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Inflammatory biomarkers derived from whole blood cell count in atrial fibrillation patients

Aim	This study aimed to evaluate the potential relationships between atrial fibrillation (AF) and hematological indices, such as neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), platelet/lymphocyte ratio (PLR), mean platelet volume/platelet (MPV/PLT), neutrophil/monocyte ratio (NMR), lymphocyte/monocyte ratio (LMR), systemic immune inflammation index (SII, platelet x neutrophil/lymphocytes), and monocyte/high-density lipoprotein ratio (MHR), that can be obtained from the complete blood count (CBC test).
Material and method	This retrospective study included 150 patients aged 40–80 yrs who were diagnosed with AF, and 91 age- and gender-matched controls. Hematological indices and inflammation markers were evaluated.
Results	In the AF group, NLR, PLR, SII, MHR, and MPV/PLT were elevated, and LMR was low. Multivariate regression analysis showed that hematological indices NLR, SII, and MHR were significant, independent, predictive factors for AF. ROC curves revealed the following significant sensitivity and specificity values: NLR 75%, 52.3%; LMR 61.3%, 67.3%; SII 67.4%, 64.6%; MHR 100%, 56%.
Conclusion	NLR, PLR, LMR, SII, MPV/PLT, and MHR may be useful in the early prediction of AF development. It is strongly emphasized that among these variables, MHR, may be the best independent variable that can be used to predict AF.

Keywords	Atrial Fibrillation; MHR; MPV/PLT; NMR; LMR; SII
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Introduction

The mechanism responsible for the onset of AF is multifactorial, e.g., a prothrombotic state, inflammation, and/or oxidative stress [3]. Recently, there has been a wealth of evidence blaming oxidative stress and inflammation as the cause of AF in metabolically stressed hearts [4]. AF and inflammation are closely linked; inflammation exacerbates AF, and inflammation in the presence of AF creates a negative spiral [5]. Also, it is clear that AF is triggered by structural and electrical remodeling of the atria. Structural remodeling involves atrial fibrosis, which is associated closely with inflammation [6].

Thromboembolism and cerebrovascular events are the most common complications of AF. They cause cardiovascular morbidity and mortality, increase the length of hospital stay, and the number of admissions and exits to and from intensive care units. These complications increase the cost of healthcare [7].

The diagnosis and follow-up of AF are based on the patient's medical history and examination and on findings of electrocardiogram and Holter monitoring. The complete blood count (CBC) is a standard blood test that is performed routinely in the clinical examination of cardiovascular diseases [7]. There is good evidence that the indices obtained by calculating ratios among lymphocytes, monocytes, neutrophils, and platelets are strongly associated with inflammation. Indeed, scientific interest in the relations between systemic inflammation and CBC indices has increased in the last decade [8]. There have been reports of relationships between the occurrence and recurrence of AF and various indices derived from CBC values [3, 6, 9–11].

Hematological indices associated with inflammation, including the neutrophil/lymphocyte ratio (NLR), the red cell distribution width (RDW), the mean platelet volume (MPV), the monocyte/high-density lipoprotein ratio (MHR), the platelet/lymphocyte ratio (PLR), and the systemic immune ınflammation ındex (SII, platelet x neutrophil/lymphocytes), have been found to be associated with non-valvular AF, cardiac surgery, cardioversion, coronary artery bypass grafting, and AF recurrence after cryoballoon-based catheter ablation [7, 9–15]. Furthermore, there are almost no studies that directly associate AF with the SII, NMR, MPV/PLT or MHR or especially with the LMR [8, 11, 14]. This comprehensive study examined the relationship between AF and various hematological indices (NLR, MPV, PLR, MPV/PLT, NMR, LMR, SII, and MHR) that can be obtained from the CBC, which is an inexpensive and reproducible test routinely used and readily performed in

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standard clinical laboratories. This study is unique in its ability to examine the direct relationship between all hematological indices and AF. It compared these hematological indices among themselves and determined which is best for predicting AF.

Material and methods

We examined the files of patients aged 40–80 yrs who applied to the Cardiology Clinic of Afyonkarahisar Health Sciences University (AHSU) between 01-01-2019 and 01-11-2021 and who were diagnosed with AF. Before the study was initiated, Ethics Committee approval was obtained from AHSU Clinical Research Ethics Committee (decision dated 03.12.2021 and number 2021/558, Ethics Committee Code: 2011-KAEK-2).

Patients diagnosed with AF according to the American Heart Association Guidelines [16] were included in this study. The study sample consisted of a total of 241 individuals, 150 of whom were patients with AF and 91 participants without AF as controls. The inclusion criteria of all patients and controls were ECGs and transthoracic echocardiography during routine examinations in the Cardiology Clinic of AHSU Faculty of Medicine. The history and physical examination records of the patients with AF and those of the control group were examined in detail. The demographic data, e.g., age and gender, of the AF patients and the control patients were obtained from the patients' files along with their clinical characteristics, e.g., smoking, anticoagulant use, hypertension, diabetes mellitus, congestive heart failure, dyslipidemia, cerebrovascular accident, and myocardial infarction history. The inclusion criteria for the AF group was a diagnosis of AF. For the control group, those outside the age range of 40–80 yrs and those with conditions associated with inflammation, acute coronary syndrome, cardiothoracic surgery, valvular heart diseases, thyroid diseases, autoimmune and inflammatory diseases, pregnancy, malignancy, and infection were excluded. All control patients were required to have no history of bleeding, and to have normal blood cell count, sedimentation rate, C-reactive protein (CRP), and sinus rhythm.

Statistical analysis

The data were analyzed statistically with SPSS 21.0 Software for Windows. Qualitative data were compared with the chi-square test. All data were tested for normal distribution with Kolmogorov-Smirnov and Shapiro-Wilk tests. Comparisons of variables between two groups (control vs. AF) were made with a parametric, independent t-test procedure or the non-parametric, Wilcoxon procedure. Binary logistic regression analysis was used to determine whether the hematological indices (NLR, PLR, MPV/PLT, NMR, LMR, SII, MHR) were associated with AF. Variables with p<0.10 in the univariate analysis were included in a multivariate, binary logistic-regression analysis in which the Hosmer-Lemeshow test was used for goodness-of-fit. The results of these analyses are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The optimal cut-off values of NLR, LMR, SII, and MHR were determined by receiver operating characteristics (ROC) curve analysis and identified as the values that maximized the Youden Index (sensitivity + specificity – 1). P values <0.05 were used as the level of statistical significance.

Table 1. Baseline characteristics of the subjects

Parameters	Control (n = 91)	AF (n = 150)	Total (n = 241)	p
Gender				
Female	44 (48.4)	82 (54.7)	126 (52.3)	0.341*
Male	47 (51.6)	68 (45.3)	115 (47.7)	
Age (yr)	65.03±9.95	66.14±9.87	65.72±9.89	0.34 #
Smoking	19 (20.9)	35 (29.9)	54 (25.7)	0.161 *
Hypertension	28 (30.8)	56 (38.1)	84 (35.3)	0.25 *
Diabetes mellitus	36 (39.6)	54 (40)	90 (39.8)	0.947 *
Congestive heart failure	8 (8.8)	24 (16.6)	32 (13.6)	0.09 *
Cerebrovascular accident	1 (1.1)	7 (4.9)	8 (3.4)	0.125 *
Dyslipidemia	15 (16.5)	17 (12.1)	32 (13.9)	0.351 *
Myocardial infarction	0 (0)	6 (4.1)	6 (2.8)	0.09 *
Anticoagulant drugs	18 (20.9)	102 (72.9)	120 (53.1)	< 0.001 *

Data are number (percentage) or mean±standard deviation.
* Chi-square test. #Mann–Whitney U test.

Results

General characteristics of the study population

The general characteristics of the study population are presented in Table 1. Except for the use of anticoagulants, all other clinical characteristics did not differ significantly between the groups.

Clinical characteristics of the AF and control groups

The clinical characteristics of the subjects are shown in Table 2. Compared to the control group, heart rate, hemoglobin, leukocytes, neutrophil, monocytes, MPV, RDW-CV, sedimentation, CRP, NLR, PLR, SII, MHR, and MPV/PLT were significantly higher in the AF group, while HDL and LMR were lower.

Univariate and multivariate analysis of hematological indices as predictors for AF

Table 3 shows univariate and multivariate analyses of predictive factors for AF. Univariate regression analysis showed that NLR (OR: 1.326; 95% CI: 1.082–1.624;

Table 2. Clinical characteristics of AF patients and controls

Parameters	Control (n = 91)	AF (n = 150)	Total (n = 241)	*p
Systolic blood pressure (mmHg)	134.53 ±16.81	129.45±17.51	132.27±17.34	0.359
Diastolic blood pressure (mmHg)	80.21±13.02	77.03±10.65	77.8±11.31	0.177
Heart rate (beats/min)	75.53±10.03	85.63±17.67	83.33±16.77	< 0.001
Hemoglobin (g/dl)	12.56±2.03	13.25±1.91	13±1.98	0.012
Lymphocyte (103/µl)	1.97±0.91	1.87±0.88	1.91±0.89	0.407
Leukocyte (103/µl)	6.45±1.18	7.81±2.39	7.44±2.21	< 0.001
Neutrophil (103/µl)	4.07±1.06	5.19±1.96	4.86±1.82	< 0.001
Eosinophil (103/µl)	0.13±0.07	0.14±0.1	0.14±0.10	0.503
Basophil (103/µl)	0.05±0.02	0.04±0.03	0.04±0.03	0.369
Monocyte (103/µl)	0.5±0.14	0.64±0.21	0.6±0.2	< 0.001
Platelet (103/µl)	229.13±39.81	243.27±74.07	239.08±66.01	0.076
MPV (fl)	9.70±1.08	10.55±1.03	10.25±1.12	< 0.001
RDW-CV (%)	12.85±0.66	14.71±1.99	14.48±1.97	< 0.001
HDL (mg/dl)	50.81±7.31	41.13±10.93	43.6±10.96	< 0.001
Sedimentation (mm/hr)	9.54±5.59	24.25±17.81	22.85±17.56	< 0.001
CRP (mg/dl)	0,24±0.15	3.96±5.52	3.4±5.26	< 0.001
NLR	2.54±1.49	3.39±2.1	3.15±1.98	0.005
PLR	134.68±55.89	157.41±80.74	150.74±74.9	0.046
NMR	8.49±3.7	8.4±3.08	8.42±3.25	0.859
LMR	4.01±1.7	3.19±1.83	3.47±1.83	0.001
SII	551.78±291.76	817.86±553.08	757.64±517.38	< 0.001
MHR	0.01±0.003	0.017±0.007	0.015±0.007	< 0.001
MPV/PLT	0.044±0.009	0.05±0.021	0.048±0.018	0.046

Data are mean±standard deviation. *Independent samples t test. MPV, mean platelet volume; RDW-CV, red blood cell distribution width-coefficient of variation; HDL, high density lipoprotein; CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; NMR, neutrophil/monocyte ratio; LMR, lymphocyte/monocyte ratio; SII, systemic inflammatory index (platelet x neutrophil/lymphocyte); MHR, monocyte/HDL ratio; MPV/PLT, MPV/platelet ratio.

p=0.007), PLR (OR: 1.005; 95% CI: 1.001–1.009; p=0.049), LMR (OR: 0.785; 95% CI: 0.672–0.916; p=0.002), SII (OR: 1.002; 95% CI: 1.001–1.003; p=0.005), MHR (OR: 2.603; 95% CI: 1.762–3.840; p<0.001), and MPV/PLT (OR: 1.004; 95% CI: 1.001–1.006; p=0.05) were potential predictive factors for AF. Multivariate regression analysis identified NLR (OR: 0.764; 95% CI: 0.568–0.991; p=0.042), SII (OR: 1.014; 95% CI: 1.001–1.026; p=0.03), and MHR (OR: 2.352; 95% CI: 1.184–4.815; p=0.01) as independent predictive factors for AF.

ROC Curve Analyses of hematological indices in predicting AF

Figure1 and Table 4 show ROC curves and prognostic accuracy of derived hematological indices. The ROC curves

Table 3. Univariate and multivariate analyses of predictive factors for AF

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
NLR	1.326	1.082-1.624	0.007	0.764	0.568-0.991	0.042
PLR	1.005	1.001-1.009	0.049	1.011	0.989-1.033	0.318
NMR	0.991	0.901-1.090	0.858	-	-	-
LMR	0.785	0.672-0.916	0.002	1.821	0.919-3.606	0.086
SII	1.002	1.001-1.003	0.005	1.014	1.001-1.026	0.03
MHR	2.603	1.762-3.840	<0.001	2.352	1.184-4.815	0.01
MPV/PLT	1.004	1.001-1.006	0.05	0.996	0.987-1.004	0.395

OR, odds ratio; CI, confidence interval; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; NMR, neutrophil/monocyte ratio; LMR, lymphocyte/monocyte ratio; SII, systemic inflammatory index (platelet x neutrophil/lymphocyte); MHR, monocyte/HDL ratio; MPV/PLT, mean platelet volume/platelet ratio.

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revealed that the optimal cut off value of NLR was 2.78 with a sensitivity of 75% and a specificity of 52.3%; the optimal cutoff value of LMR was 3.494 with a sensitivity of 61.3% and a specificity of 67.3%; the optimal cutoff value of SII was 533.4 with a sensitivity of 67.4% and a specificity of 64.6%; the optimal cutoff value of MHR was 0.015 with a sensitivity of 100% and a specificity of 56%.

Discussion

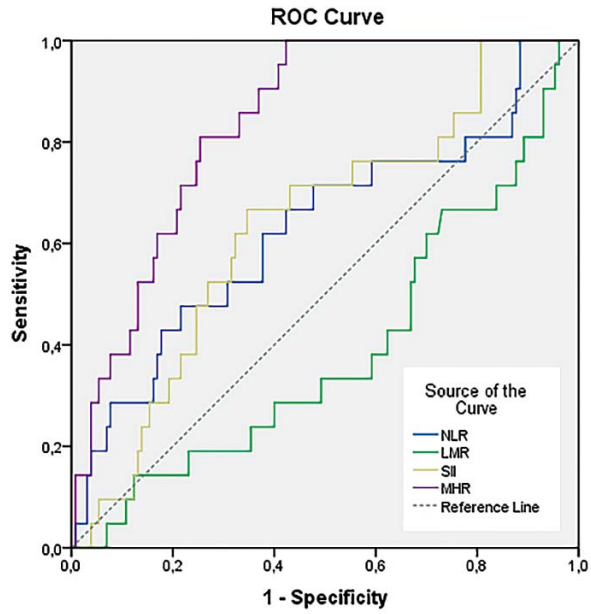
AF is the most common atrial arrhythmia affecting patients' quality of life. AF can cause serious complications, e.g., heart failure and stroke [6, 9, 10]. Inflammation and oxidative stress, which are considered to be associated with the onset of AF, trigger AF by reshaping the atria structurally and electrically [6, 17]. Inflammatory factors cause the emergence and re-entry of ectopic activity contributing to the initiation and maintenance of AF. Inflammatory biomarkers are characteristic of AF; therefore, anti-inflammatory treatment strategies reduce the risk of AF [6]. However, the results of current therapeutic approaches and preventive treatments for AF have been disappointing.

In the present study, although the NLR, PLR, SII, MHR, and MPV/PLT, were found to be elevated in patients with AF, the LMR was low. Multivariate logistic regression analysis showed that, among these variables, NLR, LMR, SII, and MHR were the best predictors of AF.

The lymphocyte count did not differ significantly in the AF group, but leukocytes, neutrophils, and NLR were higher in AF. The numbers of leukocytes and their subtypes are accepted as markers of inflammation and stress in various diseases [10]. Since neutrophil and lymphocyte counts change in the presence of inflammation, NLR is an index of systemic inflammation. NLR is used in the differential diagnosis of diseases or in the prediction of prognosis [18, 19]. For this reason, NLR has emerged as a novel systemic inflammatory marker in the prognostic follow-up of cardiovascular diseases.

A previous study reported that increased monocytes and NLR were associated with the prevalence of AF [10]. That study found that NLR could be a predictor of early recurrence of AF in patients who undergo radiofrequency catheter ablation [10]. In another study on AF, increased NLR after coronary artery bypass grafting was identified as a risk marker for AF [20]. However, some other reports contradicted these conclusions [12, 13].

Figure 1. Receiver operating characteristic (ROC) curves



NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; SII, systemic inflammatory index (platelet × neutrophil/lymphocyte); MHR, monocyte/HDL ratio.

The development of thromboembolism, which can be AF's fatal complication, is also associated with inflammatory activity [21]. Blood stagnates in the atria during AF, and the slowly flowing blood easily contributes to atrial thrombus formation. For this reason, the incidence of stroke and systemic embolism in AF patients is very high [14]. MPV is an important indicator of platelet activity since it reflects granule secretion and thromboxane synthesis in platelets. Elevating MPV is considered a risk marker for thrombogenesis in AF [6]. MPV and MPV/PLT were found to be high in patients with nonvalvular AF and with acute ischemic stroke [22]. In this context, the significant increase in MPV and MPV/PLT in the AF group in our study is consistent with previous studies [22].

In the present study, the platelet count and the PLR ratio differed significantly in the AF and the control group and were higher in AF. PLR is predicted to be a potential marker that can be employed to detect inflammation [23]. Zhang et al. stated that high PLR is associated with poor prognosis in

Table 4. ROC curves and prognostic accuracy of the derived hematological indices

Risk Factor	AUC	95% CI	p	Cut-off	Sensitivity (%)	Specificity (%)
NLR	0.646	0.562-0.73	0.001	> 2.78	75	52.3
LMR	0.659	0.584-0.734	< 0.001	< 3.494	61.3	67.3
SII	0.662	0.574-0.749	0.001	> 533.4	67.4	64.6
MHR	0.797	0.731-0.863	< 0.001	> 0.015	100	56

AUC, area under the curve; CI, confidence interval; NLR, neutrophil/lymphocyte ratio;
LMR, lymphocyte/monocyte ratio; SII, systemic inflammatory index (platelet x neutrophil/lymphocyte); MHR, monocyte/HDL ratio.

cardiovascular diseases. High PLR in the preoperative period may not only prepare the ground for the formation of AF in the postoperative period but may also increase the existing inflammation or exacerbate existing AF [24].

SII, the novel parameter for AF was initially defined in oncological studies as a prognostic inflammatory marker in infective endocarditis recently [11]. Studies conducted to understand the possible relations between AF and SII are limited. Bagci et al. speculated that SII can be used as one of the independent predictors in new-onset AF after ST-segment elevation myocardial infarction [25]. The findings of the present study indicate that a high SII is significantly associated with AF risk. To the best of our knowledge, this is the first study to examine the relation between SII and AF.

The activation of monocytes plays important roles in chronic inflammation and cardiovascular diseases, including AF. Increased monocyte count and AF were reported to be associated with each other [10]. LMR, like other index, is a marker of systemic inflammation that is inexpensive for routine use and easily calculated from a white blood cell test. LMR was proven to be a prognostic factor in patients with malignancy and tuberculosis [23]. It was argued in a recent study that LMR is an independent risk factor for cardiovascular diseases and a predictor of lesion severity in coronary artery disease [26]. Zhang et al. speculated that LMR would be a systematic inflammatory predictor for patients who have cardiovascular disease [24]. However, there is no direct evidence regarding a relation between LMR and AF [24, 26]. A study conducted by Yu et al. was the first to explain the association between AF and LMR [27]. In that study, the relation between LMR and mortality in patients with AF was questioned. In this respect, low LMR was associated with a risk of mortality in patients with AF [27]. According to the findings of the study, although the monocyte count was elevated in AF, the LMR ratio was low. In our study, LMR was low in the patient group with AF. Although the control group and patients diagnosed with AF were compared in our study, LMR was low in the patient group with AF, similar to this study [27].

Monocytes are the primary sources of proinflammatory and prooxidant cytokines in inflammation [14, 28]. The result obtained by dividing the number of circulating monocytes by HDL cholesterol is the MHR. The MHR has been proposed as a new inflammatory biomarker and a prognostic indicator for cardiovascular diseases based on the pro-inflammatory effect of monocytes and the anti-inflammatory effect of HDL [29]. As a new indicator, MHR has been investigated in a limited number of cardiovascular diseases in which inflammation and oxidative stress are common, including AF [18, 25]. Although MHR has a prognostic value in paroxysmal AF, reports of MHR in AF after radiofrequency ablation are conflicting [14]. One of these studies suggested that MHR could be used as a predictor of AF recurrence after cryoballoon-based catheter ablation [15]. In another study, it was noted that MHR is also important in predicting the development of AF after coronary artery bypass grafting [14]. Among the inflammation indices examined in the current study, MHR was found to be the best predictor of AF risk. In fact, increased MHR in AF patients was the most powerful and independent predictor of AF among the hematological indices examined. In clinical practice, using MHR can identify high-risk patients for AF early, and, thus, this can reduce unnecessary interventions.

Red cell distribution width (RDW) is a measure of the variation in the sizes of erythrocytes and is routinely obtained in the CBC. An increased RDW shows chronic inflammation, and the presence of anisocytosis, which reflects high oxidative stress. It was reported previously that RDW increases in hypertensive patients with new-onset and recurrent AF [3, 7, 9]. In the present study, RDW values were higher in the AF group, which is consistent with the literature.

Although CRP has a high sensitivity to inflammation, it is a non-specific marker. Clinical data have shown a significant relationship between CRP and AF [21, 30]. It was reported that CRP can indicate the possibility of developing new-onset AF since plasma CRP is increased in patients with AF when compared to patients who are in sinus rhythm [11]. CRP is employed as systemic inflammation markers in routine clinical follow-up. In the current study, these variables were in the reference range for the control group, but they were higher in the AF group. This was similar to the findings of previous studies [11, 30].

Conclusion

Some of the hematological inflammatory indices evaluated in this report have been associated in previous studies of AF developing after cardiac surgery, cardioversion, and catheter ablation. It has been suggested that these indices can be used in the predetermination of AF and in the follow-up prognosis. However, in this study for the first time, we found that MHR is more powerful than other hematological indices for predicting AF.

Limitations of the study

This study is retrospective, and it has some additional, potential limitations. The number of subject in the study was statistically sufficient, but the fact that this study was conducted in a single center prevented it from reaching a larger sample size. Therefore, subtyping of AF could not be done.

No conflict of interest is reported.

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