Journal of Geriatric Cardiology (2018) 15: 725–731

Research Article · Open Access ·

Value of cystatin C in predicting atrial fibrillation recurrence after radiofrequency catheter ablation

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Abstract

Backgroud Recent studies have demonstrated that cystatin C is a valuable risk marker for cardiovascular disease morbidity and mortality. Therefore, we hypothesized that the pre-ablation cystatin C level was associated with post-ablation atrial fibrillation (AF) recurrence. **Methods** 207 patients were enrolled and completed in this prospective observational study. Patients with AF scheduled for receive radiofrequency catheter ablation (RFCA) therapy were screened for the study. Before ablation therapy, electrocardiogram, 24 h holter monitor, transesophageal echocardiography, serum cystatin C, high-sensitivity C-reactive protein, creatinine levels, and routine blood examinations were examined. After ablation, patients were followed up every week for the first month, and then at 2, 3, 6, 9, and 12 months. Thereafter, patients came back to out-patient clinic every six months regularly. Electrocardiogram or 24 h holter monitor were repeated if the patient experienced palpitations or every six months. AF recurrence was defined as atrial fibrillation/atrial flutter or atrial tachycardia lasting ≥ 30 seconds within three months after therapy. **Results** Compared to patients with no AF recurrence, patients with recurrence had longer AF history ($P = 0.007$), more early recurrence ($P = 0.000$), a larger left atrium ($P = 0.004$), and higher pre-ablation cystatin C levels ($P = 0.000$). Multivariate regression analysis revealed that cystatin C and left atria (LA) diameter were risk factors for AF recurrence. After adjusting for LA diameter, the risk of AF recurrence increased 30% with every milligram cystatin C elevation (95% CI: 1.117–1.523). **Conclusions** Pre-ablation cystatin C levels were associated with AF recurrence after RFCA therapy, an optimal cut-off value of 1.190 mg/L (sensitivity = 0.576; specificity = 0.851).

J Geriatr Cardiol 2018; 15: 725–731. doi:10.11909/j.issn.1671-5411.2018.12.008

Keywords: Atrial fibrillation; Catheter ablation; Cystatin C; Recurrence

1 Introduction

Atrial fibrillation (AF) is a common supraventricular cardiac arrhythmia in clinical practice, with high morbidity and mortality.[1,2] Treatments commonly include multiple choices to reach either rate or rhythm controls.[3,4] In addition to control pharmacological antiarrhythmic medications, radiofrequency catheter ablation (RFCA) therapy is a recommended treatment option for symptomatic and drug-refractory AF.[5] However, AF recurrence after RFCA therapy is still a problem nowadays.[6] Previous studies demonstrated that various factors, including myocardial injury markers, inflammatory factors, and atrial structural remodeling could predict patients with a high risk for recurrence after ablation therapy.[7–9] Further investigations are required to determine factors that could predict AF recurrence after ablation therapy, to select appropriate treatment options for these patients.[10]

Cystatin C is a cysteine protease inhibitor and mainly produced by macrophages and dendritic cells during inflammation.[11] Recent studies have demonstrated that cystatin C is a better risk marker than creatinine-based estimates of glomerular filtration for cardiovascular disease morbidity and mortality.[12,13] Therefore, we hypothesized that the pre-ablation level of cystatin C is associated with the post-ablation recurrence of AF. This finding has not been previously reported to the best of our knowledge.

In this study, we investigated whether pre-ablation cystatin C levels are associated with the AF recurrence after RFCA therapy.

2 Methods

2.1 Study design

The study was a prospective observational study, involving 207 patients with paroxysmal ($n = 98$) and persistent AF

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Received: September 6, 2018 **Revised:** November 13, 2018
Accepted: November 19, 2018 **Published online:** December 28, 2018

(n = 109) between April 2013 and May 2018, and was performed at an urban academic hospital. The study protocol was approved by the hospital ethics committee, and all study participants signed informed consent.

The inclusion criteria was as follows: (1) symptomatic paroxysmal (self-terminated within seven days) or persistent (≥ 7 days) AF; (2) never received RFCA therapy before, and they were refractory to antiarrhythmic drugs; and (3) decided by primary treating physicians to receive RFCA therapy.

The exclusion criteria was as follows: (1) moderate or severe cardiac valvular disease; (2) acute myocardial infarction or acute coronary syndrome; (3) hepatic (transaminase is ≥ 3 fold the normal value) or renal insufficiency (glomerular filtration rate ≤ 30 mL/min); (4) contraindication to anticoagulation; (5) uncontrolled thyroid dysfunction; (6) left atrial diameter > 50 mm (in PLAX view) under echocardiography examination; and (7) severe heart failure (left ventricular ejection fraction < 30%).

2.2 Study protocol

After the informed consent process, patients' baseline characteristics of age, gender, medical history, and medication intakes were recorded. AF was confirmed with electrocardiogram or 24 h holter monitor. Cardiac functions and left atrial appendage thrombosis were assessed by transesophageal echocardiography. Serum cystatin C levels were measured by latex immunoturbidimetric assays (Hitachi, Japan, 008AS). Serum creatinine levels were measured by Jaffe's assay (Roche, USA, Cobas8000). In addition, high-sensitivity C-reactive protein (hs-CRP) was measured using immunoturbidimetric assay (Roche, USA, Cobas8000).

All patients underwent CT examination before ablation to clarify the size and structure of the left atrium and the shape of the pulmonary veins. In the 3D CARTO system, the model of left atrium and pulmonary veins was quickly established using Lasso or PentaRay (FAM). Then, we merged the model with the CT map. According to the merged 3D map and X-ray images, the ostia of pulmonary veins were determined. The ablation site which we chose needed to meet the following requirements: 0.5–1.0 cm away from the ostia of the pulmonary veins in the atrial side, and we could detect the endocardial potential and pulmonary vein potential.

Circumferential pulmonary vein isolation was conducted under sedation using fentanyl citrate. RFCA therapy was performed by first puncturing the left or right femoral vein with Seldinger technique. A steerable electrode catheter (BARD, USA) was introduced to the coronary sinus. Then, a 6-F PACEL bipolar pacing catheter (St. Jude Medical, USA) was placed into the right ventricle. Thermocool Smarttouch (3.5 mm, spacing 1-6-2, Biosense Webster, USA) was used as the irrigated-tip catheter during pulmonary vein isolation. We also used Lasso (Biosense Webster) or PentaRay (Biosense Webster) to confirm the isolation of each pulmonary vein. Radiofrequency energy was released to every site at a power of 30 Watts. The irrigation rates were 17 mL/min. Blood pressure, finger pulse oxygen saturation, and electrocardiogram were monitored during the entire procedures.

After RFCA therapy, all patients received electrocardiogram to confirm their normal sinus rhythm. Then, all patients were invited to come back to the outpatient clinic every week for the first month, and then at 2, 3, 6, 9, and 12 months. Thereafter, patients came back to outpatient clinic every six months until the patient was lost to follow-up or dead. Patients received an electrocardiogram and 24 h holter monitor examination if symptoms of palpitations were noted. Those patients with no symptoms received an electrocardiogram and 24 h holter monitor examination every six months. AF recurrence was defined as AF/atrial flutter or atrial tachycardia lasting ≥ 30 s within three months after RFCA therapy.

2.3 Statistical analysis

Continuous variables were presented as the mean ± SD. Categorical variables were presented as percentage (%). The independent sample t-test or Mann-Whitney U test was used to compare continuous variables between two groups depending on normality test results. The chi-square test was used to compare categorical variables between groups. Correlation analyses between cystatin C level and other baseline characteristics were performed using Spearman's rank test. Univariate and multivariate Cox proportional hazards regression analyses were used to identify the predictors for AF recurrence. A receiver operating characteristic (ROC) curve analysis was used to investigate the diagnostic value of cystatin C as the predictive indicator for AF recurrence. The rate of freedom of AF recurrence was determined by Kaplan-Meier (KM) survival curves. Log-rank test was used to confirm the effect of cystatin C on the AF recurrence. A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics, version 16.0.

3 Results

Statistical analysis was performed in 207 patients. During a mean follow-up period of 21.99 ± 8.84 months, 59 patients (28.50%) experienced AF recurrence. Their baseline characteristics are listed in Table 1. Compared with patients

Table 1. Patients' baseline characteristics.

Parameters	Total *n* = 207	Recurrence (+) *n* = 59	Recurrence (-) *n* = 148	*P*
Clinical Parameters				
Gender, male	118 (57.00%)	32 (54.24%)	86 (58.11%)	0.612
Age, yrs	59.69 ± 9.39	60.14 ± 7.06	59.51 ± 10.19	0.777
History of CAD,	21 (10.14%)	4 (6.78%)	17 (11.49%)	0.449
Hypertension,	104 (50.24%)	35 (59.32%)	69 (46.62%)	0.099
Diabetes	32 (15.46%)	11 (18.64%)	21 (14.19%)	0.424
Smoking	47 (22.71%)	16 (27.12%)	31 (20.95%)	0.339
Alcohol	34 (16.43%)	12 (20.34%)	22 (14.86%)	0.337
HR	82.96 ± 20.94	82.95 ± 22.76	82.97 ± 20.24	0.720
AF history; yrs	39.35 ± 54.98	51.47 ± 64.92	34.52 ± 49.91	0.007*
Persistent AF	109 (2.66%)	34 (57.63%)	75 (50.68%)	0.366
Statins	56 (27.05%)	15 (25.42%)	41 (27.70%)	0.739
ACEI/ARB	29 (14.01%)	10 (16.95%)	19 (12.84%)	0.442
Echocardiography Parameters				
LA diameter, mm	44.06 ± 1.71	40.14 ± 5.19	37.89 ± 5.03	0.004*
LVEF	59.91 ± 5.89	58.85 ± 6.65	60.34 ± 5.53	0.079
Laboratory Parameters				
WBC, $\times 10^9$	6.41 ± 1.42	6.60 ± 1.40	6.34 ± 1.43	0.211
NE, $\times 10^9$	3.90 ± 1.28	4.11 ± 1.33	3.82 ± 1.26	0.104
LY, $\times 10^9$	1.87 ± 0.56	1.79 ± 0.57	1.90 ± 0.55	0.137
Cystatin C, mg/L	1.34 ± 0.70	1.41 ± 1.25	1.02 ± 0.19	0.000*
Serum creatinine, μmol/L	71.19 ± 16.39	74.79 ± 17.98	69.76 ± 15.54	0.081
Hs-CRP, mg/L	3.11 ± 4.84	3.15 ± 3.68	3.10 ± 5.24	0.535
Cystatin C, quartiles (Qs)				
Q1: < 0.93	51 (24.64%)	8 (13.56%)	43 (29.05%)	0.020*
Q2: 0.93–1.07	54 (26.09%)	10 (16.95%)	44 (29.73%)	0.059
Q3: 1.08–1.20	51 (24.64%)	10 (16.95%)	41 (27.70%)	0.105
Q4: > 1.20	51 (24.64%)	31 (52.54%)	20 (13.51%)	0.000*
Follow-up Parameters				
Early recurrence	36 (17.39%)	14 (23.73%)	12 (8.18%)	0.000*

Values are presented as means ± SD or *n* (%), *$P < 0.05$. ACEI: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; CAD: coronary artery disease; HR: heart rate; Hs-CRP: high sensitivity C-reactive protein; LA: left atrium; LVEF: left ventricular ejection fraction; LY: lymphocyte count; NE: neutrophils count; Qs: quartiles; WBC: white blood cell count.

in the non-recurrence group, patients in the recurrence group exhibited more early recurrence, longer AF history, larger left diameters and higher cystatin C levels. We divided cystatin C into four levels according to quartiles. Significant differences were noted between the non-recurrence group and recurrence group in Q1 and Q4.

Table 2 presented the results from Spearman rank correlation analysis. Pre-ablation cystatin C level was associated with demographic characteristics (age, gender), medical history (hypertension and persistent AF history), cardiac structure (left atrial diameter), and renal function index (creatinine).

Results from univariate and multivariate Cox proportional hazards regression analyses are presentedin Table 3. Left atrial diameter diameters, hypertension and cystatin C were correlated with the AF recurrence in the univariate regression analysis. However, in the multivariate regression analysis, both cystatin C (HR: 1.304; 95% CI: 1.117–1.523) and left atrial diameter diameters (HR: 1.081; 95% CI: 1.027–1.137) were risk factors for the AF recurrence. The risk of AF recurrence increased 30% with every milligram increase in cystatin C levels.

Figure 1 presents the ROC curve of cystatin C. The AUC (area under the curve) was 0.740 (95% CI: 0.658–0.821; $P = 0.000$), with an optimal cut-off value of 1.190 mg/L (sensitivity = 0.576, 1-specificity = 0.149). The KM analysis

Table 2. Spearman rank correlations analysis between cystatin C and patients' baseline characteristics.

Baseline characteristics	Correlation Coefficient	*P*	Baseline characteristics	Correlation Coefficient	*P*
Gender	0.223	0.001*	Persistent AF	0.230	0.001*
Age	0.250	0.000*	Statins	0.138	0.047
History of CAD	–0.012	0.863	ACEI/ARB	0.078	0.264
Hypertension	0.259	0.000*	LA diameter	0.277	0.000*
Diabetes	0.102	0.142	LVEF	–0.217	0.002
Smoking	0.199	0.004	WBC, $\times 10^9$	0.002	0.975
Alcohol	0.198	0.004	NE, $\times 10^9$	0.037	0.592
HR	0.050	0.470	LY, $\times 10^9$	–0.085	0.226
AF history	0.012	0.869	Serum creatinine	0.437	0.000*
Early recurrence	0.119	0.086	Hs-CRP	0.103	0.139

Correlation coefficient < 0.2 means very weak correlation or no correlation, *P < 0.05. ACEI: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; CAD: coronary artery disease; HR: heart rate; Hs-CRP: high sensitivity C-reactive protein; LA: left atrium; LVEF: left ventricular ejection fraction; LY: lymphocyte count; NE: neutrophils count; WBC: white blood cell count.

Table 3. Univariate and multivariate proportional hazards regression results of AF recurrence after PV isolation.

Parameters	Univarite model			Multivarite model		
	HR	95% CI	*P*	HR	95% CI	*P*
Clinical parameters						
Gender	1.001	0.596–1.682	0.997			
Age	1.006	0.979–1.034	0.674			
History of CAD	0.564	0.204–1.564	0.271			
Hypertension	1.801	1.056–3.072	0.031*			
Diabetes	1.278	0.684–2.389	0.442			
Smoking	1.333	0.749–2.371	0.328			
Alcohol	1.604	0.849–3.032	0.145			
HR	0.999	0.987–1.011	0.872			
AF history	1.003	1.000–1.007	0.089			
Persistent AF	1.373	0.818–2.304	0.230			
Statins	0.985	0.547–1.775	0.960			
ACEI/ARB	1.300	0.657–2.570	0.451			
Echocardiography parameters						
LA diameter	1.073	1.020–1.127	0.006*	1.081	1.027–1.137	0.003*
LVEF	0.963	0.929–0.998	0.040			
Laboratory parameters						
WBC, $\times 10^9$	1.095	0.917–1.308	0.315			
NE, $\times 10^9$	1.131	0.940–1.361	0.192			
LY, $\times 10^9$	0.668	0.399–1.118	0.125			
Cystatin C	1.238	1.072–1.430	0.004*	1.304	1.117–1.523	0.001*
Serum creatinine	1.014	0.999–1.029	0.059			
Hs-CRP	0.998	0.947–1.051	0.931			
Follow-up parameters						
Early recurrence	1.576	0.863–2.877	0.139			

Dependent value was defined as AF recurrence, *P < 0.05. ACEI: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; CAD: coronary artery disease; CI: confidence interval; HR: heart rate; Hs-CRP: high sensitivity C-reactive protein; LA: left atrium; LVEF: left ventricular ejection fraction; LY: lymphocyte count; NE: neutrophils count; WBC: white blood cell count.

revealed that patients with lower baseline cystatin C levels presented a significantly increased freedom of AF recurrence rates after RFCA in Figure 2. (Log-rank $P = 0.000$).

4 Discussion

The current study demonstrated that patients with higher

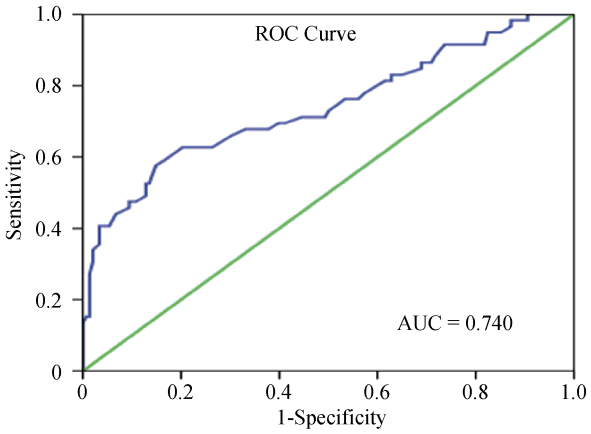

Figure 1. ROC curve of baseline level of cystatin C for predicting AF recurrence after RFCA. The cur-off level is 1.190 mg/mL, the sensitivity is 0.576 and the specificity is 0.851. AF: atrial fibrillation; RFCA: radiofrequency catheter ablation; ROC: receiver operating characteristic.

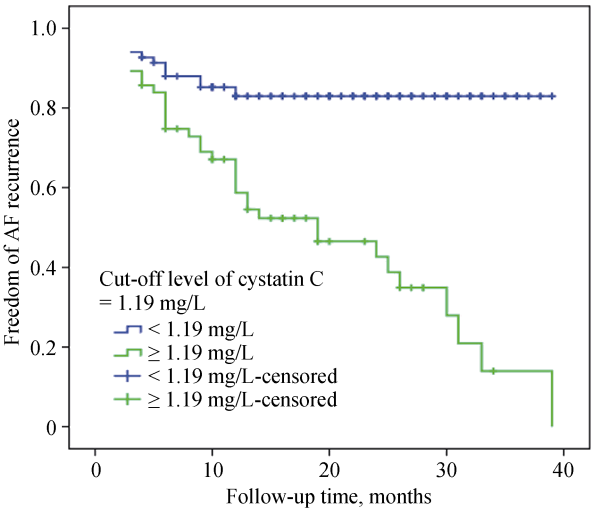

Figure 2. Kaplan-Meier curve for freedom of AF recurrence based on the baseline levels of cystatin C. AF: atrial fibrillation.

pre-ablation cystatin C levels were at increased risk for AF recurrence after radiofrequency catheter ablation therapy. We analysed cystatin C based on quartiles. We found that the lower the cystatin C level was, the less likely AF was to recur. With increased cystatin C levels, the number of recurrent patients increased, significantly. KM survival curves revealed that patients with lower baseline cystatin C levels (<cut-off level = 1.190 mg/L) presented a reduced AF recurrence rates after RFCA.

Compared with the patients in the non-recurrence group, patients in the recurrence group exhibited more early recurrence. It is generally believed that reconnection of PV-LA is the main mechanism of AF recurrence after RFCA. Early recurrence indicates PV-LA reconnection. However, in Cox regression model, early recurrence was not correlated with AF recurrence.

Previous studies have demonstrated that cardiac function impairment and structural remodeling are the risk factors for AF recurrence after RFCA therapy.[14] Our study demonstrated that cystatin C level and left atrial (LA) diameter were correlated with AF recurrence. We put all of the variables into the multivariable proportional hazards regression model, cystatin C and LA diameter were the only two risk factors for AF recurrence. Our correlation analysis revealed that serum cystatin C was associated with LA diameter, persistent AF and hypertension. It is well known that persistent AF and hypertension have negative effects on the atrial structure. We found that compared with the patients in the non-recurrence group, patients in the recurrence group had a longer AF history. The longer the AF history was, the more adverse effect on the left atrium. Enlarged LA is considered to be closely related to AF recurrence. Atrial structure remodeling typically occurs after myocardial cell injury and it is accompanied by inflammations. Cystatin C is mainly produced by nucleated cells during inflammations.[11] Inflammation increases the risk for AF recurrence after ablation.[15,16] The relationship between LA remodeling and inflammatory markers is complex, including apoptosis, atrial fibrosis, calcium handing abnormalities, gap junction modulation, connexin dysregulation and so on.[17] It is believed that inflammatory markers are associated with AF recurrence.[15] Cystatin C is an inflammatory marker which is mostly produced by macrophages and dendritic cells.[11] As one of the markers of systemic inflammation, cystatin C participates in atrial remodeling and it plays an adverse role in the myocardium. Changes in cystatin C levels are generally more easily detected by biomedical assays compared with changes in cardiac structure detected by imaging studies. Pre-ablation cystatin C level might be used as a marker which is more sensitive than cardiac structural changes, to predict post- ablation AF recurrence. However, a Mendelian randomization study showed that therapeutics targeted at lowering circulating cystatin C were unlikely to be effective in preventing cardiovascular disease.[18]

Cystatin C levels are also affected by gender and age.[19] In our study, we observed the correlation between age and cystatin C level; with elderly patients exhibiting increased cystatin C level. A previous study demonstrated that age could be a predictor for the AF recurrence.[20] Researchers found that patients exhibited an age related, but heterogeneous decline in cystatin C derived renal function; and the ageing effect was more pronounced in men.[21] However, in our regression model, gender and age were not correlated

with AF recurrence.

Cystatin C level is considered to be a marker for renal function. Correlation analysis revealed the relationship between serum cystatin C and creatinine levels (correlation coefficient = 0.437). However, no statistically significant differences between creatinine levels were noted between patients with or without AF recurrence. Regression analysis also showed no relationship between AF recurrence and serum creatinine level. Contrary to previous research conclusions demonstrating that renal insufficiency were an important factor for the prediction of rhythm outcomes in patients with atrial fibrillation, especially in patients with an estimated GFR < 60 mL/min.[22,23] Our results may be due to the fact that creatinine could not represent the real renal function, and most of the patients in this study had normal renal function.

Cystatin C is an index of inflammation as well as renal function.[24] It has been found that in peripheral arterial disease patients with normal renal function, cystatin C was related with all-cause and cardiovascular mortality.[25] This finding may be attributed to the fact that cystatin C is less affected by other factors, such as age and gender than GFR.[26] Recently, some researchers have combined cystatin C with GFR as one observational index: cystatin C estimated GFR. One study demonstrated[27] that reducing cystatin C estimated GFR was related with cardiovascular and all-cause mortality. However, therapeutics aimed to reduce circulating cystatin C levels was unlikely to be functional in preventing cardiovascular disease.[19]

4.1 Limitations

The limitations of the current study include that it was a single centre study with a small sample size. We repeated 24 h holter monitor for patients without symptoms at 6 months and 12 months, regularly. This timing might miss the detection of AF recurrence in these patients with asymptomatic AF and paroxysmal AF. If the patient experienced palpitations, he/she underwent the holter monitor immediately at the nearest hospital. Due to economic reasons, some of the patients with symptoms selected to undergo ECG examination instead of 24 h holter minitor. However, unfortunately, the ECG results that patients may not have captured AF recurrence. There must be a 12-lead ECG or 24 h holter monitor evidence for each patient with recurrence in our study. Therefore, the AF recurrence rate in this study was likely to be lower than the actual situation.

4.2 Conclusions

To sum up, our study demonstrated that pre-ablation cystatin C levels were associated with AF recurrence after RFCA with an optimal cut-off value of 1.190 mg/L. Cystatin C might be more sensitive than cardiac structure changes or other inflammatory markers to predict AF recurrence after ablation.

Acknowledgments

All authors report no conflicts of interest, this work was supported by major research and development projects in Hebei province (17277729D).

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