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Study on the correlation between red cell distribution width, homocysteine, lipoprotein(a), and left atrial diameter in newly diagnosed nonvalvular atrial fibrillation patients

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Abstract. – OBJECTIVE: This study aims to investigate the correlations between red cell distribution width (RDW), homocysteine (Hcy), lipoprotein(a) [Lp(a)], and left atrial diameter (LAD) measured by echocardiography in newly diagnosed nonvalvular atrial fibrillation (NVAF) (referred to as "new-onset AF") patients and their predictive value for new-onset AF. The findings of this study provide a basis for early clinical identification of the risk of new-onset AF.

PATIENTS AND METHODS: Eighty-nine newly diagnosed NVAF patients (46 males and 43 females) admitted to the Department of Cardiology, First Affiliated Hospital of Nanchang University, from January 2017 to January 2023 were included in the new-onset AF group. Over the same time, 88 sinus rhythm patients (44 males and 44 females) were included in the control group. Data, including demographic information, routine blood test parameters, biochemical indicators, and relevant values from cardiac color Doppler ultrasound, were recorded for all study subjects. Logistic regression analysis was used to explore the clinical characteristics of the indicators mentioned above in patients with new-onset AF. Receiver operating characteristic (ROC) curves were drawn to assess the predictive ability of these indicators for new-onset AF.

RESULTS: Univariate analysis of biochemical indicators revealed differences between the two groups ($p<0.05$) in RDW, Hcy, and Lp(a). The univariate analysis also revealed differences ($p<0.05$) in RDW, Lp(a), Hcy, left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST), and left ventricular ejection fraction (LVEF). Multivariable logistic regression analysis identified RDW (OR=2.38, 95% CI: 1.65-3.67), Hcy (OR=1.57, 95% CI: 1.37-1.86), and Lp(a) (OR=1.01, 95% CI: 1.00-1.01) as independent risk factors for the new-onset AF. In the subgroup analysis dichotomizing patients around the LAD cutoff value, the high-LAD group had higher RDW, Hcy, and Lp(a) (13.4 *vs.* 12.7, 15.0 *vs.* 10.9, 144.0 *vs.* 101.3, respectively).

CONCLUSIONS: RDW, Hcy, and Lp(a) are elevated in patients with new-onset AF. They are positively correlated with LAD in these patients, indicating their role as risk factors for new-onset AF.

Key Words:
Nonvalvular atrial fibrillation, Red cell distribution width, Homocysteine, Lipoprotein(a), Left atrial diameter.

Introduction

Atrial fibrillation (AF) is one of the most common types of cardiac arrhythmias, and its incidence has steadily increased. AF is recognized as a leading cause of cardiovascular events globally[1]. The pathogenesis of AF has yet to be fully understood, though it has traditionally been attributed to micro reentry. Recent studies[2] have discovered the involvement of inflammation and oxidative stress in the development and progression of AF. Several biochemical markers, including red blood cell distribution width (RDW), homocysteine (Hcy), and lipoprotein(a) [Lp(a)], are associated with the onset and progression of AF, though there are variations in published results[3-5]. RDW is a parameter that reflects the heterogeneity of red blood cell volume and size, which has been associated with the occurrence, progression, and prognosis of AF[6]. Hcy, a sulfur-containing amino acid, serves as a marker reflecting the inflammatory state of oxidative stress. It has been associated with cardiovascular and cerebrovascular diseases and is closely correlated with the occurrence of AF[7]. Lp(a) is a complex consisting of apolipoprotein A and apolipoprotein B linked by disulfide bonds. Elevated serum Lp(a) has been confirmed8 as an independent risk factor for atherosclerosis and co-

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ronary heart disease and has been associated with the occurrence of AF. The above three biomarkers may potentially affect atrial electrical activity or structure, leading to the occurrence of AF through inflammation or oxidative stress responses. This study analyzed the correlations between left atrial diameter (LAD) and RDW, Hcy, and Lp(a) in newly diagnosed AF patients.

Definition

Nonvalvular AF (NVAF) is defined as AF that occurs in the absence of mechanical prosthetic heart valves or moderate to severe mitral valve stenosis (typically of rheumatic origin)[9]. NVAF includes all three types of AF (paroxysmal AF, persistent AF, and permanent AF), with arbitrary durations. New-onset AF is defined as the first occurrence of AF diagnosed through electrocardiography and/or through 24-hour Holter monitoring after initial presentation or during hospitalization.

Patients and Methods

A total of 89 newly diagnosed AF patients admitted to the Cardiology Department of the First Affiliated Hospital of Nanchang University from January 2017 to January 2023 were included in the AF group. Among them were 46 male patients and 43 female patients. A total of 88 sinus rhythm patients admitted during the same period were enrolled as the control group. Among these were 44 male patients and 44 female patients.

Inclusion Criteria

The AF group met the diagnostic criteria for new-onset AF[10], which included a lack of prior history of AF and confirmation of AF through routine electrocardiography or 24-hour Holter monitoring during the current hospitalization. For the control group, the inclusion criterion was sinus rhythm patients who did not meet the diagnostic criteria for AF. Their exclusion criteria were 1. incomplete case information; 2. patients with coronary heart disease, structural heart disease, cardiomyopathy, heart valve disease, congenital heart disease, etc; 3. patients with recent severe heart failure, postcardiac surgery, or other major surgery; 4. severe liver and kidney insufficiency; 5. stroke (last three months) or malignant tumor; 6. autoimmune disease; 7. acute or chronic inflammatory disease; 8. hyperthyroidism 9. recent use of uric acid reduction.

Data Collection

(1) Collection of basic information: Relevant data, including hospital admission number, age, sex, body weight, blood pressure, and heart rate, were retrieved from our hospital's medical records system. Each patient's past medical history was thoroughly assessed, including the history of hypertension, diabetes, and coronary heart disease. (2) Collection of laboratory parameters: The following laboratory parameters were collected: red blood cells, white blood cells, hemoglobin, neutrophil count, lymphocyte count, red cell distribution width, uric acid, homocysteine, lipid profile, lipoprotein(a), apolipoprotein A1, and apolipoprotein B. (3) Collection of echocardiographic data: The following echocardiographic parameters were collected: left ventricular end-diastolic diameter (LVEDD), left atrial diameter (LAD), left ventricular posterior wall thickness (LVPWT), interventricular septal thickness (IVST), and left ventricular ejection fraction (LVEF).

Statistical Analysis

Statistical analysis was performed using IBM SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA). Normally distributed continuous data are presented as mean ± standard deviation ($\bar{x}\pm s$), and the *t*-test was used for comparisons between the two groups. Nonnormally distributed continuous data are presented as median (interquartile range) "M (*p25, p75*)", and nonparametric tests were used for comparisons between the two groups. Count data are presented as frequency (%), and two groups were compared using the Chi-square or Fisher's exact test. Logistic regression analysis was performed to explore independent risk factors for the development of NVAF. Receiver operating characteristic (ROC) curves were used to evaluate the predictive ability of RDW, Hcy, Lp(a), and LAD for NVAF patients. The optimal cutoff value, sensitivity, and specificity for LAD were calculated. Statistical significance was set at a two-tailed $p<0.05$.

Results

No statistically significant differences were observed between the two groups in general characteristics, including sex, weight, blood pressure, and history of diabetes ($p>0.05$). There were statistically significant differences between the two groups in mean age, heart rate, and history of hypertension ($p<0.05$) (Table I).

Table I. Comparison of general characteristics between the two groups.

Characteristic	AF group (N=89)	Control group (N=88)	*p*
Age/years	68.2±11.2	56.2±13.8	<.001
Sex			
Male	46 (51.7%)	44 (50%)	0.941
Female	43 (48.3%)	44 (50%)	
Weight (kg)	60.0 (54.0-70.0)	60.5 (55.0-68.5)	0.927
SBP (mmHg)	123.0 (114.0-141.0)	123.5 (113.0-142.5)	0.979
DBP (mmHg)	79.0 (71.0-88.0)	78.5 (71.5-87.5)	0.679
Heart rate (bpm)	89.0 (78.0-100.0)	83.0 (72.5-90.0)	0.004
History of hypertension			
Yes	51 (57.3%)	33 (37.5%)	0.013
No	38 (42.7%)	55 (62.5%)	
History of diabetes			
Yes	6 (6.7%)	2 (2.3%)	0.278
No	83 (93.3%)	86 (97.7%)	

SBP: systolic blood pressure; DBP: diastolic blood pressure.

Comparison of biochemical indicators between the two groups showed that the absolute neutrophil/absolute lymphocyte ratio (NLR), RDW, Hcy, Lp(a), uric acid, and creatinine were significantly different between the two groups ($p<0.05$). Erythrocytes, leukocytes, hemoglobin, absolute lymphocyte value, absolute neutrophil value, total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein were not significantly different between the two groups in the indexes of apolipoprotein A1, apolipoprotein B, and the apolipoprotein A1/apolipoprotein B ratio ($p>0.05$) (Table II).

Multivariable Logistic Regression Analysis of Factors Influencing the Occurrence of New-Onset AF

The dependent variable was the presence of newly diagnosed AF (assigned values: 2=No, 1=Yes). Based on the results of the univariate analysis and baseline data adjustments, the following variables were included as independent variables: age, sex (female=2, male=1), hypertension (No=2, Yes=1), diabetes (No=2, Yes=1), LAD, RDW, Hcy, NLR, and Lp(a). The results revealed that NLR, RDW, Hcy, and Lp(a) were independent risk factors for the development of newly diagnosed AF (OR>1, $p<0.05$) (Table III).

The ROC curves for RDW, Hcy, and Lp(a) had area under the curve (AUC) values of 0.851, 0.712, and 0.674, respectively. The sensitivity of RDW was 78.7%, and the specificity was 55.7%, with the optimal cutoff point of 12.75 (95% CI: 0.641-0.791, $p<0.001$). The sensitivity of Hcy was 61.8% and the specificity was 96.6%, with the optimal cutoff point of 14.15 (95% CI: 0.798-0.911, $p<0.001$). The sensitivity of Lp(a) was 53.9% and the specificity was 73.9%, with the optimal cutoff point of 155.25 (95% CI: 0.592-0.750, $p<0.001$). The sensitivity of LAD was 76.4% and the specificity was 89.8%, with the optimal cutoff point of 37 (95% CI: 0.834-0.937, $p<0.001$) (Table IV, Figure 1).

Based on the optimal cutoff point of LAD, all eligible patients were divided into two groups: a low-LAD group (LAD<37 mm) and a high-LAD group (LAD≥37 mm). RDW, Hcy, and Lp(a) values were analyzed in patients divided by LAD (Table V).

Discussion

AF is one of the most common cardiac arrhythmias encountered in clinical practice and has emerged as a significant socioeconomic burden worldwide. It is estimated that there are at least 33.5 million individuals with AF globally, and its incidence is increasing at a rate of 5 million new cases per year, with a prevalence ranging from 2.5% to 3.2%[11]. In the United States, over 3 million people have AF, while in China, this number has already exceeded 10 million[12]. AF patients have a higher incidence of thromboembolism, which is one of the major complications of AF and a leading cause of their mortality and disability[13]. Therefore, early detection of AF is particularly important. The pathogenesis of AF is complex and appears to involve interactions between inflammatory responses[14,15], oxidative stress[16,17], and the development of atrial fibrosis[18]. In the past, AF was predominantly believed to be driven by micro reentry. In recent years, growing evidence[14-18] has suggested a potential relationship

Table II. Comparison of general characteristics between the two groups.

Characteristic	AF group (N=89)	Control group (N=88)	p
WBC (x10^9/L)	5.7 (4.7-6.8)	5.5 (4.9-6.4)	0.533
RBC (x10^9/L)	4.5 (4.1-4.8)	4.4 (4.1-4.8)	0.483
Hb (g/L)	136.0 (123.0-148.0)	134.0 (122.0-145.5)	0.480
Lymphocytes (x10^9/L)	1.5 (1.1-1.8)	1.6 (1.3-2.0)	0.116
Neutrophile granulocyte (x10^9/L)	3.7 (2.8-4.3)	3.4 (2.6-4.2)	0.300
NLR	2.4 (1.9-3.3)	2.2 (1.6-2.7)	0.032
RDW (fL)	13.3 (12.8-14.0)	12.6 (12.3-13.3)	<.001
UA (μmol/L)	352.0 (299.0-416.0)	310.1 (270.5-403.5)	0.044
Creatinine (μmol/L)	79.7 (63.6-91.0)	61.7 (53.0-80.1)	<.001
Cholesterol (μmol/L)	4.1 (3.6-4.9)	4.2 (3.8-4.7)	0.691
TG (μmol/L)	1.1 (0.8-1.6)	1.2 (0.8-1.7)	0.121
LDL-C (μmol/L)	2.5 (1.9-3.0)	2.4 (2.0-2.9)	0.981
HDL-C (μmol/L)	1.2±0.3	1.2±0.3	0.416
Lp(a) (μmol/L)	162.0 (84.0-319.0)	85.0 (49.0-172.5)	<.001
Apolipoprotein A1 (g/L)	1.2±0.2	1.2±0.2	0.735
Apolipoprotein B (g/L)	0.8 (0.7-1.0)	0.8 (0.6-0.9)	0.209
Hcy (μmol/L)	15.0 (12.5-20.0)	10.3 (9.0-12.0)	<.001
Apo A1/Apo B	1.4 (1.2-1.7)	1.5 (1.2-1.9)	0.400
LAD (mm)	41.0 (37.0-45.0)	31.5 (29.0-34.0)	<.001
LVPW (mm)	9.0 (9.0-10.0)	9.0 (8.0-10.0)	0.124
LVEDD (mm)	46.0 (43.0-50.0)	45.0 (42.0-48.0)	0.033
IVST (mm)	10.0 (9.0-10.0)	9.0 (9.0-10.0)	0.032
LVEF (%)	60.0 (58.0-63.0)	62.0 (60.0-65.0)	<.001

NLR: neutrophil-to-lymphocyte ratio; RDW: red cell distribution width; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Lp(a): lipoprotein(a); Hcy: homocysteine; Apo A1/Apo B: apolipoprotein A1/apolipoprotein B ratio; LAD: left atrial diameter; LVPW: left ventricular posterior wall thickness; LVEDD: left ventricular end-diastolic diameter; IVST: Interventricular septal thickness; LVEF: left ventricular ejection fraction.

Table III. Multivariable logistic regression analysis of factors influencing new-onset AF.

Characteristics	OR[1]	95% CI[1]	p
Age (years)	0.94	0.91, 0.98	0.002
NLR	1.29	0.95, 1.80	0.117
RDW (fL)	2.38	1.65, 3.67	<0.001
Hcy (μmol/L)	1.57	1.37, 1.86	<0.001
Lp(a) (mmol/L)	1.01	1.00, 1.01	<0.001

NLR: neutrophil-to-lymphocyte ratio; RDW: red cell distribution width; Hcy: homocysteine; Lp(a): lipoprotein(a). [1]: The presence of new-onset atrial fibrillation was used as the dependent variable (assignment: 2=no, 1=yes), and age, sex, hypertension, diabetes mellitus, left atrial internal diameter, RDW, Hcy, neutrophil-to-lymphocyte ratio, and lipoprotein(a) were used as the independent variables after adjusting for the results of the univariate analysis and the baseline data (assignment: original values of the continuous variables were carried forward; sex: female=2, male=1; hypertension: 2=no, 1=yes; Diabetes: 2=no, 1=yes). The analysis was performed using the forward LR method, which showed that age, NLR, RDW, Hcy, and lipoprotein a were independent risk factors for new-onset AF (OR>1, p<0.05).

Table IV. ROC curve analysis of Lp(a), Hcy, and RDW.

Characteristics	AUC	95% CI	p
RDW (fL)	0.716	0.641-0.791	<0.001
Lp(a) (mmol/L)	0.671	0.592-0.750	<0.001
Hcy (μmol/L)	0.854	0.798-0.911	<0.001
LAD (mm)	0.885	0.834-0.937	<0.001

RDW: red cell distribution width Hcy: homocysteine Lp(a): lipoprotein(a), LAD: left atrial diameter.

between certain biochemical markers and inflammatory and oxidative stress reactions in the body. Felker et al[19] first reported in 2007 that elevated RDW is a novel predictor of morbidity and mortality in patients with chronic heart failure. RDW, as part of blood cell analysis, is readily available in clinical practice. It is a measure of the variation in red blood cell size and reflects the heterogeneity in cell volume and size. In other words, a higher RDW value indicates more significant variability in red blood cell size. Currently, RDW is used to evaluate different types of anemia. For example, RDW is a valuable tool for distinguishing between thalassemia and iron deficiency anemia[20]. However, a large population-based cohort study by Adamsson Eryd et al[21] demonstrated an association between RDW and the incidence of AF. Even after adjusting for dietary intake of folate, iron, and B12 in the model, the increasing risk of AF remained essentially unchanged. Recently, a large cross-sectional study[22] involving 106,998 Chinese participants revealed that the odds ratios for AF in the tertiles of RDW were 1.00, 1.08, and 2.65 (p<0.001). These findings suggest a significant association between increased RDW and the incidence of AF in the general Chinese population. These results suggest that RDW is a novel risk factor for AF development. The underlying mechanisms behind this relationship are not yet fully understood. The association is likely due to the direct impact of changes in red blood cell volume and heart function. It could also reflect the independent effects of other pathological and physiological processes that act on both red blood cells and the heart. Indeed, red blood cells not only play a crucial role in oxygen delivery to tissues but also contribute to cardiovascular regulation through the release of extracellular nucleotides and other mediators. Therefore, alterations in red blood cell function could have a direct impact on the heart[23]. Hemolysis can increase the release of free radicals, which can be harmful to the heart. It has been suggested[24,25] that this process, which includes oxidative stress and inflammation, may be associated with increased RDW. Inflammation may increase RDW by altering iron metabolism or inhibiting

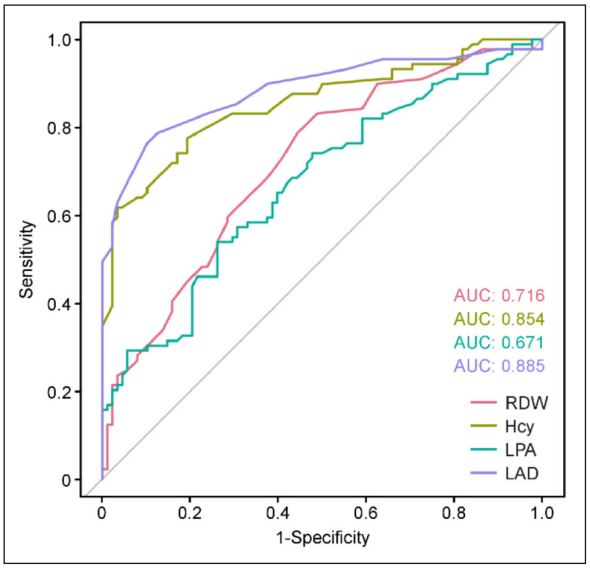

Figure 1. ROC curves of Lp(a), Hcy, RDW and LAD. RDW: red cell distribution width Hcy: homocysteine Lp(a): Lipoprotein(a) LAD: left atrial diameter.

the production of erythropoietin or the response to erythropoietin[26]. In this study, we found a significant association between RDW and LAD (p<0.01). The AUC of RDW was 0.716, which is greater than 0.5 and, therefore, indicates a statistically significant association with new-onset AF. These results are consistent with the significant positive correlation observed between the prevalence of AF and increased LAD[27]. Indeed, RDW appears to be a simple and easily accessible marker, suggesting[21] its promise as a tool for the diagnosis and prevention of AF and its adverse outcomes.

Hcy is an essential component of the methionine cycle and an intermediate product of metabolism. Hcy, a marker of oxidative stress discovered in recent years, is involved in the onset, development, prognosis, and recurrence of AF. Elevated serum/plasma Hcy levels have been moderately associated with an increased risk of AF, as observed in the prospective population-based ARIC and MESA cohort studies[28]. Another clinical study[29] has shown that serum/plasma Hcy levels can influence atrial electrical activity. The meta-a-

Table V. Grouping according to LAD truncation values.

Characteristics	<37 mm (N=100)	≥37 mm (N=77)	p
RDW (fL)	12.7 (12.4-13.3)	13.4 (12.8-14.1)	<0.001
Lp(a) (mmol/L)	101.3 (56.0-193.5)	144.0 (68.0-253.0)	<0.050
Hcy (μmol/L)	10.9 (9.3-12.2)	15.0 (13.0-19.0)	<0.001

RDW: red cell distribution width Hcy: homocysteine Lp(a): lipoprotein(a).

nalysis conducted by Dong et al[7], which covered five clinical studies, demonstrated a significant association between Hcy and AF. The role of Hcy in patients with AF should not be overlooked in clinical practice. The clinical study by Yao et al[30] showed that Hcy is an independent risk marker for the early recurrence of AF after catheter ablation. The AUC of LAD in our study (95% CI: 0.834-0.937, $p<0.001$) suggests a significant correlation between Hcy and LAD, consistent with a clinical study by Marcucci et al[31], who found a mild correlation between LAD and Hcy levels in patients with AF. Many pathophysiological mechanisms can explain the effect of Hcy on LAD; in normal blood vessels and heart walls, elastin and collagen act as a solid protective barrier, and it is only when this barrier fails or is disrupted that dilatation of the atria or ventricles, and eventual aneurysms of the blood vessels occur. Some in vitro studies[32,33] suggest that Hcy may be involved in the pathogenesis of left atrial enlargement by increasing the activity of matrix metalloproteinases and may be involved in the mechanisms of AF maintenance, recurrence, and risk of ischemic attack during AF. In summary, increased Hcy may cause structural changes in the left atrium and electrical activity, leading to the development of AF.

Whether Lp(a) is associated with the onset and progression of AF has not been established. A prospective community study[34] of 10,127 participants without AF at baseline found no significant linear trend between AF and Lp(a) quartile. The results of another observational and Mendelian randomization study[5] of elevated Lp(a) and AF risk indicated that Lp(a) is a causal mediator in the development of AF. Importantly, these studies did not include Asian participants. A published Mendelian randomization study[35] in a Chinese Han population showed that genetically elevated Lp(a) was negatively associated with AF risk. These results suggest that the risk of Lp(a) for AF may be related to ethnicity and sex. Lp(a) plays a role in atherosclerotic cardiovascular disease and is a recognized risk factor for coronary artery disease, aortic stenosis, and ischemic stroke[36-38]. Some studies[39,40] have found that both ischemic heart disease and aortic stenosis were consequences of elevated Lp(a) and risk factors for AF; this is one mechanism by which Lp(a) contributes to the development of AF. In addition, an observational and Mendelian randomization study by Mohammadi-Shemirani et al[5] indicated a role for Lp(a) in myocardial tissue beyond atherosclerotic cardiovascular disease, suggesting Lp(a) as a potential causal mediator in the development of AF. This suggests that although coronary artery disease itself is a risk factor for AF, Lp(a) particles have additional thrombogenic and inflammatory properties that may provide other mechanisms independent of atherosclerotic cardiovascular disease. In this study, Lp(a) was significantly higher in the experimental group than in the control group (162.0 *vs.* 85.0, $p<0.01$), and Lp(a) was higher in the LAD≥37 mm group than in the low-LAD group (144.0 *vs.* 101.3, $p<0.05$), which also suggests that Lp(a) may affect the structure of the left atrium through inflammation or oxidative stress and thus contribute to the development of AF, in line with existing studies[41]. In summary, the effect of Lp(a) on AF may be related to various factors, such as ethnicity, sex, inflammation, and oxidative stress response. More rigorous prospective clinical studies are still needed to validate this hypothesis.

Limitations

Retrospective nature: The study design was retrospective, introducing the possibility of information bias and limitations in data collection. Single-center nature: Conducting the study in a single center may have reduced the generalizability of the findings to a broader population, and the limited sample size may have weakened the statistical power and the ability to draw definitive conclusions. Further research is needed on the clinical implications of ROC curve analysis. The determination of critical values through ROC curve analysis requires additional research to establish its significance and applicability in clinical practice.

Conclusions

RDW, Hcy, and Lp(a) were all elevated in patients with new-onset AF and significantly and positively correlated with LAD in patients with new-onset AF, suggesting that RDW, Hcy, and Lp(a) may contribute to the development of AF by affecting the electrical activity and structure of the left atrium and are risk factors for the development of new-onset AF.

Ethics Approval

This study was approved by The First Affiliated Hospital of Nanchang University Review Board. The ethical approval number is IIT2023315.

Informed Consent
The Ethics Committee waived the need to obtain an informed consent.

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Authors' Contributions
Libing Zhang analyzed the data, drafted the manuscript and was the primary contributor to writing this manuscript. Zhi Zhao collected the data. Yongnan Fu conceived and designed the study, provided funding support, and made substantial revisions and critical reviews of the article.

Data Availability
The dataset used and analyzed in this study can be obtained from the corresponding authors upon reasonable request.

Conflict of Interest
All authors declare that they have no conflicts of interest.

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