uptake in the cardiac atria of patients with atrial fibrillation. Int J Cardiol 2019;283:171-7.
13. Xie B, Chen BX, Nanna M, Wu JY, Zhou Y, Shi L, Wang Y, Zeng L, Wang Y, Yang X, Liu X, Yang MF. 18F-fluorodeoxyglucose positron emission tomography/computed tomography imaging in atrial fibrillation: a pilot prospective study. Eur Heart J Cardiovasc Imaging 2021;23:102-12.
14. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609-78.
15. Mazurek T, Kiliszek M, Kobylecka M, Skubisz-Głuchowska J, Kochman J, Filipiak K, Królicki L, Opolski G. Relation of proinflammatory activity of epicardial adipose tissue to the occurrence of atrial fibrillation. Am J Cardiol 2014;113:1505-8.
16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group,

American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.

17. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, 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;42:373-498.

18. Ding WY. Residual Stroke Risk in Atrial Fibrillation. Arrhythm Electrophysiol Rev 2021;10:147-53.

19. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. JAMA 2019;321:1261-74.

20. Pranata R, Henrina J, Yonas E, Putra ICS, Cahyadi I, Lim MA, Munawar DA, Munawar M. BMI and atrial fibrillation recurrence post catheter ablation: A dose-response meta-analysis. Eur J Clin Invest 2021;51:e13499.

21. Pallisgaard JL, Gislason GH, Hansen J, Johannessen A, Torp-Pedersen C, Rasmussen PV, Hansen ML. Temporal trends in atrial fibrillation recurrence rates after ablation between 2005 and 2014: a nationwide Danish cohort study. Eur Heart J 2018;39:442-9.

22. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Europace 2016;18:1455-90.

23. Lüscher TF. Atrial fibrillation: from biomarkers to CABANA. Eur Heart J 2019;40:1243-6.

24. Casali M, Lauri C, Altini C, Bertagna F, Cassarino G, Cistaro A, et al. State of the art of (18)F-FDG PET/CT application in inflammation and infection: a guide for image acquisition and interpretation. Clin Transl Imaging 2021;9:299-339.

25. Lu Y, Grant C, Xie K, Sweiss NJ. Suppression of Myocardial 18F-FDG Uptake Through Prolonged High-Fat, High-Protein, and Very-Low-Carbohydrate Diet Before FDG-PET/CT for Evaluation of Patients With Suspected Cardiac Sarcoidosis. Clin Nucl Med 2017;42:88-94.

26. Vitali F, Serenelli M, Airaksinen J, Pavasini R, Tomaszuk-Kazberuk A, Mlodawska E, Jaakkola S, Balla C, Falsetti L, Tarquinio N, Ferrari R, Squeri A, Campo G, Bertini M. CHA2DS2-VASc score predicts atrial fibrillation recurrence after cardioversion: Systematic review and individual patient pooled meta-analysis. Clin Cardiol 2019;42:358-64.

27. Kabra R, Girotra S, Vaughan Sarrazin M. Refining Stroke Prediction in Atrial Fibrillation Patients by Addition of African-American Ethnicity to CHA2DS2-VASc Score. J Am Coll Cardiol 2016;68:461-70.

28. Chen BX, Xie B, Zhou Y, Shi L, Wang Y, Zeng L, Liu X, Yang MF. Association of Serum Biomarkers and Cardiac Inflammation in Patients With Atrial Fibrillation: Identification by Positron Emission Tomography. Front Cardiovasc Med 2021;8:735082.

29. Xie B, Chen BX, Wu JY, Liu X, Yang MF. Factors relevant to atrial (18)F-fluorodeoxyglucose uptake in atrial fibrillation. J Nucl Cardiol 2020;27:1501-12.

30. Kupusovic J, Weber M, Bruns F, Kessler L, Pesch E, Bohnen J, Dobrev D, Rassaf T, Wakili R, Rischpler C, Siebermair J. PET/CT-identified atrial hypermetabolism is an index of atrial inflammation in patients with atrial fibrillation. J Nucl Cardiol 2023;30:1761-72.