The European Research Journal 2023;9(4):674-679 Original Article

DOI: 10.18621/eurj.1038532 *Cardiology*

C-reactive protein to albumin ratio in atrial fibrillation

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ABSTRACT

Objectives: Atrial fibrillation (AF) may cause thromboembolism and cardiac morbidity and mortality. Patients with cardiovascular diseases are at risk for developing AF. In this study, the relationship between inflammation markers and AF was examined.

Methods: Among 689 people followed up in the cardiology outpatient clinic for reasons such as hypertension, coronary artery disease, and rheumatic valve disease, 88 patients with AF and 601 patients without AF were compared. The blood parameters of the AF group were examined during the period when AF developed in the patients. Hemogram and biochemistry parameters of AF and non-AF groups were compared.

Results: C-reactive protein to albumin ratio (CAR), neutrophil count to albumin ratio, neutrophil count to lymphocyte count ratio, and monocyte count to lymphocyte count ratio were significantly higher in the AF group than in the non-AF group ($p < 0.001$, $p < 0.001$, $p = 0.001$, $p < 0.001$; respectively). According to the Receiver Operating Characteristics analysis, it was found that the CAR value of cut-off: 0.0533 could diagnose AF with 74% sensitivity (AUC: 0.789, CI 95%: 0.726-0.853, $p < 0.001$). Albumin value of cut-off: 3.75 was found to be able to diagnose AF with 82% specificity (AUC: 0.772, CI 95%: 0.707-0.836, $p < 0.001$).

Conclusions: AF is an arrhythmia that should be recognized early due to the complications it causes, and the CAR value can be used in the diagnosis of AF in individuals with cardiac disease.

Keywords: Atrial fibrillation, C-reactive protein, albumin

Atrial fibrillation (AF) is one of the most critical and most frequent arrhythmias, accelerating mortality and morbidity such as hemodynamic instability, thromboembolism, and stroke, increasing hospital readmissions and thus health care costs. In general, AF affects patients' quality of life in negative way [1]. AF alone increases mortality risk by 1.5% to 1.9% in a broad age group in both gender [2].

The pathophysiological mechanism in AF is quite complex and multifactorial. Prothrombotic state, inflammation, and oxidative stress may play essential roles in the formation of supraventricular arrhythmias. Complete blood count (CBC) and biochemical examination are necessary blood tests routinely used in clinical practice to examine cardiovascular diseases. However, the diagnostic performance of blood parameters for AF alone and in combination with other diseases is still unknown [3].

C-reactive protein (CRP)/albumin ratio (CAR) is a recently used marker and is used in the follow-up of infections, malignancies, rheumatic diseases, and serious diseases. It has been emphasized that CAR can also be used to determine the severity of coronary artery disease. It is thought that the CAR value alone gives more significant results than the ratio of CRP or albumin [4].

Received: ***December 19, 2021;*** *Accepted:* ***March 26, 2022;*** *Published Online:* ***September 27, 2022***

How to cite this article: *Abuş S. C-reactive protein to albumin ratio in atrial fibrillation. Eur Res J 2023;9(4):674-679. DOI: 10.18621/eurj.1038532*

e-ISSN: 2149-3189

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Many methods are used to determine the severity of AF, and CBC parameters are the essential tools that can be easily accessed and applied among these. Our information on the use of lymphocyte ratios in AF, which has been the subject of research in many fields recently and can be used as a diagnostic tool and follow-up tool of diseases, is limited.

In this study, we aimed to investigate the relationship between AF and inflammation values, especially CAR, neutrophil to albumin ratio (NAR), monocyte to lymphocyte ratio (MLR), neutrophil to lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR).

METHODS

Study Design and Population

This research is a cross-sectional study. A total of 689 consecutive patients are followed up in the cardiology outpatient clinic for hypertension, coronary artery disease, and rheumatic valve disease whom are at risk of developing AF were enrolled in this study. All patients were followed for the six-month in term of developing AF. The patients were divided into two groups according to presence of AF at the end of the follow up. Venous blood of the patients who developed AF was taken when AF developed.

Exclusion criteria of this study were follows: 1) patients with hematological malignancies or cancer or thyroid hormone abnormalities. 2) usage of any drug which can affect laboratory parameters. 3) patients with active inflammation 4) Patients with a history of stroke or a recent surgical operation.

Electrocardiography

The diagnosis of AF is made by the absence of P waves on electrocardiography (ECG) and irregular R-R wave distances. 12-lead ECG recordings (25 mm/sec, 10 mm/mV) were obtained in the supine position using the CardioFax S device (Nihon Kohden, Tokyo, Japan).

Laboratory Analysis

Venous blood samples were examined regularly at hospital admission. Total white blood cell count and neutrophil, lymphocyte, monocytes, eosinophil, and basophil counts were measured using a device (CELL-DYN Ruby; Abbott Diagnostics, Abbott Park, IL) and given as x 103 cells/mm^3. Hemoglobin, hematocrit, platelet counts, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet (PLT), mean platelet volume (MCV), platelet distribution width (PDW), red blood cell distribution width (RDW) were also calculated. Albumin and CRP levels were analyzed using biochemistry kits (Abbott Diagnostics) and an Architect c8000 Chemistry System (Abbott Diagnostics) machine.

Statistical Analysis

All analyzes were performed in SPSS26.0 for Mac (SPSS Inc., Chicago, IL). In the findings, categorical data were expressed as numbers and percentages. The conformity of the data to the normal distribution was evaluated using the Kolmogorov-Smirnov test. The mean and standard deviation values of the continuous data were given. Student t-test was used to assess the difference between groups of normally distributed data. The Mann-Whitney U test evaluated the difference between the two groups of non-normally distributed data. The chi-square test was performed to assess the difference in categorical data between groups. Receiver Operating Characteristics (ROC) analysis was performed to evaluate the sensitivity and specificity of data that differed significantly between groups for the diagnosis of AF. A p - value of < 0.05 was considered statistically significant.

RESULTS

The comparison of the laboratory parameters of the AF group and the non-AF group is shown in Table 1. There was no significant difference between groups regarding mean age and gender distribution. The AF group's white blood cell, MCV, RDW, neutrophil count, lymphocyte count, monocyte count, PDW, and CRP values were significantly higher than the non-AF group ($p = 0.049$, $p = 0.006$, $p = 0.002$, $p < 0.001$, $p = 0.011$, $p = 0.003$, $p = 0.03$, and $p = 0.023$; respectively).

The albumin level of the AF group was significantly lower than the non-AF group ($p < 0.001$). In addition, the lymphocyte count was significantly lower in the AF group than in the non-AF group ($p = 0.011$). NLR, MLR, CAR, and NAR values of the AF group

Table 1. Comparison of baseline demographic and laboratory parameters of the study population

	AF Group (n = 88)	Non-AF Group (n = 601)	*p* value
Age	69.60 ± 8.52	68.76 ± 7.61	0.562[1]
Female gender	43 (49%)	264 (44%)	0.478[3]
WBC (1/μL)	7968 ± 628	7524 ± 1530	**0.049[1]**
RBC (10^3/μL)	5001 ± 609	5290 ± 609	**0.002[1]**
HCT (%)	43.61±4.4	44.36 ± 5.42	0.284[1]
HGB (g/dL)	14.13 ± 1.48	14.52 ± 2.04	0.121[1]
MCV (fL)	111.76	89.25	**0.006[2]**
MCH (pg)	107.38	93.63	0.093[2]
MCHC (g/dL)	98.84	102.16	0.685[2]
RDW (%)	112.96	88.04	**0.002[2]**
PLT (1/μL)	97.47	103.54	0.838[2]
Neutrophil (10^3/μL)	113.06	87.95	**< 0.001**
Lymphocyte (1/μL)	2155 ± 832	2488 ± 987	**0.011[1]**
Monocyte (1/μL)	112.63	88.38	**0.003[2]**
Eosinophil (1/μL)	95.29	105.72	0.203[2]
Basophil (1/μL)	100.96	100.04	0.910[2]
PCT (%)	104.98	96.02	0.274[2]
MPV (fL)	108.15	92.86	0.062[2]
PDW (fL)	109.36	91.65	**0.03[2]**
Albumin (g/dL)	3.57 ± 0.32	3.92 ± 0.26	**< 0.001[1]**
CRP (mg/dL)	105.56	95.44	**0.023[2]**
NLR	114.28	86.72	**0.001[2]**
MLR	117.56	83.44	**< 0.001[2]**
PLR	108.51	92.49	0.05[2]
CAR	129.45	71.55	**< 0.001[2]**
NAR	120.11	80.89	**< 0.001[2]**

WBC = White blood cells, RBC = Red blood cells, HCT = Hematocrit, HGB =Hemoglobin, MCV = Mean corpuscular volume, MCH = Mean corpuscular hemoglobin, MCHC = Mean corpuscular hemoglobin concentration, PLT = Platelet, PCT = Plateletcrit, MPV = Mean platelet volume, PDW = Platelet distribution width, RDW = Red blood cell distribution width, CRP = C-reactive protein, NLR = Neutrophil lymphocite ratio, MLR = Monocyte to lymphocite ratio PLR = Platelet to lymphocite ratio, CAR = C-reactive protein to albumin ratio, NAR = Neutrophil to albumin ratio

[1]Student's t test was performed and data were given as mean ± standard deviation.

[2]Mann-Whitney u tests were applied and the data were given as sequence numbers.

[3]Chi-square test was applied and data were given as percentages.

were significantly higher than the non-AF group (p = 0.001, $p < 0.001$, $p < 0.001$, and $p < 0.001$; respectively).

The evaluation of the parameters that differed between the groups by ROC analysis is shown in Table 2. According to the ROC analysis, when the CAR marker was above the cut-off value of 0.0533, its sensitivity was the highest (sensitivity: 74%, specificity: 77%) (AUC: 0.789, CI 95%: 0.726-0.853, $p < 0.001$). According to ROC analysis, albumin of cut-off: 3.75

Table 2. Evaluation of laboratory parameters by ROC analysis

		95% Confidence Interval					
Parameters	**AUC**	**Lower**	**Upper**	**Cut-off**	**Sensitivity**	**Specifity**	***p* value**
CAR	0.789	0.726	0.853	0.0533	74%	77%	**< 0.001****
NAR	0.696	0.624	0.768	1237.18	63%	64%	**< 0.001****
NLR	0.638	0.561	0.714	2.0495	61%	61%	**0.001****
MLR	0.671	0.597	0.745	0.2161	64%	64%	**< 0.001****
WBC (1/µL)	0.579	0.500	0.658	N/A	N/A	N/A	0.053
Neutrophil (10^3/µL)	0.626	0.549	0.703	4631.50	57%	59%	**0.002****
Monocyte (1/µL)	0.621	0.544	0.699	495.50	59%	59%	**0.003****
MCV (fL)	0.613	0.535	0.691	85.19	%60	60%	**0.006****
RDW (%)	0.625	0.542	0.702	11.51	62%	62%	**0.002****
PDW (fL)	0.589	0.510	0.667	19.49	56%	56%	**0.03***
Lymphocite (1/µL)	0.592	0.513	0.670	2277.50	55%	56%	**0.025***
Albumin (g/dL)	0.772	0.707	0.836	3.75	65%	82%	**< 0.001****
CRP (mg/dL)	0.551	0.471	0.630	N/A	N/A	N/A	0.216
RBC (10^3/µL)	0.637	0.560	0.714	5136.50	63%	60%	**0.001****

WBC = White blood cells, RBC = Red blood cells, MCV =Mean corpuscular volüme, PDW = Platelet distribution width, RDW = Red blood cell distribution width, CRP = C-reactive protein, NLR = Neutrophil to lymphocite ratio, MLR = Monocyte to lymphocite ratio, CAR = C-reactive protein to albümine ratio, NAR = Neutrophil to albumine ratio, AUC = Area under curve

ROC analysis was applied. $p < 0.05$ was accepted as statistical significance.

was found to have the highest specificity (sensitivity: 65%, specificity: 82%) (AUC: 0.772, CI 95%: 0.726-0.853, $p < 0.001$).

DISCUSSION

Our study found significant differences between the AF group and the non-AF group. We obtained the most sensitive data for the diagnosis of AF according to the ROC analysis of the CAR value, which has recently come to the fore as a new marker of inflammation.

Since AF is the most common arrhythmia in clinical practice and causes diseases such as stroke and heart failure and significantly increases cardiovascular mortality, early diagnosis and treatment are valuable in disease progression. In addition, AF is known as the most common arrhythmia in hospitalized patients. It has been emphasized in previous studies that AF occurs after an inflammatory process, and the presence of interstitial fibrosis and inflammatory cells in the atrial tissues of AF patients indicates the presence of an inflammatory process. The incidence of AF increases with increasing age [5]. In this sense, our study is compatible with the literature, and the mean age of the AF group was 69.60 ± 8.52 years. But there was no significant age difference between the AF and non-AF groups.

CRP value has been known for a long time as an inflammation marker and has been associated with the risk of atherosclerosis and stroke due to vascular damage in studies. A study found that the incidence of AF increased fourfold in the presence of CRP and microalbuminuria [6]. A study conducted on patients who had an acute myocardial infarction and subsequently developed AF found a higher CRP value in these patients [7]. On the other hand, albumin is decreased in oxidative stress and inflammation as a negative acute-phase reactant. A study conducted in Copenhagen found a relationship between hypoalbuminemia and the development of AF in women, independent of other risk factors [8].

The CAR value has emerged as a marker showing

the inflammatory state and body hunger level and can be elevated in many clinical situations. A study found that the CAR value may predict the risk of new-onset AF in patients with COVID-19 [9]. A survey conducted in 2020 reported that patients who developed AF after bypass surgery had a significantly higher CAR value in the preoperative period [10]. In a study conducted on patients who had a stroke, it was found that the CAR value could predict mortality within 90 days [11]. Çınar *et al*. found that CAR value in ST-elevation myocardial infarction could predict mortality risk better than CRP and albumin alone [4].

In recent studies, NAR value has come to the fore as a new inflammation marker. Yu *et al*. [12] reported that NAR value could be used to predict mortality in patients with cardiogenic shock. In another study, the NAR value was written as a mortality predictor in sepsis and septic shock [13]. In our research, CAR and NAR values were high in the patient group, and it was concluded that they could significantly diagnose the disease according to the ROC analysis.

Chavarria *et al*. [14] found that NLR increased statistically in cases with new-onset AF developing after percutaneous coronary intervention in acute ST-elevation myocardial infarction. Many studies have shown increased inflammation associated with AF. Although CRP is the most widely used indicator of inflammation, NLR has recently been shown to be a marker of inflammation in certain conditions. Karavelioglu *et al*. [15] found that NLR could significantly predict recurrence in AF patients undergoing medical cardioversion with amiodarone.

It has been suggested that neutrophil reflects inflammation, and lymphopenia indicates general health status and physiological stress [16]. Based on this idea, Gibson *et al*. [17] showed that NLR could be a significant predictor in the preoperative and postoperative AF periods that occur after coronary artery grafting.

NLR has been studied for some time in inflammatory diseases, and NLR has been emphasized as an independent predictor of coronary artery disease. In addition, a relationship was found between the frequency of thromboembolic stroke in AF and NLR [18]. Shao *et al*. found that NLR and RDW values were higher in AF patients [19].

MLR, as an inflammation marker, was found to be higher in coronary artery patients [20]. MLR study in AF patients has not been found in the literature. In our research, the MLR value was higher in AF patients, like other inflammation markers.

Limitations

The relatively small study population is the first limitation. As a second limitation, being a single-center study may limit the interpretation of results. The cross-sectional nature of the study may limit the clear relationship between cause and effect. There are needs for more larger and prospective studies to confirm this relationship.

CONCLUSION

Our most striking result is that new inflammation markers such as CAR and NAR values were significantly higher in the AF group, and especially the CAR value had the most heightened diagnostic sensitivity. The CAR value may be used as a suggestive marker in AF that needs to be diagnosed early.

Authors' Contribution

Study Conception: SA; Study Design: SA; Supervision: SA, FE; Funding: SA; Materials: SA; Data Collection and/or Processing: SA; Statistical Analysis and/or Data Interpretation: SA; Literature Review: SA; Manuscript Preparation: SA and Critical Review: SA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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