Therapeutics and Clinical Risk Management Dovepress

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Atrial Fibrillation Types and Chronic Kidney Disease are Independent Predictors of Atrial Fibrillation Recurrence After Radiofrequency Ablation

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Purpose: Atrial fibrillation (AF) is classified into paroxysmal, persistent, long-term persistent, and permanent types. It is commonly treated by radiofrequency ablation (RFA), which is more successful than conventional anti-arrhythmic drugs, but it is still largely unknown whether these beneficial effects are equally present for all AF types. Here, we evaluated the impact that AF type has on post-RFA patient conditions and identified underlying factors affecting AF prognoses.

Patients and Methods: Three hundred and twenty-nine AF patients who underwent RFA were retrospectively examined (221 paroxysmal, 56 persistent, 52 long-term persistent), during a post-RFA follow-up period, from 3-months to 2-years. Cardiac functional parameters, such as left atrial (LA), ventricular (LV), and pulmonary artery diameters, as well as ejection fraction (EF) and end-diastolic/systolic diameter ratio, were measured using echocardiography. Additionally, chronic kidney disease (CKD) was diagnosed among these AF patients, using the Modification of Diet in Renal Disease (MDRD) formula, and its impact on post-RFA patient outcomes was examined. Logistic regression analysis identified differences between AF and non-AF recurrence groups.

Results: In terms of functional parameters, persistent AF had significantly smaller LA, and larger EF, compared to paroxysmal and long-term persistent groups, while paroxysmal had significantly larger LV versus persistent and long-term persistent after RFA. For post-RFA patient conditions, paroxysmal, compared to persistent and long-term persistent, had significantly lower AF recurrence (18.10% versus 30.36% and 36.54%) and re-hospitalization rates (6.79% versus 14.29% and 19.23%); however, no significant difference was present between the 3 groups in terms of post-operative stroke rates, as well as re-hospitalization duration. Additionally, CKD patients, versus non-CKD, were more prone to AF recurrence and re-hospitalization, being 3.268 times more likely.

Conclusion: AF types and CKD were independent factors influencing AF recurrence, serving as highly sensitive predictors to monitor prognoses and guide treatments. Therefore, personalized treatment regimens should be recommended for different AF patients.

Keywords: atrial fibrillation, radiofrequency ablation, chronic kidney disease

Introduction

Atrial fibrillation (AF) is the most common tachycardia arrhythmia,[1] and it is associated with increased risk for stroke,[2–4] heart failure, mortality,[5,6] and dementia.[7–9] In fact, AF individuals have a 5-fold increased risk of stroke, doubled mortality risk,[6] as well as 2–3-fold higher risk of dementia development,[7] as found in studies of Indian and Taiwanese patients.[7,9] As a result, anticoagulants have been an important preventative strategy for non-valvular AF patients with

Received: 20 August 2024
Accepted: 23 November 2024
Published: 3 December 2024

high risk of stroke risk or systemic embolism. However, their use also increases bleeding risk,[10] which has spurred the search for alternative AF treatment approaches, such as radiofrequency ablation (RFA).

The conventional method of AF classification is based on their clinical presentation, particularly in terms of episode duration. AF can thus be classified into 4 different types: paroxysmal, persistent, long-term persistent, and permanent, with wide variations in their clinical course; individuals with longer AF durations are more at risk of atrial remodeling, entailing structural changes and myocardial damage that contributes to increased likelihood of thrombosis and heart failure.[11] Furthermore, persistent AF patients, compared to paroxysmal AF, have been documented under electro-anatomical mapping studies to have larger left atrial dimensions, lower atrial voltages, slower atrial conduction velocities, higher electrogram grades, and shorter AF cycle lengths.[11] Additionally, long-term persistent AF patients are more likely to develop heart failure, compared to those with persistent, paroxysmal, or first-episode AF,[12] while non-paroxysmal AF have been found in large-scale clinical trials to possess higher stroke risk, compared to paroxysmal individuals.[13]

Longer AF durations were also observed by Yu et al to be associated with higher AF recurrence,[14] which itself could be owed to multiple factors, one of which is inflammation. Indeed, correlations between higher levels of inflammatory markers C-reactive protein (CRP),[15] interleukin-2, 6, 8, tumor necrosis factor-α, as well as neutrophil and platelet/lymphocyte ratios[16] and AF recurrence were observed. This was further reinforced by AF recurrence being able to be lowered by colchicine administration, which inhibits the NLR family pyrin domain containing 3 inflammasome, in a randomized trial by Deftereos et al.[17] Likewise, higher levels of fibrosis markers have also been linked with AF recurrence, such as transforming growth factor-β1 and galectin-3, which is secreted by activated macrophages, serving as a possible link between increased inflammation, fibrosis, and AF recurrence.[16] However, the precise association of these factors with AF severity and recurrence need further investigation.

RFA, compared to antiarrhythmic drugs, has been documented to be more successful for treating AF, along with lower mortality and recurrence rates;[18,19] it has also been found to significantly lower dementia risk, as seen in a study of 136774Taiwanese individuals.[9] Furthermore, AF patients who underwent RFA also have improved hospitalization rates for cardiovascular disease, which is owed to improved cardiac function post-RFA, as indicated by lowered left atrial (LA) and ventricular (LV) inner diameters under echocardiography, along with increased LV ejection fraction (EF).[20] However, the full extent of the beneficial effects of RFA, as well as whether these benefits are equally present for the different AF types, are still largely unknown. In this study, we aimed to fill in this gap in knowledge by collecting relevant data from AF patients who underwent RFA in our hospital from 2017 to 2022, and examined post-RFA effects among different AF types, for AF recurrence, stroke incidence, as well as AF re-hospitalization rate and duration. The main focus was on examining the predictive power of factors affecting AF recurrence post-RFA among 3 AF types: paroxysmal, persistent, and long-term persistent, which could serve as sensitive predictors to monitor prognoses and guide treatments.

Materials and Methods

Patient Recruitment

AF patients were admitted to the Second Affiliated Hospital of Guangzhou Medical University between August 1, 2017-July 31, 2022, and underwent RFA, were recruited. Inclusion criteria were as follows: 1) AF diagnostic criteria were met, along with being clinically confirmed by both medical history and electrocardiograms (ECGs), 2) Consent provided for RFA, 3) Being 18–85 years old, 4) Atrial/atrial appendage thrombi were absent under transesophageal echocardiography (TEE)/left atria and LA appendage computed tomography (CT)/intra-cardiac echocardiography (ICE), 5) No serious procedural complications present, and 6) Patient follow-up for ≥12–24 months. Exclusion criteria were as follows: 1) Intra-cardiac thrombosis present under TEE/CT/ICE, 2) Left ventricular ejection fraction (LVEF)<35% associated with other severe heart diseases, including congenital, valvular, hypertensive, coronary, or dilated/hypertrophic cardiomyopathy, 3) Uncontrolled hyper-/hypothyroidism, 4) History of severe lung disease, liver failure, malignant tumor, or unfavorable hematology, 5) Presence of psycho-neurological diseases, intellectual disability, arthritis, ankle/knee joint/spinal injury, muscle atrophy, limb movement disorder, or otherwise being unable to cooperate, 6) Being pregnant, lactating, or trying to conceive, 7) Previous RFA history, 8) LA diameter >50 mm under preoperative cardiac ultrasound,

or 9) Loss to follow-up during the ≥12-24-month follow-up period post-RFA. Upon applying inclusion and exclusion criteria, 329 patients were included, as shown in Figure 1.

For all patients, medical histories and ECGs were used to identify AF type; they fell into 3 groups: paroxysmal, persistent, and long-term persistent. Paroxysmal AF was defined as lasting <7 days, while persistent AF were >7 days, and long-term persistent AF lasting for ≥1 year.[21] Additionally, biochemical indicators, such as creatinine and brain natriuretic peptide (BNP), were measured. The study protocol was approved by the ethics committee of the Second Affiliated Hospital of Guangzhou Medical University (REB#: 2023-hg-ks-48). The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Conducting RFA and Follow-Up

RFA involves a catheter electrode being inserted into precise areas of the heart, via the blood vessel, followed by the release of a current, at a precisely delineated voltage, to cause coagulative necrosis of the local muscle, thereby quickly blocking the conductive bundle and its origin point. It is one of the main ablation methods used in the Second Affiliated Hospital of Guangzhou Medical University, along with cryo-ablation, and compared to traditional drug treatment, it is more effective for treating AF.

All patients undergoing RFA had previously been on anti-coagulants for ~2 months prior to the procedure, and within 24 h pre-RFA, TEE was performed to exclude their LA thrombi. After echocardiography, RFA was performed, in which

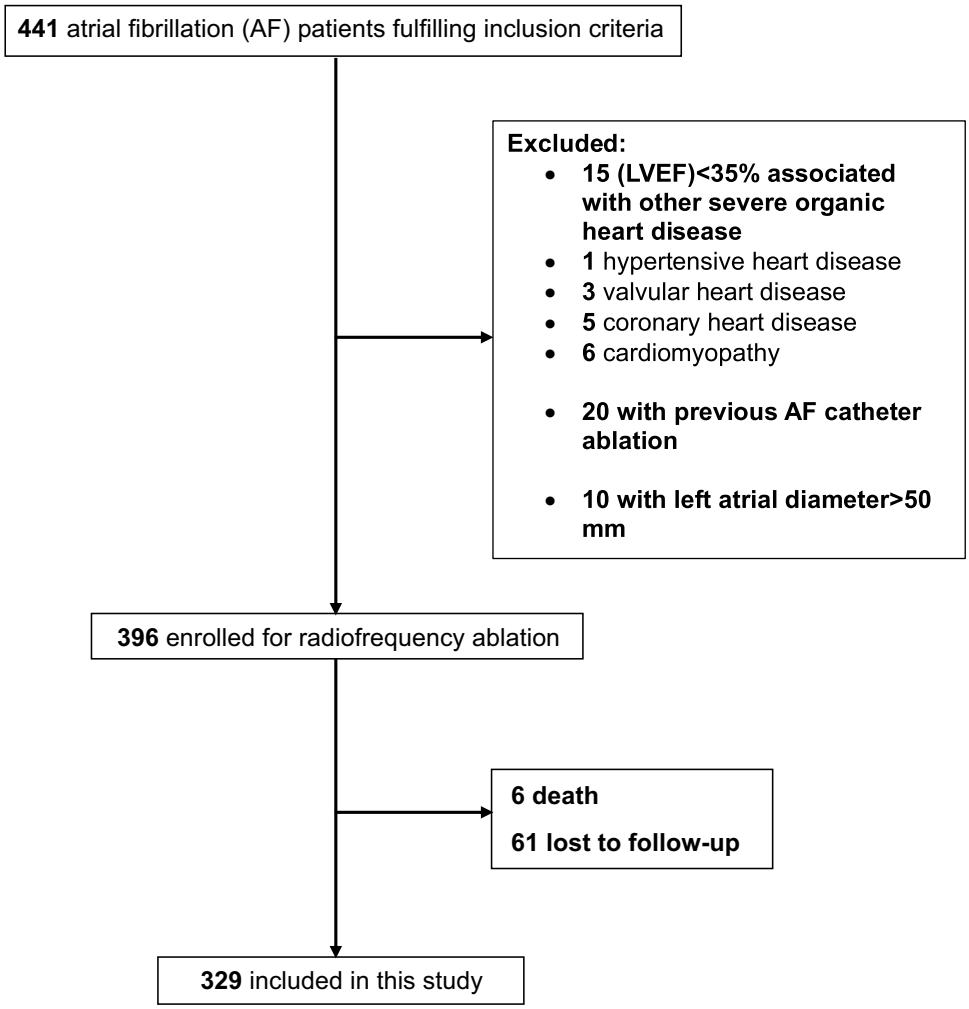

Figure 1 Flow chart showing recruitment of 329 atrial fibrillation (AF) patients in the study, after applying inclusion and exclusion criteria. LVEF, left ventricular ejection fraction.

a fixed-curve 6F catheter (Biosense Webster) was first placed in the coronary sinus (CS). Two long sheaths within the catheter were then advanced into the LA, guided by fluoroscopy, followed by insertion of a circular catheter (Lasso^{TM}, Abbott Laboratories) into the LA, through 1 of those long sheaths to carry out the ablation. Heparin was administered intravenously to prevent blood clot formation.

After RFA, patients were followed-up by phone calls, and their state of health, with respect to cardiac condition, stroke, re-hospitalization for cardiovascular reasons, etc., were recorded from 3 months to 2 years post-procedure. The primary endpoint is AF recurrence, while secondary endpoint indicators were the occurrence of re-hospitalization and number of days post-AF recurrence, as well as post-RFA stroke presence. Furthermore, during that follow-up period, 164 of the 329 patients also underwent echocardiography in our hospital, and cardiac functional parameters, such as LA, LV, and pulmonary artery (PA) diameters, as well as EF and end-diastolic/systolic diameter ratio, were measured.

With respect to the presence of CKD, the Modification of Diet in Renal Disease (MDRD) formula was used to calculate glomerular clearance, in which the estimated glomerular filtration rate (eGFR)=186×serum creatinine (Cr)-1.154×Age-0.203 [×0.742 (if female)]. Patients with eGFR<60 were categorized as having CKD, while those with eGFR>60 were non-CKD.

Statistical Analyses

All variables were expressed as either mean ± SD, or numbers with percentages. Continuous data with normal distribution were compared using the paired *t*-test, while for non-normal distribution, the rank-sum test was used. χ^2 and Fisher's exact test was used to compare frequencies. Both univariate analysis and multivariate logistic regression analysis were carried out for patient parameters between AF recurrence and non-AF recurrence groups, in which univariate analysis was first used to identify associations between different factors and AF recurrence, followed by multivariate logistic regression to determine AF recurrence predictors. A stratified analysis was conducted to identify possible confounding factors and control their bias on the results. All statistical tests were two-tailed. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics of Patients with Paroxysmal, Persistent, or Long-Term Persistent AF

The average age of the 329 AF patients, who underwent RFA for the first time, was ~66–68 years old. Out of these patients, 221 had paroxysmal, 56 had persistent, and 52 had long-term persistent AF. Cardiac parameters were compared at baseline, prior to and during RFA, including LA, LV, and PA diameters, EF, valvular, coronary artery (CAD), and congenital heart diseases, as well as heart failure, cardiomyopathy, hypertension, diabetes, cerebrovascular incident, CKD, and hospitalization in days. Significant differences in body mass index (BMI), cardiac structural parameters LA, LV, PA, EF, mitral/tricuspid regurgitation, amiodarone treatment, creatinine, as well as the presence of heart failure, cerebrovascular incidents, CKD, plus the average hospitalization stay length, were present among the 3 groups pre-RFA (Table 1).

Comparing Pre- and Post-RFA Cardiac Ultrasound Parameters Among the 3 AF Patient Groups

We then examined 164 patients (99 paroxysmal, 31 persistent, 34 long-term persistent), within the 329-patient total, who underwent cardiac ultrasound, both pre- and post-RFA, with respect to LA, LV, and PA diameters, as well as EF, to determine RFA therapeutic effectiveness among the 3 AF groups. We found that for LA diameter, a significant decrease was present only for persistent, but not paroxysmal or long-term persistent AF (Table 2). On the other hand, for LV diameter, paroxysmal, but not persistent or long-term persistent AF, had a significant increase pre- to post-RFA (Table 2). As for PA diameter, no significant differences, from pre- to post-RFA, were present among the 3 AF groups (Table 2). In terms of EF, a significant increase was only present for persistent, but not paroxysmal or long-term persistent AF (Table 2). Therefore, changes in cardiac ultrasound parameters, pre- and post-RFA, were only present for persistent AF in terms of LA diameter and EF, as well as paroxysmal AF in terms of LV diameter.

Table 1 Baseline Characteristics of Patients with Different Types of Atrial Fibrillation (AF)

	AF type			P
	Paroxysmal (N=221)	Persistent (N=56)	Long-Term Persistent (N=52)	
Age	68.6±10.5	68.1±11.6	66.3±10.3	0.416
Number of patients (female)	221 (121)	56 (15)	52 (20)	0.000
Body mass index	23.8±3.2	25.9±3.9	24.9±4.1	0.003
Left atrium diameter (mm)	34.2±5.7	39.3±4.6	38.2±5.4	0.000
Left ventricle diameter (mm)	44.1±4.8	46.9±4.9	46.2±7.0	0.001
Pulmonary artery diameter (mm)	18.9±2.7	19.7±2.9	20.8±2.9	0.000
Left ventricular ejection fraction (%)	63.8±6.7	58.6±8.7	60.5±8.6	0.000
Mitral regurgitation (%)	135 (61.1%)	49 (87.5%)	46 (88.5%)	0.000
Tricuspid regurgitation (%)	135 (61.1%)	47 (83.9%)	44 (84.6%)	0.000
Amiodarone treatment (%)	55 (24.9%)	28 (50.0%)	24 (46.2%)	0.000
Creatinine (μmol/L)	85.4±48.1	95.8±44.6	106.3±48.5	0.001
Atrial flutter (%)	21 (9.5%)	2 (3.6%)	4 (7.7%)	0.349
Heart failure (%)	19 (8.6%)	25 (44.6%)	10 (19.2%)	0.000
Coronary artery disease (%)	38 (17.2%)	5 (8.9%)	5 (9.6%)	0.159
Cardiomyopathy (%)	9 (4.1%)	0 (0%)	1 (1.9%)	0.250
Valvular heart disease (%)	14 (6.3%)	1 (1.8%)	3 (5.8%)	0.407
Congenital heart disease (%)	11 (5.0%)	0 (0%)	0 (0%)	0.062
Hypertensive (%)	99 (44.8%)	20 (35.7%)	16 (30.8%)	0.122
Diabetes mellitus (%)	30 (13.6%)	7 (12.5%)	4 (7.7%)	0.513
Cerebrovascular incidents (%)	10 (4.5%)	0 (0%)	0 (0%)	0.080
Chronic kidney disease (%)	11 (5.0%)	6 (10.7%)	10 (19.2%)	0.008
Average hospitalization stay length (days)	9.45±4.8	12.0±6.1	9.12±3.1	0.002

Table 2 Comparing Pre- and Post-RFA Cardiac Ultrasound Parameters Among the 3 AF Patient Groups

	Paroxysmal		P	Persistent		P	Long-Term Persistent		P
	Pre-Treatment	Post-Treatment		Pre-Treatment	Post-Treatment		Pre-Treatment	Post-Treatment	
Left atrial diameter (mm)	34.4±6.2	34.0±5.8	0.402	39.5±3.3	36.4±5.3	0.001	38.0±5.3	37.3±7.2	0.399
Left ventricular diameter (mm)	43.9±5.4	45.0±5.2	0.05	46.7±4.9	45.4±4.1	0.667	47.0±7.6	46.5±6.8	0.632
Pulmonary artery diameter (mm)	19.1±2.9	19.0±2.2	0.987	20.1±3.2	19.5±2.6	0.878	20.6±2.8	22.4±9.3	0.489
Ejection fraction (%)	63.9±7.0	64.7±4.7	0.259	58.4±8.7	62.6±6.2	0.01	60.4±9.0	57.3±14.9	0.695

Comparing Post-RFA AF Recurrence, Stroke, Re-Hospitalization Rate and Duration Among the 3 AF Groups

We then compared the post-operative conditions of all patients during the follow-up period, in terms of AF recurrence, post-operative stroke incidence, as well as AF re-hospitalization rate and number of days (Table 3). We found that AF recurrence was the highest among the long-term persistent AF group, at 36.54% (19/52), compared to, respectively, 18.10% (40/221) in paroxysmal, and 30.36% (17/56) in the persistent group (Table 3). Indeed, a significant difference was present between paroxysmal and long-term persistent AF groups, paroxysmal vs persistent, but not for persistent vs

Table 3 Comparing Post-Radiofrequency Ablation (RFA) Conditions Among the 3 AF Types

	Paroxysmal			P (Paroxysmal vs Persistent)	Persistent			Long-Term Persistent			P (Paroxysmal vs long-term persistent)	P (Persistent vs long-term persistent)
	Yes	No	Rate		Yes	No	Rate	Yes	No	Rate		
AF recurrence	40	181	18.10%	0.043	17	39	30.36%	19	33	36.54%	<0.01	0.496
Postoperative stroke	25	196	11.31%	0.540	8	48	14.29%	4	48	7.69%	0.446	0.276
Re-hospitalization rate	15	206	6.79%	0.099	8	48	14.29%	10	42	19.23%	0.013	0.491
Re-hospitalization duration				1.0000							0.8490	0.8968

long-term persistent. For post-operative stroke, though, no significant difference was present among the 3 AF groups, with paroxysmal having an incidence of 11.31% (25/221), persistent with 14.29% (8/56), and long-term persistent with 7.69% (4/52) (Table 3). As for re-hospitalization rates, the highest rate was present among long-term persistent AF, at 19.23% (10/52), compared to 6.79% (15/221) among paroxysmal, and 14.29% (8/56) among persistent groups (Table 3). There, significant differences were present between paroxysmal vs long-term persistent, but not for paroxysmal vs persistent and persistent vs long-term persistent. However, average hospitalization length was similar between the 3 AF groups, at ~14.45, ~12.00, and ~16.30 days for, respectively, paroxysmal, persistent, and long-term persistent AF (Table 3); no significant difference was present. Overall, compared to paroxysmal AF, long-term persistent AF patients were more likely to have recurrent AF, as well as subsequently being re-hospitalized.

Comparing Patient Parameters Between AF Recurrence and Non-AF Recurrence Groups

We then compared the AF recurrence group to the non-AF recurrence group using univariate analysis and found that no significant differences were present in terms of age, gender, BMI, as well as history of CAD, diabetes mellitus, hypertension, and AF duration. Furthermore, no significant differences were present between the 2 groups for LA, LV, and PA diameters, as well as for moderate-to-severe mitral or tricuspid regurgitation. Significant differences, though, were present with respect to EF, renal function, BNP (normal levels <150), as well as paroxysmal vs non-paroxysmal AF (Table 4). We then conducted a multivariate logistic regression analysis on those 4 parameters, and found that they were still significantly associated with AF recurrence. In particular, patients with non-paroxysmal AF were 1.841 times, and

Table 4 Comparing Patient Parameters Between AF Recurrence and Non-AF Recurrence Groups Using Univariate Analysis

	AF Recurrence (N=76)	No AF Recurrence (N=253)	P
Age	69.5±10.6	67.7±10.7	0.179963
Number of patients (female)	76 (38)	253 (118)	0.606991
Body mass index	24.8±4.1	24.1±3.4	0.510076
Coronary artery disease (%)	14 (18.4%)	34 (13.4%)	0.280586
Diabetes mellitus (%)	13 (17.1%)	28 (11.1%)	0.162241
Hypertensive (%)	33 (43.4%)	102 (40.3%)	0.629419
Left atrium diameter (mm)	36.6±5.8	35.5±5.9	0.090052
Left ventricle diameter (mm)	45.5±5.5	44.7±5.2	0.308955
Pulmonary artery diameter (mm)	19.4±3.1	19.3±2.7	0.988184
Left ventricular Ejection fraction (%)	61.7±5.9	62.6±8.1	0.030147
Mitral regurgitation (middle-heavy, %)	10 (13.2%)	31 (12.3%)	0.834093
Tricuspid regurgitation (middle-heavy, %)	13 (17.1%)	36 (14.2%)	0.536866
Average AF duration	30.4±63.0	31.0±62.2	0.996154
Estimated glomerular filtration rate<60 (%)	30 (39.5%)	39 (15.8%)	0.000011
Brain natriuretic peptide>150 (%)	43 (62.3%)	106 (48.4%)	0.043656
Paroxysmal AF (%)	40 (52.6%)	181 (71.5%)	0.00208

those with CKD were 3.268 times more likely to have AF recurrence, compared with those with paroxysmal AF, or without CKD, respectively (Table 5).

Renal Function Effects on RFA Outcomes

We further examined the effects of renal function on RFA outcomes. Out of the 329 AF patients in this study, 323 had their creatinine levels and eGFR recorded, of which 217 were classified as having paroxysmal, 55 persistent, and 51 long-term persistent AF. These patients were categorized as having CKD, or non-CKD, based on them having eGFR of, respectively, < or >60.[22,23] We found that in terms of AF recurrence, individuals with CKD within all 3 AF groups had significantly higher rates than non-CKD individuals. These rates were 30%, 63.64%, and 61.11% for CKD, compared to 15.82%, 22.73%, and 24.24% for non-CKD, among, respectively, paroxysmal (P=0.0367), persistent (P=0.0239), and long-term persistent (P=0.0093) AF patients (Figure 2A). By contrast, no significant difference between CKD and non-CKD patients were observed among the 3 AF groups in terms of post-operative stroke (P=0.4203 for paroxysmal, 0.6538 for persistent, 0.607 for long-term persistent AF; Figure 2B).

As for re-hospitalization rates, a significant difference was only found for the long-term persistent AF group (P=0.0228), in which it was significantly higher among CKD, at 38.89%, compared to non-CKD, at 9.09%; no such difference was found for paroxysmal, in which the rates were, respectively, 12.5% for CKD and 5.65% for non-CKD (P=0.1605), or for persistent AF (P=0.3349), where CKD had a re-hospitalization rate of 27.27%, while it was 11.36% for non-CKD (Figure 2C). However, no significant difference in re-hospitalization duration was present among the 3 AF groups (P=0.951, 0.763, and 0.646 for, respectively, paroxysmal, persistent, and long-term persistent AF; Figure 2D). Therefore, patients with CKD were significantly more likely to have AF recurrence, no matter the AF type. Furthermore, those CKD patients with long-term persistent AF were more likely to be re-hospitalized.

Discussion

In this study, we examined whether different AF types influenced the therapeutic effects of RFA, via comparing AF recurrence, post-operative stroke occurrence, as well as AF re-hospitalization rates and duration in days, among paroxysmal, persistent, and long-term persistent AF groups. We found that paroxysmal, compared to persistent and long-term persistent AF, had lower AF recurrence and re-hospitalization rates post-RFA. However, for post-operative stroke occurrence and duration of re-hospitalization, no significant differences were present among the 3 AF types. All these findings thus indicated that RFA was most beneficial for paroxysmal AF patients, in terms of avoiding future AF recurrence and subsequent re-hospitalization. However, little difference was present, in terms of post-operative complications, such as stroke, for all 3 AF types.

Our findings of lower AF recurrence among paroxysmal patients was in line with a previous study, which found that within 5 years post-RFA, the lowest recurrence rates were present among paroxysmal AF patients, and the highest among long-term persistent AF, with persistent AF in between. These observations seem to suggest that longer AF durations

Table 5 Multivariate Logistic Regression Analysis of 4 Patient Parameters Between AF Recurrence and Non-AF Recurrence Groups

Patient Parameter	Category	B	SE B	Wald χ^2	df	Sig.	Exp(B)	95% CI for Exp(B)	
								Lower	Upper
Chronic kidney disease	No*								
	Yes	1.183	0.314	14.193	1	<0.01	3.265	1.764	6.043
AF type	Paroxysmal*								
	Non-paroxysmal	0.61	0.306	3.981	1	0.046	1.841	1.011	3.353
Brain natriuretic peptide	Normal*								
	High	0.269	0.31	0.755	1	0.385	1.309	0.713	2.401
Ejection fraction	N/A	−0.012	0.02	0.353	1	0.553	0.988	0.951	1.027

Note: *Indicates control group.
Abbreviation: CI, confidence interval.

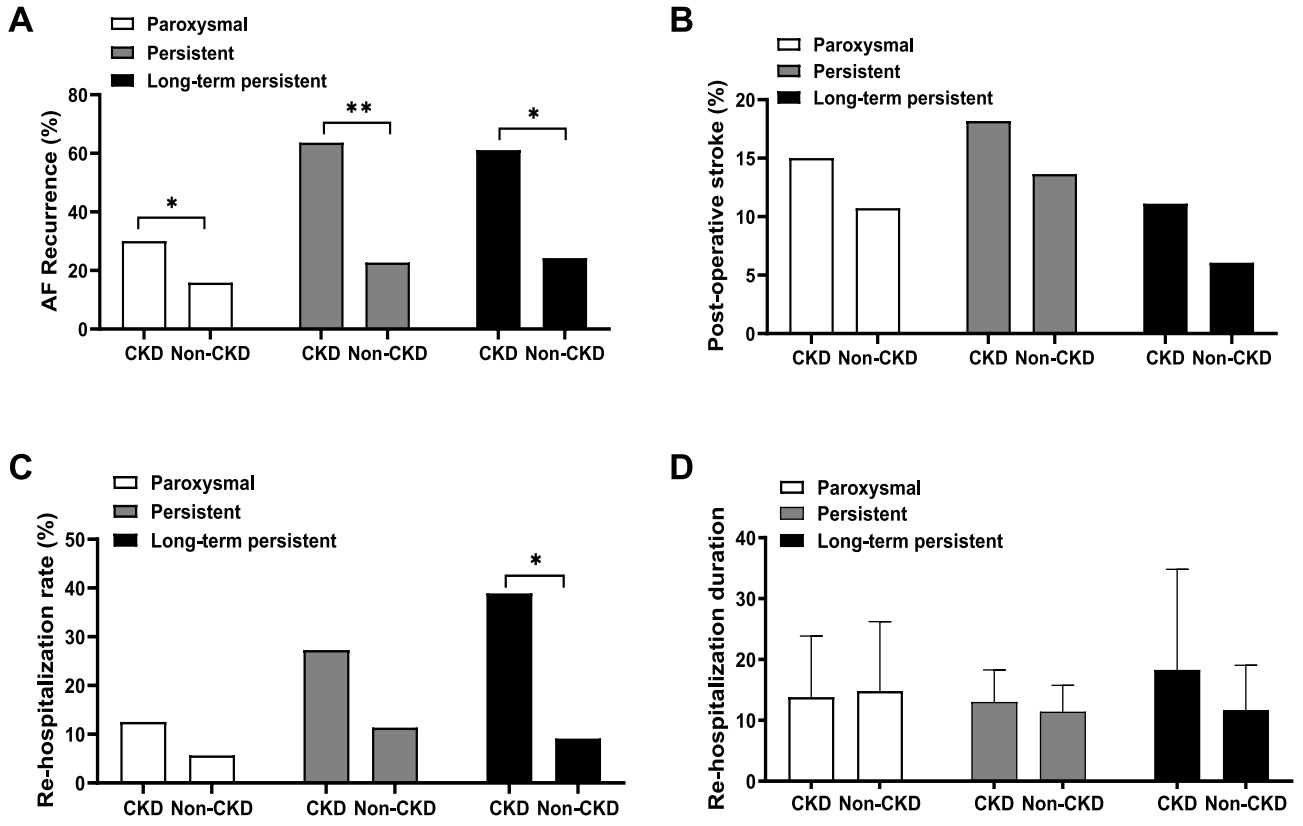

Figure 2 Comparing patient outcomes after undergoing radiofrequency ablation (RFA) between chronic kidney disease (CKD) and non-CKD groups, in terms of (**A**) AF recurrence, (**B**) stroke incidence, (**C**) re-hospitalization rate, and (**D**) re-hospitalization duration in days. *P<0.05, **P<0.01.

corresponded to higher recurrence likelihoods post-RFA, which may be owed to multiple factors. One major factor is that AF induces cardiac remodeling, particularly at the LA, owing to lowered Ca^{2+} release stemming from Ca^{2+} channel down-regulation and sarcomere loss, or myolysis, leading to LA dilation,[24] thereby creating a larger cardiac space that perpetuates fibrillation waves.[25] LA dilation also fosters a pro-thrombotic and fibrotic environment, which eventually could lead to ventricular dysfunction and heart failure.[26] In fact, patients with persistent and long-term persistent AF have been identified as possessing larger LA dimensions, owing to myocardial hypertrophy, and are more likely to display rapid and irregular heartbeats.[27] As a result, they are more susceptible for heart failure, compared to paroxysmal AF.[11] On the other hand, heart failure itself could cause increases in atrial pressures, which promotes atrial scarring and fibrosis, leading to further electrical conduction abnormalities and AF in a vicious cycle.[28] In particular, fibrosis has been closely associated with lowered RFA effectiveness for treating AF, and correspondingly, increased AF recurrence risk.[29] Furthermore, with respect to atrial fibrotic structural changes, longer AF durations have generally been associated with greater interstitial fibrosis, serving as the likely basis for increased AF recurrence after RFA.[30] These longer AF durations have also been linked to lower LA reservoir strain (LASr), which may stem from increased fibrosis. In fact, Khan et al observed that LASr was lower among the AF recurrence group, 3 months post-ablation, compared to patients with sinus rhythm.[31] Moreover, Vincenti et al found that AF patients, even with sinus rhythm, did not recover proper LA mechanical activity, as the LA was enlarged and stiffer, leading to increased endo-cavity pressure. As a result, these patients are likely at greater thromboembolic risk.[32] These studies therefore indicate that longer AF duration corresponds with greater interstitial fibrosis and smaller LASr. Consequently, lower pre-RFA LASr is associated with higher likelihood for post-RFA AF recurrence.

Increased AF recurrence among patients with longer AF durations was also coupled with increased re-hospitalization rates. This may be due to shorter-term AF having less impact on atrial structural changes. As a result, RFA was able to reverse whatever atrial remodeling was present, via restoring the sinus rhythm of the atrium.[33] However, for longer-term

AF, greater changes are present, which are harder to recover from even after RFA. Another significant factor contributing to AF occurrence and recurrence is CAD, which could be owed to both diseases sharing similar risk factors and pathophysiology. In fact, CAD and AF "feed" upon each other in a vicious cycle, where AF increases atherosclerosis, a prominent pathological development in CAD, due to endothelial dysfunction and inflammation. This increased atherosclerosis promotes thrombi formation, exacerbating ischemia and electrical signaling disruption as part of CAD. Consequently, atrial ischemia and electrical inhomogeneity promotes re-entry and increased tissue excitability in CAD, thereby worsening AF.[34,35] Indeed, the close connection between AF and CAD has been documented in a group of 70 persistent AF patients, of which 70% had CAD, and among those who did not, a large proportion still had slowed blood flow.[36] On the other hand, those without CAD had significantly lower AF recurrence, post-RFA, than those who did,[37] and treating CAD individuals with percutaneous coronary intervention prior to RFA also reduced AF recurrence, as it helped to improve LV diastolic function.[38] Therefore, CAD was a significant risk factor for AF recurrence, and likewise, treating CAD aided in counteracting against that adverse post-RFA outcome.

The involvement of inflammation in AF was further supported by studies measuring levels of CRP, in which increases in CRP levels were found to be predictive for AF occurrence,[39] as well as recurrence,[40] in which CRP levels >1.9 mg/L were found to be moderately accurate for predicting AF recurrence in a meta-analysis by Yo et al.[15] Another inflammatory marker was NT-proBNP, which Carballo et al identified, in a multi-center study, to be higher among patients with AF recurrence post-RFA, versus those who did not;[40] this was in line with our observations, in which the presence of BNP levels >150 were significantly higher among post-RFA AF recurrence patients, compared to those with no recurrence. Higher CRP and BNP among those patients, after undergoing RFA, may be reflective of inflammation altering the ratio between atrial fibroblasts and cardiomyocytes, resulting in adverse atrial remodeling and AF recurrence.[41]

By contrast, we did not find any significant differences among the 3 AF types regarding post-operative stroke occurrence and re-hospitalization duration. Our observation on post-operative stroke contradicts a number of previous findings where non-paroxysmal AF was associated with higher stroke incidence and worse survival rates, compared to paroxysmal AF.[42–44] This discrepancy may be due to the small sample size in this study, as well as loss of some patients to follow-up. Furthermore, re-hospitalization durations could be affected by multiple confounding factors present in AF patients, rather than the AF type alone.

Aside from AF type, we also examined other underlying factors that may affect AF prognoses. In our logistics regression analysis, we found that CKD was the other parameter significantly affecting AF recurrence. With respect to kidney function, CKD patients, no matter the AF type, had significantly higher AF recurrence rates, compared to non-CKD. Moreover, CKD patients with long-term persistent AF were more likely to be re-hospitalized versus their non-CKD counterparts, suggesting that kidney deficiencies could negatively impact post-RFA recovery. In fact, a 2-way relationship has been documented between AF and CKD, in which the latter could induce the former,[45,46] and the former could worsen kidney function,[47,48] in a vicious cycle. Furthermore, CKD is often linked to inflammation, to the point where a hallmark feature of this disease is a sustained, low-level inflammatory response, which may be due to inflammasome activity and intestinal flora imbalances.[49] Indeed, in agreement with this study, Guo et al, in their analysis of 88,312 patients, found that AF incidence was higher among CKD, compared to non-CKD patients; increased AF risk was also associated with higher levels of CRP.[50] Additionally, Qiu et al, using a rat CKD model, found that significant differences in AF induction and duration were present between those subject to nephrectomy versus the sham group, which is related to NLRP3 inflammasome activation and connexin remodeling.[51] CKD has also been linked to the renin-angiotensin-aldosterone system, leading to increased atrial pressure, atrial fibrosis, and ultimately, AF.[48] All of these observations thus illustrate that CKD could induce AF, via increasing inflammatory responses and increasing intra-atrial pressure, resulting in such patients possessing higher AF recurrence rates post-RFA, compared to non-CKD individuals, as demonstrated by our findings. Likewise, AF worsens CKD, which may be due to renal hypo-perfusion and micro-thrombi formation. Therefore, AF treatment should account for the presence of CKD, as well as the impact that anti-fibrillary medications may have on kidney function.

Study Limitations

There are a number of limitations for this study, one of which is its limited sample size of patients from a single hospital. Another limitation is the retrospective nature of the study, meaning that there may be biases introduced in the analysis of the findings, which may not be fully reflective of AF patients who underwent RFA. Furthermore, only 4 post-RFA endpoints were examined: AF recurrence, post-operative stroke rate, as well as re-hospitalization rate and duration, even though other adverse events, such as local inflammation, could occur. Additionally, the impact of only 1 concurrent disease with AF, CKD, was examined, despite AF also being associated with other diseases, such as CAD. Therefore, future studies with larger sample sizes, as well as examining other post-RFA endpoints and the impacts of other concurrent diseases aside from CKD, are required to further verify our findings.

Conclusion

In this study, we examined whether different AF types influenced patient outcomes post-RFA. Our key findings were that post-procedural AF recurrence and re-hospitalization rates were significantly lower for paroxysmal, compared to persistent and long-term persistent AF. Additionally, CKD patients, compared to non-CKD ones, were more likely to have AF recurrence and be re-hospitalized. All these findings suggest that variable outcomes for RFA are present, depending on AF type, and that CKD is an independent predictor for AF recurrence. Therefore, CKD can be used in conjunction with AF types to identify patients with high AF recurrence risk, and subsequently aid in developing personalized treatment strategies.

Data Sharing Statement

Data are available on request to the corresponding author, Chongyu Zhang.

Ethics Approval and Consent Statements

The study protocol was approved by the ethics committee of the Second Affiliated Hospital of Guangzhou Medical University (REB #:2023-hg-ks-48) and was undertaken according to the ethical standards of the Declaration of Helsinki. All patients provided written informed consent.

Acknowledgments

We thank Alina Yao for her assistance in revising and editing the manuscript before publication.

Funding

This study was supported by National Natural Science Foundation of China (C. Z., 82200559; J.C., 82000246), the Guangzhou Municipal Science and Technology Project (C.Z., 2023A04J0586; J.C., 202102020094) and the Innovation Team of General Universities in Guangdong Province (2023KCXTD025).

Disclosure

The authors declare no conflicts of interest.

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