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The role of IL-6, IL-10, TNF-α and PD-1 expression on CD4 T cells in atrial fibrillation

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ABSTRACT

Backgrounds: While not completely understood, the electrical, structural, and communication pathways that play a role in the onset and progression of atrial fibrillation (AF) seem to be connected to the intricate interplay between neurohormones and cellular mediators. Our study's objective was to examine how the expression profiles of the inflammatory cytokines interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor (TNF), and programmed death 1 (PD-1) changed in Cluster of Differentiation 4 (CD4) T cells depending on whether atrial fibrillation was paroxysmal or permanent. This analysis would provide new diagnostic markers for the detection and management of atrial fibrillation.

Methods: In a cross-sectional study, 60 healthy controls, 49 patients with persistent atrial fibrillation, and 50 patients with paroxysmal atrial fibrillation were compared. Serum biomarker levels are found using the ELISA method, which uses enzyme-linked immunosorbent assay. Echocardiography was used to assess heart function.

Results: Patients with atrial fibrillation had serum concentrations of IL-6, TNF-a, and IL-10 that were considerably higher than but PD-1 was lower those in the non-AF control group and those in patients with persistent atrial fibrillation. According to the diameter of LA and the serum level of NT-proB-type natriuretic peptide (NT-proBNP) is greater than that of patients with paroxysmal atrial fibrillation than control group. Patients with persistent atrial fibrillation had increased serum levels of low-density lipoprotein cholesterol (LDL-C) compared with those without atrial fibrillation. While PD-1 in patients with paroxysmal atrial fibrillation is closely related to C-reactive protein (CRP), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and very low density lipoprotein cholesterol. In addition, PD-1 in patients with persistent atrial fibrillation is closely related to IL-6, TNF-a, and IL-10.

Conclusion: Higher blood concentrations of NT-proBNP, IL-6, IL-10, TNF-, and LDL-C but low level of PD-1 are associated with progression from paroxysmal or chronic AF.

1. Introduction

The most prevalent chronic arrhythmia in the elderly is atrial fibrillation (AF), which has been linked to a potential 5-fold increase in the risk of ischemic stroke in the general population [1]. Atrial fibrillation's pathogenic processes are still not fully understood, although mounting data suggests that the immunosuppressive response plays a significant role [2,3]. The quantity of serum

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inflammatory markers affects both the occurrence and prognosis of atrial fibrillation [2,4,5]. Patients with atrial fibrillation are impacted significantly by inflammatory infiltration of the vestibular tissue [6]. Inflammation is related to a variety of pathological processes related to atrial fibrillation, including oxidative stress, fibrosis, and thrombosis [4]. Our findings suggest that inflammation variables may be connected to the pathophysiology of AF, to put it simply. To characterize the molecular and cellular processes of the AF immune response, nevertheless, requires further research.

A member of the CTLA-4 family of negative immunoreceptors, programmed death-1 (PD-1) is a CD28/cytotoxic T-lymphocyte antigen. Lack of PD-1 raises T-cell activation and inflammatory levels [7]. A related CD28 costimulatory molecule, programmed death-1 (PD-1, CD279) is produced upon activation of $CD4^+$ and $CD8^+$ T cells, NK cells, B cells, and monocytes. PD-1 is also implicated in the pathophysiology of cardiovascular illnesses such arteriosclerosis, immune-mediated myocarditis, and dilated cardiomyopathy, according to growing body of research [8–11]. It is unclear, nevertheless, whether the PD-1 pathway influences how the immune system controls AF. Atrial myocytes from PD-1 (-/-) mice exhibit increased amounts of oxidative stress and inflammatory substances, which results in electrical and structural remodeling of the atria [12]. Reduced PD-1/PD-L1 levels in AF patients may enhance T cell activity and hasten the onset of AF [13]. It is unclear, nevertheless, if the PD-1 pathway influences the immune system's control of AF and whether PD-1 is connected to other inflammatory elements. For instance, alterations in PD-L1 may not be associated with TNF-, a significant inflammatory cytokine.

The previous study looked at the connection between atrial fibrillation (AF) and the rise of plasma cytokines in patients [14]. According to evidence, cardiovascular illness and the burden of atrial fibrillation have been linked to inflammation (AF). Independent of clinical risk variables, IL-6 is linked to a greater risk of stroke and severe bleeding, and both indicators are linked to a higher risk of vascular mortality and the composite of thromboembolic events [15]. The additional pro-inflammatory cytokines (interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF)), chemoattractant proteins, and selectins levels in blood and tissue contribute to the maintenance of inflammation in the AF [16], however it is unclear how these inflammatory variables and AF are related.

The goal of this experiment was to identify novel diagnostic markers for the detection and management of atrial fibrillation by analyzing changes in the expression profiles of IL-6, IL-10, TNF-, and PD-1 in CD4 T cells in relation to clinical outcomes of paroxysmal or persistent atrial fibrillation. We also investigated the relationship between PD-1 and IL-6, IL-10, and TNF-, three additional inflammatory indicators.

2. Materials and methods

2.1. Patients

Each patient and control participant provided their informed permission, and the research was authorized by the First Affiliated Hospital of Xinjiang Medical University's Ethics Committee (Number: LE20180223).

In all, 102 patients who received an AF diagnosis at our institutions between May 2012 and December 2018 were included in this research. The patients with paroxysmal AF ($n = 52$) and those with persistent AF ($n = 50$) were divided into two groups. The diagnostic standards for atrial fibrillation were created based on the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee (ACC/AHA/ESC) 2006 guidelines. 62 healthy volunteers without a history of arrhythmias who were undergoing a routine clinical assessment for a health certificate made up the control group. The exclusion criteria included coronary heart disease, myocardiopathy, rheumatic heart disease, valvular heart disease, heart failure, chronic lung illnesses, hepatic and renal disorders, malignancy, immunological diseases, anti-inflammatory or immunosuppressive medications, recent trauma and surgery. Clinical histories, electrocardiograms, and common biochemical tests were gathered for the research. 52 individuals with paroxysmal AF (occasional paroxysms) matched the following criteria: I bouts of paroxysmal AF lasting no more than 6 h each, and (ii) a total of paroxysmal AF lasting no more than 30% of the time. 50 patients who had at least one of the following conditions were included in the group with frequent paroxysms (Persistent AF): I a total duration of recurrent paroxysmal AF lasting more than 30% of the whole time; and (ii) at least one episode of AF lasting more than 6 h. ECG, Holter monitor, or palpitation symptoms were the main factors in determining the length of paroxysms. The burden of arrhythmia and the risk of unfavorable outcomes may be shown using this grouping method [17].

2.2. Sample preparation and peripheral blood mononuclear cell isolation

Each patient received a complete blood sample by venepuncture of the antecubital vein on the first day of admission, and normal procedures were followed to measure the serum cholesterol, C-reactive protein (CRP), lymphocytes, and white blood cell counts. Peripheral blood mononuclear cells (PBMCs) were isolated from fresh heparinized blood using Ficoll-Hypaque (Sigma-Aldrich, St. Louis, MO, USA) density gradient centrifugation. For further research, they were viably frozen in FCS (80%; Gibco, Grand Island, NY, USA), 10% dimethylsulfoxide, and 10% RPMI 1640 medium (Gibco).

As monoclonal antibodies, we used CD3-FITC (isotype, mouse IgG2a), CD8-PE (isotype, mouse IgG2a), CD4-APC (isotype, mouse IgG1), and PD-1-PE-cy7 (isotype, mouse IgG1) (mAbs). It was determined if PD-1 was expressed on T cells using recently heparinized peripheral blood. The cells were then frozen, subjected to a FACSCalibur four-color flow cytometry analysis, and treated with FACS lysing solution (BD Pharmingen, San Diego, CA, USA) to eliminate RBC (BD Biosciences). A total of 1*105 cells were counted in each study. FCS express V3 software was used to evaluate the results and compute the percentage of positive cells.

2.3. ELISA test

Using an ELISA Kit, the blood levels of four cytokines (IL-2, IL-6, IL-10, NT-proBNP, TGF-beta and TNF-a) were determined (eBioscience). Everything was done in accordance with the manufacturer's instructions. The absorbance was calculated using an automated plate reader. The sensitivity of the IL-10 ELISA kit is 1 pg/ml, IL-2 is 2 pg/ml, TNF-a is 3 pg/ml, NT-proBNP is 2 pg/ml, TGF-beta is 3 pg/ml and IL-6 is 4 pg/ml.

2.4. Statistical methods

The statistical analysis was performed using SPSS 11.0 for Windows. The Kolmogorov-Smirnov test is used to confirm if the distribution is normal before the data are given as mean SD. The Mann-Whitney *U* test was used to assess differences between any two groups, and the Kruskal-Wallis test with Bonferroni correction was employed to compare more than two groups due to the anomalous distribution. To compare categorical data between two or more groups, the Pearson's st was utilized. The Pearson's chi-square test was employed to analyze categorical variable differences across study groups. Evaluations were made of the ROC curve's area under it, as well as its sensitivity and specificity. The highest joint sensitivity and specificity served as the basis for determining the cut-off value. The Kaplan-Meier technique and log-rank test were used to examine the follow-up data. A probability value of P0.05 was considered significant.

3. Results

3.1. Characteristics of the study individuals

The characteristics of the participants in this study are listed in Table 1. There was no discernible difference between the three groups in terms of age, gender, hypertension, body mass index (BMI), hyperlipidemia, diabetes, external artery disease, and the use of angiotensin-converting enzyme. Angiotensin-converting enzyme inhibitors, calcium channel blockers, statins, carotid artery disease, lymphocytes, and white blood cells (all $P > 0.05$) (Table 1; Fig. 1).

3.2. Clinical outcome

None of the investigated parameters in the gender-based comparison of individuals with paroxysmal atrial fibrillation indicated any discernible differences between men and women. While women often had higher median values for several characteristics in the group with persistent atrial fibrillation than males, the difference is not statistically significant. The HDL-C values of patients with paroxysmal atrial fibrillation was both considerably lower and the LDL-C values of patients with persistent atrial fibrillation was higher significantly than the preoperative blood lipid value of the control group (Table 2).

Naturally, patients with atrial fibrillation had greater LA diameters than those in the control group without the condition, and patients with persistent atrial fibrillation had bigger LA diameters than those with paroxysmal atrial fibrillation ($P < 0.001$). A crucial biomarker of atrial fibrillation is the vasoactive peptide NT-proBNP. Our result found that atrial fibrillation patients had considerably higher levels of circulating IL-6, TNF-α, TGF-β, NT-proBNP, IL-10, PD-1, and left ventricular ejection fraction. The control group progressed from paroxysmal to persistent atrial fibrillation and did not have any atrial fibrillation (Table 3).

TNF-a, PD-1, and IL-6 each had an areas under the ROC curve (AUC) of 0.075 (95% CI: 0.458 to 0.885), 0.039 (95% CI: 0.625 to

Table 1
Characteristic of studied population.

	Control (n = 60)	Paroxysmal AF (n = 52)	Persistent AF (n = 50)	P value
Age (years)	65.2 ± 5.6	63.5 ± 6.8	64.2 ± 4.6	0.625
Men (N., %)	32 (53.33)	22 (42.31)	23 (46.0%)	0.359
BMI (kg/m^2)	28.36 ± 2.65	27.81 ± 3.65	26.51 ± 5.25	0.362
Past history (N., %)				
Hypertension (BP > 139/89 mmHg)	15 (25)	10 (19.23)	9 (18.00)	0.625
Diabetes mellitus (DM)	21 (35.0)	19 (36.53)	18 (36.0)	0.784
Hyperlipidemia	15 (25.0)	16 (30.7)	12 (24.0)	0.524
Carotis artery lesion	5 (8.3)	4 (7.6)	4 (8.0)	0.865
Periferal artery disease	4 (6.7)	5 (9.6)	4 (8.0)	0.251
Angina pectoris	32 (53.3)	28 (53.8)	27 (54.0)	0.622
Myocardial infarction	8 (13.3)	9 (17.3)	7 (14.5)	0.425
Beta-blocker use	28 (46.7)	27 (51.9)	25 (50.0)	0.321
Statins use	11 (18.3)	11 (21.2)	10 (20.0)	0.856
CCBs use	7 (11.7)	6 (11.5)	6 (12.0)	0.597
COPD (using steroid)	5 (8.3)	4 (7.6)	4 (8)	0.365
Family history	8 (13.3)	7 (13.4)	5 (10.0)	0.251

BMI, Body Mass Index; BP, blood pressure; CCBs, Calcium antagonists; COPD, chronic obstructive pulmonary disease. P value is Chi-square testing among three groups.

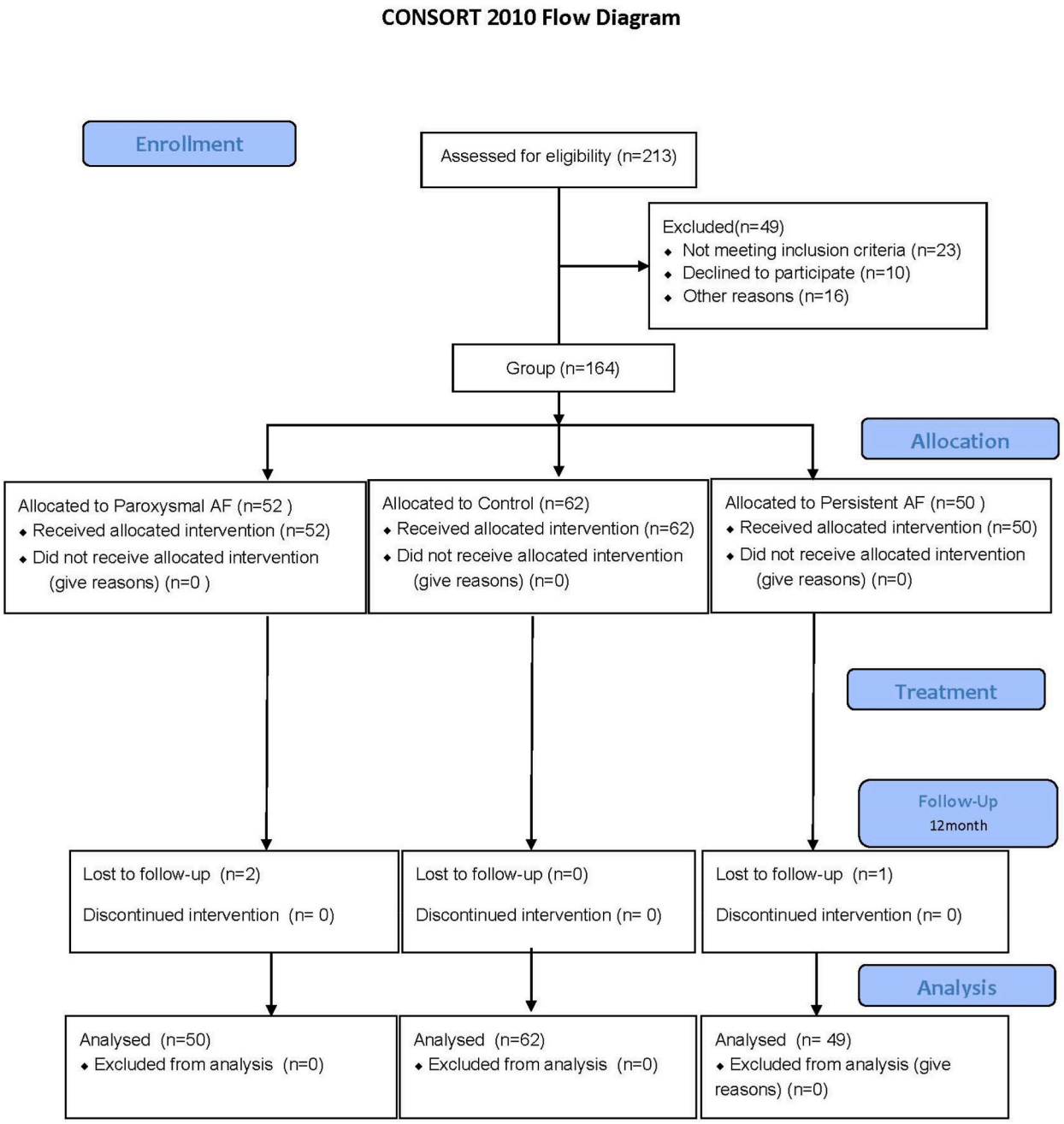

Fig. 1. Flow diagram.

0.995), and 0.028 (95% CI: 0.335 to 0.780), respectively. More than 1.2 pg/mL TNF-a (H-TNF-a) relapse prediction values had a sensitivity and specificity of 48.25% and 69.0%, respectively. More than 2.49 ng/mL IL-6 (H- IL-6) had a sensitivity and specificity of 78.62% and 59.36%, respectively. More than 27.25% PD-1 (H-PD-1) had a sensitivity and specificity of 65.25% and 53.62%, respectively. When the follow-up data was examined using the Kaplan-Meier method, there was no discernible difference between paroxysmal and chronic AF ($P = 0.327$). Patients with high TNF-a (H-TNF-a) had a non-significant tendency of AF recurrence ($P = 0.075$) in contrast to low TNF-a (L-TNF-a: 1.2 pg/mL). Patients with H-PD-1 showed a higher recurrence of AF ($P = 0.039$) compared to those with low PD-1, in a non-significant trend. A log-rank test revealed that H-IL-6 significantly enhanced the likelihood of AF recurrence after catheter ablation ($P = 0.028$) (Fig. 2).

Regression plots using data that had been logarithmically transformed and matching to the variables under study were also computed. In patients with paroxysmal and chronic AF, the correlations between serum biomarkers, LA diameter, and LVEF were examined. It won't go away for AF. Regression plots showed the relationship between PD-1 and IL-6, TNF-a, and IL-10. Moreover, PD-

Table 2
Comparison of preoperative lipid profiles and biochemical examinations between the groups.

	Control (n = 60)	Paroxysmal AF (n = 52)	P* value	Persistent AF (n = 50)	P# value
WBC count (per lL)	9.36 ± 2.11	9.25 ± 1.56	0.234	9.05 ± 2.26	0.651
Hemoglobin	13.52 ± 2.95	14.02 ± 4.25	0.123	13.14 ± 3.18	0.477
Hematocrit	38.22 ± 4.89	37.05 ± 5.62	0.342	37.99 ± 4.15	0.524
Platellet	265.22 ± 54.28	289.67 ± 61.02	0.321	275.68 ± 75.26	0.895
Creatinine, mg/dl	1.15 ± 0.62	1.20 ± 0.45	0.455	1.09 ± 0.63	**0.012**
BUN, mg/dl	20.96 ± 11.25	21.68 ± 12.62	0.883	22.63 ± 11.02	0.625
Glucose, mg/dl	135.62 ± 54.86	135.96 ± 41.26	0.234	139.24 ± 62.51	0.236
AST, mg/dl	22.63 ± 11.02	23.69 ± 9.86	0.563	24.99 ± 12.62	0.958
ALT, mg/dl	31.25 ± 13.27	32.92 ± 14.02	0.183	35.91 ± 14.95	0.645
GGT, U/L	29.86 ± 11.26	28.61 ± 9.55	0.732	29.86 ± 8.64	0.154
LDH, mg/dl	296.15 ± 85.64	286.64 ± 89.26	0.234	302.58 ± 56.84	0.362
CRP, mg/dl	2.15 ± 1.21	2.95 ± 2.36	0.123	3.11 ± 1.25	**0.025**
TGF-β, pg/mL	28.22 ± 2.68	55.84 ± 6.25	**0.027**	62.68 ± 4.91	**0.022**
NT-proBNP, pg/mL	112.18 ± 25.68	162.25 ± 15.67	**0.024**	155.42 ± 35.61	**0.038**
Total cholesterol, mg/dl	186.25 ± 25.64	195.63 ± 42.61	0.442	186.62 ± 26.53	0.265
LDL-C, mg/dl	118.25 ± 21.05	105.66 ± 20.65	**0.014**	125.68 ± 23.61	**0.025**
HDL-C, mg/dl	35.22 ± 5.91	33.69 ± 6.25	**0.032**	34.64 ± 4.52	0.258
Triglyceride, mg/dl	157.25 ± 61.74	162.35 ± 64.95	0.123	158.46 ± 56.66	0.856
VLDL-C, mg/dl	28.66 ± 11.56	24.86 ± 12.69	0.348	25.61 ± 11.24	**0.035**

WBC, white blood cell; BUN, Blood urea nitrogen; AST, Aspartate aminotransferase; ALT, glutamic-pyruvic transaminase; GGT, Glutamyl transferase; LDH, lactate dehydrogenase; CRP, C-reaction protein; TGF-β1, Transforming growth factors - β; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol, ; VLDL-C, very low-density lipoprotein cholesterol; *compare Control group and Paroxysmal AF.; # compare Control group and Persistent AF.

Table 3
Comparison of preoperative inflammation factors, PD-1 and biochemical examinations between the groups.

	Control (n = 60)	Paroxysmal AF (n = 52)	P* value	Persistent AF (n = 50)	P# value
IL-6 (pg/mL)	2.36 ± 0.27	2.99 ± 0.85	**0.013**	2.86 ± 1.15	**0.026**
TNF-α (pg/mL)	1.30 ± 0.25	2.65 ± 0.31	**0.043**	2.89 ± 0.15	**0.005**
IL-10 (pg/mL)	1.11 ± 0.52	1.85 ± 0.24	**0.045**	2.15 ± 0.14	**0.048**
PD-1 (%)	30.25 ± 2.89	26.58 ± 8.11	**0.028**	20.66 ± 4.57	**0.021**
Left ventricular ejection fraction (%)	52.23 ± 11.25	50.61 ± 9.27	**0.023**	51.21 ± 12.06	**0.041**
LA diameter	34.23 ± 3.24	44.01 ± 4.66	**0.048**	48.23 ± 7.32	**0.042**

IL-6, Interleukin-6; TNF-α, Tumor necrosis factor alpha; IL-10, Interleukin-10; LA, left atrium; *compare Control group and Paroxysmal AF.; # compare Control group and Persistent AF.

1, TNF-a, and IL-10 were shown to be connected to LDL-C. It was discovered that IL-6, TNF-a, TGF-b, and NT-proBNP are all related to HDL-C. IL-6 and VLDL-C were related as well. In patients with paroxysmal AF, we found that PD-1 closure was related to TGF-b, AST, CRP, LDL-C, HDL-C, and VLDL-C. PD-1 was not connected to any of the other variables (Table 4, supplement figure S2).

4. Discussion

The relationship between IL-6, TNF-a, PD-1, and IL-10 is described in this study for the first time that we are aware of. Patients with paroxysmal and chronic atrial fibrillation are given biomarkers like IL-6, TNF-, PD-1, and IL-10, and there is a connection between NT-proBNP, LVEF, and LA diameter (called atrial fibrillation predictors). Interestingly, the biomarkers under investigation exhibited a range of functions and structures. As a consequence, TGF-b and LDL-C cause atrial fibrosis, PD-1 is linked to inflammation, and NT-proBNP has a specific hormonal effect. Sometimes, it might be difficult to release these markers since fibrosis and inflammation are so closely related. The following are the study's primary conclusions: In accordance with NT-proBNP serum levels and LA diameter, serum IL-6, TNF-a, and IL-10 levels were significantly higher in AF patients compared to non-AF controls, and in persistent AF compared to paroxysmal AF; (ii) serum LDL-C and TGF-1 levels were higher in persistent AF and paroxysmal AF than controls group; (iii) In groups with chronic AF, PD-1 was significantly linked with IL-6, TNF-a, and IL-10, but in groups with paroxysmal AF, it was connected with CRP, LDL-C, HDL-C, and VLDL-C.

Atrial fibrillation develops and persists as part of the remodeling of the atrial anatomy. Inflammation (pro-inflammatory cytokines that may activate TGF-1 signaling), lipid metabolism (LDL-C), fast atrial stimulation rate, and atrial dilatation are all stimulated along with hemodynamics and neurohormones (natriuretic peptides) [18,19].

In recent years, researchers have created and studied biomarkers that may predict AF in people who have had ischemic strokes. It has been shown that inflammatory activity is connected to AF and associated complications [20]. C-reactive protein and interleukin-6, two inflammatory indicators, have shown a substantial correlation between the burden of AF and suboptimal sinus rhythm maintenance. A number of haematological indicators obtained from white blood cells (WBC) and its components may be used to measure the

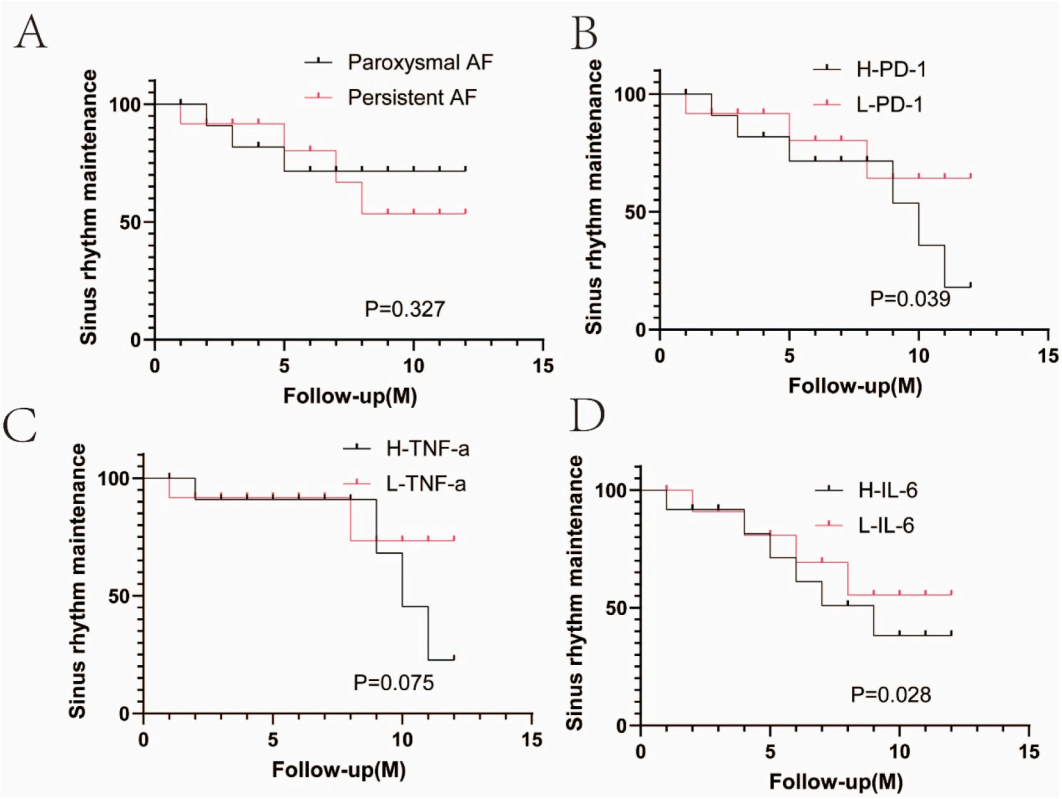

Fig. 2. Follow-up data. The Kaplan-Meier curve of sinus rhythm maintenance 11.25 ± 2.61 months after catheter rablation and the log-rank test for the comparison of the type of atrial fibrillation(A), PD-1(C), tumournecrosisfactor-a (C), IL-6(D) (D). AF = atrial fibrillation, H-IL-6 level more than 766 ng/mL, H-TNF-a = tumournecrosis factor-a level larger than 1.2 pg/mL, L-TNF-a = tumor necrosis factor-a level less than 1.2 pg/mL.

Table 4
Correlation between biomarker and atrial fibrillation.

	IL-6	TNF-α	IL-10	PD-1	TGF-β	NT-proBNP	AST	ALT	CRP	LDL-C	HDL-C	VLDL-C
IL-6	1	0.322	0.423	0.123	0.112	0.342	0.311	0.123	0.103	0.233	0.342	0.523
TNF-α	0.832	1	0.193	0.653	0.234	0.233	0.842	0.212	0.833	0.674	0.763	0.342
IL-10	0.123	0.341	1	0.322	0.423	0.112	0.183	0.187	0.873	0.733	0.764	0.632
PD-1	**0.032**	**0.023**	**0.012**	1	**0.032**	0.342	**0.032**	0.113	**0.038**	**0.013**	**0.012**	**0.034**
TGF-β	**0.033**	0.932	0.245	0.463	1	0.377	0.932	0.673	0.563	0.462	0.342	0.763
NT-proBNP	0.234	0.654	0.552	0.832	0.832	1	0.231	0.673	0.234	0.122	0.338	0.423
AST	0.123	0.342	0.125	0.193	0.932	0.873	1	0.235	0.238	0.341	0.421	0.984
ALT	0.134	0.663	0.233	0.452	0.863	0.832	0.773	1	0.343	0.966	0.483	0.873
CRP	0.763	0.312	**0.012**	0.983	0.342	0.334	0.765	0.897	1	0.742	0.873	0.874
LDL-C	0.982	**0.022**	**0.011**	**0.036**	0.991	0.323	0.342	0.123	0.322	1	0.349	0.273
HDL-C	**0.042**	**0.033**	0.312	0.342	**0.021**	**0.034**	0.342	0.583	0.874	0.344	1	0.412
VLDL-C	**0.023**	0.562	0.984	0.311	0.341	0.763	0.342	0.123	0.112	0.158	0.198	1

Blue is shown that correlation between different biomark in persistent AF. Red is shown that correlation between different biomark in paroxysmal AF.

level of inflammatory activity. Atrial fibrillation is primarily a risk factor for metabolic aging syndrome (MS). Dyslipidemia is one of its primary symptoms, although clinical observation and research are still unsure of how it relates to atrial fibrillation [21]. According to Stephanie et al. research's the negative link between raised HDL-C and atrial fibrillation is only present in individuals under the age of 75, but the negative correlation between high LDL-C/HDL-C and atrial fibrillation is present only in senior individuals [22]. Moreover, an inverse connection between serum TC, LDL, and HDL-C levels and AF risk was discovered by a meta-analysis of extensive cohort

studies [23]. These outcomes are in line with the information gathered throughout our research.

Atrial fibrillation and inflammation have been linked for more than 20 years, as shown by the high frequency of atrial fibrillation (20–50%) after cardiac surgery [24]. Between two to three days after surgery, postoperative atrial fibrillation incidence reaches its peak. It has to do with the mechanisms that cause systemic inflammation. C-reactive protein (CRP), a sensitive but non-specific indicator of systemic inflammation, is increased in plasma along with early interleukin 1 (IL-1), IL-6, and other inflammatory cytokines [25]. Patients with postoperative atrial fibrillation had greater levels of IL-6 in the pericardial drainage fluid [26]. Patients with postoperative atrial fibrillation had greater levels of IL-6 in the pericardial drainage fluid [27]. Moreover, Hidekazu et al. discovered that treating IL-10 may slow the development of atrial fibrillation brought on by HFD-induced obesity [28]. Tumor necrosis factor-alpha (TNF-), which is implicated in atrial remodeling, is supported by a growing body of research [29]. Physical signs are also significant biomarkers for AF. For instance, left atrial stain was regarded as a helpful indicator in atrial fibrillation and also connected with left atrial pressures [30,31].

The pathophysiology of AF may include the programmed route of death-1 (PD-1)/PD-1 ligand (PD-L) pathway [13]. Atrial electrical and structural atrophy is caused by greater levels of oxidative stress and inflammatory substances in the atrial myocytes of PD-1 (-/-) mice. PD-1 (-/-) mice are more susceptible to atrial fibrillation because of atrial remodeling [12]. The key components of an inflammatory response are immunological response and immune control. The body's immune system is significantly influenced by T lymphocytes and their subtypes, which take part in a variety of pro- and anti-inflammatory activities that have an impact on the development and maintenance of AF [32]. According to pertinent evidence, atrial adipose tissue has considerably more $CD3^+$ cells in AF patients, and the amount of atrial dysfunction may change the type of AF [33]. A CD28 homolog and costimulatory molecule, programmed death-1 (PD-1, CD279) is expressed on activated $CD4^+$ and $CD8^+$ T cells, NK cells, B cells, and monocytes. Recent research has emphasized the importance of the PD-1/PD-L signaling pathway (belonging to the B7:CD28 family) as key regulators for preserving this vital balance [13]. Moreover, several studies have shown that the PD-1/PD-L pathway largely regulates T cell activation, proliferation, and cytokine generation in a negative manner [34,35]. Besides that, PD-L1 (the ligand of PD-1) and Programmed cell death-1 (PD-1) are regulatory molecules with negative costimulatory signals that play a crucial role in regulating numerous immune system functions, including infection immunity, autoimmunity, and tumor immunity [36,37]. One of these, the PD-1 with PD-L1 axis, is widely expressed in the cardiovascular system, although it is not yet clear how this route is connected to the pathological development of AF or how it is connected to an inflammatory response.

4.1. Limitations

It is important to note several restrictions on our study. The most glaring issue in our idea is that it does not chronologically correspond to the survey of those who have switched from paroxysmal to chronic atrial fibrillation. The fact that none of our patients had an atrial biopsy to assess the degree of atrial fibrosis is another disadvantage. The groupings vary and are homogenized (paroxysmal atrial fibrillation, chronic atrial fibrillation, and atrial fibrillation control group). However, the study's limited sample size of AF patients prevents it from demonstrating the variability of other predictors, such as heart size, heart ejection fraction, and other markers. As a result, certain systematic indications could be exaggerated. Anti-inflammatory medicines and ARBs were maintained during the follow-upperiod, although ideally all medications, including AADs, would be stopped for the duration of the follow-up period.

5. Conclusion

In conclusion, our findings show that a constant rise in blood levels of NT-proBNP, IL-6, IL-10, TNF-α, and LDL-C ratio is associated with AF onset and progression (from paroxysmal to permanent). Moreover, this research shows that in groups with chronic AF, PD-1 was significantly associated to IL-6, TNF-α, PD-1, and IL-10, but in groups with paroxysmal AF, PD-1 was linked to CRP, LDL-C, HDL-C, and VLDL-C. The results need to be confirmed by other research. The findings of this research will help to elucidate the relationship between AF and inflammatory factors, which might result in the development of a more comprehensive and successful plan for the prevention and treatment of AF.

Consent for publication

We all agree to publication.

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Author contribution statement

1 - Conceived and designed the experiments: Muhuyati; Wen Bai; Zhi-Qiang Liu; Peng-Yi He.
2 - Performed the experiments: Muhuyati; Wen Bai.

3 - Analyzed and interpreted the data: Zhi-Qiang Liu; Peng-Yi He.
4 - Contributed reagents, materials, analysis tools or data: Muhuyati; Wen Bai; Zhi-Qiang Liu; Peng-Yi He.
5 - Wrote the paper: Muhuyati; Wen Bai; Zhi-Qiang Liu; Peng-Yi He.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e18818.

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