

Comparison of the Relationship Between Inflammatory Markers and Atrial Fibrillation Burden

ABSTRACT

Background: Atrial fibrillation is a complex disease with irregular ventricular response and tachycardia as a result of irregular and rapid contraction of the atria, with poor cardiovascular outcomes unless treated. Various mechanisms are involved in its pathophysiology. Inflammation has an important place among these mechanisms. Many cardiovascular events accompany inflammation. Understanding and correct evaluation of inflammation in current situations contribute to the diagnosis and severity of the disease. The aim of our study was to understand the role of inflammatory biomarkers in patients with atrial fibrillation and to evaluate the difference between whether the disease is paroxysmal and persistent (atrial fibrillation burden).

Methods: The study was done retrospectively, and a total of 752 patients who were admitted to the cardiology outpatient clinic were recruited. The normal sinus rhythm group of the study consisted of 140 patients, and the atrial fibrillation group consisted of 351 [permanent atrial fibrillation (n=206) and paroxysmal atrial fibrillation (n=145)] patients. Inflammation markers were evaluated by dividing the patients into 3 groups.

Results: Higher permanent atrial fibrillation [209.71 (40.73-604.0)], paroxysmal atrial fibrillation [188.51 (53.95-617.46)], normal sinus rhythm [629.47 (104-4695)]; permanent atrial fibrillation [4.53 (0.27-17.94)], paroxysmal atrial fibrillation [3.09 (0.40-11.0)], normal sinus rhythm [2.34 (0.61-13.51)] ($P < .05$); and permanent atrial fibrillation [1569.54 (139-6069)], paroxysmal atrial fibrillation [1035.09 (133-4013)], normal sinus rhythm [130.40 (26.42-680.39)] ($P < .05$) were detected in the systemic immune inflammation index, neutrophil-lymphocyte ratio, and platelet/lymphocyte ratio atrial fibrillation groups compared to normal sinus rhythm group. Correlation between C-reactive protein and systemic immune inflammation index ($r = 0.679$, $r = 0.483$ $P < .05$, respectively) was found in the permanent atrial fibrillation and paroxysmal atrial fibrillation groups.

Conclusion: Systemic immune inflammation index, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio were found to be higher in permanent atrial fibrillation compared to paroxysmal atrial fibrillation and in the whole atrial fibrillation group compared to the normal sinus rhythm group. This indicates that inflammation is associated with AF burden and the SII index is successful in reflecting this.

Keywords: Atrial fibrillation, systemic immune inflammation index, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, C-reactive protein

INTRODUCTION

Atrial fibrillation (AF) is a rapid and irregular contraction of the atria characterized by an abnormal heart rhythm.¹ Atrial fibrillation is the most common serious abnormal heart rhythm disorder.² In Europe and North America, it affects approximately 2%-3% of the population as of 2014.³ Current estimates suggest that approximately 1 in 4 people will develop AF during their lifetime.^{4,5} Atrial fibrillation begins as short-term abnormal heartbeats (paroxysmal) that will become longer and possibly permanent over time.³ Therefore, determining and predicting AF durations of patients will contribute to the understanding of the pathophysiology of AF.

Inflammatory activity can be evaluated with a range of hematological indices derived from white blood cells (WBC) and their elements. Neutrophil-lymphocyte

ORIGINAL INVESTIGATION

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ratio (NLR) and platelet–lymphocyte ratio (PLR) have shown an enhanced predictive potential in the detection of cardiovascular diseases (CVDs) and related mortality.^{6,7} Recently, a new immune and inflammation index calculated from platelet, neutrophil, and lymphocyte counts, namely the systemic immune inflammation index (SII), has been able to provide additional information in the risk assessment and prognosis of CVDs such as hypertension, coronary artery disease (CAD), and pulmonary embolism.⁸ After it was understood that inflammation can trigger CVD diseases, it was thought that inflammatory activity might be associated with AF in studies. Subsequent studies have reported that NLR, PLR, and lymphocyte–monocyte ratio are associated with systemic inflammation and AF progression.⁹ Certain inflammatory markers such as C-reactive protein (CRP) and interleukin-6 have shown a strong relationship between AF and poor sinus rhythm control.^{10,11} This gave us the opinion that SII, a new inflammatory marker, may be associated with the burden of AF. This study aimed to determine the relationships between hematological inflammation markers (SII, NLR, PLR) and AF burden, which do not require additional cost and their relationship with other defined inflammation markers in AF patients.

METHODS

Study Design Study Population

This retrospective study was conducted with 612 AF patients and 140 age- and sex-matched volunteers (NSR) who attended a Local University Hospital Cardiology Outpatient Clinic between June 2020 and June 2022, with a total of 752 participants. The study complies with the principles outlined in the Declaration of Helsinki and was approved by the Local University Hospital Ethics Committee.

Patients were included in the study by scanning the local hospital system database. A total of 20 patients were excluded from the study due to lack of data. Two hundred forty-one AF patients were excluded from the study because they did not meet the study inclusion criteria. The detection of AF (absence of prominent repetitive P waves and irregular atrial activation) in the documented 12-lead electrocardiography was checked, and the follow-up time required for diagnosis was taken as at least 30 seconds to diagnose AF with rhythm Holter for at least 72 hours.¹ Patients included in

the paroxysmal AF group were defined as having been diagnosed with AF at least once in their history (less than 7 days in duration).¹ In the diagnosis of permanent AF, the diagnosis of AF was considered to mean that the effort to convert AF to sinus rhythm was abandoned.¹ Patients in the normal sinus rhythm group (NSR) were selected from patients who had no AF attack defined at any time in their lives.

The patient group consisted of a total of 351 patients (permanent AF n=206, paroxysmal AF n=145) diagnosed with permanent and paroxysmal AF. The control group consisted of 140 patients with NSR. The NSR group was matched with the AF group in terms of age and gender.

Patients with acute infection or sepsis, heart failure (HF), pulmonary embolism, severe valvular disease (moderate mitral stenosis and all other serious valve diseases and prosthetic valve disease), malignancy, coagulation disorder, patients younger than 18 years of age, acute or chronic stroke, depot diseases (glycogen, lipid, and lysosomal), acute kidney disease, mechanical valve, end-stage renal disease, severe anemia, recent acute patients with coronary syndrome (first 6 months) or CAD leading to stenosis, which may be significant, were excluded from the study.

Echocardiography and Electrocardiography Evaluation

Echocardiographic evaluations of the patient and control groups were performed in the echocardiography (ECO) unit of our center with the Vivid S5 ECO device (General Electric, Milwaukee, Wis, USA) using a 2.5-3.5 MHz transducer in the left decubitus position for all participants. Ejection fractions (EFs) of all participants were performed using the modified Simpsons method as per the American Society of Echocardiography and the European Society of Cardiovascular Imaging criteria.¹² Left ventricular hypertrophy (LVH) was evaluated by ECO and values above 95 g/m² for women and 115 g/m² for men¹³ were considered LVH.

A 12-lead ECG (Cardiofax V; Nihon Kohden Corp., Tokyo, Japan; 10 mm/mV and 25 mm/s) was taken with all participants in the supine position at rest. Electrocardiograms obtained from all participants were sent to the computer via a scanner and analyzed and evaluated at ×400% using Adobe Photoshop CS2 program (Adobe Systems Inc., San Jose, Calif, USA).

Laboratory and Demographic Data

Biochemical parameters were evaluated automatically with the aid of the Beckman Coulter LH-750 Hematology Analyzer (Beckman Coulter, Inc., Fullerton, Calif, USA). The lipid panel of the patients was evaluated using standard methods. For the diagnosis of hypercholesterolemia, patients were asked to have an LDL value above 130 mg/dL and to have been treated or diagnosed with hypercholesterolemia before. Patients who received medical treatment for diabetes mellitus (DM) or whose laboratory results were diagnosed with DM according to current criteria¹⁴ were evaluated as DM. Repeated systolic/diastolic blood pressure measurements were made for the diagnosis of hypertension, and patients whose measurements were above 140/90 mm Hg or who were previously diagnosed with hypertension and

HIGHLIGHTS

- The effect of inflammation on amnesia is being investigated.
- The study was designed for this purpose.
- Higher systemic immune inflammation index (SII), neutrophil–lymphocyte ratio (NLR), and platelet–lymphocyte ratio (PLR) was detected in the atrial fibrillation (AF) groups compared to the normal sinus rhythm (NSR) group.
- SII, NLR, and PLR were found to be higher in permanent AF compared to paroxysmal AF and in the whole AF group compared to the NSR group.

started treatment were considered hypertensive. Patients who had smoked for the last 6 months were considered smokers. Mild mitral stenosis rheumatic valve with <5 mm Hg gradient was accepted. Patients treated for acute coronary syndrome (ACS) (with stent or balloon) and at least 6 months after ACS or with <50% stenosis in any coronary artery were accepted as CAD.

Inflammation Marker and Risk Score

The SII index was calculated as peripheral platelet count $\times$ neutrophil count/lymphocyte count, NLR was calculated as neutrophil count/lymphocyte count, and PLR as peripheral platelet count/lymphocyte count. CHA₂DS₂-VASc [C: congestive HF or left ventricular systolic dysfunction, H: hypertension, A: ≥ 75 years, D: diabetes mellitus, S: previous stroke, V: vascular disease, A: 65–74 years, and Sc: female gender] scores of all groups were calculated.

Statistics Analysis

The data obtained from our study were evaluated with the Statistical Package for the Social Sciences (SPSS) 25.0 (SPSS, Inc., Chicago, Ill, USA) program. The probability value of $P < .05$ was taken in the tests for statistical significance. Categorical variables were expressed as numbers and percentages [n (%)], and continuous variables were expressed as median, and interquartile range [median (IQR)] by the distribution of data. The normality of the data was checked with the Kolmogorov–Smirnov test. If the data were parametric (data obtained with range, ratio scale and normal distribution), the Kruskal–Wallis H test was used. The Games–Howell test was used for those who met the homogeneity assumption and did not provide the Tukey homogeneity assumption to determine which group was different from the others. The chi-square test was used to evaluate the categorical data. The Spearman test was used in correlation analysis to determine the relationship between CRP and SII.

RESULTS

The basic characteristics, age, body mass index (BMI), comorbidities, ECG rhythm, and smoking habits of the patients and control group included in the study were noted. The basic characteristics of the patients are given in Table 1 in detail. One hundred forty patients [76 women and 64 men, mean age: 63.66 (20–88) years] as the NSR group and 351 patients as the AF group [permanent AF n=206 (110 females and 96 males mean age: 68.25 (42–93)] and paroxysmal AF n=145 (76 female and 69 male mean age: 66.38 (22–90)] were included in the study. Considering the mean age between the groups, the mean age in the permanent AF group was higher in the other 2 groups, but it was not statistically significant. When the groups were evaluated separately, the BMI was highest in the NSR group, but there was no statistical difference. No statistically significant difference was found between the groups in terms of comorbidities (Table 1).

Except for hemogram parameters, AF group and NSR group exhibited similar properties in terms of other chemical parameters. When the CRP value shown in Table 2 [permanent AF 18.52 (2.0–95.0), paroxysmal AF 12.83 (5.0–91.25), NSR 5.90 (1–40), $P < .05$] was evaluated between the groups,

Table 1. Distribution of the Main Characteristics of the Groups

Variables	Permanent AF (n=206)	Paroxysmal AF (n=145)	NSR (n=140)
Age (years)	68.25 (42–93)	66.38 (22–90)	63.66 (20–88)
BMI (mean $\pm$ SD)	30.21 (6.20)	32.72 (8.08)	33.46 (7.05)
Gender (female), n (%)	110 (53.39)	76 (52.41)	76 (54.3)
Weight (mean $\pm$ SD)	80.86 (11.97)	86.44 (17.41)	86.09 (16.72)
Height (mean $\pm$ SD)	164.26 (10.9)	163.20 (8.89)	160.09 (7.95)
DM, n (%)	71 (34.5)	49 (33.8)	47 (33.6)
HT, n (%)	100 (48.54)	71 (48.96)	68 (48.6)
COPD, n (%)	19 (9.22)	14 (9.65)	15 (10.71)
Asthma, n (%)	10 (4.85)	8 (5.51)	6 (4.28)
CAD, n (%)	65 (31.55)	46 (31.7)	43 (30.7)
HL (%)	51 (24.75)	40 (27.58)	35 (25.0)
Smoking (%)	69 (33.5)	45 (31)	44 (31.4)
Heart rate (bpm)	109.42 ^a (56–161)	116.71 ^b (56–158)	74.46 ^c (45–115)
LBBB, n (%)	10 (4.85)	7 (4.82)	5 (3.57)
Mild mitral stenosis, n (%)	5 (2.42)	3 (2.06)	3 (2.14)
LVH, n (%)	18 (8.73)	12 (8.3)	10 (7.1)

^{a,b,c}The same letters show that there is no statistically significant difference between them, and different letters show that there is a statistically significant difference.

Table 2. Comparison of Laboratory and Echocardiographic Features of the Groups

Variables	Permanent AF (n = 206)	Paroxysmal AF (n = 145)	NSR (n = 140)	P
AAD (cm)	37.57 (32-48)	37.06 (32-47)	35.89 (28-48)	.002
EF	56.48 (45-65)	58.27 (50-65)	60.07 (50-70)	<.001
LA (cm)	48.52 (34-57)	43.28 (30-59)	37.59 (36-72)	<.001
Hemoglobin (g/dL)	13.99 (1.53)	13.37 (1.53)	13.46 (1.20)	.053
Sodium (mmol/L)	139.00 (3.11)	139.38 (4.00)	139.85 (4.41)	.054
Potassium (mmol/L)	4.58 (0.61)	4.43 (0.57)	4.44 (0.66)	.220
Neutrophil ($\times 10^3/\mu\text{L}$)	7.43 ^a (2.44-14.67)	5.47 ^b (1.33-9.76)	4.79 ^c (1.93-10.13)	<.001
Lymphocyte ($\times 10^3/\mu\text{L}$)	2.19 ^a (0.62-9.92)	2.17 ^a (0.59-6.23)	2.39 ^b (0.47-5.39)	<.001
WBC ($\times 10^3/\mu\text{L}$)	8.74 ^a (4.0-15.0)	7.69 ^b (4.0-13.0)	6.97 ^c (4-15)	<.001
Platelet ($\times 10^3/\mu\text{L}$)	358.66 ^a (98-571)	336.11 ^a (110-617)	269.28 ^b (93-697)	<.001
CRP (mg/L)	18.52 ^a (2.0-95.3)	12.83 ^b (5.0-91.25)	5.90 ^c (1-40)	<.001
Creatinine (mg/dL)	1.19 (0.36)	1.13 (0.51)	1.27 (0.57)	.224
CHA ₂ DS ₂ -VASc	3.47 (0-7)	3.11 (0-7)	2.94 (0-8)	.123
SII	1569.54 ^a (139-6069)	1035.09 ^b (133-4013)	629.47 ^c (104-4695)	<.001
PLR	209.71 ^a (40.73-604)	188.51 ^b (53.95-617.46)	130.40 ^c (26.42-680.39)	<.001
NLR	4.53 ^a (0.27-17.94)	3.09 ^b (0.40-11.0)	2.34 ^c (0.61-13.51)	<.001
TSH (ng/dL)	1.66 (0.45-4.78)	1.50 (0.44-4.0)	1.52 (0.43-4.1)	.225
T4 (ng/dL)	1.58 (0.56-5.66)	1.56 (0.45-4.0)	1.52 (0.45-4.2)	.200
LDL cholesterol (mg/dL)	117.66 (52-180)	115.02 (42-170)	118.36 (102-178)	.076
ALT (U/L)	22.47 (5.3-42.5)	23.91 (5-75)	23.42 (4.0-73)	.591
AST (U/L)	22.05 (8.0-41)	25.27 (6.0-45.0)	23.45 (6.0-70)	.510

^{a,b,c}The same letters show that there is no statistically significant difference between them, and different letters show that there is a statistically significant difference.

AAD, ascending aortic diameter; AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHA₂DS₂-VASc [C: congestive heart failure or left ventricular systolic dysfunction, H: hypertension, A: ≥ 75 years, D: diabetes mellitus, S: previous stroke, V: vascular disease, A: 65-74 years, and Sc: female gender]; CRP, C-reactive protein; EF, ejection fraction; LA, left atrium; LDL, low-density lipoprotein; NLR, neutrophil-lymphocyte ratio; NSR, normal sinus rhythm; PLR, platelet-lymphocyte ratio; SII, systemic immune inflammation index; T4, tetraiodothyronine; TSH, thyrotrophin-stimulating hormone; WBC, white blood cell.

($P < .001$) relationship was found between SII and CRP in permanent AF (Figure

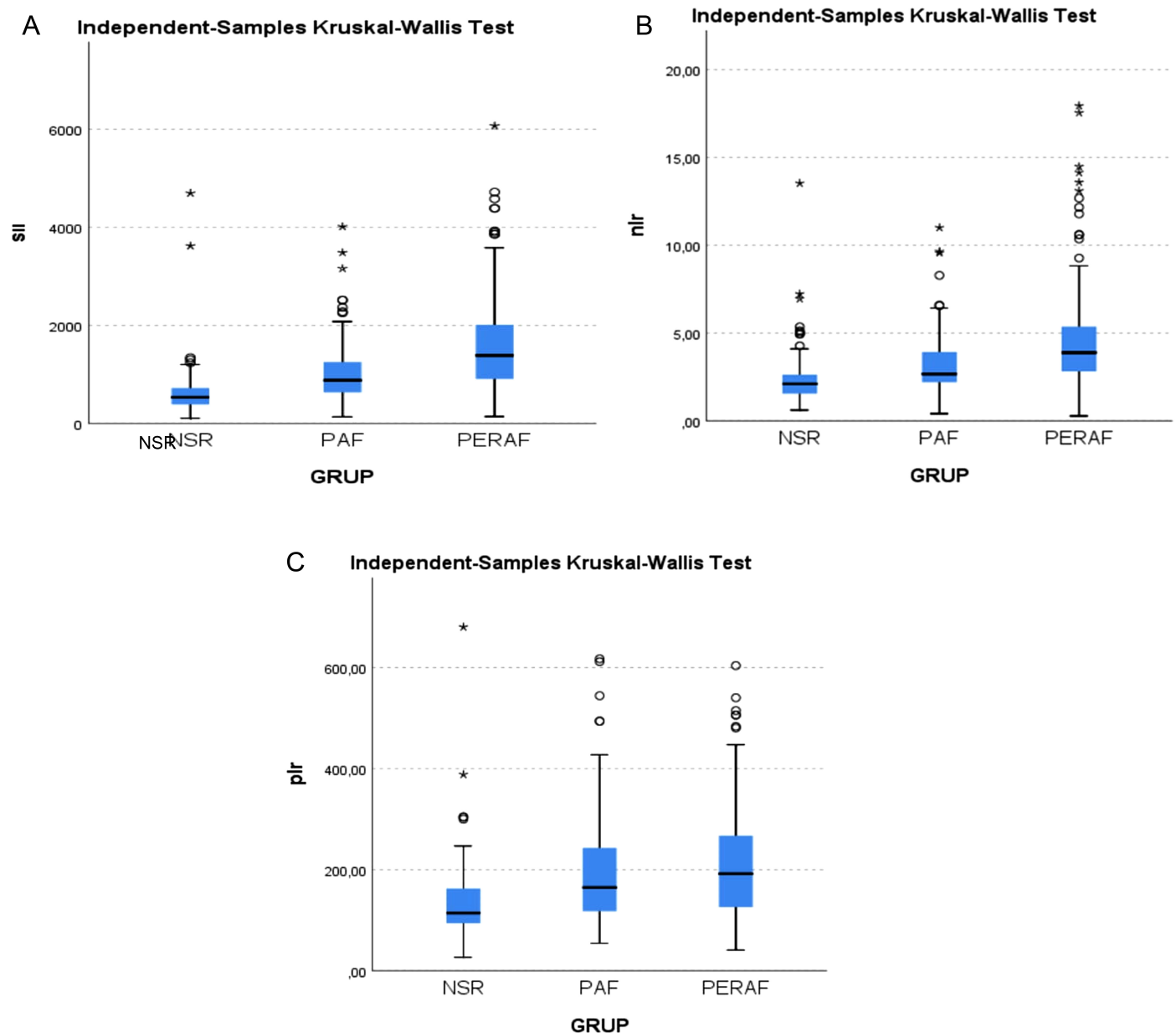


Figure 1. Intergroup evaluation of systemic immune inflammation index, neutrophil–lymphocyte ratio, and platelet–lymphocyte ratio.

stress, and it even showed that NLR was more significant in the permanent AF group than in the paroxysmal AF group.

Inflammation and hypercoagulation cause platelet activation and endothelial dysfunction. Von Willebrand factor and asymmetric dimethyl arginine are biomarkers of endothelial dysfunction and both were found to be predictors of stroke in patients with AF in a prospective cohort.^{22,23} Proinflammatory cytokines originating from immune cells and leukocyte–platelet interactions also mediate prothrombotic states.¹⁷ Proinflammatory cytokines released from immune cells induce platelets and this induction causes spontaneous echo contrast and adverse cardiovascular events.^{24–26} One study found that it would induce platelet–leukocyte interactions at the onset of acute AF.²⁷ In this context, the role of PLR,

which combines thrombocyte and leukocyte subgroup lymphocyte, in systemic inflammation has been examined and it was shown that it can detect inflammation in AF.⁹ In our study, in accordance with the literature data, the PLR value in AF patients was found to be higher in the persistent AF group compared to both groups, and the lowest value was found in the NSR group. In this case, our findings statistically stated that one of the valuable parameters in the chronic inflammation process is PLR. Our contribution showed that inflammatory markers were associated with AF burden, rather than merely determining the presence of AF with high inflammatory markers.

Although the NLR and PLR can help assess inflammation, these 2 indices integrate only 2 cell types. Systemic immune

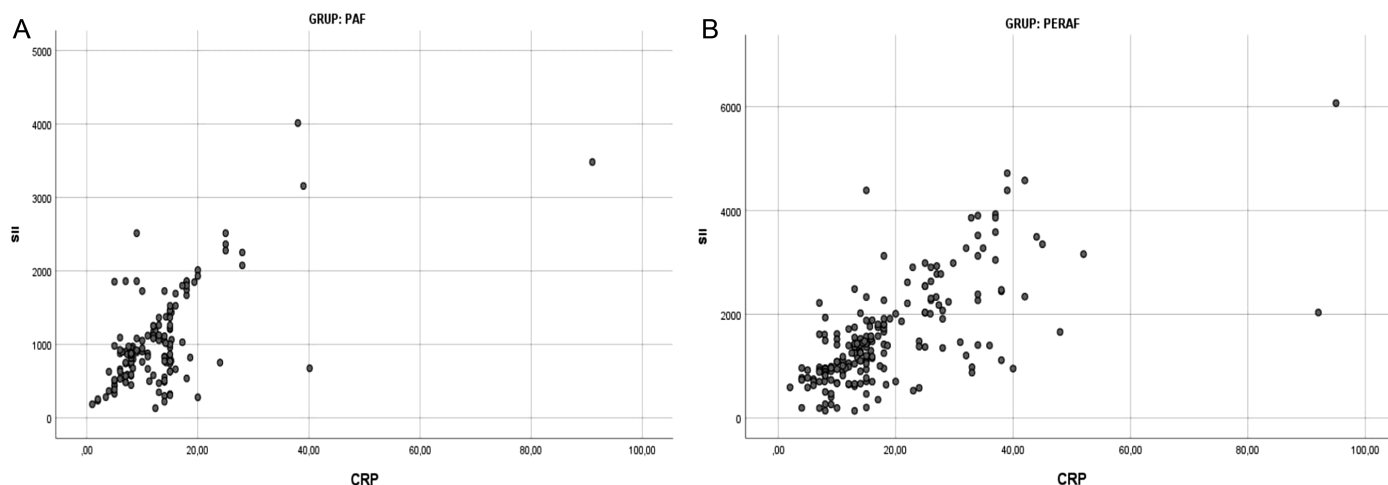


Figure 2. Correlation between systemic immune inflammation index (SII) and C-reactive protein (CRP). A positive ($r = 0.483$) and significant ($P < .05$) correlation was found between SII and CRP in paroxysmal atrial fibrillation (AF). A positive ($r = 0.679$) and significant ($P < .05$) correlation was found between SII and CRP in permanent AF.

inflammation index is an innovative inflammatory biomarker that combines neutrophil, lymphocyte, and platelet counts to reflect the overall inflammatory status of the body. The SII value mathematically potentiates the strength of inflammatory markers and is a more sensitive marker. The predictive value of this index has been evaluated in the follow-up of prognosis in individuals suffering from various cancers.^{28,29} Besides, a previous study by Seo et al³⁰ demonstrated the predictive accuracy of SII for mortality in cases of chronic HF. Also, some previous studies have compared the prognostic importance of this index with NLR and PLR components and revealed that SII is a stronger marker. For example, a recent study showed that SII levels predicted severe coronary obstruction hemodynamically better than NLR or PLR in patients with chronic coronary syndrome (CCS).³¹ In another study, Yang et al³² demonstrated that SII predicts major cardiovascular events better than traditional risk factors in cases of CCS after an invasive coronary arterial intervention.³² We decided to evaluate the status of SII, which reflects the inflammatory state, in patients with AF, putting this situation as the basis of our study. Therefore, we excluded HF, ACS, and other causes of inflammation based on current studies and included only AF patients in our study. Our findings showed that patients with permanent AF had a higher level of SII and showed that these patients were exposed to inflammation more than paroxysmal and NSR groups. Changing or suppressing the inflammation process with the evaluations to be made will also contribute to the treatment with new studies to be conducted in AF patients.

A 1 mg/dL increase in plasma CRP levels increases the risk of paroxysmal AF approximately 7 times and the risk of permanent AF approximately 12 times. Plasma CRP, an acute phase reaction protein, has been found to be directly related to the inflammatory process, which is also a cardiovascular risk factor.^{33,34} It was found in many studies that inflammation and infections play a role in the pathogenesis of CAD.^{33,34} The theory of the effect of infection on the development of AF can be considered as a possible piece of a complex

puzzle. Increased CRP levels are successful in demonstrating inflammation and remain high in chronic infections.³⁴ In other recent studies carried out, it was found that CRP increased in AF patients.³⁵ In this study, permanent AF patients had higher CRP than paroxysmal AF patients, and higher CRP levels were found in both groups than controls.³⁵ Our findings were also consistent with studies.^{35,36} and the literature, and higher CRP levels were detected in the AF group compared to the NSR group in our study. Also, our study showed similar findings between paroxysmal AF and Permanent AF and found higher CRP levels in favor of permanent AF. Thus, it was determined that CRP may contribute to the prediction of AF. It was observed in our study that SII acts just like CRP (permanent AF > paroxysmal AF > NSR) and in our analysis based on the idea that CRP and SII might be correlated in patients with AF, a positive correlation was found between SII and CRP. A close correlation was found especially in permanent AF. This shows us the ability of SII to detect inflammation and that it should be evaluated in the ongoing chronic inflammatory process in AF.

Study Limitations

Our study has some limitations. Among these, first of all, there is a single-center and retrospective study of the study. The patients were not followed up for a long time and their mortality rates were not evaluated. The patients did not have follow-up inflammatory markers, the evaluation was based on a single inflammation parameter. We do not know how the inflammatory parameters will progress when the patients in the -paroxysmal atrial fibrillation group return to permanent AF.

CONCLUSION

Through our study, the importance of chronic inflammation in AF was once again highlighted. This contributed to the prediction of AF and the understanding of its pathophysiology. Thereafter, our study should be repeated with larger patient groups and multicenter enrollments, and perhaps AF treatment options should be expanded.

Ethics Committee Approval: The study complies with the principles set forth in the Declaration of Helsinki and was approved by the Local University Hospital Ethics Committee – Decision Date: 28.07.2022 – Decision number: 22-KAEK-153.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.E.Ö.; Design – Ç.Z.; Supervision – M.Y.; Resources – S.E.Ö.; Materials – M.Y.; Data Collection and/or Processing – Ç.Z.; Analysis and/or Interpretation – S.E.Ö.; Literature Search – Ç.Z.; Writing – S.E.Ö.; Critical Review – Ç.Z.

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Declaration of Interests: The authors have no conflict of interest to declare.

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