RENAL FAILURE
2025, VOL. 47, NO. 1, 2466824
https://doi.org/10.1080/0886022X.2025.2466824

Taylor & Francis
Taylor & Francis Group

CLINICAL STUDY

The association between the cystatin C- and creatinine-based estimated GFR ratio and post-ablation outcomes in patients with atrial fibrillation

Wenchao Huang[a], Luxiang Shang[b,c], Yan Luo[a], Shiqiang Xiong[a], Shuwei Suo[a], Zhen Zhang[a], Hanxiong Liu[a] and Huaxin Sun[a]

[a]Department of Cardiology, The Third People's Hospital of Chengdu, Chengdu, Sichuan, China; [b]Department of Cardiology, The First Affiliated Hospital of Shandong First Medical University and Shandong Provincial Qianfoshan Hospital, Shandong Medicine and Health Key Laboratory of Cardiac Electrophysiology and Arrhythmia, Jinan, Shandong, China; [c]Medical Science and Technology Innovation Center, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, Shandong, China

ABSTRACT

Background: The difference between the cystatin C-based eGFR (eGFRcys) and the creatinine-based eGFR (eGFRcr) is associated with the risk of developing atrial fibrillation (AF) risk. However, its impact on AF ablation outcomes is unknown.

Methods: The associations between the baseline eGFR ratio (eGFRcys/eGFRcr) and the risk of experiencing post-ablation endpoints were evaluated on a continuous scale (restricted cubic splines) and by a priori defined centile categories with Cox proportional hazards regression models. The primary endpoints were AF recurrence and adverse events; the secondary endpoint was rehospitalization.

Results: Among 989 participants (49.2% women; mean age 65.7 years), 313 experienced AF recurrence after a median follow-up of 28 months. After full adjustment for confounding factors, a U-shaped association was observed between eGFR ratio and AF recurrence risk (minimum risk at 0.797). Although a U-shaped trend was observed, there was no statistically significant association between the eGFR ratio and adverse events or rehospitalization. Hazard ratios for AF recurrence, compared to the second quartile, were 1.68 (1.20–2.37) for the first quartile, 1.64 (1.15–2.34) for the third quartile, and 1.96 (1.37–2.80) for the fourth quartile. According to the subgroup analysis, the above association was strongly U-shaped for males and linear for females.

Conclusion: In the AF population, both low and high eGFR ratios were associated with an increased risk of post-ablation AF recurrence.

ARTICLE HISTORY
Received 11 October 2024
Revised 5 February 2025
Accepted 9 February 2025

KEYWORDS
Atrial fibrillation; ablation; estimated glomerular filtration rate; cystatin C; creatinine

1. Introduction

Atrial fibrillation (AF) is the most common persistent arrhythmia, with an estimated global prevalence of 50 million in 2020, and its incidence and prevalence are increasing worldwide [1]. There are two major problems associated with AF: symptoms that affect quality of life and serious cardiovascular events such as ischemic stroke, congestive heart failure, and mortality [2]. Given the known association between the maintenance of sinus rhythm and survival [3], catheter ablation as a rhythm control strategy can not only improve the symptoms of patients [4] but also reduce the incidence of adverse cardiovascular events [5–7]. However, the precise factors and mechanisms contributing to poor prognosis remain unclear.

The co-occurrence of AF and chronic kidney disease is associated with poor prognosis, including a higher rate of postoperative recurrence [8], adverse events [9] and readmission [10]. Currently, serum creatinine is widely used as a marker of renal function in clinical practice. However, several studies have shown that the cystatin C-based eGFR (eGFRcys) is more strongly associated with incident AF than is the creatinine-based eGFR (eGFRcr) [11,12]. Malmgren et al. [13] suggest that if only creatinine-based GFR-estimating equations are used, a significant number of patients with severe kidney disorders will be missed, which may have serious health implications. Interestingly, the creatinine/cystatin C ratio is useful for describing the muscle mass of different patient groups to identify sarcopenia and frailty [14–16].

CONTACT Hanxiong Liu clin999@163.com Department of Cardiology, The Third People's Hospital of Chengdu, Chengdu Cardiovascular Disease Research Institute, 82 Qinglong St., Chengdu, Sichuan, China; Huaxin Sun gracekelly1994@163.com Department of Cardiology, The Third People's Hospital of Chengdu, Chengdu Cardiovascular Disease Research Institute, 82 Qinglong St., Chengdu, Sichuan, China

Supplemental data for this article can be accessed online at https://doi.org/10.1080/0886022X.2025.2466824.

Furthermore, recent studies have shown that the eGFRcys/eGFRcr ratio (eGFR ratio) is associated with the risk of experiencing poor prognosis in HF [17] and cardiac surgery [18] patients and an increased risk of right ventricular systolic dysfunction [19], which is a significant predictor of AF development [20]. On the other hand, a large prospective cohort study showed that the difference between the eGFRcys and eGFRcr was associated with the risk of developing AF [21]. Despite these associations, no previous study has explored the relationship between the eGFR ratio and AF ablation prognosis. Therefore, we investigated the associations between the eGFR ratio and the risk of experiencing long-term recurrence, AF-related adverse events and rehospitalization after AF ablation.

2. Methods

2.1. Study population

We performed a single-centre, prospective, observational cohort study of consecutive patients with drug-refractory AF who underwent radiofrequency ablation for the first time at the Third People's Hospital of Chengdu (Sichuan, China) from July 2017 to February 2023. Patients were excluded if they (1) were aged less than 18 years; (2) had a history of AF ablation; (3) had left atrial appendage thrombosis or other absolute contraindications for catheter ablation; (4) had AF caused by reversible or pathological factors, including but not limited to hyperthyroidism, acute alcoholism, electrolyte disturbance, drugs, and cardiac surgery; or (5) had left ventricular dysfunction (<30%) or severe cardiac valvular disease. Patients with incomplete key variables, including cystatin C and creatinine concentrations, were also excluded. A total of 32 patients were excluded because of missing follow-up data despite at least five separate attempts to contact them. Ultimately, 989 patients were included in the final analyses. This study was approved by the local institutional review boards and strictly complied with the Declaration of Helsinki. Informed consent was obtained from all patients.

2.2. Ablation strategy and follow-up

All patients were given anticoagulation therapy, and left atrial thrombosis was excluded by transoesophageal echocardiography. All patients underwent ablation under general anesthesia using a three-dimensional imaging system (CARTO-3 system, Version 6) with continuous intraoperative monitoring of vital signs. Patients with paroxysmal AF underwent circumferential ablation along the left and right pulmonary veins, achieving conduction block between the pulmonary veins and the atrium. Adjuvant left atrium ablation beyond pulmonary vein isolation was allowed in persistent AF patients. Ablation was performed using 50-W power for pulmonary vein isolation and left atrium ablation, while 40-W power was used for cavotricuspid isthmus ablation if needed.

Anticoagulation therapy with new oral anticoagulants or warfarin was continued for at least 3 months if there was no contraindication. To reduce the recurrence rate, all patients were asked to take antiarrhythmic drugs for 3 months if there were no contraindications. During the blanking period (within 3 months after ablation), no further ablation was performed. All patients were regularly followed-up at 3, 6, and 12 months after ablation by outpatient follow-up physicians who were blinded to the study design, were monitored by 24-h Holter electrocardiogram, and were asked about any symptoms associated with arrhythmia. When patients had symptoms suggestive of arrhythmia, 24-h Holter monitoring at the nearest hospital is strongly recommended as soon as possible.

2.3. Formulas for estimating the glomerular filtration rate

Serum samples were obtained at baseline. Cystatin C and serum creatinine concentrations were detected by using a COBAS automatic biochemical analyzer (Roche Diagnostics, Basel, Switzerland) before the procedure. We calculated the eGFRcr using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation with race coefficients [22]. eGFRcys were calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2012 equation [23]. The exposure of interest was the baseline eGFR ratio.

2.4. Assessment of endpoints

The primary endpoints were post-ablation AF recurrence and adverse events, and the secondary endpoint was rehospitalization after ablation. AF recurrence was defined as the occurrence of atrial tachycardia (AT) or AF events lasting over 30 s after a single procedure, excluding recurrence during the blanking period. Adverse events included heart failure, stroke, and cardiogenic death after ablation. Endpoints were assessed from the first assessment date to the date of death or the last follow-up visit. All patients were followed-up for at least 1 year after the procedure.

2.5. Assessment of covariates

Analyses were adjusted for covariates that might confound the association between the eGFR ratio and the risk of primary endpoints, including sex, age (in years), body mass index (calculated as weight in kilograms divided by height in meters squared), AF type, duration from AF diagnosis to ablation, fasting blood glucose concentrations, triglyceride concentrations, cholesterol concentrations, brain natriuretic peptide concentrations, left ventricular ejection fraction, left atrial diameter, antiarrhythmic drug use status, oral anticoagulant drug use status, high blood pressure status, diabetes status, and history of vascular disease (peripheral artery disease or coronary heart disease), chronic obstructive pulmonary disease, congestive heart failure, stroke, and dyslipidaemia.

2.6. Statistical analysis

The baseline characteristics are presented as the mean and standard deviation for continuous variables and as numbers

and percentages for categorical variables in different subgroups stratified by quartiles of the eGFR ratio. Multivariate Cox proportional hazards regression models adjusted for potential confounders were used to estimate hazard ratios (HRs) for endpoints associated with the eGFR ratio. We used restricted cubic spline models fitted for univariate Cox proportional hazards models to examine the nonlinear or irregular shapes of the hazard functions. If the associations between endpoints were nonlinear, we further analyzed the variables using restricted cubic spline curves based on multivariate Cox proportional hazards models. Knots between 3 and 7 were selected as the lowest value for the Akaike information criterion.

To further evaluate the effects of the eGFR ratio on the endpoints of interest, Kaplan–Meier curves of event-free patients in the four groups were plotted and then compared with the log-rank test. We used multivariate Cox proportional hazards to estimate the HRs and 95% confidence intervals (CIs) of the different groups at the endpoints of interest compared with those of the reference group. Furthermore, we conducted post-hoc subgroup analyses to explore potential effect modification by sex, age, and the presence of hypertension or diabetes in the associations between clinical endpoints and the eGFR ratio. Statistical analyses were performed using R (version 4.3.1; R Foundation, Vienna, Austria). A value of $p < 0.05$ (two-tailed) was considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics of the study cohort

The study included 989 individuals with a mean age of 65.7 ± 10.6 years, 49.2% (487/989) of whom were female. According to the eGFR quartiles, the patients were divided into Q1 (eGFR ratio < 0.715), Q2 (0.715 ≤ eGFR ratio < 0.818), Q3 (0.818 ≤ eGFR ratio < 0.930), and Q4 (eGFR ratio ≤ 0.930) groups. Table 1 shows the baseline characteristics of the participants according to the eGFR ratio categories. The eGFR ratio ratios were 0.63 ± 0.07, 0.77 ± 0.03, 0.87 ± 0.03 and 1.03 ± 0.10 in the four subgroups, respectively. During a median follow-up of 28 months (IQR 17–42), AF recurrence was detected in 318 (32.2%) of 989 patients, and 671 (67.8%) were free from AF. The APPLE score, as a predictive model for AF recurrence, showed a decreasing trend among the four subgroups, which means that the probability of AF recurrence inferred from common risk factors gradually decreased.

3.2. Association between the eGFR ratio and the risk of experiencing the endpoints

When we transformed the eGFR ratio as the categorical variable according to its quartered distribution (Q1, eGFR ratio <0.715; Q2, 0.715 ≤ eGFR ratio <0.818; Q3, 0.818 ≤ eGFR ratio <0.930; Q4, eGFR ratio ≤ 0.930), we employed Cox proportional hazards model to evaluate the stratification effect of eGFR ratio on AF recurrence. As shown in Table 2, the AF recurrence increased with the incremental quartile of eGFR ratio with or without adjusting the additional covariates ($p < 0.001$). We found U-shaped associations between the eGFR ratio and the risk of AF recurrence ($p < 0.001$) and adverse events ($p = 0.041$) but no significant nonlinear associations between the eGFR ratio and the risk of rehospitalization ($p = 0.115$) (Figure S1 in the Supplementary Materials). Therefore, we further analyzed the associations between the eGFR ratio and the risk of AF recurrence and adverse events by restricted cubic spline models based on multivariate Cox proportional hazards models. As shown in Figure 1, after fully correcting for the previously mentioned covariates, the results showed a statistically significant U-shaped association for the eGFR ratio and the risk of AF recurrence ($p < 0.001$); however, the associations between the eGFR ratio and the risk of adverse events ($p = 0.113$) did not reach statistical significance (Figure S2 in the Supplementary Materials).

3.3. Association between the eGFR ratio and the risk of AF recurrence

Figure 1 shows the inflection points (cutoff values) of the U-shaped curve indicating the lowest risk of AF recurrence, with an eGFR ratio of 0.797 identified as the inflection point after full adjustment for confounding factors. The predicted AF recurrence had a strong U-shaped relationship with the eGFR ratio, and the curve showed that the risk of AF recurrence was significantly reduced for individuals with an eGFR in the lower range. When the eGFR ratio was 0.797, the risk of recurrence was the lowest, and it increased thereafter (nonlinear $p = 0.001$). When the eGFR was greater than 0.797, the HR per standard deviation of the predicted AF ratio was 1.23 (1.07 to 1.41). When the eGFR was lower than 0.797, the HR per standard deviation greater than the predicted lean body mass was 0.83 (0.71 to 0.98). After full adjustment for all covariates, additional adjustments were made for the creatinine and cystatin C concentrations. The eGFR ratio showed a U-shaped relationship with the risk of AF recurrence after adjusting for creatinine concentrations (Figure 2A) and a J-shaped relationship after adjusting for cystatin C concentrations (Figure 2B); therefore, the main outcome did not change.

The cutoff value of the eGFR ratio was 0.797, which was between 0.715 and 0.818; therefore, the second quartile array of the eGFR ratio was used as the reference group. Kaplan–Meier survival curves revealed that the reference group had lower AF recurrence rates than did the other three groups ($p = 0.001$) (Figure 3). Compared with those of the reference group, the HRs (and 95% CIs) for AF recurrence were as follows: first quartile, 1.68 (1.20 to 2.37); third quartile, 1.64 (1.15 to 2.34); and fourth quartile, 1.96 (1.37 to 2.80).

3.4. Association between the eGFR ratio and the risk of AF recurrence in subgroups

According to our subgroup analysis, we observed a strong U-shaped association between the eGFR ratio and the risk of AF recurrence in men. In women, although the eGFR ratio

Table 1. Baseline characteristics of patients with AF based on quartiles of the eGFR ratio.

Parameters	Q1 ($n=248$)	Q2($n=247$)	Q3 ($n=247$)	Q4 ($n=247$)	All ($n=989$)
Demographics					
Age, years	68.2 ± 9.6	67.0 ± 10.7	65.0 ± 10.2	62.7 ± 10.6	65.7 ± 10.6
Female sex, n (%)	109 (44.0)	131 (53.0)	116 (47.0)	131 (53.0)	487 (49.2)
Body-mass index, kg/m^2	24.6 ± 3.4	24.9 ± 3.4	24.7 ± 3.7	24.5 ± 2.9	24.7 ± 3.4
Current Smoker, n (%)	39 (15.7)	31 (12.6)	35 (14.2)	35 (14.2)	140 (14.2)
High alcohol consumption, n (%)	35 (14.1)	25 (10.1)	32 (13.0)	33 (13.4)	125 (12.6)
Duration after AF diagnosis, days	484 (97, 1740)	423 (90, 1508)	700 (92, 1516)	446 (93, 1504)	453 (90, 1556)
Persistent atrial fibrillation, n (%)	133 (53.6)	102 (41.3)	112 (45.3)	103 (41.7)	450 (45.5)
Previous medical history, n (%)					
Hypertension	151 (60.9)	137 (55.5)	131 (53.0)	129 (52.2)	548 (55.4)
Diabetes mellitus	53 (21.4)	47 (19.0)	54 (21.9)	50 (20.2)	204 (20.6)
Vascular disease	42 (16.9)	29 (11.7)	34 (13.8)	37 (15.0)	142 (14.4)
Heart failure	54 (21.8)	46 (18.6)	33 (13.4)	32 (13.0)	165 (16.7)
Previous stroke	21 (8.5)	18 (7.3)	15 (6.1)	15 (6.1)	69 (7.0)
Dyslipidemia	44 (17.7)	53 (21.5)	56 (22.7)	45 (18.2)	199 (20.1)
Chronic obstructive pulmonary disease	10 (4.0)	12 (4.9)	9 (3.6)	5 (2.0)	36 (3.6)
Laboratory data					
Fasting blood glucose, mmol/L	5.4 ± 1.1	5.6 ± 1.7	5.6 ± 1.4	5.6 ± 1.5	5.5 ± 1.5
Brain natriuretic peptide, pg/mL	160 (84, 311)	108 (67, 237)	108 (60, 210)	108 (58, 190)	111 (66, 235)
Creatinine, umol/L	79.0 ± 26.1	73.9 ± 15.6	77.2 ± 17.1	77.1 ± 21.6	76.8 ± 20.6
cystatin C, mg/L	1.36 ± 0.43	1.10 ± 0.17	1.02 ± 0.17	0.90 ± 0.19	1.10 ± 0.31
Blood uric acid, umol/l	388 ± 104	361 ± 87	367 ± 91	344 ± 100	365 ± 97
Cholesterol, mmol/L	4.12 ± 1.09	4.33 ± 0.97	4.23 ± 1.05	4.16 ± 0.98	4.21 ± 1.02
Triglyceride, mmol/L	1.48 ± 0.88	1.43 ± 0.98	1.46 ± 0.77	1.43 ± 0.94	1.45 ± 0.89
Imaging					
Left atrial diameter, mm	42.2 ± 5.4	41.3 ± 5.5	41.2 ± 5.8	40.8 ± 5.7	41.4 ± 5.6
Left ventricular end diastolic diameter, mm	46.1 ± 4.9	45.6 ± 5.0	45.6 ± 4.5	46.4 ± 4.8	45.9 ± 4.8
Left ventricular ejection fraction, %	58.7 ± 5.7	59.4 ± 5.8	59.7 ± 5.4	59.3 ± 5.3	59.3 ± 5.6
Medication at discharge, n (%)					
New oral anticoagulants	198 (79.8)	201 (81.4)	216 (87.4)	199 (80.6)	814 (82.3)
Vitamin K antagonist oral anticoagulant	37 (14.9)	35 (14.2)	28 (11.3)	38 (15.4)	138 (14.0)
Platelet inhibitor	35 (14.1)	31 (12.6)	31 (12.5)	33 (13.4)	130 (13.1)
Class III antiarrhythmic drugs	175 (70.6)	175 (70.9)	163 (66.0)	173 (70.0)	686 (69.4)
Beta blocker	41 (16.5)	35 (14.2)	41 (16.6)	41 (16.6)	158 (16.0)
Calcium channel blocker	9 (3.6)	10 (4.0)	8 (3.2)	13 (5.3)	40 (4.0)
CHA2DS2-VASc score	2.81 ± 1.58	2.63 ± 1.74	2.38 ± 1.59	2.28 ± 1.66	2.53 ± 1.66
APPLE score	1.90 ± 1.05	1.60 ± 1.04	1.58 ± 1.04	1.40 ± 1.10	1.62 ± 1.07
$eGFR_{Cys}$	53.1 ± 13.0	67.4 ± 12.6	75.3 ± 14.2	90.1 ± 19.7	71.5 ± 20.2
$eGFR_{cre}$	84.6 ± 17.6	87.6 ± 15.8	86.5 ± 15.9	87.2 ± 19.2	86.5 ± 17.2
eGFR ratio	0.63 ± 0.07	0.77 ± 0.03	0.87 ± 0.03	1.03 ± 0.10	0.83 ± 0.16

Patients were divided into four groups according to the quartile of eGFR ratio (Q1, eGFR ratio < 0.715; Q2, 0.715 ≤ eGFR ratio <0.818; Q3, 0.818 ≤ eGFR ratio <0.930; Q4, eGFR ratio ≤ 0.930).

Vascular disease, denotes peripheral artery disease or coronary heart disease; CHA2DS2-VASc score, calculated by congestive heart failure, hypertension, age >75, diabetes, stroke or transient ischemic attack, vascular disease, age >65, sex category; APPLE score, calculated by age >65 years, Persistent atrial fibrillation, $eGFR_{cre}$ < 60 mL/min/1.73 m^2, Left atrial diameter ≥43mm, and Left ventricular ejection fraction <50%; eGFR ratio, $GFR_{cys}/eGFR_{cre}$. Abbreviations: AF, atrial fibrillation; $eGFR_{cys}$, estimated glomerular filtration rate based on cystatin C; $eGFR_{cr}$, estimated glomerular filtration rate based on creatinine.

Values are means (±standard deviation) or medians (25th–75th interquartile range).

Table 2. HRs (95% CIs) For AF recurrence according to the eGFR ratio.

Quartile of eGFR ratio	Recurrence, No./Total No.	Hazard ratio (95% CI)			
		Model 1	Model 2	Model 3	Model 4
Q1	95/248	1.80 (1.30 to 2.51)	1.81 (1.30 to 2.53)	1.81 (1.30 to 2.53)	1.68 (1.20 to 2.37)
Q2	56/246	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Q3	80/248	1.60 (1.14 to 2.26)	1.66 (1.18 to 2.34)	1.69 (1.20 to 2.39)	1.64 (1.15 to 2.34)
Q4	87/247	1.79 (1.28 to 2.50)	2.06 (1.44 to 2.92)	2.06 (1.45 to 2.94)	1.96 (1.37 to 2.80)

Patients were divided into four groups according to the quartile of eGFR ratio (Q1, eGFR ratio < 0.715; Q2, 0.715 ≤ eGFR ratio <0.818; Q3, 0.818 ≤ eGFR ratio <0.930; Q4, eGFR ratio ≤ 0.930).

Model 1: Cox proportional hazards model without adjustment; Model 2: Model 1 with adjustment for age, sex and body mass index; Model 3: Model 2 with additional adjustment for comorbidities (hypertension, diabetes, vascular disease, heart failure, previous stroke, dyslipidemia and chronic obstructive pulmonary disease); Model 4: Model 3 with additional adjustment for laboratory measurements (brain natriuretic peptide, fasting blood glucose, triglyceride and cholesterol), imaging parameters (left atrial diameter and ejection fraction), atrial fibrillation type, antiarrhythmic drugs, oral anticoagulants and duration after atrial fibrillation diagnosis. Vascular disease, denotes peripheral artery disease or coronary heart disease.

Abbreviations: AF, atrial fibrillation; eGFR, estimated glomerular filtration rate.

was significantly associated with the risk of AF recurrence, a linear association was observed (Figure 4A). In addition, we observed U-shaped associations between the eGFR ratio and the risk of AF recurrence among participants aged ≥65 years and those aged <65 years (Figure 4B). We also examined the associations stratified by high blood pressure (Figure 4C) and diabetes (Figure 4D). We observed a similar U-shaped association between the eGFR ratio and the risk of AF recurrence

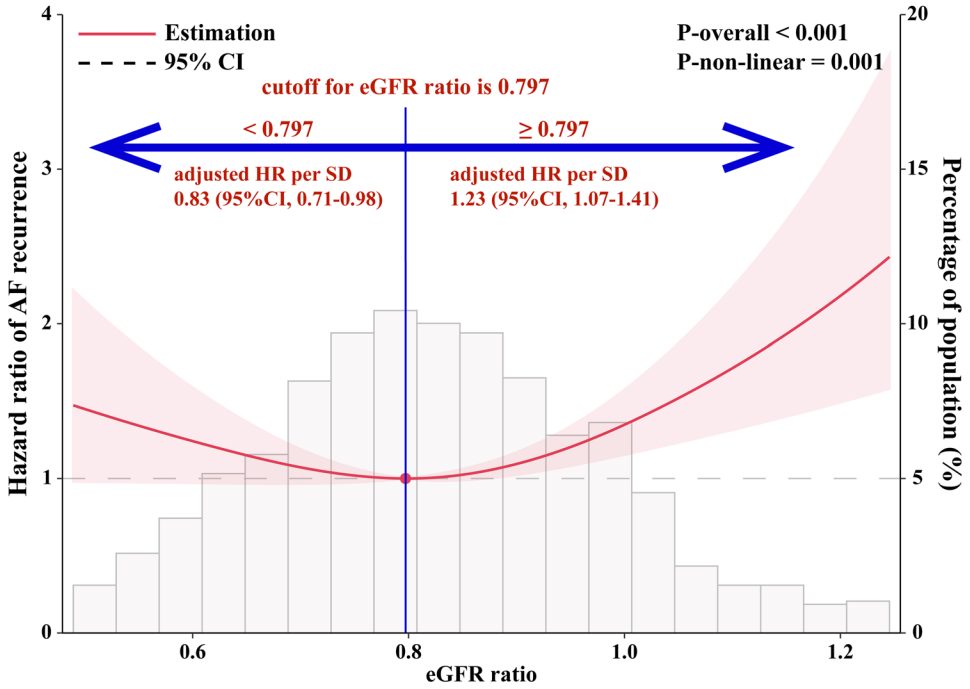

Figure 1. Restricted cubic spline for the associations between the eGFR ratio and the risk of experiencing AF recurrence.
The results are presented as hazard ratios (HRs, solid lines) and 95% confidence intervals (CIs, light red areas) after multivariate adjustment for all the covariates, including sex, age, body mass index, AF type, duration from AF diagnosis to ablation, fasting blood glucose, triglyceride, cholesterol, brain natriuretic peptide, left ventricular ejection fraction, left atrial diameter, antiarrhythmic drugs, oral anticoagulants, high blood pressure, diabetes, and history of vascular disease, chronic obstructive pulmonary disease, congestive heart failure, stroke, and dyslipidaemia. The knots were set at the 10th, 50th, and 90th percentiles of the eGFR ratio. The histograms represent the distribution of the eGFR ratio in our study. Abbreviations: AF, atrial fibrillation.

across the four subgroups. On the other hand, we observed a stronger U-shaped association between the eGFR ratio and the risk of AF recurrence in patients with diabetes than in those without diabetes.

4. Discussion

In this single-centre prospective study, after full adjustment for identified confounders, we found a U-shaped association between the preoperative eGFR ratio and the risk of AF recurrence after a single radiofrequency ablation, with both low and high eGFR ratios associated with increased risk. The eGFR ratio associated with the lowest risk of AF recurrence was 0.797. In addition, we investigated this association among different subgroups of participants, the results further indicated a strong U-shaped association between the eGFR ratio and the risk of AF recurrence in male patients but a positive linear association in female patients. This finding suggests that the eGFRcys and eGFRcr are influenced by nonrenal factors and that their ratio is a useful marker for identifying individuals at greater risk of post-ablation AF recurrence.

Although creatinine is currently the most commonly used biomarker to assess the glomerular filtration rate in clinical practice, its limitations include its susceptibility to factors other than the kidney and the considerable amount of creatinine excreted by the renal tubules [13]. Therefore, cystatin C has received extensive attention as an alternative marker, and as a marker of the GFR, cystatin C is commonly superior to creatinine [24]. Because cystatin C and creatinine are often analyzed separately, the individual differences in eGFRcys and eGFRcr, which have been ignored for a long time in the past, are now gradually attracting increasing attention in various diseases. Previous studies have shown that individual differences in the eGFRcys and eGFRcr are closely related to heart failure [25], frailty [26] and death [27] and can also be used to predict the risk of contrast-associated acute kidney injury [28]. Although there are many studies on the relationship between renal function and the risk of AF, most of them have not focused on the impact of cystatin C on this relationship, especially the impact of the differences between eGFRcys and eGFRcr. Recently, a large cohort study showed that the difference between the eGFRcys and eGFRcr was associated with the risk of developing AF, and the difference was greater with a lower risk of developing AF [21]. The eGFR ratio is strongly associated with differences in the eGFRcys and eGFRcr, so it is understandable that the results of this study showed that the eGFR ratio was independently associated with the risk of post-ablation AF recurrence.

Grubb et al. [19] reported a low eGFR ratio (≤0.6) as 'shrunken pore syndrome' to explain the possible causes of the abnormal components of glomerular filtration fluid and the corresponding changes in plasma levels of some proteins. Shrunken pore syndrome is associated with long-term mortality and morbidity in patients [29,30], even in the absence of a reduced GFR [31], and these poor outcomes predominantly manifest as cardiovascular disease. Consistently, the results of this study revealed that an eGFR

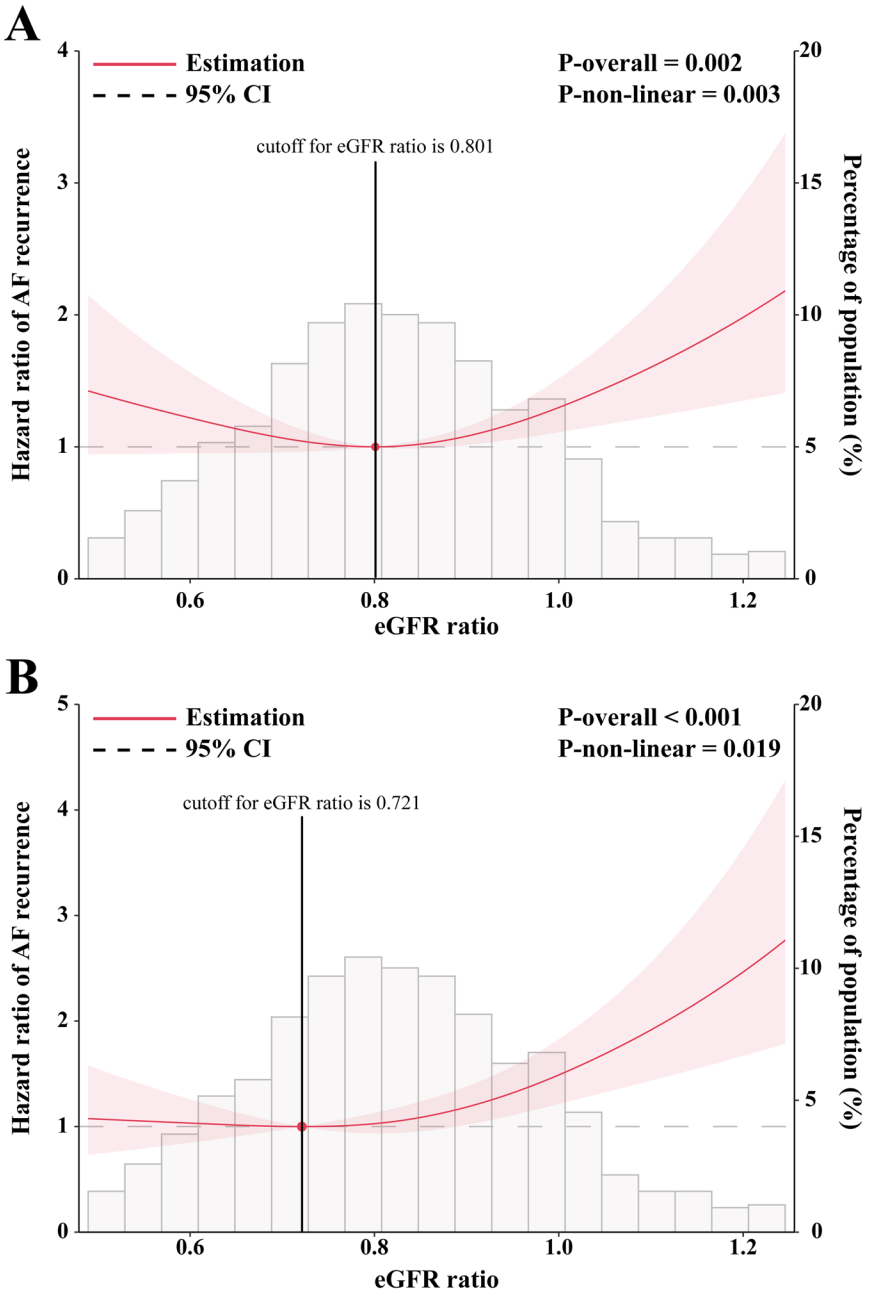

Figure 2. Restricted cubic spline for the associations between the eGFR ratio and the risk of AF recurrence after additional adjustment for (A) creatinine and (B) cystatin C concentrations.
The results are presented as hazard ratios (HRs, solid lines) and 95% confidence intervals (CIs, light red areas), with additional adjustment for creatinine concentrations (A) and cystatin C concentrations (B), respectively, after full adjustment for all covariates. The histograms represent the distribution of the eGFR ratio in our study. Abbreviations: AF, atrial fibrillation.

ratio ≤ 0.6 was independently associated with a higher AF recurrence rate, and the association remained after adjusting for creatinine and cystatin C concentrations separately. Several potential mechanisms could explain the observed association between shrunken pore syndrome and the risk of AF recurrence, attributed to decreased left ventricular contraction, which are associated with the risk of AF recurrence [32,33]. However, a decreased pore size is not the only possible mechanism leading to a reduced eGFR ratio. Oberg et al. also suggested that thickening of the glomerular basal membrane, which increases the diffusion length of cystatin C, decreases the eGFR ratio in kidney biopsies of patients with diabetic nephropathy [34]. In addition, a limitation of shrunken pore syndrome is its low prevalence in the study population, and binary classification can lead to missing key information; therefore, we used the eGFR ratio as a continuous variable in our study.

Inconsistent with most previous studies, our results showed that poor prognosis was associated not only with a low eGFR ratio but also with a high eGFR ratio, suggesting the following plausible reasons. The eGFRcr is impacted by muscle mass, consumption of meat with high creatinine

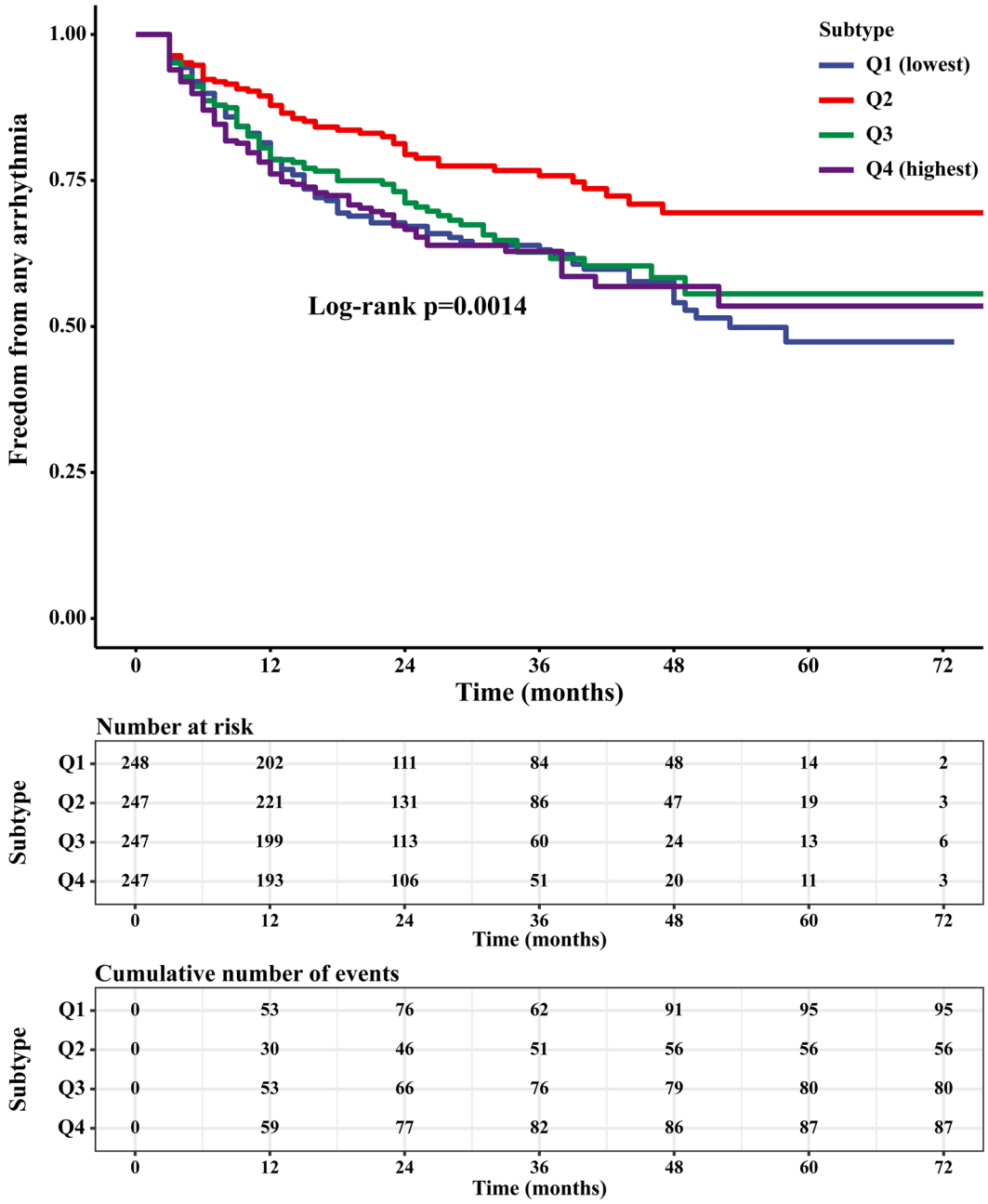

Figure 3. Kaplan–meier survival curve of freedom from AF recurrence after a single procedure in various AF subgroups.
During a median follow-up of 28 (IQR 17–42) months, the cumulative incidence of freedom from AF was significantly greater in the second quartile cohort (77.2%) than in the other three cohorts (61.7% to 67.7%) (log-rank test $P = 0.001$). Abbreviations: AF, atrial fibrillation.

content, advanced age, and physical activity, whereas the eGFRcys is susceptible to the effects of glucocorticoid therapy, thyroid function, inflammation, and obesity, all of which may contribute to different eGFR ratios [13,35]. Several studies have shown that an eGFRcr greater than the eGFRcys is often associated with frailty [26,36]. In this study, the baseline eGFR cohort with the lowest quartile showed higher age, more comorbidities, and frailty. Additionally, the CHA2DS2-VASc and APPLE scores were higher in this group, with the APPLE score gradually decreasing between groups. This suggests that the association between a high eGFR ratio and a high AF recurrence rate cannot be fully explained by clinically common risk factors [37]. In fact, this is not the first time that this phenomenon has been observed. The results of a study that explored the association between the eGFRcys and eGFRcr difference and acute kidney injury showed a similar U-shaped association. Consistent with previous research, this study further categorized variables, which may have led to the loss of important information [28].

We found that the difference between the eGFRcys and eGFRcr was very common, and as an independent predictor of AF recurrence, the proportion of AF patients with an eGFRcys < 60 was significantly greater than that of patients with an eGFRcr < 60, which may have been underestimated

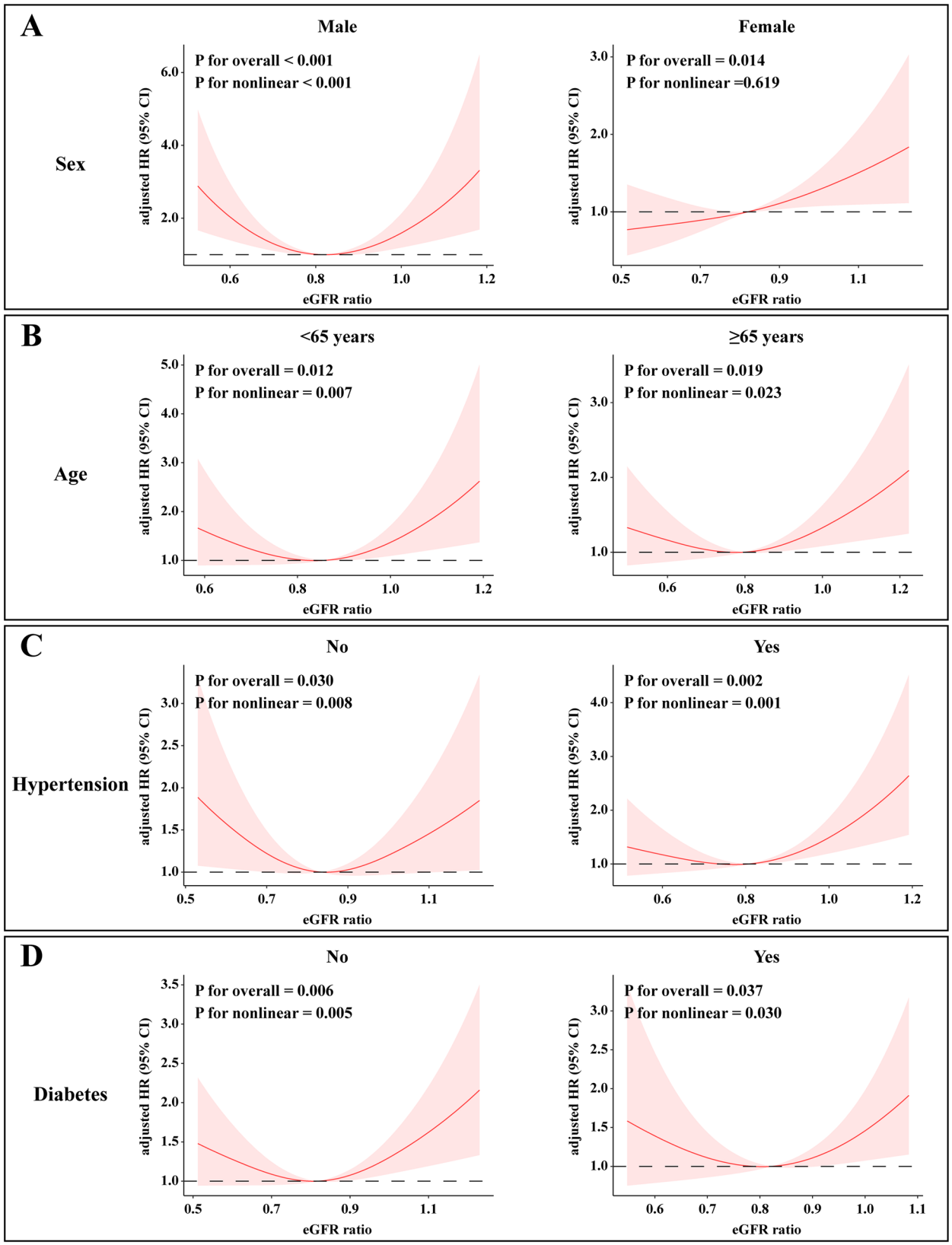

Figure 4. Association between the eGFR ratio and the risk of AF recurrence stratified by sex (a), age (B), high blood pressure status (C) and diabetes status (D). The results are presented as hazard ratios (HRs, solid lines) and 95% confidence intervals (CIs, light red areas) after multivariate adjustment for all the covariates except the self-grouping variable. Abbreviations: AF, atrial fibrillation.

in the initial risk assessment. A prospective study involving 9,228 participants showed that the eGFRcys was more strongly associated with AF development than was the eGFRcr [12]. Furthermore, according to our findings, the association between the eGFR ratio and the risk of AF recurrence after radiofrequency ablation was independent of creatinine and cystatin C levels. Another finding in our study was that there was a significant U-shaped association between the eGFR ratio and the risk of AF recurrence in men but a linear association in women. There are many sex-related differences in the risk and pathophysiology of AF, and the reasons often include hormone levels, height, obesity or fat distribution [38,39]. These findings emphasize the need for gender-specific approaches in AF management and risk stratification.

The mechanisms underlying the eGFR ratio-AF recurrence association likely involve complex interactions between renal function, systemic inflammation, and neurohormonal activation. Low ratios may predispose to AF through age-related factors and frailty, while high ratios may contribute to arrhythmogenesis through chronic inflammation and metabolic stress. These mechanisms may be modulated by gender-specific factors, resulting in the distinct association patterns observed. Future research should focus on elucidating the molecular pathways linking eGFR ratio to atrial remodeling, investigating the role of inflammatory markers and neurohormonal activation, and exploring targeted interventions to modify these pathways.

This study has both strengths and limitations. The main strength of this study is that, to our knowledge, this is the first study to examine the association between the eGFR ratio and the risk of AF recurrence after radiofrequency ablation. In addition, restricted cubic spline curves based on multivariate Cox proportional hazards models with full adjustment for identified confounders were used to investigate potential nonlinear associations, and our approach allowed for the determination of optimal eGFR ratios. Notably, this study also focused on the association between the eGFR ratio and the risk of experiencing post-ablation adverse events and rehospitalization.

Our study has several limitations. First, this was a single-centre, observational study, which has inherent limitations. It is thus necessary to confirm these results in a multicenter, large-scale, international study. Second, the presence of residual confounders cannot be included despite adjusting for potential confounders as much as possible. Third, the serum creatinine and cystatin C levels were measured at baseline and only once, and we were not able to monitor changes in the eGFR ratio over time. Fourth, the study participants were mainly elderly Chinese individuals. Therefore, caution is needed when generalizing our findings to other populations. Furthermore, this study did not evaluate left atrial strain, which is a significant predictor of AF recurrence following ablation [40,41]. Future investigations should incorporate this critical parameter to enhance the comprehensive evaluation of clinical outcomes in AF patients. Lastly, subgroup analyses were conducted post-hoc, which may limit their interpretability.

5. Conclusion

Our results demonstrate a U-shaped association between eGFR ratio and AF recurrence risk post-ablation, with both low and high ratios showing increased risk. The association pattern differed by gender, showing a strong U-shaped relationship in males and a linear trend in females. These findings suggest that the eGFR ratio may reflect important pathophysiological processes related to AF recurrence, warranting further investigation into the underlying mechanisms.

Authors' contributions

W.H. designed the research study; H.L., Z.Z., and S.S. performed the research; H.S., L.S., and Y.L. analyzed the data; W.H., H.S., and S.X. wrote the paper; all authors discussed the results and contributed to the final manuscript; and all authors have participated in drafting the article or revising it critically for important intellectual content.

Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics statement

The studies involving human participants were approved by local ethics committees, and all patients gave informed consent.

Funding

This work was supported by Chengdu High-level Key Clinical Specialty Construction Project (2021YJ0215), Chengdu famous doctor Liu Hanxiong studio (20240216) and Natural Science Foundation of China (82400390).

ORCID

Huaxin Sun http://orcid.org/0000-0002-1975-8722

Data availability statement

The original contributions presented in the study are included in the article, and further inquiries can be directed to the corresponding author.

References

[1] Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation. 2024;149(1):e1–e156.
[2] Kornej J, Börschel CS, Benjamin EJ, et al. Epidemiology of atrial fibrillation in the 21st century: novel methods

and new insights. Circ Res. 2020;127(1):4–20. doi: 10.1161/CIRCRESAHA.120.316340.

[3] Corley SD, Epstein AE, Dimarco JP, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study . Circulation. 2004;109(12):1509–1513. doi: 10.1161/01.CIR.0000121736.16643.11.

[4] Hagens VE, Ranchor AV, Van Sonderen E, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) study. J Am Coll Cardiol. 2004;43(2):241–247. doi: 10.1016/j.jacc.2003.08.037.

[5] Packer DL, Mark DB, Robb RA, 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(13):1261–1274. doi: 10.1001/jama.2019.0693.

[6] Modin D, Claggett B, Gislason G, et al. Catheter ablation for atrial fibrillation is associated with lower incidence of heart failure and death. Europace. 2020;22(1):74–83. doi: 10.1093/europace/euz264.

[7] Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. Eur Heart J. 2016;37(31):2478–2487. doi: 10.1093/eurheartj/ehw087.

[8] Deng H, Shantsila A, Xue Y, et al. Renal function and outcomes after catheter ablation of patients with atrial fibrillation: the Guangzhou atrial fibrillation ablation registry. Arch Cardiovasc Dis. 2019;112(6–7):420–429. doi: 10.1016/j.acvd.2019.02.006.

[9] Lip GY, Laroche C, Ioachim PM, et al. Prognosis and treatment of atrial fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). Eur Heart J. 2014;35(47):3365–3376. doi: 10.1093/eurheartj/ehu374.

[10] Tripathi B, Atti V, Kumar V, et al. Outcomes and resource utilization associated with readmissions after atrial fibrillation hospitalizations. J Am Heart Assoc. 2019;8(19):e013026. doi: 10.1161/JAHA.119.013026.

[11] Mcmanus DD, Corteville DC, Shlipak MG, et al. Relation of kidney function and albuminuria with atrial fibrillation (from the heart and soul study). Am J Cardiol. 2009;104(11):1551–1555. doi: 10.1016/j.amjcard.2009.07.026.

[12] Van Der Burgh AC, Geurts S, Ikram MA, et al. Bidirectional association between kidney function and atrial fibrillation: a population-based cohort study. J Am Heart Assoc. 2022;11(10):e025303. doi: 10.1161/JAHA.122.025303.

[13] Malmgren L, Öberg C, Den Bakker E, et al. The complexity of kidney disease and diagnosing it – cystatin C, selective glomerular hypofiltration syndromes and proteome regulation. J Intern Med. 2023;293(3):293–308. doi: 10.1111/joim.13589.

[14] Fu X, Tian Z, Wen S, et al. A new index based on serum creatinine and cystatin C is useful for assessing sarcopenia in patients with advanced cancer. Nutrition. 2021;82:111032. doi: 10.1016/j.nut.2020.111032.

[15] Lin YL, Chen SY, Lai YH, et al. Serum creatinine to cystatin C ratio predicts skeletal muscle mass and strength in patients with non-dialysis chronic kidney disease. Clin Nutr. 2020;39(8):2435–2441. doi: 10.1016/j.clnu.2019.10.027.

[16] Kusunoki H, Tabara Y, Tsuji S, et al. Estimation of muscle mass using creatinine/cystatin C ratio in Japanese community-dwelling older people. J Am Med Dir Assoc. 2022;23(5):902.e21–e31. doi: 10.1016/j.jamda.2021.07.029.

[17] Xhakollari L, Grubb A, Jujic A, et al. The Shrunken pore syndrome is associated with poor prognosis and lower quality of life in heart failure patients: the HARVEST-Malmö study. ESC Heart Fail. 2021;8(5):3577–3586. doi: 10.1002/ehf2.13485.

[18] Herou E, Dardashti A, Nozohoor S, et al. The mortality increase in cardiac surgery patients associated with shrunken pore syndrome correlates with the eGFR(cystatin C)/eGFR(creatinine)-ratio. Scand J Clin Lab Invest. 2019;79(3):167–173. doi: 10.1080/00365513.2019.1576101.

[19] Grubb A, Lindström V, Jonsson M, et al. Reduction in glomerular pore size is not restricted to pregnant women. Evidence for a new syndrome: 'Shrunken pore syndrome'. Scand J Clin Lab Invest. 2015;75(4):333–340. doi: 10.3109/00365513.2015.1025427.

[20] Aziz EF, Kukin M, Javed F, et al. Right ventricular dysfunction is a strong predictor of developing atrial fibrillation in acutely decompensated heart failure patients, ACAP-HF data analysis. J Card Fail. 2010;16(10):827–834. doi: 10.1016/j.cardfail.2010.05.004.

[21] Heo GY, Koh HB, Jung CY, et al. Difference between estimated GFR based on cystatin C versus creatinine and incident atrial fibrillation: a cohort study of the UK Biobank. Am J Kidney Dis. 2024;83(6):729–738.e1. doi: 10.1053/j.ajkd.2023.11.004.

[22] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–612. doi: 10.7326/0003-4819-150-9-200905050-00006.

[23] Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20–29. doi: 10.1056/NEJMoa1114248.

[24] Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis. 2002;40(2):221–226. doi: 10.1053/ajkd.2002.34487.

[25] Chen DC, Shlipak MG, Scherzer R, et al. Association of intra-individual differences in estimated GFR by creatinine versus cystatin C with incident heart failure. Am J Kidney Dis. 2022;80(6):762–772.e1. doi: 10.1053/j.ajkd.2022.05.011.

[26] Potok OA, Ix JH, Shlipak MG, et al. The difference between cystatin C- and creatinine-based estimated GFR and associations with frailty and adverse outcomes: a cohort analysis of the Systolic Blood Pressure Intervention Trial (SPRINT). Am J Kidney Dis. 2020;76(6):765–774. doi: 10.1053/j.ajkd.2020.05.017.

[27] Chen DC, Shlipak MG, Scherzer R, et al. Association of intraindividual difference in estimated glomerular filtration rate by creatinine vs cystatin C and end-stage kidney disease and mortality. JAMA Netw Open. 2022;5(2):e2148940. doi: 10.1001/jamanetworkopen.2021.48940.

[28] Zhang LW, Luo MQ, Zeng JL, et al. The association of intraindividual difference between cystatin- and creatinine-based estimated GFR and contrast-associated

acute kidney injury. Clin Interv Aging. 2024;19:411–420. doi: 10.2147/CIA.S447042.

[29] Purde MT, Nock S, Risch L, et al. The cystatin C/creatinine ratio, a marker of glomerular filtration quality: associated factors, reference intervals, and prediction of morbidity and mortality in healthy seniors. Transl Res. 2016;169:80–90.e1-2. doi: 10.1016/j.trsl.2015.11.001.

[30] Dardashti A, Nozohoor S, Grubb A, et al. Shrunken pore syndrome is associated with a sharp rise in mortality in patients undergoing elective coronary artery bypass grafting. Scand J Clin Lab Invest. 2016;76(1):74–81. doi: 10.3109/00365513.2015.1099724.

[31] Purde MT, Nock S, Risch L, et al. Ratio of cystatin C and creatinine-based estimates of the glomerular filtration rate predicts mortality in healthy seniors independent of kidney function. Scand J Clin Lab Invest. 2016;76(4):341–343. doi: 10.3109/00365513.2016.1149882.

[32] Almén MS, Björk J, Nyman U, et al. Shrunken pore syndrome is associated with increased levels of atherosclerosis-promoting proteins. Kidney Int Rep. 2019;4(1):67–79. doi: 10.1016/j.ekir.2018.09.002.

[33] Christensson A, Grubb A, Molvin J, et al. The shrunken pore syndrome is associated with declined right ventricular systolic function in a heart failure population – the HARVEST study. Scand J Clin Lab Invest. 2016;76(7):568–574. doi: 10.1080/00365513.2016.1223338.

[34] Öberg CM, Lindström M, Grubb A, et al. Potential relationship between eGFR(cystatin C)/eGFR(creatinine) -ratio and glomerular basement membrane thickness in diabetic kidney disease. Physiol Rep. 2021;9(13):e14939. doi: 10.14814/phy2.14939.

[35] Stevens LA, Coresh J, Greene T, et al. Assessing kidney function–measured and estimated glomerular filtration rate. N Engl J Med. 2006;354(23):2473–2483. doi: 10.1056/NEJMra054415.

[36] Potok OA, Katz R, Bansal N, et al. The difference between cystatin C- and creatinine-based estimated GFR and incident frailty: an analysis of the Cardiovascular Health Study (CHS). Am J Kidney Dis. 2020;76(6):896–898. doi: 10.1053/j.ajkd.2020.05.018.

[37] Kornej J, Hindricks G, Shoemaker MB, et al. The APPLE score: a novel and simple score for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation. Clin Res Cardiol. 2015;104(10):871–876. doi: 10.1007/s00392-015-0856-x.

[38] Camm CF, Lacey B, Massa MS, et al. Independent effects of adiposity measures on risk of atrial fibrillation in men and women: a study of 0.5 million individuals. Int J Epidemiol. 2022;51(3):984–995. doi: 10.1093/ije/dyab184.

[39] Westerman S, Wenger NK. Women and heart disease, the underrecognized burden: sex differences, biases, and unmet clinical and research challenges. Clin Sci (Lond). 2016;130(8):551–563. doi: 10.1042/CS20150586.

[40] Barilli M, Mandoli GE, Sisti N, et al. Potential role of left atrial strain to predict atrial fibrillation recurrence after catheter ablation therapy: a clinical and systematic review. J Cardiovasc Dev Dis. 2024;11(7):203. doi: 10.3390/jcdd11070203.

[41] Kiliszek M, Uziębło-Życzkowska B, Krzyżanowski K, et al. Value of left atrial strain in predicting recurrence after atrial fibrillation ablation. J Clin Med. 2023;12(12):4034. doi: 10.3390/jcm12124034.