

ORIGINAL ARTICLE

Association between adiponectin-to-leptin ratio and heart rate variability in new-onset paroxysmal atrial fibrillation: A retrospective cohort study

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Abstract

Background: The adiponectin-to-leptin (A/L) ratio has been identified as a potential surrogate biomarker for metabolic disorders. However, it remains unknown whether the serum A/L ratio is associated with heart rate variability in paroxysmal atrial fibrillation (AF).

Methods: For this retrospective study, we included consecutive patients who underwent 24-h long-range electrocardiogram examination in our center for paroxysmal AF. The results of echocardiography, heart rate variability tests, and blood tests were also retrieved. Multivariate line regression analysis was performed to evaluate identify factors independently associated with heart rate variability.

Results: Among the 85 included patients with paroxysmal AF, the median A/L ratio was 1.71. Univariate analysis indicated that patients with a low A/L ratio (<1.71 , $n = 42$) had a lower high-frequency (HF) power and a higher hs-CRP level, low-frequency (LF) power, and LF/HF ratio than those with a high A/L ratio (≥ 1.71 , $n = 43$). Multivariate linear regression analysis showed that the serum leptin concentration was independently and positively associated with LF ($\beta = 0.175$, $p = .028$), while the serum adiponectin concentration was independently and positively associated with HF ($\beta = 0.321$, $p = .001$). Moreover, the A/L ratio was independently and negatively associated with the LF/HF ratio ($\beta = -0.276$, $p = .007$).

Conclusions: The A/L ratio was independently and negatively associated with the LF/HF ratio in patients with new-onset paroxysmal AF.

KEYWORDS

adiponectin, autonomic function, heart rate variability, leptin, paroxysmal atrial fibrillation

1 | INTRODUCTION

Patients with atrial fibrillation (AF), particularly those with paroxysmal AF, often have an unstable clinical status and increased risks

of morbidity, mortality, and disability (Beaser Andrew & Cifu, 2019; Morillo Carlos et al., 2017). The pathogenesis of AF centers on autonomic nervous system activation and atrial structural remodeling (Chen et al., 2014; Liu et al., 2019). However, it is well established

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that obesity adversely affects cardiovascular hemodynamics, as well as cardiac structure and function, resulting in an increased prevalence of AF mediated by the altered secretion of a variety of adipokines such as leptin, adiponectin, and others (Lavie et al., 2017). Adipokines play complex roles in the process of AF via their activities related to inflammation, autonomic function, and myocardial fibrosis (Kershaw & Flier, 2004; Lin et al., 2013; Prior Sarah et al., 2009; Zhou et al., 2020).

Adiponectin, one of the most abundant adipokines in human plasma, was shown to exert cardioprotective effects via its insulin-sensitizing, anti-inflammatory, and antioxidant effects (Li et al., 2009; Ouchi et al., 2011; Prior Sarah et al., 2009). However, in patients with paroxysmal AF, a high circulating adiponectin level was confirmed to be independently associated with a poor clinical outcome after treatment by catheter ablation (Kim et al., 2018). Additional experimental data indicate that interactions between adiponectin and the intrinsic cardiac autonomic nervous system may contribute to AF (Kershaw & Flier, 2004). Leptin is another important adipocytokine that regulates the physiological functions of the heart and has been linked to AF in the contexts of inflammation, myocardial remodeling, and sympathetic nervous system stimulation (Jenne & Tschopp, 1992; Jiang et al., 2020; Li & Liu, 2009; Lin et al., 2012).

Recent studies showed that the serum leptin/adiponectin ratio, which incorporates two major subgroups of adipokines, may offer prognostic value in many diseases based on findings that this ratio can reflect the presence of metabolic disturbances in obesity, the extent and severity of coronary artery disease, and idiopathic pulmonary fibrosis (Enomoto et al., 2019; Larsen et al., 2018; Rahmani et al., 2020). Vega and Grundy found that the adiponectin/leptin (A/L) ratio is a marker of adipose tissue dysfunction (Lena & Grundy, 2013), and Frühbeck et al. reported a negative correlation between the A/L ratio and biomarkers of low-grade chronic inflammation (Frühbeck et al., 2018). Overall, the current clinical and experimental data support interaction between inflammation and cardiac autonomic nervous system that facilitates both the initiation and perpetuation of cardiovascular disease (Pizzi et al., 2010; Williams et al., 2019). However, the potential relationships between the A/L ratio and measures of autonomic imbalance in new-onset paroxysmal AF have not been characterized in the literature. Therefore, in the present study, we investigated the associations between the A/L ratio and heart rate variability in patients with new-onset paroxysmal AF.

2 | MATERIALS AND METHODS

2.1 | Study population

This retrospective study included 85 consecutive patients with a first diagnosis of paroxysmal AF who were scheduled to receive radiofrequency ablation at the Renmin Hospital of Wuhan University

from March 2019 to December 2020. A total of 85 matched individuals with normal sinus rhythm (NSR) were included as controls. Paroxysmal AF was diagnosed according to the guidelines established by the European Society of Cardiology (Hindricks et al., 2021). Patients with a history of any of the following clinical conditions were excluded, as these factors may affect the A/L ratio: previous paroxysmal AF, acute coronary syndrome, any structural heart disease, stroke, cardiac failure (left ventricular ejection fraction [LVEF] <50%), implantation of pacemaker, other arrhythmias (e.g., bradycardia, sick sinus syndrome, atrioventricular block, or ventricular arrhythmias), abnormal $\geq 5\%$ effective rhythm according to 24-h long-range electrocardiographic examination, cancer, any autoimmune disease, any hematological disease, renal failure, any hepatic disease (e.g., nonalcoholic fatty liver disease or cirrhosis), thyroid insufficiency, any systemic acute disease, and any chronic infectious disease. All methods were performed in accordance with the relevant guidelines and regulations.

2.2 | Blood sampling and laboratory analyses

Venous blood samples were collected after fasting, centrifuged, and stored at -80°C until analysis. Samples for the measurement of fasting blood glucose, lipid levels, uric acid, N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), and creatinine were analyzed by a Siemens Healthcare Diagnostics instrument. Plasma adiponectin and leptin levels were determined by enzyme-linked immunosorbent assay (ELISA) using kits from Millipore.

2.3 | Echocardiography

A transthoracic echocardiography exam with color Doppler echocardiography was performed for all participants by the same skilled ultrasound physician. The left ventricular end-diastolic diameter (LVEDD), and left atrial anteroposterior diameter (LAD) were measured using standard M-mode echocardiography. The left ventricle ejection fraction (LVEF) was calculated with the modified Simpson method.

2.4 | Holter monitoring and heart rate variability analysis

For all participants, 24-h long-range 12-channel electrocardiographic recordings (DMS300-4A, DM Software, Inc.) were obtained upon admission. To simulate actual clinical use and cardiac sympathetic activity throughout the day and night, no attempt was made to control patient or environmental factors. Therefore, we expect that continuous monitoring with 24-h long-range 12-channel electrocardiography provides information about shifting HRV throughout the

day. All 24-h long-range electrocardiographic recordings were saved with a sampling frequency of 1 kHz (signal bandwidth 0.04–387 Hz) and a resolution of 1 μ V/bit. After classifying the QRS morphology, the R–R intervals (longest and shortest) were confirmed manually until no QRS sequences were incorrectly labeled. Only sequences with normal QRS characteristics during 24 h (sinus rhythm) were analyzed for the HRV study. During analysis, patients with sinoatrial node dysfunction and a large number of abnormal rhythms (abnormal $\geq 5\%$ effective rhythm) were excluded. The specific signal processing steps for computation of the HRV parameters are detailed elsewhere (El Aarbaoui et al., 2017). HRV, which reflects cardiac autonomic function, was analyzed using commercial software (H-Scribe Analysis System, Mortara Instrument, Inc.). The following parameters of HRV were calculated according to previously published methods and using customized and validated software (Circulation, 1996). HRV indexes included both time-domain parameters (i.e., standard deviation of all normal sinus R–R intervals [SDNN], standard deviation average of normal-to-normal (NN) intervals [SDANN], percentage of the number of times that the difference between adjacent normal R–R intervals > 50 ms in the total number of NN intervals [pNN50], and root mean square successive difference [rMSSD]) and frequency-domain parameters (i.e., high-frequency power [HF, 0.15–0.4 Hz], low-frequency power [LF, 0.04–0.15 Hz], and low-frequency/high-frequency [LF/HF] ratio). The rMSSD in NN intervals is considered an estimate of the short-term components of HRV. The pNN50 is derived by dividing NN50 (the number of interval differences of successive NN intervals > 50 ms) by the total number of NN intervals. The SDNN is the standard deviation of all intervals between adjacent QRS complexes resulting from sinus node depolarization (NN), that is, the square root of variance, and reflects the cyclic components responsible for variability in the period of recording. The SDNN is considered as an estimate of overall HRV, encompassing vagal and sympathetic influences. SDANN is the standard deviation of the averages of NN intervals in all 5-min segments of the 24-h recording. For frequency-domain variables, fast Fourier transformation was used to convert the different successive RR intervals in the frequency domain. HF generally reflects cardiac parasympathetic nerve activity. Accordingly, the LF/HF ratio provides an indicator of the balance between sympathetic and parasympathetic activities, with higher LF/HF ratio values indicating increased sympathetic nerve excitability (Circulation, 1996). Analysis of the LF/HF ratio rather than either single component is widely accepted as a preferred technique for assessing cardiac autonomic nervous system balance and sympathetic activity (Xhyheri et al., 2012).

2.5 | Statistical analysis

All statistical analyses were carried out using SPSS 22.0 software (SPSS, Inc.). The included patients were assigned to two groups according to the median value of the A/L ratio among the study population, and comparisons were made between the groups with low and high A/L ratios. Continuous data are presented as

mean \pm standard deviation (SD) or median (interquartile range), and categorical data as number and percentage. The two-sample *t* test was used to compare variables that showed a normal distribution, and the Mann-Whitney *U* test was used to compare variables that showed non-normal distributions. Categorical data are reported as count (proportion) and were compared using the χ^2 test or Fisher's exact test. The Spearman correlation analysis was performed to evaluate the correlations between A/L ratio and indices of heart rate variability (i.e., LF, HF, and LF/HF ratio). Variables for which a significant correlation was found ($p < .05$) were included in the subsequent multivariate logistic regression analysis. For all analyses, statistical significance was recognized if $p < .05$.

3 | RESULTS

3.1 | Clinical characteristics of patients with AF and controls with normal sinus rhythm

A total of 85 patients with new-onset paroxysmal AF and 85 people with NSR were included, and the baseline characteristics of the included participants are presented in Table 1. Significant differences were detected for NT-proBNP, LDL-cholesterol, total cholesterol, triglycerides, adiponectin, A/L ratio, LAD, LVEF, SDNN, rMSSD, PNN50, LF, HF, LF/HF ratio, and heart rate between the two groups. Patients with new-onset paroxysmal AF were more likely to have lower values of LDL-cholesterol, total cholesterol, triglycerides, and LVEF and higher values of NT-proBNP, adiponectin, A/L ratio, LAD, SDNN, rMSSD, PNN50, LF, HF, LF/HF ratio and heart rate compared to those with NSR (all $p < .05$).

3.2 | Characteristics of patients according to A/L ratio

Overall, 85 patients with new-onset paroxysmal AF were included, and the characteristics of the included participants are presented in Table 2. Those with a higher A/L ratio (≥ 1.71 , $n = 43$) were more likely to be male and to have a lower body mass index (BMI), triglyceride level, uric acid level, heart rate, hs-CRP level, LF, and LF/HF ratio but a higher HF compared with those with a lower A/L ratio (< 1.71 , $n = 42$; all $p < .05$). However, with the grouping of patients according to A/L ratios, no correlation was detected between adipokine levels and time-domain HRV indices. The patient groups with low and high A/L ratios showed no significant differences in the other observed characteristics.

3.3 | Association between leptin and LF

The results of Spearman correlation analysis showed that coronary heart disease, BMI, hs-CRP level, leptin concentration (Figure 1a), A/L ratio, LAD, LVEF, and heart rate were significantly correlated

	New-onset PAF group	Normal sinus rhythm group	<i>t/z/χ²</i>	<i>p</i>
Men (n/%)	57 (67.1)	55 (64.7)	0.105	.746
Age (years)	60.8 ± 11.1	60.8 ± 10.9	0.007	.994
Hypertension (n/%)	41 (48.2)	45 (52.9)	0.377	.539
Diabetes mellitus (n/%)	76 (89.4)	67 (78.8)	3.566	.059
Smoking (n/%)	65 (76.5)	59 (69.4)	1.073	.300
Drinking (n/%)	68 (80.0)	61 (71.8)	1.575	.209
CHD (n/%)	71 (83.5)	61 (71.8)	3.389	.066
BMI (kg/m ²)	25.3 ± 3.6	24.3 ± 3.0	1.888	.061
NT-proBNP	480.1 ± 578.3	76.9 ± 71.9	5.748	<.001
Fasting glucose (mmol/L)	5.40 ± 1.89	6.04 ± 5.40	1.007	.315
HDL-cholesterol (mmol/L)	1.17 ± 0.45	1.14 ± 0.33	0.518	.605
LDL-cholesterol (mmol/L)	2.38 ± 0.69	2.61 ± 0.83	1.987	.049
Total cholesterol (mmol/L)	4.12 ± 0.88	4.52 ± 1.03	2.629	.009
Triglycerides (mmol/L)	1.86 ± 1.14	2.31 ± 1.64	2.028	.044
Creatinine (μmol/L)	72.01 ± 17.80	70.56 ± 23.06	0.380	.704
Uric acid (μmol/L)	386.05 ± 93.97	400.49 ± 123.13	0.848	.398
hs-CRP	1.17 (0.56, 3.19)	0.91 (0.50, 2.38)	0.714	.475
Aiponectin (μg/ml)	7.07 (4.59, 9.09)	5.28 (3.31, 7.74)	3.123	.002
Leptin (ng/ml)	3.60 (1.85, 5.35)	3.05 (1.89, 5.45)	0.268	.789
A/L ratio	1.72 (1.16, 3.84)	1.00 (0.90, 2.42)	2.149	.032
LAD (mm)	40.38 ± 5.71	34.42 ± 4.10	7.808	<.001
LVEDD (mm)	45.11 ± 5.78	43.91 ± 3.64	1.619	.107
LVEF (%)	57.39 ± 4.21	59.89 ± 1.90	4.996	<.001
SDNN (ms)	172 ± 82	133 ± 35	3.914	<.001
SDANN (ms)	110 (95, 140)	108 (92, 126)	0.600	.549
rMSSD (ms)	90 (44, 152)	44 (31, 65)	4.854	<.001
PNN50 (ms)	11 (33, 72)	8 (3, 17)	5.990	<.001
LF (ms ²)	1043 (575, 2398)	863 (574, 1211)	2.029	.042
HF (ms ²)	797 (281, 1157)	575 (393, 919)	8.134	<.001
LF/HF ratio	2.0 (1.1, 5.0)	1.65 (1.11, 2.21)	8.565	<.001
Heart rate (beats/min)	75.05 ± 10.54	67.70 ± 7.59	4.978	<.001

TABLE 1 Clinical characteristics of patients with AF and controls with normal sinus rhythm

Note: Continuous variables are presented as mean ± SD or median and IQR; categorical variables are presented as number (percentage); values of *p* < .05 are indicated in bold.

Abbreviations: A/L, Adiponectin/Leptin; BMI, body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein; HF, high frequency; hs-CRP, high-sensitivity C-reactive protein; LAD, left atrial diameter; LDL, low-density lipoprotein; LF, low frequency; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricle ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PNN50, percent of the number of times that the difference between adjacent normal R-R intervals >50 ms in the total number of NN intervals; rMSSD, root mean square successive difference of normal R-R intervals; SDANN, standard deviation average of NN intervals; SDNN, standard deviation of normal R-R intervals.

with LF (all *p* < .05, Table 3). Subsequent multivariate analysis also identified coronary heart disease, BMI, hs-CRP level, leptin concentration, and heart rate as independently associated with LF among all study participants (*p* < .05, Table 4).

3.4 | Association between adiponectin and HF

Univariate line regression analysis identified hs-CRP level, adiponectin concentration (Figure 1b), leptin concentration, A/L ratio, and

TABLE 2 Characteristics of patients with new-onset paroxysmal AF according to A/L ratio

Clinical characteristics	All patients (n = 85)	A/L ratio <1.71 (n = 42)	A/L ratio ≥1.71 (n = 43)	t/z/χ ²	p
Men (n/%)	57 (67.1)	22 (52.4)	35 (81.4)	8.097	.004
Age (years)	60.8 ± 11.1	61.9 ± 9.8	59.8 ± 12.2	0.857	.394
Hypertension (n/%)	41 (48.2)	19 (45.2)	22 (51.2)	0.299	.585
Diabetes mellitus (n/%)	76 (89.4)	36 (85.7)	40 (93.0)	0.551	.458
Smoking (n/%)	65 (76.5)	33 (78.6)	32 (74.4)	0.204	.652
Drinking (n/%)	68 (80.0)	35 (83.3)	33 (76.7)	0.577	.448
CHD (n/%)	71 (83.5)	36 (85.7)	35 (81.4)	0.288	.591
BMI (kg/m ²)	25.3 ± 3.6	26.0 ± 2.9	24.0 ± 3.6	2.893	.005
NT-proBNP (pg/ml)	480.1 ± 578.3	502.4 ± 631.5	455.8 ± 522.8	0.332	.741
Fasting glucose (mmol/L)	5.40±1.89	5.62 ± 2.48	5.17 ± 0.96	1.075	.287
HDL-cholesterol (mmol/L)	1.17 ± 0.45	1.20 ± 0.59	1.14 ± 0.26	0.573	.568
LDL-cholesterol (mmol/L)	2.38 ± 0.69	2.34 ± 0.71	2.41±0.67	0.424	.673
Total cholesterol (mmol/L)	4.12 ± 0.88	4.24 ± 1.00	4.02 ± 0.75	1.144	.256
Triglycerides (mmol/L)	1.86 ± 1.14	2.18±1.18	1.56 ± 1.01	2.566	.012
Creatinine (μmol/L)	72.01 ± 17.80	74.17 ± 22.95	69.48 ± 10.76	1.191	.239
Uric acid (μmol/L)	386.05 ± 93.97	407.8 ± 99.06	364.29 ± 84.25	2.142	.035
hs-CRP (mg/L)	1.17 (0.56, 3.19)	2.19 (0.64, 3.83)	1.00 (0.51, 2.01)	2.462	.014
Aiponectin (μg/ml)	7.07 (4.59, 9.09)	5.19 (3.18, 7.78)	8.40 (6.66, 9.88)	4.052	<.001
Leptin (ng/ml)	3.60 (1.85, 5.35)	5.11 (3.90, 6.48)	2.11 (1.47, 3.17)	6.513	<.001
A/L ratio	1.72 (1.16, 3.84)	1.16 (0.83, 1.47)	3.78 (2.59, 5.21)	7.937	<.001
LAD (mm)	40.38 ± 5.71	40.76 ± 5.28	40.00 ± 6.13	0.613	.542
LVEDD (mm)	45.11 ± 5.78	45.74 ± 4.29	44.49 ± 6.93	0.996	.322
LVEF (%)	57.39 ± 4.21	57.64 ± 2.69	57.14 ± 5.32	0.552	.583
SDNN (ms)	172 ± 82	166 ± 71	177 ± 92	0.598	.552
SDANN (ms)	110 (95, 140)	101 (93, 141)	114 (95, 139)	1.226	.220
rMSSD (ms)	90 (44, 152)	91 (53, 158)	90 (40, 129)	0.264	.792
PNN50 (ms)	11 (33, 72)	31 (15, 72)	34 (9, 72)	0.171	.864
LF (ms ²)	1043 (575, 2398)	1326 (648, 3618)	884 (516, 1458)	2.127	.033
HF (ms ²)	797 (281, 1157)	453 (133, 917)	854 (508, 1280)	2.813	.005
LF/HF ratio	2.0 (1.1, 5.0)	4.8 (1.8, 6.9)	1.6 (0.6, 2.8)	4.043	<.001
Heart rate (beats/min)	75.05 ± 10.54	77.50 ± 11.71	72.65 ± 8.73	2.160	.034

Note: Continuous variables are presented as mean ± SD or median and IQR; categorical variables are presented as number (percentage); values of $p < .05$ are indicated in bold.

Abbreviations: A/L, Adiponectin/Leptin; BMI, body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein; HF, high frequency; hs-CRP, high-sensitivity C-reactive protein; LAD, left atrial diameter; LDL, low-density lipoprotein; LF, low frequency; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricle ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PNN50, percent of the number of times that the difference between adjacent normal R-R intervals >50 ms in the total number of NN intervals; rMSSD, root mean square successive difference of normal R-R intervals; SDANN, standard deviation average of NN intervals; SDNN, standard deviation of normal R-R intervals.

heart rate as significantly associated with HF ($p < .05$, Table 5). Of these factors, only hs-CRP concentration and adiponectin concentration were independently associated with HF in the overall cohort according to the subsequent multivariate analysis ($p < .05$, Table 6).

3.5 | Association between A/L ratio and LF/HF ratio

Univariate logistic regression analysis identified hypertension, gender, hs-CRP concentration, A/L ratio (Figure 1c), and LAD as factors

significantly correlated with the LF/HF ratio ($p < .05$, Table 7). On the subsequent multivariate analysis, only hs-CRP concentration and A/L ratio were independently associated with the LF/HF ratio in the overall patient cohort ($p < .05$, Table 8).

4 | DISCUSSION

In this case-control study of AF patients and NSR controls, we found that the serum adiponectin levels, A/L ratio, SDNN, rMSSD, PNN50, LF, HF, and LF/HF ratio were significantly higher in

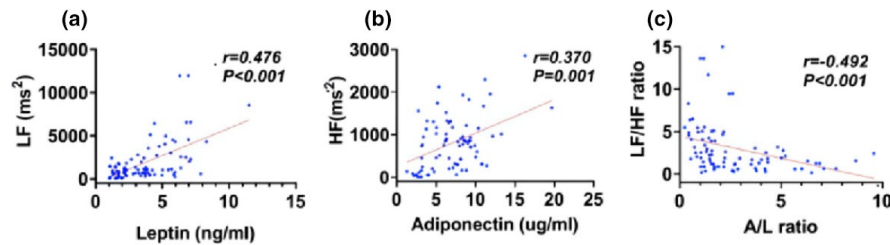


FIGURE 1 Correlation analyses between Adipocytokines and HRV in the included new-onset paroxysmal AF participants; (a) Association between leptin and LF; (b) correlation of adiponectin with HF; (c) correlation of A/L ratio with LF/HF ratio. HRV, heart rate variability; AF, atrial fibrillation; LF, low frequency; HF, high frequency; A/L, Adiponectin/Leptin

TABLE 3 Univariate linear regression model for LF

Variables	Univariate		
	B	t	p
Women (n/%)	0.100	0.914	.363
Age (years)	-0.013	0.122	.903
Hypertension (n/%)	0.185	1.717	.090
Diabetes mellitus (n/%)	-0.047	0.428	.670
Smoking (n/%)	-0.093	0.855	.395
Drinking (n/%)	-0.140	1.285	.202
CHD (n/%)	-0.509	5.391	<.001
BMI (kg/m ²)	0.502	5.293	<.001
NT-proBNP (pg/ml)	0.216	1.813	.074
Fasting glucose (mmol/L)	-0.021	0.187	.852
HDL-cholesterol (mmol/L)	0.138	1.246	.217
LDL-cholesterol (mmol/L)	0.112	1.004	.318
Total cholesterol (mmol/L)	0.087	0.784	.436
Triglycerides (mmol/L)	-0.119	1.068	.289
Creatinine (μmol/L)	-0.093	0.848	.399
Uric acid (μmol/L)	-0.030	0.266	.791
hs-CRP (mg/L)	0.576	6.417	<.001
LAD (mm)	0.424	4.269	<.001
LVEDD (mm)	0.131	1.207	.231
LVEF (%)	-0.214	1.992	.049
Adiponectin (μg/ml)	0.156	1.443	.153
Leptin (ng/ml)	0.512	5.426	<.001
A/L ratio	-0.320	3.072	.003
Heart rate (beats/min)	0.457	4.679	<.001

Note: Values of $p < .05$ are indicated in bold. All abbreviations are presented in Table 1.

new-onset paroxysmal AF patients than in control individuals with NSR. Among the included patients with new-onset paroxysmal AF, we found that those with a higher A/L ratio had a higher HF power but lower LF power and LF/HF ratio compared to those with a lower A/L ratio. This finding was further verified by the results of Spearman correlation analysis showing correlations between the A/L ratio and LF, A/L ratio and HF, A/L ratio and the LF/HF ratio.

Subsequent multivariate analysis identified a significant independent association between the A/L ratio and LF/HF ratio in the overall study population. Moreover, the results of multivariate linear regression analysis showed that the serum leptin concentration was independently and positively associated with LF, while the serum adiponectin concentration was independently and positively associated with HF. Taken together, our results demonstrate that the A/L ratio is correlated with cardiac autonomic function in patients with new-onset paroxysmal AF.

4.1 | Cardiac autonomic function and AF

Despite the availability of many studies on the subject, the pathogenesis of AF remains unclear. Its pathogenesis has been primarily attributed to mechanisms involving the cardiac autonomic function system (Chen et al., 2014; Liu et al., 2019). The current understanding is that sympathetic and vagal activation work together to create a more pronounced new-onset paroxysmal AF substrate than sympathetic or parasympathetic stimulation alone (Khan et al., 2019). Acute conditions related with the transient imbalance of cardiac autonomic function activation may cause a dynamic arrhythmogenic substrate and provide the trigger and initiator for AF (Linz et al., 2019). Complex interactions exist between cardiac autonomic function activation and AF that may further perpetuate the progression of the arrhythmia of AF (Linz et al., 2019). Moreover, prognostic information regarding mortality risk can be derived from the balance of the cardiac autonomic nervous system by measuring the HRV index in a single 5-min ECG recording in patients with AF (Hämmerle et al., 2020). In comparison with the previous study, although the collection of HRV indices in routine ambulatory 5-min ECG recordings is simple, easy to perform, and can be applied to practical problems, it cannot provide information about cardiac sympathetic activity all day, which can be obtained using 24-h long-range 12-channel electrocardiography (Hämmerle et al., 2020). Therefore, our study, using 24-h long-range 12-channel electrocardiography, provides current information on cardiac autonomic function in new-onset paroxysmal AF. Our study further indicated that the HRV index, which reflects cardiac autonomic nervous system modulation, was associated with new-onset paroxysmal AF. Moreover, our study showed low serum

TABLE 4 Multivariate linear regression model for LF

Variables	B	SE	β	t	p
Constant	-6323.072	3677.070		1.720	.090
CHD (n/%)	-2192.437	499.727	-0.323	4.387	<.001
BMI (kg/m ²)	187.361	55.699	0.266	3.364	.001
hs-CRP (mg/L)	675.285	180.169	0.314	3.748	<.001
Leptin (ng/ml)	0.201	0.090	0.175	2.237	.028
A/L ratio	-43.000	36.217	-0.087	1.187	.239
Heart rate (beats/min)	34.999	15.891	0.167	2.202	.031
LAD (mm)	12.662	38.043	0.028	0.333	.740
LVEF (%)	9.851	50.342	0.016	0.196	.845

Note: Values of $p < .05$ are indicated in bold. All abbreviations are presented in Table 1.

TABLE 5 Univariate linear regression model for HF

Variables	Univariate		
	B	t	p
Women (n/%)	-0.136	1.251	.215
Age (years)	-0.13	0.116	.908
Hypertension (n/%)	-0.143	1.317	.192
Diabetes mellitus (n/%)	0.069	0.632	.529
Smoking (n/%)	-0.022	0.205	.838
Drinking (n/%)	-0.108	0.988	.326
CHD (n/%)	0.146	1.345	.182
BMI (kg/m ²)	-0.024	0.217	.828
NT-proBNP (pg/ml)	-0.013	0.105	.917
Fasting glucose (mmol/L)	-0.065	-0.579	.564
HDL-cholesterol (mmol/L)	0.080	0.717	.475
LDL-cholesterol (mmol/L)	0.141	1.274	.206
Total cholesterol (mmol/L)	-0.001	0.008	.994
Triglycerides (mmol/L)	-0.083	0.744	.459
Creatinine (μ mol/L)	-0.081	0.736	.464
Uric acid (μ mol/L)	0.029	0.263	.793
hs-CRP (mg/L)	-0.459	4.709	<.001
LAD (mm)	0.127	0.166	.247
LVEDD (mm)	0.104	0.952	.344
LVEF (%)	-0.147	1.354	.179
Adiponectin (μ g/ml)	0.419	4.203	<.001
Leptin (ng/ml)	-0.307	2.926	.003
A/L ratio	0.301	2.895	.005
Heart rate (beats/min)	0.316	3.002	.001

Note: Values of $p < .05$ are indicated in bold. All abbreviations are presented in Table 1.

levels of LDL-cholesterol, total cholesterol, and triglycerides were found in new-onset paroxysmal AF patients, which is consistent with previous studies showing that hypolipidemia may be related to paroxysmal AF (Annoura et al., 1999). However, further research is needed to evaluate the potential mechanisms underlying the association between hypolipidemia and AF.

4.2 | A/L ratio and heart rate variability

Obesity has consistently emerged as a risk factor for AF and the progression of paroxysmal to permanent AF, which is related to the release of adipokines by adipose tissue (Badimon et al., 2017). Accordingly, dysfunction among adipose tissue as indicated by a low A/L ratio may represent a hallmark of obesity and metabolic syndrome, with increased levels of proinflammatory factors serving as potential mediators in the relevant pathophysiological processes (Frühbeck et al., 2017). Therefore, it has been proposed that a low A/L ratio may be a novel and reliable surrogate biomarker of inflammation and a diagnostic factor for new-onset paroxysmal AF. Also, links between epicardial adipose tissue and AF were demonstrated in recent studies based on the interaction between adipose tissue and inflammation, further supporting our conclusions (Tran et al., 2019). Indeed, previous studies showed significant association between the L/A (leptin/adiponectin) ratio and the severity of coronary lesions in patients with coronary artery disease patients according to the Gensini score (Rahmani et al., 2020). Similarly, use of the L/A ratio as a clinically useful biomarker was reported as a promising alternative for detecting early obesity-related metabolic disturbances of any kind (Larsen et al., 2018). Moreover, because the A/L ratio reflects the functionality of adipose tissue, this ratio may be a valuable index for identifying patients at risk for cardiometabolic diseases (Frühbeck et al., 2017). In the present study, the balance of cardiac autonomic tone was evaluated by applying power spectral analysis of heart rate variability, and the results provide a pathophysiological basis underlying the association between A/L ratio and cardiac autonomic tone. Our previous study found that adiponectin acts on adiponectin receptor (Adipor) of cardiac ganglionated plexus (GP) neurons to activate the Adipor/AMPK/NF- κ B signaling pathway, reducing the expression of proinflammatory factors, and preventing the occurrence of AF by inhibiting the activity of GP neurons, further confirming the protective effect of adiponectin in AF (Zhou et al., 2020). Taken together, our findings have further confirmed that an abnormal A/L ratio may serve as a novel index to predict the risk of new-onset paroxysmal AF or as a prognostic marker in AF. Further studies are needed to confirm these findings and expand our understanding of the potential role of the A/L ratio in risk stratification for new-onset paroxysmal AF patients.

Variables	B	SE	β	t	p
Constant	13845.174	3937.406		3.516	.001
hs-CRP (mg/L)	-1385.132	352.280	-0.368	-3.932	<.001
Adiponectin (μ g/ml)	0.602	0.178	0.321	3.377	.001
Leptin (ng/ml)	-0.361	0.263	-0.125	-1.377	.172
A/L ratio	179.821	103.259	0.161	1.741	.085
Heart rate (beats/min)	-96.044	49.555	-0.174	-1.938	.056

TABLE 6 Multivariate linear regression model for HF

Note: Values of $p < .05$ are indicated in bold. All abbreviations are presented in Table 1.

TABLE 7 Univariate linear regression model for LF/HF ratio

Variables	Univariate		
	B	t	p
Women (n/%)	0.223	2.083	.040
Age (years)	0.027	0.245	.807
Hypertension (n/%)	0.243	2.281	.025
Diabetes mellitus (n/%)	-0.043	0.392	.696
Smoking (n/%)	0.011	0.098	.922
Drinking (n/%)	0.047	0.429	.669
CHD (n/%)	-0.175	1.622	.109
BMI (kg/m^2)	-0.081	0.745	.459
NT-proBNP (pg/ml)	0.217	1.819	.073
Fasting glucose (mmol/L)	-0.010	0.092	.927
HDL-cholesterol (mmol/L)	0.050	0.449	.655
LDL-cholesterol (mmol/L)	-0.107	0.966	.337
Total cholesterol (mmol/L)	0.016	0.145	.885
Triglycerides (mmol/L)	-0.024	0.219	.827
Creatinine (μ mol/L)	0.022	0.202	.841
Uric acid (μ mol/L)	-0.083	0.747	.457
hs-CRP (mg/L)	0.394	3.910	<.001
LAD (mm)	0.253	2.386	.019
LVEDD (mm)	-0.021	0.194	.847
LVEF (%)	-0.124	1.139	.258
Adiponectin (μ g/ml)	0.062	0.565	.574
Leptin (ng/ml)	-0.037	0.333	.740
A/L ratio	-0.334	3.227	.002
Heart rate (beats/min)	-0.081	0.745	.459

Note: Values of $p < .05$ are indicated in bold. All abbreviations are presented in Table 1.

4.3 | Adiponectin and heart rate variability

Previous studies have reported inconsistent results regarding the association between adiponectin level and AF risk (Macheret et al., 2015). Two cross-sectional studies showed that compared to the serum adiponectin level in individuals with sinus rhythm, those in patients with persistent AF are significantly higher (Shimano et al., 2008), while those in patients with paroxysmal AF are significantly lower (Choi et al., 2012). These conflicting results may be explained

by the presence of a significantly larger pericardial fat volume in persistent AF patients compared with that in paroxysmal AF patients (Al Chekakie et al., 2010). Moreover, previous research indicated that a high plasma level of adiponectin is related to a smaller body size in elderly women, which corresponds to a larger left atrial volume index, and can serve as a predictive factor for AF recurrence after catheter ablation among patients with paroxysmal AF (Kim et al., 2018). Our results showed that the serum adiponectin level was independently and positively associated with HF power in patients with new-onset paroxysmal AF. Therefore, we speculate that adiponectin may be an active participant in the pathogenesis of new-onset paroxysmal AF.

4.4 | Leptin and heart rate variability

The mechanism of AF by which leptin regulates atrial muscle cell activity remains incompletely understood (Jenne & Tschopp, 1992; Jiang et al., 2020; Li & Liu, 2009; Lin et al., 2012, 2013). The literature related to the association of blood leptin level and heart rate variability parameters indicates a possible link between the leptin concentration and disturbances of the autonomic nervous system for some ethnicities (Pieterse et al., 2014). One study reported that hyperleptinemia may be related to cardiac autonomic dysfunction in patients with type 2 diabetes and visceral obesity (Kurajoh et al., 2015). In male patients with cardiac infarction, Piestrzeniewicz et al. showed that leptin was positively associated with LF and the LF/HF ratio, but negatively correlated with HF (Piestrzeniewicz et al., 2008). The results of the present study are inconsistent with those of previous studies in that leptin was only positively associated with LF in our patients with new-onset paroxysmal AF. Overall, the present study and those in the current literature illustrate the role of increased leptin secretion, which will contribute to autonomic imbalance. Therefore, the circulating adiponectin level may be a potential biomarker of AF or an independent predictor for recurrence of atrial arrhythmia after catheter ablation for AF. Potential interactions among these pathways are of potential significance and warrant further investigation.

4.5 | Study limitations

Several limitations of the present study should be noted. First, this was a retrospective observational study with a limited sample size,

TABLE 8 Multivariate linear regression model for LF/HF ratio

Variables	B	SE	β	t	p
Constant	-1.293	0.553		-2.339	.022
Hypertension (n/%)	0.151	0.124	0.118	1.219	.227
Women (n/%)	0.201	0.131	0.151	1.533	.129
hs-CRP (mg/L)	0.130	0.040	0.331	3.259	.002
LAD (mm)	0.015	0.012	0.136	1.326	.189
A/L ratio	-0.031	0.011	-0.276	2.766	.007

Note: Values of $p < .05$ are indicated in bold. All abbreviations are presented in Table 1.

and the findings must be confirmed in prospective studies with larger samples. Second, it remains unclear whether an elevated A/L ratio is a cause or consequence of heart rate variability in patients with paroxysmal AF, and therefore, the associations between the A/L ratio and parameters of heart rate variability should be evaluated in future studies. Third, no control group of healthy people was included in the present study, and thus, we could not examine the differences between paroxysmal AF patients and a control group of healthy people. Finally, without longitudinal follow-up data, we could not assess the clinical impact of the A/L ratio and heart rate variability analysis on future events.

5 | CONCLUSION

The results of the present study indicate that the A/L ratio, as well as the individual adiponectin and leptin levels correlated with cardiac autonomic function in new-onset paroxysmal AF patients. However, given the known limitations of HRV analysis during new-onset paroxysmal AF, the potential value of adipokine levels for the identification and evaluation of new-onset paroxysmal AF deserves further investigation.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHORS CONTRIBUTIONS

Conceived and designed the study: HJ. Data collection and analyzed the data: TZ and MW. Quality control the study and revision: MC, ZW, SW, and HH. Wrote the paper: TZ and MC. TZ, MC, and MW contributed to the work equally and should be regarded as co-first authors. Corresponding Author: KM and HJ. The manuscript was approved by all the above authors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Because this was a retrospective observational study and no treatment was tested in patients by the authors of this article, the Renmin Hospital of Wuhan University Ethics Committee granted an exemption from requiring ethics approval and waived the requirement to obtain informed consent from eligible patients. All methods

were performed in accordance with the relevant guidelines and regulations.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Renmin Hospital of Wuhan University. However, restrictions apply to the availability of these data, which were used under license for the current study, and accordingly, they are not publicly available. Data are, however, available from the authors upon reasonable request from the corresponding author Kezhong Ma (E-mail: makezhong2020@163.com) and with permission of the Renmin Hospital of Wuhan University.

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