Effect of Insulin Resistance on Recurrence After Radiofrequency Catheter Ablation in Patients with Atrial Fibrillation

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Abstract

Background

Recurrence after atrial fibrillation(AF) ablation has many risk factors. the relationship between the recurrence rate after ablation and IR in the non-diabetic patients with AF is not clear.

Methods

Retrospective cohort study enrolled AF patients without diabetes who underwent ablation between 2018~2019 in the first affiliated hospital of zhengzhou university. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated and a value of ≥2.69 was defined as insulin resistant(IR). The patients were categaried into two groups: those with HOMA-IR<2.69 in group 1(n=163); HOMA-IR≥2.69 in group 2 (n=69). Multivariable adjusted Cox proportional hazard models were performed to compare the risk of AF recurrence after ablation. The definition of AF recurrence was documented AF, atrial flutter, or atrial tachycardia lasting >30 seconds recorded in ECG or 24-hour Holter monitoring after 3 months blanking period.

Results

232 AF patients receiving ablation were enrolled and the median age was 59.5±11.3 years . There were 166 cases of paroxysmal AF and 66 cases of persistent AF. Patients with IR (n=69)were more likely to have Dyslipidemia, higher fasting blood glucose and fasting insulin than those in non-IR group. Patients with IR also were more likely to recieve antiarrhythmic drugs before ablation. After a mean follow-up of 322±85 days, 62(26.7%) patients had documented recurrence of AF. Multivariable analysis showed that HOMA-IR value and left atrial diameter（LAD）were independent risk factors for recurrence after AF ablation (HR: 1.259, 95% CI:1.086~1.460, P=0.002; HR: 1.043, 95% CI:1.005~1.083, P=0.025; respectively).

Conclusions

HOMA-IR and LAD are independent risk factors for AF recurrence after ablation in patients without diabetes.

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmic cardiovascular diseases in clinical practice, AF can significantly increase the risk of heart failure, renal impairment and so on[1]. Radiofrequency catheter ablation (RFCA) is the main treatment for AF. However, patients with AF have a certain recurrence rate after ablation. The success rate remained at 70%~90% at 1-year follow-up after RFCA in patients with paroxysmal atrial fibrillation(PAF) and the success rate was even lower at 65%~75% for persistent atrial fibrillation(PAF)[2, 3].risk factors associated with recurrence of AF after RFCA were hypertension, metabolic syndrome, sleep apnea syndrome and other diseases[4].

Insulin resistance(IR) is a state of decreased insulin response, which shows signs including obesity, elevated blood glucose, dyslipidemia and elevated blood pressure[5].IR is generally a component of metabolic syndrome and a precursor of diabetes mellitus(DM),metabolic syndrome and diabetes mellitus are independent risk factors for recurrence after AF ablation[6, 7],IR also could increase the susceptibility to AF[8-10].At present, the relationship between the recurrence rate after ablation and IR in patients with AF is not clear, the aim of this study was to investigate the effect of IR on the recurrence after RFCA in patients with AF.

Methods

Study population

This single-center prospective cohort study was carried out at the first affiliated hospital of Zhengzhou university between January 2018 and July 2019.A total of 321 patients with AF underwent successful RFCA were screened for eligibility. The inclusion criteria were age≧18 years and hospitalized for first RFCA. Exclusion criteria were those with DM, congenital heart disease, hypertrophic cardiomyopathy, and valvular heart disease, treatment with glucocorticoids or non-steroidal anti-inflammatory drugs, patients with thyroid dysfunction and hepatorenal insufficiency. A participant was considered to have DM if he/she had previously been diagnosed with DM or was currently taking medications for DM or had a glycated hemoglobin (HbA1c) level >6.5%. The present study fully complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China .

Date collection

Demographic parameters and comorbidities were collected from patients' medical records. AF duration, AF type, body mass index(BMI), including dyslipidemia, hypertension, cerebrovascular disease, antiarrhythmic drugs(AADs) and statins before procedure, left atrial diameter(LAD), left ventricular end diastolic diameter(LVEDD), left ventricular ejection fraction (LVEF) and heart rate(HR) in electrocardiography (ECG) were collected. Blood samples were obtained after at least eight hours fasting; creatinine, uric acid, high sensitivity C-reactive protein(HS-CRP), erythrocyte sedimentation rate (ESR), glycated hemoglobin(HbA1c), fasting plasma glucose(FPG), fasting insulin(FINS),total cholesterol, triglycerides, high-and low-density lipoprotein cholesterol levels were measured.Intraoperative parameters including linear ablation and superior vena cava (SVC) ablation were recorded. The CHA_2DS_2-VASc score of each patient was calculated [11].

Definition of IR

IR was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) as follows: HOMA-IR=FPG(mmol/L)×FINS(μU/mL)/22.5[12]. FPG was measured by hexokinase method and FINS was measured by electrochemiluminescence method.

Ablation protocol and peri-procedure management

Details of the RFCA procedure have been described in published studies[13].Briefly, circumferential pulmonary vein isolation(CPVI) was performed in all patients with PAF, and isthmus line ablation was performed when typical atrial flutter was documented preoperatively or intraoperatively. For all patients with PeAF, the endpoint of ablation was CPVI, followed by bidirectional block of linear ablation across the left atrial roof, mitral isthmus, cavotricuspid isthmus. If AF could not be terminated after the above ablation, and synchronous direct current cardioversion was converted to sinus rhythm. In addition, all patients with AF, electrical isolation of the SVC was performed if induced tachycardia suggested an origin of the SVC or if the potential of the SVC was active.Last, if no AF induction was confirmed via coronary sinus electrode burst pacing of, the procedure was deemed completed.

The patients received AADs for 3 months after ablation to prevent early recurrence of AF. Besides, all the patients has been taking new oral anticoagulants (NOACs or warfarin(INR of 2.0-3.0)for at least 3 months. Continuation of anticoagulation therapy was determined according to the AHA/ACC/HRS guidelines[14],and was decided jointly by patient and physician.

Outcome and Follow-up

The definition of AF recurrence was documented AF, atrial flutter, or atrial tachycardia(AT) lasting >30seconds recorded in ECG or 24-hour Holter monitoring after 3 months blanking period. follow-up was performed at 3, 6, 9, and 12 months after ablation in outpatient and/or by telephone. ECG and/or 24-hour Holter monitoring were performed at each visit. When the patient had symptoms of arrhythmia outside the hospital, he/she timely visited the outpatient department of the nearby hospital for examination. If recurrence occurred, the time of AF recurrence was recorded.

Statistical analysis

continuous data were expressed by the mean±standard deviation (SD) and categorical variables were presented as counts and percentages. Continuous variables were compared between the two groups using Student's t-test or Mann-Whitney test depending on whether the data were normally distributed or not. Categorical variables were compared between two groups was by χ^2 test or Fisher's exact test. The Kaplan-Meier curve was used to analyze the AF-free survival rate after ablation and group comparisons were based on the log-rank test. The patients were categaried into two groups: those with HOMA-IR<2.69 in group 1(n=163); HOMA-IR≥2.69 in group 2 (n=69).Univariate and multivariate Cox proportional hazards regression models were used to evaluate the risk of AF on recurrence. In the multivariate Cox proportional hazard analysis, to prepare for potential confounding ,the following important clinical factors were adjusted : AF type, duration of AF, HS-CRP, LAD and HOMA-IR. The subgroup analyses for risk factors of AF ,with and without recurrence of AF. All collected data were statistically analyzed using SPSS 21.0 and GraphPad Prism 9.all statistical tests were two-sided and a value of P<0.05 was considered significant.

Results

Patient characteristics

A total of 321 AF patients underwent ablation were screened, of which 232 patients were eligible for inclusion in the present analysis (Figure 1).The baseline characteristics of the two groups are shown in Table 1.The mean age was 59.50±11.32 years, and 87 (38.50%) were female. Compared to the patients without IR，patients with IR were more likely to have dyslipidemia(63.8% vs 48.5%, P=0.033)and to take AAD before procedure (86,52.8% vs 49,71.0%, P=0.010). Both FPG and FINS were significantly higher in group 2 than in group 1 (5.7±1.2 vs 4.8±0.9,P<0.001; 14.9±4.8 vs 7.9±2.6,P<0.001;respectively).

The incidence of AF recurrence

During the follow-up period of 322±85 days, the incidence of AF recurrence was more frequently in group 2 (40.6% vs 20.9%,P=0.002).The Kaplan-Meier showed that the HR for the recurrence was 2.25 in group 2 compared to group 1(log-rank P=0.001), as shown in Figure 2 .

Risk factors associated with AF recurrence

All patients with AF were divided into recurrence of AF group (n=62,26.7%) and no-recurrence of AF group(n=170,63.8%) according to the follow-up results (Supplementary Material Table 2). In the Univariable analysis, patients with AF had higher HOMA-IR (P=0.001)and LAD (P=0.015). There were no significant differences in AF type, dyslipidemia, duration of AF (>5 years), and BMI between the two groups.(Table 2) In the multivariable Cox regression hazard analysis, HOMA-IR(HR: 1.259, 95% CI:1.086~1.460, P=0.002) and LAD(HR:1.043,95%CI:1.005~1.083,P=0.025) remained an independent predictor of AF recurrence .

Subgroup analysis

The association between HOMA-IR and the recurrence risks of AF was evaluated in the subgroup. HOMA-IR and LAD were risk factors on recurrence of PAF (P=0.023 ,P=0.020, respectly; Figure 3),HOMA-IR and HS-CRP were risk indicators in the recurrence of PeAF (P=0.002,P=0.010,respectly;Figure 4).

Discussion

The findings of this study provide important information about the risk of recurrence of AF in patients without diabetes. IR is associated with a high recurrence rate after ablation in patients with AF. the association between high HOMA-IR value and recurrence of AF after ablation remained in the subgroup analysis based on type of AF . This could be an important information in clinical decision making in treating patients with AF ablation.

AF ablation has a certain recurrence rate, and many risk factors may increase its recurrence rate.Previous studies have shown that increased of the LAD leads to left atrial remodeling, making recurrence rates

higher after ablation in patients with AF[15, 16].The results of this study also showed that the larger LAD in AF patients are associated with high recurrence rates after ablation, which was consistent with the previous study.However, the impact of IR on recurrence after AF ablation is not clear. There had been a previous study showing that IR was a predictor of PAF recurrence after CPVI[17]. Our finding that high HOMA-IR levels in patients with AF were associated with a higher recurrence rate after ablation whether PAF or PeAF,which was first reported and included 232 AF patients more than 114 AF patients in the previous study.

IR is a common feature of metabolic syndrome and diabetes mellitus and it is a potential mechanism for the development of abnormal glucose metabolism[18].In the National Health and Nutrition Examination Survey (NHANES III) study, aged≧20 years of 8608 people with non-diabetic had HOMA-IR values≧2.68, were defined as IR[19].HOMA-IR values≧2.69 in 10147 non-diabetic Chinese people, aged 25 to 74 years, were defined as IR[20].revious studies have found subtle differences in the defined values of IR, which are attributed to different ethnic groups with different constitution, and we defined HOMA-IR value≧2.69 as IR in combination with the physical condition of Chinese people[21]. IR is associated with abnormal obesity, obesity and hyperlipidemia can cause massive fat accumulation in the body, causing the release of cytokines related to IR and resulting in abnormal production of signaling pathways in which insulin acts [22].IR combined with obesity can aggravate the cardiac burden of patients, and poor weight control is one of the main causes of IR[23].In this study, BMI was higher than normal weight in both groups, may be that all patients with AF, obesity is associated with the occurrence and development of AF[24].There was no significant difference in LAD, LVEDD and HS-CRP between the two groups , possibly because IR has little effect on atrial structural remodeling.IR was found not to significantly alter atrial fibrosis and structural remodeling[25].

Shigematsu et al suggested that IR accounted for a significantly higher proportion of non-diabetic hypertrophic cardiomyopathy patients with AF than hypertrophic cardiomyopathy patients with sinus rhythm , which had shown that impaired fasting glucose and impaired glucose tolerance could lead to delayed electrical conduction in the atria and the formation of low-voltage areas,suggesting that IR may be a potential mechanism mediating the development of AF[26].Lee et al found that high HOMA-IR levels were independently associated with an increased risk of AF in non-diabetic patients, high HOMA-IR levels were one of the main causes of AF in the non-diabetic population[27].The recurrence rate of AF after ablation in diabetic patients is higher than that in non-diabetic patients, and metabolic abnormalities in diabetes play a role in promoting arrhythmia[28].The recurrence of AF in the abnormal glucose metabolism group after catheter ablation was also significantly higher than that in patients in the normal glucose metabolism group[7].IR leads to the slowing of conduction velocity in the left atrium, the formation of reentry, aggravating atrial electrical remodeling, and promoting recurrence after AF ablation[20].In this study, HOMA-IR levels in patients with AF in the recurrence group were significantly higher than those in patients without AF recurrence. It may be because IR exacerbates the process of delayed atrial conduction velocity in patients with AF, which leads to continuous atrial electrical remodeling and causes an increase in the recurrence of AF.

Limitations

Several limitations existed in our study. This paper is a retrospective study that cannot avoid information bias, the duration of AF, is sometimes reported by patients themselves and no data regarding use drugs after 3 months blanking period. In addition, this study was a single-center study with a small sample size,which may limit the generalizability of the results. Finally, it is possible that patients with asymptomatic recurrence of AF may have been missed since we used the intermittent rather than continuous rhythm monitoring strategies. Whether IR is an independent predictor of recurrence of AF needs to be supported by more evidence-based in the future, and whether interventions to treat IR help reduce the recurrence rate after AF ablation.

Conclusion

HOMA-IR and LAD were independent risk factors for recurrence after RFCA in AF patients without diabetes.. IR in patients with AF is associated with high recurrence rate after ablation.

Declarations

Author contributions

ZW, ZYL , YJW and QL:Designed the study and wrote the first draft of the manuscript. JZD and YHS:Verified data extraction,and reviewed the manuscript. YWC:Supervised the data acquisition, data analysis and interpretation. YWK participated in data analysis. All authors read and approved the final manuscript.

Data Availability

The data supporting the findings of this study are available on request.

Conflict of interest

The authors declare that they have no competing interests.

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None

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Tables

Table 1. Baseline characteristics of patients with and without insulin resistance

	Group 1 (HOMA-IR<2.69)	Group 2 (HOMA-IR≧2.69)	*P*
Female	61(37.4)	26(37.7)	0.970
Age,years	59.8±11.7	58.9±10.3	0.606
BMI,kg/m^2	24.6±2.8	25.1±2.4	0.220
Current Smoker	52(31.9)	19(30.2)	0.510
AF type			0.906
Paroxysmal	117(71.8)	49(71.0)	
Persistent	46(28.2)	20(29.0)	
Hypertension	77(47.2)	39(56.5)	0.196
Cerebrovascular disease	15(9.2)	8(11.6)	0.577
Dyslipidemia	79(48.5)	44(63.8)	0.033
Duration of AF,>5 years	37(22.7)	22(31.9)	0.142
AADs	86(52.8)	49(71.0)	0.010
Statins	72(44.2)	28(40.6）	0.614
HR,bpm	78.72±17.39	79.57±18.99	0.743
Cr,μmol/l	74(64-85)	84(63-72)	0.379
UA,mmol/l	305(252-368)	284(233-366)	0.376
TG,mmol/l	1.3(0.9-1.9)	1.6(1.0-2.2)	0.136
TC,mmol/l	3.7±1.0	3.9±0.9	0.258
HDL-C,mmol/l	1.2(0.9-1.8)	1.7(1.1-2.5)	0.706
LDL-C ,mmol/l	2.6(1.9-3.3)	2.7(2.0-3.5)	0.712
HS-CRP,mg/l	3.1(1.6-5.5)	3.9(1.6-6.2)	0.322
ESR,mm/l	10.8(8.0-14.0)	11.8(9.7-13.9)	0.134
HbAlc,%	5.8±0.6	5.9±0.6	0.625
FPG,mmol/L	4.8±0.8	5.8±1.3	<0.001
FINS,μU/mL)	7.9±2.6	14.9±4.8	<0.001
HOMA-IR	1.7±0.6	3.8±1.3	<0.001
LAD,mm	39.5±6.5	40.4±6.6	0.356
LVEF,%	60.8±6.6	60.5±7.8	0.776
LVEDD,mm	47.6±5.3	48.2±6.1	0.418

Note: Continuous data are presented as means±standard deviation (SD) or median (interquartile range) and categorical data was shown as n (%)

Abbreviations: AF: atrial fibrillation; BMI: body mass index; ADDs:antiarrhythmic drugs;HbA1c: glycated hemoglobin; HR:heart rate;Cr:creatinine;UA:Uric Acid;TC:total cholesterol;TG:triglyceride;HDL-C:high-density lipoprotein cholesterol;LDL-C:low-density lipoprotein cholesterol;HS-CRP:High Sensitivity C-reactive protein;ESR:erythrocyte sedimentation rate; HbA1c: glycated hemoglobin;FPG:fasting plasma glucose;FINS:fasting insulin;HOMA-IR:homeostasis model assessment of insulin resistance;LAD:1eft atrial diameter;LVEF:1eft ventricular ejection fraction;LVEDD:1eft ventricular end diastolic diameter.

Table 2. Univariable and multivariable Cox regression hazard analysis for AF recurrence

	Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Female	1.137	0.684~1.889	0.620			
Smoking habits	1.293	0.732~2.284	0.376			
AF type(PAF vs PeAF)	0.7675	0.401~1.135	0.138	0.643	0.377~1.096	0.104
Hypertension	0.663	0.401~1.099	0.111			
Dyslipidemia	1.229	0.744~2.030	0. 421			
Duration of AF(>5 years)	0.683	0.401~1.163	0.160	0.802	0.462~1.390	0.431
CHA_2DS_2-VASc score≧2	0.882	0.535~1.452	0.661			
Age	1.010	0.987~1.033	0.394			
BMI	1,001	0.909~1.103	0.982			
HR	1.000	0.985~1.014	0.949			
Cr	0.997	0.982~1.012	0.671			
UA	0.999	0.997~1.002	0.646			
TG	1.081	0.819~1.427	0.581			
TC	1.121	0.864~1.456	0.390			
HDL	0.771	0.525~1.133	0.185			
LDL	1.090	0.958~1.241	0.191			
HbAlc	0.826	0.531~1.286	0.397			
HS-CRP	1.047	0.984~1.114	0.150	1.050	0.983~1.121	0.145
ESR	1.016	0.968~1.067	0.514			
LAD	1.046	1.009~1.084	0.015	1.043	1.005~1.083	0.025
LVEF	1.002	0.966~1.039	0.935			
LVEDD	1.004	0.961~1.048	0.874			
Linear ablation	1.382	0.832~2.296	0.211			
SVC isolation	0.585	0.278~1.230	0.157			
FPG,mmol/L	1.165	0.951~1.427	0.139			
HOMA-IR	1.264	1.096~1.457	0.001	1,259	1.086~1.460	0.002

Note: Multivariate Cox regression analysis model included AF type,duration of AF(>5 years),HS-CRP,LAD,and HOMA-IR.

Abbreviations:AF: atrial fibrillation; PAF: paroxysmal atrial fibrillation;PeAF: persistent atrial fibrillation;BMI: body mass index;HR:heart rate;Cr:creatinine;UA:Uric Acid;TC:total cholesterol;TG:triglyceride;HDL-C:high-density lipoprotein cholesterol;LDL-C:low-density lipoprotein cholesterol;HS-CRP:High Sensitivity C-reactive protein;ESR:erythrocyte sedimentation rate; HbA1c: glycated hemoglobin;FPG:fasting plasma glucose;FINS:fasting insulin;HOMA-IR:homeostasis model assessment of insulin resistance;LAD:1eft atrial diameter;LVEF:left ventricular ejection fraction;LVEDD:1eft ventricular end diastolic diameter; SVC: superior vena cava, CI: confidence interval; HR: hazard ratio.

Figures

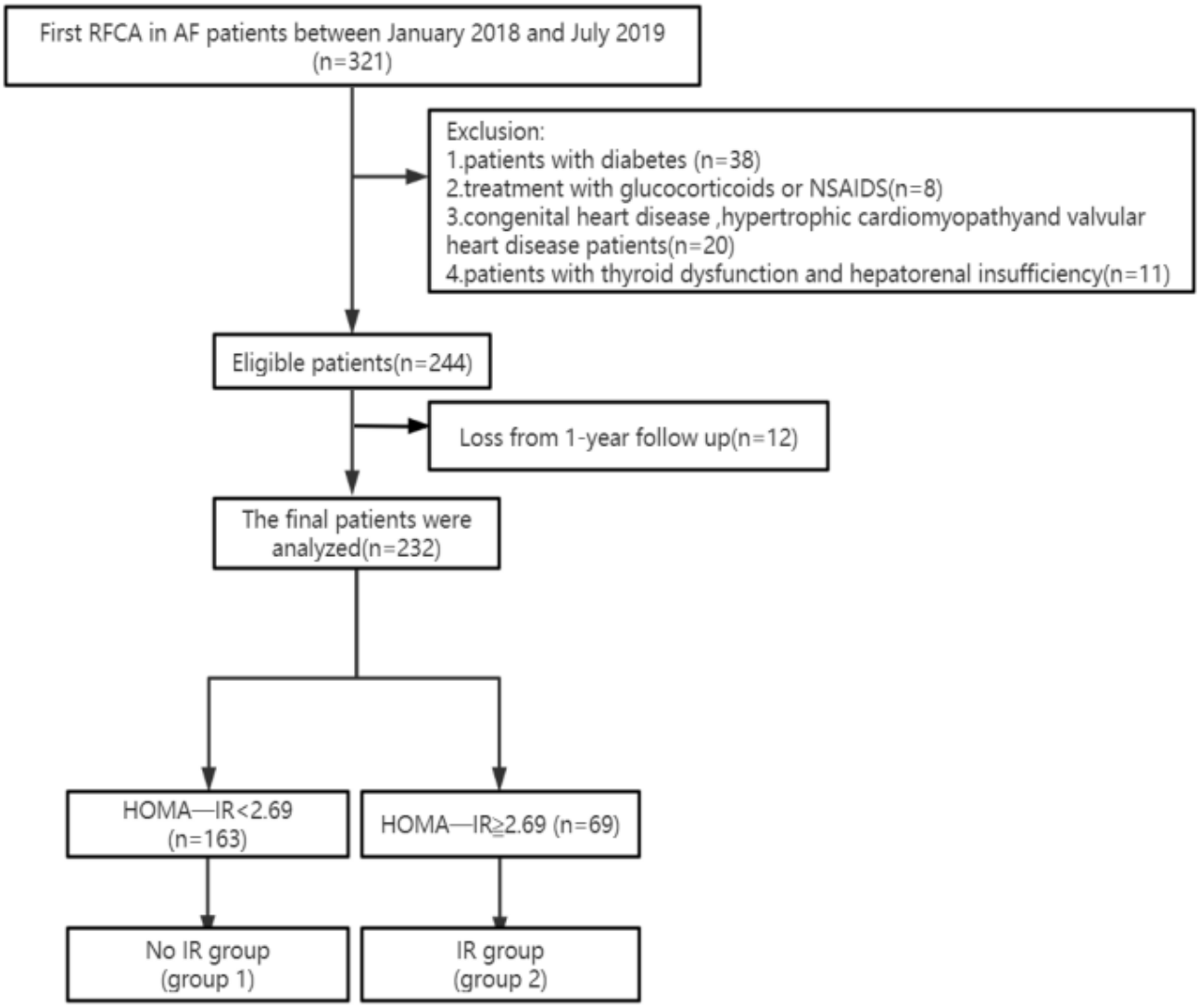
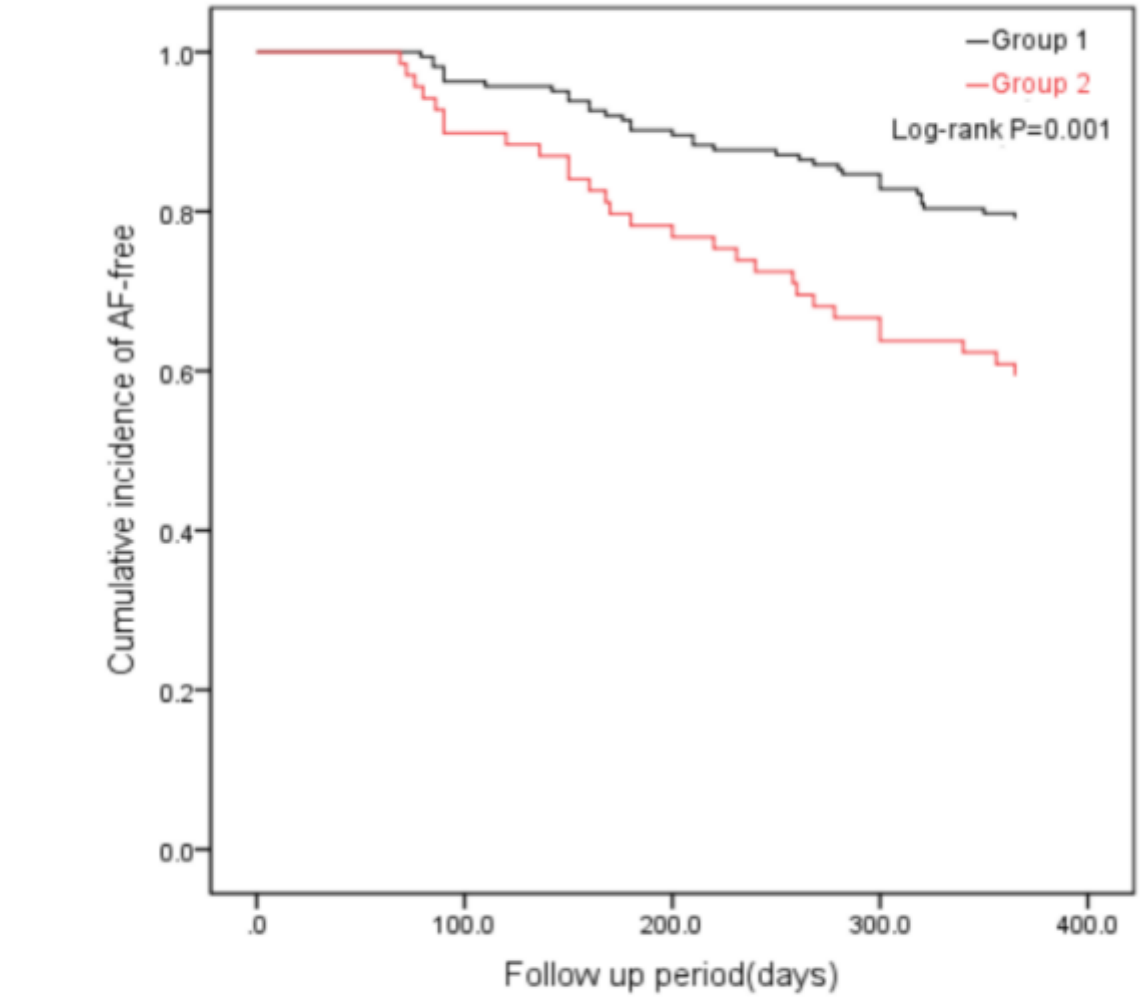


Figure 1

Patients flow chart for the study cohort. RFCA, radiofrequency catheter ablation; AF,atrial fibrillation;NSAIDS, non-steroidal anti-inflammatory drugs;HOMA IR,homeostasis model assessment of insulin resistance;IR, insulin resistance.



Number at risk					
Group 1	163	157	146	135	129
Group 2	69	62	53	44	41

Figure 2

Cumulative incidence of atrial fibrillation(AF) between two groups according to homeostasis model assessment of insulin resistance(HOMA-IR) levels; The Kaplan-Meier survival curve analysis shows a significant difference in the recurrence of AF after ablation between two HOMA-IR groups .

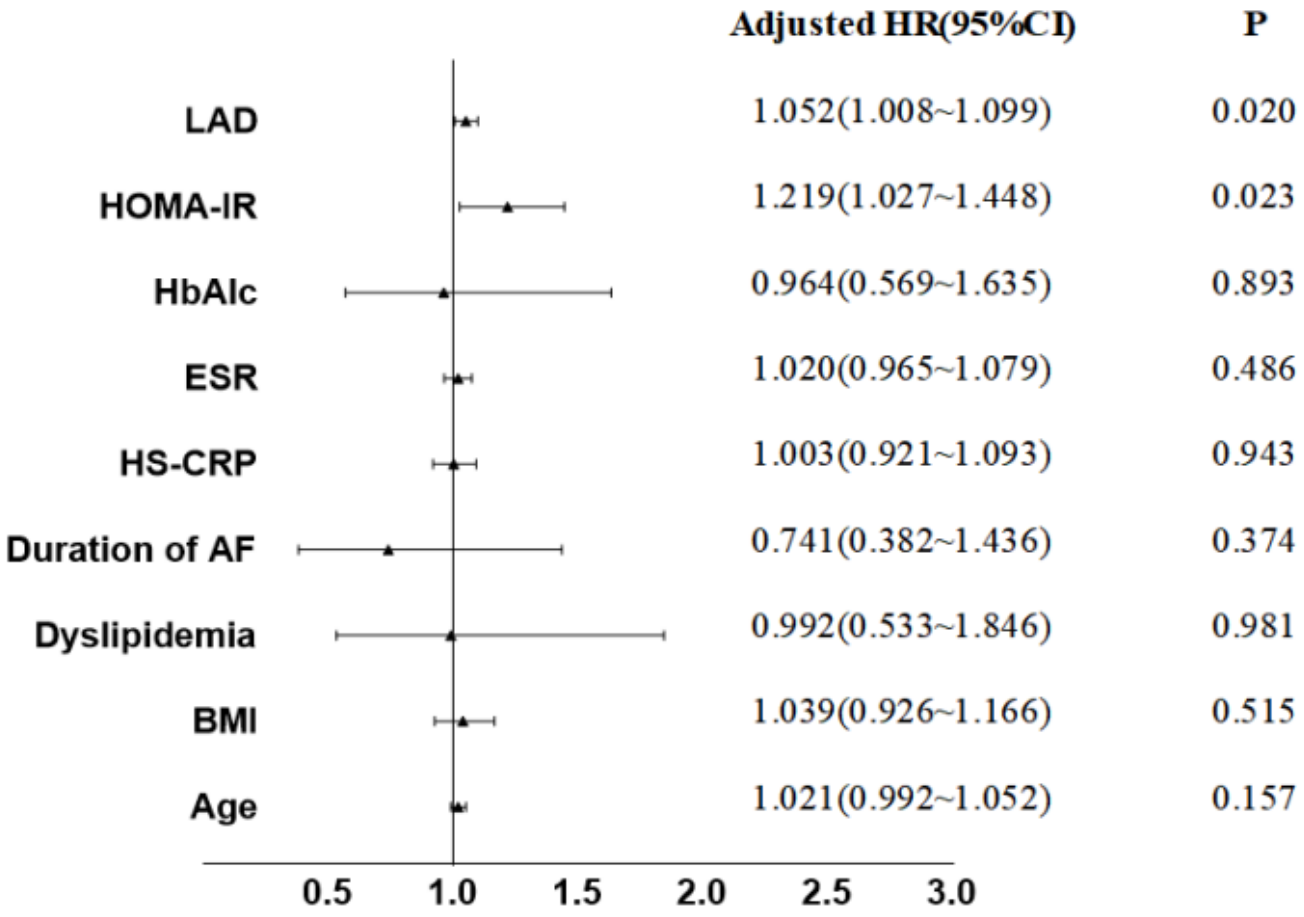


Figure 3

Subgroup analyses for risk of recurrence in paroxysmal atrial fibrillation(PAF) patients after ablation.LAD:left atrial diameter; HOMA-IR:homeostasis model assessment of insulin resistance;HbA1c: glycated hemoglobin; HS-CRP:High Sensitivity C-reactive protein;ESR:erythrocyte sedimentation rate;AF: atrial fibrillation;BMI: body mass index; HR: hazard ratio;CI: confidence interval.

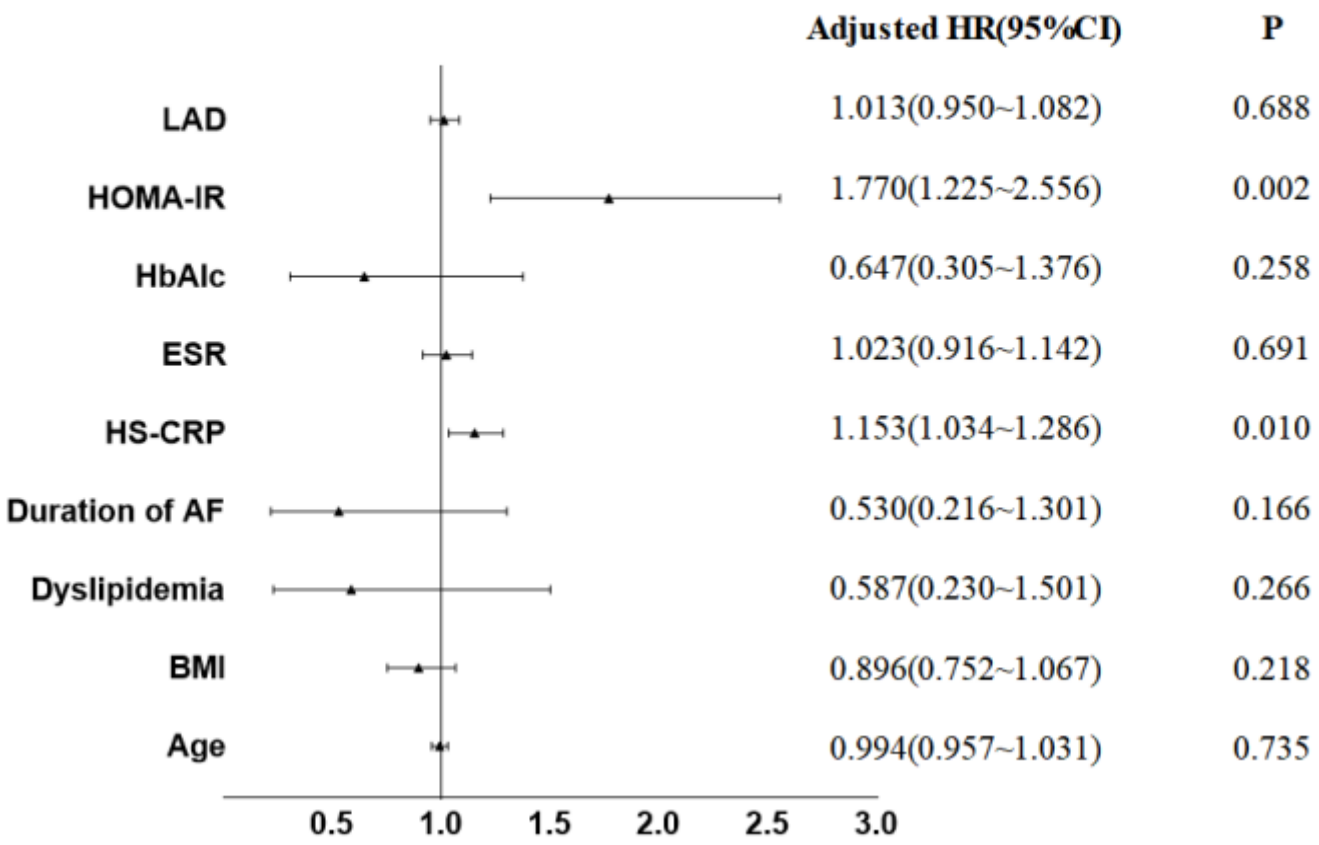


Figure 4

Subgroup analyses for risk of recurrence in peresistant atrial fibrillation(PeAF) patients after ablation.LAD:left atrial diameter; HOMA-IR:homeostasis model assessment of insulin resistance; HbA1c: glycated hemoglobin;HS-CRP:High Sensitivity C-reactive protein; ESR:erythrocyte sedimentation rate;AF: atrial fibrillation;BMI: body mass index; HR: hazard ratio; CI: confidence interval

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.pdf