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Evaluating the Prognostic Significance of Cystatin C Level Variations Pre- and Post-Radiofrequency Catheter Ablation in the Recurrence of Persistent Atrial Fibrillation

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ABSTRACT

Objective: To investigate the correlation between persistent atrial fibrillation (AF) recurrence and alterations in cystatin C levels pre- and post-radiofrequency catheter ablation (RFCA).

Methods: This study encompassed 114 patients diagnosed with persistent AF. Their serum cystatin C levels were assessed both prior to and 3 months after undergoing an RFCA procedure. The variance in cystatin C levels before and after RFCA is represented as ΔCystatin C. Subsequently, we compared these values between two groups: patients who did not experience a recurrence of AF ($n = 79$) and those who did experience a recurrence ($n = 35$).

Results: A significant reduction in cystatin C levels post-RFCA in both groups, with a more pronounced decrease observed in the non-recurrence group. Moreover, the recurrence group exhibited larger left atrial diameter and volume before RFCA compared to the non-recurrence group. Cox regression analysis indicated that smaller reductions in serum cystatin C levels and greater left atrial volumes before RFCA were associated with an increased risk of recurrence, after adjusting for covariates. The receiver operating characteristic curve indicated an elevated probability of clinical recurrence of AF post-RFCA in patients with a cystatin C decline < 0.08 mg/L (AUC 0.64). The Kaplan–Meier survival analysis revealed that patients with a cystatin C decline > 0.08 mg/L exhibited significantly higher rates of remaining free from recurrence following RFCA across a 24-month follow-up period (Log-rank test $p = 0.003$).

Conclusions: Alterations in ΔCystatin C levels pre and post-RFCA in the initial phase could independently predict the recurrence of AF.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ACT, activated clotting time; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; CPVI, circumferential pulmonary vein isolation; ECM, extracellular matrix; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LAD, left atrial diameter; LAV, left atrial volume; LDL, low-density lipoprotein; LGE-MRI, late gadolinium enhancement cardiac magnetic resonance imaging; LVDD, left ventricular end-diastolic diameter; MDRD, modification of Diet in Renal Disease; PVI, pulmonary vein isolation; RFCA, radiofrequency catheter ablation.

Yu-Yan Zhang and Ji-Yong Ge contributed equally to this work.

1 | Introduction

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia characterized by abnormal electrical impulses in the atria. Percutaneous radiofrequency catheter ablation (RFCA), specifically, circumferential pulmonary vein isolation (CPVI), is a common treatment for AF aimed at restoring normal sinus rhythm (Weerasooriya et al. 2011). However, achieving sustained therapeutic outcomes, especially in cases of persistent AF, remains challenging despite multiple procedures (Nishimura, Lupercio-Lopez, and Hsu 2019; Calkins et al. 2018). Research by Marrouche et al. (2014) revealed a correlation between atrial fibrosis, assessed via gadolinium delayed-enhanced magnetic resonance imaging, and AF recurrence post-RFCA. This suggests that atrial fibrosis may contribute to atrial remodeling, thereby perpetuating AF (Ju et al. 2018; Yamaguchi et al. 2022; Rossi et al. 2022).

Recent studies have highlighted renal dysfunction as a significant independent risk factor for AF development (Alonso et al. 2011). Chao et al. (2011) demonstrated a strong correlation between reduced estimated glomerular filtration rate (eGFR) and higher AF recurrence rates post-ablation. The outcomes from both animal models and human studies have suggested that even slight decreases in renal function could accelerate the progression of atrial fibrosis (Martin et al. 2012; Fukunaga et al. 2012; Gupta et al. 2012). Cystatin C, an inhibitor of cysteine proteases synthesized by all nucleated mammalian cells, has emerged as a potential biomarker for early kidney damage detection (Chen et al. 2020). Circulating cystatin C levels have been proposed as a more sensitive indicator, particularly in individuals with normal creatinine levels (Kar, Paglialunga, and Islam 2018; Serezlija, Serdarevic, and Begic 2017). Previous investigations have established a significant association between cystatin C levels and cardiovascular events, such as stroke, myocardial infarction, and cardiovascular mortality, across diverse populations (Shlipak et al. 2013; Shen et al. 2018; Garcia-Carretero et al. 2017). A recent study explored the relationship between cystatin C levels, left atrial volume index, and fibrosis indices in patients with AF (Zivlas et al. 2017). Nonetheless, extensive studies on the predictive efficacy of various forms of cystatin C in predicting AF recurrence post-RFCA are still limited.

In this study, we examined the relationship between AF recurrence and changes in serum cystatin C levels both before and 3 months after RFCA. Furthermore, we assessed the potential of early serum cystatin C variation as a predictor for AF recurrence.

2 | Methods

2.1 | Study Population

In this study, 114 patients diagnosed with persistent AF undergoing their first RFCA at the cardiovascular department of the Second People's Hospital of Changzhou, were enrolled. These participants were categorized into two groups based on the procedure's outcome: a non-recurrence group ($n = 79$) and a recurrence group ($n = 35$). The primary objective was to identify predictive factors associated with AF recurrence post-ablation. Exclusion criteria included paroxysmal AF lasting less than 7 days, persistent AF exceeding 3 years, presence of structural heart disease other than left ventricular hypertrophy, presence of a pacemaker, intracardiac thrombi, rheumatic valvular disease, and a history of cardiac surgery. This study adhered to the Declaration of Helsinki principles and was approved by the Ethics Committee of the Second People's Hospital of Changzhou. Informed consent was obtained from all participants before their inclusion in the study.

Information regarding patients' medical backgrounds was collected, encompassing factors such as hypertension, diabetes mellitus, and coronary artery disease, along with their smoking and alcohol consumption habits, duration of AF, and utilization of medications such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), β-blockers, and diuretics. Blood samples were obtained after the participants fasted overnight, and various biomarkers, including serum cystatin C, blood urea nitrogen, serum creatinine, serum uric acid, serum triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol, were analyzed using an automated enzymatic method on the Chemistry Analyzer AU2700 from Olympus Medical Engineering Company, Tokyo, Japan. Low-density lipoprotein (LDL) cholesterol concentrations were computed using the Friedewald formula, and the eGFR was calculated using the CKD-EPI equation (https://www.kidney.org/professionals/gfr_calculator). Three months after PVI, serum levels of cystatin C and creatinine were reassessed for all patients. All antiarrhythmic drugs were discontinued more than 5 half-lives before RFCA and were prescribed for a period of 3 months (the blanking period) after RFCA with amiodarone for all patients with persistent AF. Anticoagulation therapy with phenprocoumon or direct oral anticoagulants (rivaroxaban or dabigatran) was maintained prior to the ablation procedure. Phenprocoumon and rivaroxaban were administered once daily at 8:00 AM, while dabigatran was administered twice daily at 8:00 AM and 4:00 PM. If the afternoon dose of dabigatran was missed due to the ablation, the regular dose was to be resumed within 2 h post-RFCA. Heparin was initiated immediately following transseptal puncture during the RFCA, with doses adjusted to maintain an activated clotting time (ACT) between 300 and 400 s (Calkins et al. 2012). Prior to RFCA, both transthoracic and transesophageal echocardiography were performed to evaluate the presence of structural heart disease or left atrial thrombus. Parameters including left ventricular ejection fraction (EF, %), left atrial diameter (LAD, mm), left atrial volume (LAV, mL), and left ventricular end-diastolic diameter (LVDD, mm) were measured during this assessment. These echocardiographic parameters were then re-evaluated 3 months after pulmonary vein isolation (PVI) in all patients to monitor any changes.

2.2 | Percutaneous RFCA

During the procedure, various catheters were inserted through the femoral vein and positioned as follows: 1. A distal ten-pole catheter from St. Jude Medical, Inc. was positioned at the coronary sinus. 2. A distal four-pole catheter from Webster Fixed Curve Catheter was placed in the right ventricle for emergent pacing during cardioversion after CPVI. 3. The mapping catheter (Pentaray) from Biosense Webster Inc. was positioned at the

target pulmonary vein through an SL1 transseptal sheath from St. Jude Medical. 4. A conventional 3.5 mm irrigated-tip ablation catheter (D curve, SmartTouch) from Biosense Webster, along with the CARTO mapping system, was used to reconstruct a three-dimensional electro-anatomical left atrium via an SL1 transseptal sheath.

During the procedure, all patients underwent CPVI using irrigated radiofrequency. The maximum target temperature was set at 43°C, with a power output limited to 35 W and an infusion rate ranging from 17 to 25 mL/min. Additionally, the power output was restricted to 30 W for lesions on the posterior wall. Successful CPVI was confirmed by the absence of any PV spike potential detected by the spiral-mapping catheter placed in the lateral PVs.

Following the CPVI procedure, cardioversion was performed to restore sinus rhythm, following the STABLE-SR protocol (Yang et al. 2017). High-density bipolar voltage mapping of the left atrium was conducted during the study, generating over 500 data points per patient using a standard 3.5 mm irrigated-tip ablation catheter. This mapping enabled precise identification of areas with low-voltage (0.1–0.4 mV) and transitional zones (0.4–1.3 mV). Subsequently, tissue homogenization was performed in the low-voltage zones, while complex electrograms in the transitional zones were targeted for substrate modification.

2.3 | Follow-Up

Patients who underwent RFCA were closely monitored for 24 months post-procedure. They attended regular follow-up visits at 3, 6, 12, 18, and 24 months, during which a 12-lead ECG, 24-h Holter monitoring, and interviews were conducted. Additionally, unscheduled visits were arranged as necessary. The recurrence of AF was defined as the presence of any episode of AF or atrial tachycardia lasting at least 30 s (European Heart Rhythm Association [EHRA] et al. 2007). It is important to note that atrial arrhythmia detected within the 3-month blanking period was not considered as a recurrence according to the latest guidelines (Calkins et al. 2012). None of the patients was died or lost during the follow-up.

2.4 | Statistical Analysis

SPSS 18.0 software was employed for both database management and statistical analysis. Continuous variables are presented as mean ± standard deviation, while categorical variables are expressed as proportions. Statistical comparisons were conducted using *t*-tests for means and chi-squared tests for proportions. Changes in serum cystatin C levels before and 3 months after RFCA were assessed using a paired *t*-test. Cox regression analyses were performed to identify factors associated with AF recurrence post-RFCA, adjusting for various demographic and clinical variables, that was, age, sex, smoking habits, alcohol intake, blood pressure, lipid profile, creatinine, and medication use (ACEI, ARB, β-blocker, diuretics, and CCB). In addition, we reported the Hazard ratio per 0.1 mg/L change in Cystatin C in the Cox regression. The predictive value of serum cystatin C for AF recurrence following RFCA was evaluated using the receiver operating characteristic (ROC) curve. Kaplan–Meier survival curves and log-rank tests were utilized to analyze rates of freedom from atrial arrhythmias post-RFCA based on ROC curve-derived cutoff points. A significance level of $p < 0.05$ was considered statistically significant.

3 | Results

3.1 | Demographic and Clinical Characteristics of the Non-Recurrence and Recurrence Groups

Out of the 114 patients diagnosed with persistent AF who underwent RFCA, 63 (55.3%) were male, while 51 (44.7%) were female. Among them, 35 experienced a recurrence, accounting for 30.7% of the total. The baseline clinical characteristics of both the recurrence and non-recurrence groups are summarized in Table 1. The recurrence group exhibited larger LAD ($p = 0.001$) and LAV ($p = 0.006$) prior to RFCA compared to the non-recurrence group. However, there were no significant differences observed in age, sex distribution, smoking status, alcohol consumption, blood pressure, heart rate, renal function, serum glucose, serum cholesterol, LVDD, EF, AF duration, ablation duration, and medication history between the two groups ($p > 0.05$).

3.2 | Variations in Serum Concentrations of Cystatin c, eGFR, and LAV in the Recurrence and Non-Recurrence Groups

The paired *t*-test comparisons revealed a significant decrease in serum cystatin C concentrations following RFCA in both the recurrence (from 1.11 ± 0.22 mg/L to 1.00 ± 0.19 mg/L, $p < 0.0001$) and non-recurrence groups (from 1.19 ± 0.23 mg/L to 1.01 ± 0.21 mg/L, $p < 0.0001$) as depicted in Figure 1a. In terms of serum concentrations of eGFR, significant increases were observed after RFCA in the non-recurrence group (83.57 ± 13.50 mL/min·1.73 m^2 to 86.32 ± 14.11 mL/min·1.73 m^2, $p = 0.002$), while no differences were found in the recurrence group (84.96 ± 15.40 mL/min·1.73 m^2 to 87.06 ± 13.50 mL/min·1.73 m^2, $p = 0.051$) (Figure 1b). Additionally, there were no significant differences in LAV after RFCA in either the recurrence group (78.34 ± 32.90 mL vs. 78.11 ± 33.00 mL, $p = 0.67$) or the non-recurrence group (63.19 ± 23.36 mL vs. 62.81 ± 23.36 mL, $p = 0.25$) (Figure 1c).

The reduction in serum cystatin C levels (ΔCystatin C) before and after RFCA exhibited a significantly greater magnitude in the non-recurrence group compared to the recurrence group (0.18 ± 0.16 mg/L vs. 0.11 ± 0.10 mg/L, $p = 0.006$) (Figure 2a). However, no significant differences were observed between the two groups regarding ΔeGFR ($p = 0.66$, Figure 2b) and ΔLAV ($p = 0.80$, Figure 2c).

3.3 | Relative Risk of AF Recurrence After RFCA Utilizing Cox Regression Analyses

The Cox regression analysis presented in Table 2 indicated that a reduction in Cystatin C levels (HR = 0.620, 95% CI: 0.413–0.931,

TABLE 1 | Characteristics between non-recurrence and recurrence group.

	Non-recurrence ($n=79$)	Recurrence ($n=35$)	p
Age (years)	64.0 ± 9.5	66.1 ± 8.5	0.27
Sbp (mmHg)	130.6 ± 14.9	126.1 ± 16.6	0.15
Dbp (mmHg)	76.6 ± 8.4	78.0 ± 12.2	0.52
Heart rate (beats/min)	76.8 ± 16.2	76.0 ± 11.8	0.79
Urea nitrogen (mmol/L)	5.19 ± 1.25	5.69 ± 1.84	0.15
Creatinine (μmol/L)	75.6 ± 12.4	74.6 ± 18.6	0.78
Uric acid (mmol/L)	358.7 ± 73.9	369.3 ± 89.5	0.51
Glucose (mmol/L)	5.40 ± 1.33	5.47 ± 1.01	0.76
TCH (mmol/L)	4.31 ± 0.93	4.39 ± 1.02	0.68
Triglycerid (mmol/L)	2.01 ± 1.84	1.54 ± 0.68	0.15
HDL-C (mmol/L)	1.03 ± 0.24	1.11 ± 0.17	0.08
LDL-C (mmol/L)	2.40 ± 0.69	2.53 ± 0.83	0.38
LAD (mm)	40.1 ± 5.9	44.5 ± 7.5	0.001
LAV (mL)	63.2 ± 23.4	78.3 ± 32.9	0.006
LVDD (mm)	48.2 ± 4.6	49.9 ± 5.4	0.09
EF (%)	59.9 ± 8.2	60.1 ± 5.8	0.96
Ablation time (min)	48.9 ± 10.7	49.6 ± 15.2	0.79
AF duration (months)	19.9 ± 8.3	17.9 ± 8.7	0.24
Sex (male, %)	41 (51.9)	22 (62.9)	0.28
Smoking (%)	9 (11.4)	9 (25.7)	0.06
Alcohol intake (%)	3 (3.80)	3 (8.57)	0.29
Medications			
β-blocker (%)	23 (29.1)	13 (37.1)	0.40
ACEI (%)	2 (2.53)	2 (5.71)	0.39
ARB (%)	28 (35.4)	14 (40.0)	0.64
Diuretics (%)	9 (11.4)	7 (20.0)	0.22
CCB (%)	17 (21.5)	9 (25.7)	0.62

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Dbp, diastolic blood pressure; EF, ejection fraction; HDL-C, high-density lipoprotein cholesterol; LAD, left atrial diameter; LAV, left atrial volume; LDL-C, low-density lipoprotein cholesterol; LVDD, left ventricular end-diastolic diameter; Sbp, systolic blood pressure; TCH, total cholesterol.

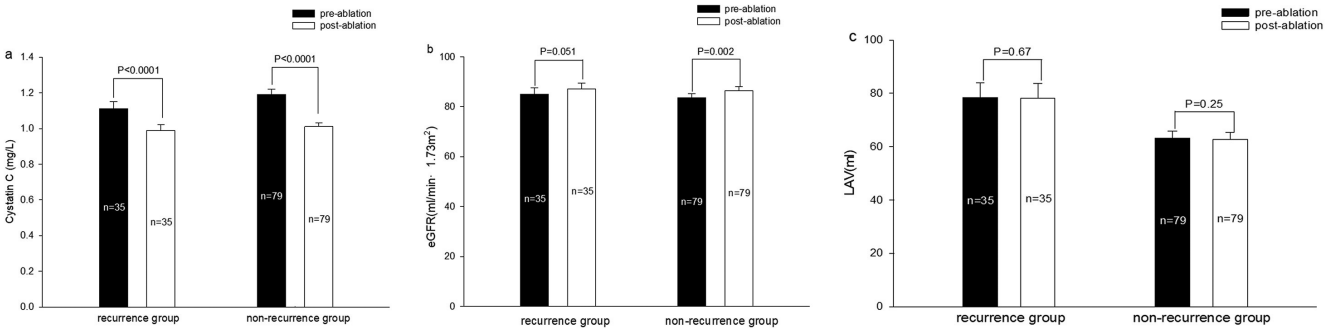

FIGURE 1 | Differences in serum cystatin C concentrations (a), eGFR (b), and LAV (c) before and after ablation in both the recurrence group (left panels) and the non-recurrence group (right panels). Mean values ± standard error are presented, and statistical significance was determined using the paired *t*-test.

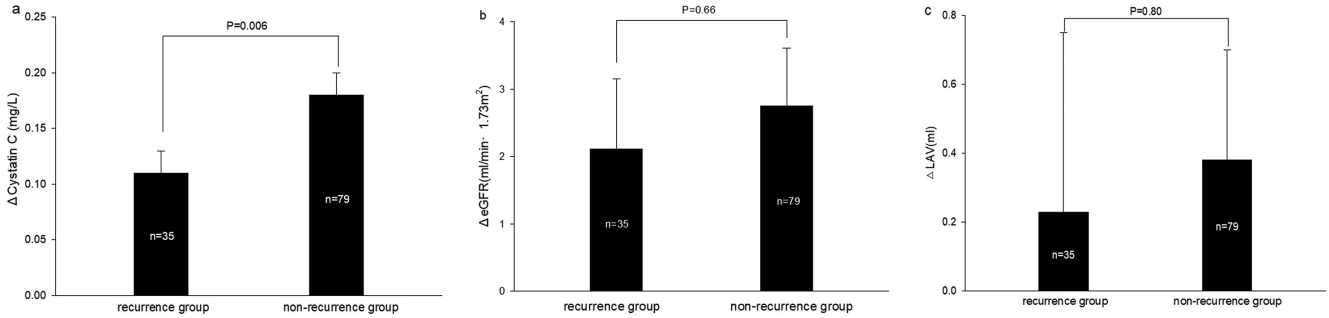

FIGURE 2 | Disparities in the changes in ΔCystatin C (a), ΔeGFR (b), and ΔLAV (c) before and after RFCA, comparing the recurrence group (left panel) and the non-recurrence group (right panel). Mean values ± standard error are presented, and statistical significance was assessed using the *t*-test.

TABLE 2 | Relative hazards of atrial fibrillation recurrence by Cox regression analyses.

	β	SE[a]	*p*	HR	95% CI
ΔCystatin C (per 0.1 mg/L)	−0.478	0.207	0.021	0.620	0.413–0.931
LAV (mL)	0.028	0.009	0.002	1.028	1.010–1.046
ΔeGFR (mL/min·1.73 m^2)	−0.023	0.030	0.456	0.978	0.921–1.037
ΔLAV (mL)	−0.042	0.074	0.568	0.959	0.830–1.107

Abbreviations: LAV, left atrial volume; ΔCystatin C, cystatin C (pre-ablation) – cystatin C (post-ablation); ΔeGFR, estimated glomerular filtration rate (post-ablation) – estimated glomerular filtration rate (pre-ablation); ΔLAV, left atrial volume (pre-ablation) – left atrial volume (post-ablation).
[a]Adjusted for age, sex, smoking, alcohol intake, systolic blood pressure, diastolic blood pressure, glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, uric acid, and medication history (ACEI, ARB, β-blocker, diuretics, and CCB).

$p = 0.021$) and higher baseline LAV (HR = 1.028, 95% CI: 1.010–1.046, $p = 0.002$) were significantly correlated with an elevated risk of AF recurrence, even after adjusting for various confounding factors such as age, sex, lifestyle habits, blood pressure, lipid profile, renal function, and medication use (ACEI, ARB, β-blocker, diuretics, and CCB). However, changes in eGFR ($p = 0.456$) and LAV ($p = 0.568$) did not exhibit a significant association with AF recurrence.

3.4 | ROC Curve of the Declined Values of Serum Cystatin C With Recurrence of AF After Radiofrequency Ablation

Following RFCA, patients with serum cystatin C levels below 0.08 mg/L exhibited a considerably elevated likelihood of clinical recurrence of AF, as revealed by the ROC curve analysis (with a sensitivity of 77.2% and a specificity of 51.4%, yielding an area under the curve (AUC) of 0.64, as depicted in Figure 3, $p = 0.016$).

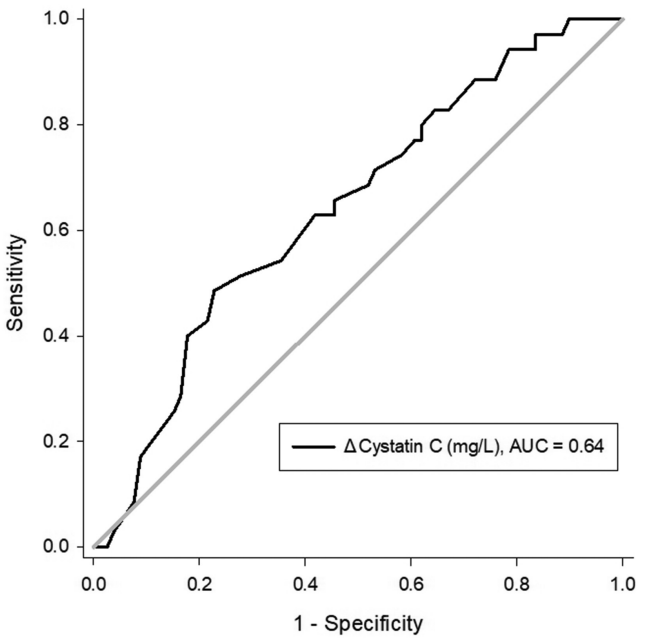

FIGURE 3 | The ROC curve illustrates the relationship between the decreased levels of serum cystatin C and the recurrence of AF following radiofrequency ablation. Patients with serum cystatin C levels below 0.08 mg/L exhibited a higher rate of clinical recurrence of AF post-RFCA, with a sensitivity of 77.2%, specificity of 51.4%, and an AUC of 0.64.

3.5 | Kaplan–Meier Survival Curve of Freedom From Atrial Arrhythmias After RFCA

The patients were divided into two groups using a cutoff value of 0.08 mg/L for ΔCystatin C based on the cutoff point at which specificity and sensitivity were optimized in the ROC curve. According to the Kaplan–Meier survival analysis, patients with ΔCystatin C > 0.08 mg/L exhibited higher rates of freedom from atrial arrhythmias following RFCA over the 24-month follow-up period (77.9% vs. 51.4%, Log-rank test $p = 0.003$, as illustrated in Figure 4).

4 | Discussion

The results of this study suggest that a reduction in ΔCystatin C 3 months post-RFCA may serve as a predictive indicator for the likelihood of AF recurrence. Furthermore, the results suggest

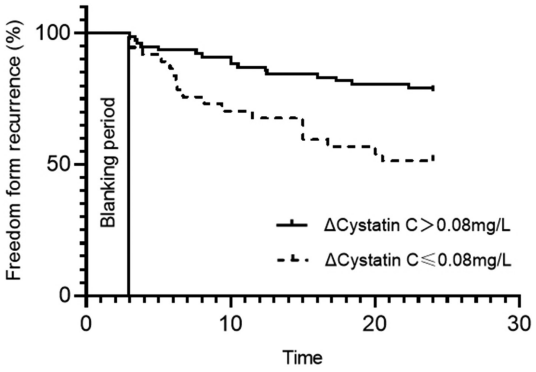

FIGURE 4 | The Kaplan–Meier survival curve depicts the freedom from atrial arrhythmias following RFCA. Patients were categorized into two groups using a threshold of 0.08 mg/L of ΔCystatin C. Those with ΔCystatin C > 0.08 mg/L exhibited higher rates of freedom from atrial arrhythmias post-RFCA over a 24-month period compared to those with ΔCystatin C ≤ 0.08 mg/L (77.9% vs. 51.4%, Log-rank test $p = 0.003$).

that changes in ΔCystatin C and LAV could predict AF recurrence independently, while changes in eGFR and LAV were not linked to AF recurrence. The utilization of ROC curves and Kaplan–Meier survival analyses further substantiated the predictive value of changes in ΔCystatin C for AF recurrence, considering potential variables. This underscores the potential utility of monitoring ΔCystatin C as a marker for predicting AF recurrence post-RFCA.

Studies have emphasized the link between renal impairment and a heightened susceptibility to AF. Furthermore, radiofrequency catheter ablation has been shown to enhance renal function in patients with AF (Iguchi et al. 2008; Takahashi et al. 2011). Navaravong et al. conducted a study involving 392 patients with AF who underwent ablation. After a median follow-up of 115 days, they noted a substantial enhancement in the eGFR when comparing pre- and post-ablation serum creatinine levels (Navaravong et al. 2015). Similarly, in our study, we observed a significant reduction in ΔCystatin C in both the recurrence and non-recurrence groups following RFCA, indicating an improvement in renal function. Interestingly, we also identified a notable disparity in the changes in ΔCystatin C between the recurrence and non-recurrence groups during the early post-RFCA period, with significantly lower variations observed in the recurrence group compared to the non-recurrence group. While the non-recurrence group showed a significant increase in eGFR following RFCA, no such differences were observed in the recurrence group. Additionally, the difference in ΔeGFR between the two groups pre- and post-RFCA was not significant. These findings corroborate previous research suggesting that cystatin C serves as a more sensitive marker for early renal damage compared to creatinine levels (Kar, Paglialunga, and Islam 2018; Serezlija, Serdarevic, and Begic 2017). Individuals diagnosed with AF commonly demonstrate impaired left atrial contractile function, decreased velocity within the left atrial appendage, and an increased propensity for spontaneous contrast echo (Providencia et al. 2013). After undergoing RFCA, there was a noted improvement in left atrial function (Muellerleile et al. 2013; Machino-Ohtsuka et al. 2013). This enhancement in renal function could potentially be attributed to improvements in left atrial function and cardiac output (Navaravong et al. 2015). LAV was identified as an independent predictor for AF recurrence prior to RFCA, based on Cox regression analyses. This indicates that changes in LAV may play a role in the enhancement of renal function in patients with AF after RFCA.

The likelihood of AF recurring following RFCA is thought to be linked to the extent of atrial fibrosis, particularly in patients with persistent AF. In a study by Takahashi et al. (2020), it was demonstrated that renal dysfunction was a significant predictor not only for the reoccurrence of AF post-ablation but also for the existence of low-voltage zones in the left atrium. Navaravong et al. (2015) discovered a link between recurrent AF and atrial fibrosis, which was assessed through late gadolinium enhancement cardiac magnetic resonance imaging (LGE-MRI). Cystatin C in circulation has emerged as a more precise indicator of eGFR compared to serum creatinine. Moreover, it has been correlated with both left ventricular structural and functional characteristics, attributed to its involvement in extracellular matrix (ECM) restructuring, which is closely linked to myocardial fibrosis (Ferguson, Komenda, and Tangri 2015; Xie et al. 2010). Cystatin C has also been associated with increased left atrial dilation and galectin-3 levels, which is considered a fibrotic index (Zivlas et al. 2017). In our study, we further validated that a ΔCystatin C < 0.08 mg/L serves as a threshold for predicting AF recurrence post-RFCA, with a sensitivity of 77.2% and specificity of 51.4%, as determined by the ROC curve. Utilizing this threshold, Kaplan–Meier survival analysis revealed a freedom rate from atrial arrhythmias of 77.9% when ΔCystatin C > 0.08 mg/L, compared to 51.4% when ΔCystatin C ≤ 0.08 mg/L. These quantitative analyses underscore the robust predictive value of ΔCystatin C for AF recurrence following RFCA.

This study is constrained by its small sample size, consisting of a select group of patients referred for RFCA. Moreover, the utilization of short-term 24-h Holter monitoring rather than the more comprehensive 7-day monitoring may have diminished the robustness of the evidence regarding AF recurrence. These constraints should be taken into account when analyzing the findings of our study. While our research indicated a potential correlation between AF recurrence and changes in serum cystatin C levels, potentially linked to atrial fibrosis, we did not include specific indices of atrial fibrosis to corroborate these associations. As the results show relatively poor prognostic prediction for Cystatin C with an AUC of 0.64, large sample size from multicenter and prospective studies are required to confirm our findings and clarify the underlying mechanisms of this relationship.

5 | Conclusion

Prior to RFCA, early-stage changes in ΔCystatin C were identified as independent predictors of AF recurrence. However, to validate this relationship, further investigation over an extended follow-up period and exploration of potential mechanisms is necessary.

Author Contributions

Conception and design of the research: Yu-Yan Zhang, Zhen-Yan Zhu. Acquisition of data: Zhen-Yan Zhu, Yuan Ji, Yi Zhu. Analysis and interpretation of the data: Fang-Fang Wang, Yuan Ji. Statistical analysis: Ji-Yong Ge, Yi Zhu. Obtaining financing: Ji-Yong Ge. Writing of the manuscript: Yu-Yan Zhang, Ji-Yong Ge. Critical revision of the manuscript for intellectual content: Fang-Fang Wang. All authors read and approved the final draft.

Ethics Statement

This study complied with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Second People's Hospital of Changzhou.

Consent

Informed consent was obtained and signed by each participant.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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