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Relationship between inflammation related index and coronary artery disease in low-to-moderate risk patients with stable chest pain

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Abstract
Aim: Coronary artery disease is the leading cause of mortality and morbidity worldwide. Recently, inflammatory markers found and measured in the complete blood count have been used as precursors in many clinical situations. In this study, we aimed to investigate the relationship between inflammatory-related hemogram parameters and coronary artery disease in low-to-moderate risk patients with stable chest pain.
Material and Methods: A total of 101 patients who underwent CT coronary angiography between 2018 and 2020 were included in the study. Patients were classified as those with normal coronaries, coronary plaques, and severe coronary stenosis. Severe coronary stenosis was represented as at least one of >50% stenotic coronary vessels and the relationship between hemogram parameters and coronary artery disease was retrospectively investigated.
Results: There was no significant difference between healthy, coronary plaque, and severe stenosis groups in terms of RDW, Platelet to Lymphocyte Ratio (PLR), and Monocyte to High Dens Lipoprotein Ratio (MHR). The only significant difference among the groups was for neutrophil/lymphocyte ratio (NLR)(p=0.015). NLR was significantly higher in the severe coronary stenosis (44.46±8.65) compared to the healthy (1.76±0.58) and coronary plaque (1.77±0.64) (p=0.005 and 0.012; respectively) groups. No difference was found between the healthy and coronary plaques in terms of NLR (p=0.989).
Discussion: Although we did not identify a parameter that could be defined as a diagnostic value among these indexes, NLR appears to be stronger than others in the low-to-moderate risk group.

Keywords
Chest Pain, Angiography, Platelet, Lymphocyte, Neutrophil, Monocyte

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Introduction

Coronary artery disease (CAD) is among the leading causes of mortality and morbidity worldwide. Morphological and functional evaluation is important for its correct treatment [1]. As is well-known, oxidative damage and inflammatory stress play an important role in the pathogenesis of CAD [2]. Conclusive determination of inflammatory markers would be helpful in the determination of cardiovascular risk and evaluation of the efficacy of the treatment. Correct determination of these inflammatory biomarkers will bring about novel treatment approaches in the future.

Coronary syndromes are associated with simple lipid accumulation. Studies have shown inflammatory cell accumulation and platelet aggregation at the site of endothelial damage and plaque rupture [3]. In this term, the Neutrophil/lymphocyte ratio (NLR) is an important marker in the diagnosis and prognosis of cardiovascular diseases. In studies related to increased NLR, it has been shown to be associated with poor prognosis and increased mortality in CAD and heart failure [4]. NLR has proven to be a strong predictor of mortality following cardiac events [5]. Considering the immune-inflammatory nature of the atherosclerotic process, it is obvious that stressors and internal and adaptive mechanisms are well-reflected by NLR [6]. Although there are numerous studies in the literature about the relationship between NLR and coronary artery disease, our knowledge of the distribution and cut-off values of NLR remains limited [7]. Again, information about whether NLR can be prognostic for CAD in patients in the low-to-moderate group is limited.

Monocytes are the main source of proinflammatory mediators in atherogenesis. High-density lipoprotein (HDL) inhibits pro-inflammatory and pro-oxidative features of monocytes. HDL also inhibits macrophage migration and efflux of low-density lipoproteins. In light of these findings, monocyte accumulation and a decrease in HDL will be expected. Considering that CAD is a chronic inflammatory process, the monocyte/HDL ratio (MHR) may have a predictor potential for CAD [8]. An increased number of platelets indicates an increase megakaryocytic proliferation and increased thrombocytosis [9]. The decreased number of lymphocytes shows immune depression and causes an increase in cardiac adverse events [10].

In this study, we aimed to investigate whether NLR, platelet/lymphocyte ratio (PLR), and MHR altered in CAD. We also investigated their prognostic significance in patients who were presented with stable chest pain and underwent computed tomographic coronary angiography (CTCA).

Material and Methods

Study Population

Since the study was intended to be retrospective, ethical approval was waived. However, the necessary permission was obtained from the hospital management for using patients' data. A total of 150 patients with clinical, laboratory, and CTCA data between 2018 and 2020 were included in the study. Based on patient data, patients with stable chest pain were categorized as low-to-moderate risk. Patients with a history of coronary intervention, severe valvular disease, heart failure, or malignancy that could change inflammatory biomarkers, autoimmune disease, renal and hepatic failure, and a history of chronic infectious disease were excluded from the study. Patients using drugs such as corticosteroids that could change NLR levels were also excluded. Finally, a total of 101 patients were involved in the present study. They were divided into three groups: those with normal coronaries, those with plaque detected, and those with severe stenosis. Severe stenosis was represented as at least one of >50% stenotic coronary vessels.

Laboratory data

Blood samples were collected from the antecubital vein with an atraumatic puncture and immediately sent to the laboratory. Ethylene-diamine-tetraacetic acid (EDTA) containing tubes were used for the hemogram. A complete blood count, including the differentials, was performed using an automated blood cell counter (Mindray BC 6800). The biochemical panel was calculated with a Cobos 6000 (Roche diagnostics) autoanalyzer. NLR was obtained by dividing the neutrophils count by the lymphocytes count, PLR by dividing the platelets count by the lymphocytes count, and MHR by dividing the monocytes number by HDL.

Computed Tomographic Coronary Angiography

All patients underwent the 128-slice CT coronary angiography procedure (Ingenuity Elite 128 Slice-PHILIPS). 100cc IV contrast agent was given at a rate of 5 mL/sec and volumetric axial sections were acquired. The volume rendering technique (VRT) was reconstructed with processing methods after maximum intensity projection (MIP) and multi-planar reformation (MPR). The axial sections and reformatted images were evaluated together. Patients with a heart rate ≥70/min were given iv beta-blockers.

Statistical Analysis

The variables were analyzed using SPSS v25 (IBM Corporation, Armonk, New York, United States) statistical software. The normality of univariate data was evaluated with the Shapiro-Wilk Francia and variance homogeneity with the Levene test. Among the parametric methods, one-way ANOVA was used to compare multiple independent groups with each other in terms of quantitative data, while Fisher's Least Significant Difference (LSD) test was used for post hoc analysis. Receiver Operating Curve (ROC) analysis was used for the diagnostic differentiation of the normal and severe coronary stenosis groups according to inflammatory biomarkers. In the tables, quantitative variables are expressed as mean±SD (Standard Deviation), while categorical variables are shown as n (%). The variables were examined at a 95% confidence interval and $p<0.05$ values were considered statistically significant.

Results

There was no statistically significant difference between healthy, coronary plaque, and severe coronary stenosis groups in terms of RDW, PLR, and MHR variables (p=0.763, p=0.082, p=0.092, and p=0.594; respectively). There was a significant difference in terms of NLR (p=0.015). The mean NLR was higher in the severe coronary stenosis group (44.46±8.65) when compared to healthy (1.76±0.58) and coronary plaque (1.77±0.64) (p=0.005 and p=0.012; respectively) (Figure 1). No significant difference was found between the healthy and coronary plaque groups in terms of NLR (p=0.989) (Table 1).

Table 1. Evaluation of the groups according to inflammatory biomarkers

Groups	n		RDW	PLR	NLR	MHR
Normal	I	65	12.75±1.63	107.9±32.4	1.76±0.58	0.015±0.006
Coronary Plaque	II	24	13.19±1.49	107.3±39.2	1.77±0.64	0.017±0.019
Severe Coronary Stenosis	III	12	13.83±1.79	132.3±47.8	4.46±8.65	0.016±0.008
Total		101	12.98±1.64	110.6±36.6	2.08±3.05	0.015±0.011
P value			0.082	0.092	0.015	0.594
Pairwise comparisons	I→II		Ns.	Ns.	0.989	Ns.
	I→III		Ns.	Ns.	0.005	Ns.
	II→III		Ns.	Ns.	0.012	Ns.

OneWay ANOVA Test; Post Hoc Test: Fisher's Least Significant Difference (LSD). Abbreviations. SD: Standard Deviation, Ns: Non-significant.

Table 2. Diagnostic value of inflammatory biomarkers in diagnostic discrimination of the normal and severe coronary stenosis groups

Groups	AUC (SE.)	p
NLR	0.548 (0.063)	0.424
RDW	0.578 (0.062)	0.196
PLR	0.538 (0.062)	0.563
MHR	0.497 (0.061)	0.966

Abbreviations. Receiver Operating Characteristic (ROC) Analysis, AUC: Area under the ROC curve, SE: Standard Error

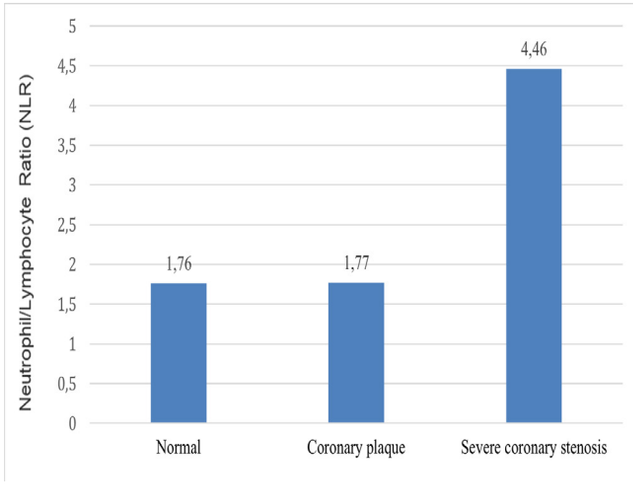

Figure 1. Comparison of the NLR among the patient groups

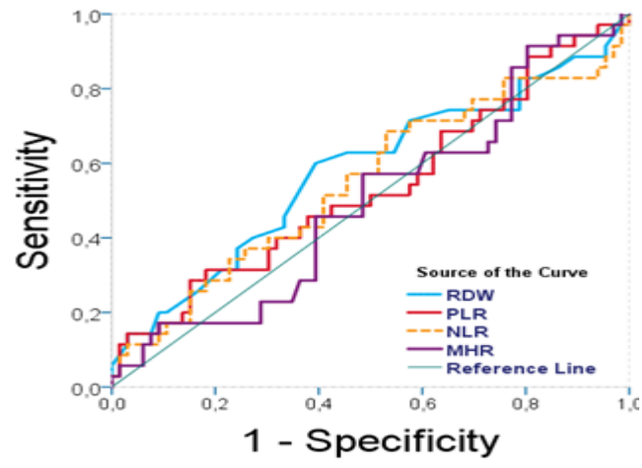

Figure 2. The ROC Curve analyzing the diagnostic value of NLR, PLR, MHR, and RDW

The results of ROC analysis performed to distinguish the healthy and coronary plaque groups according to RDW, PLR, and MHR variables were not significant (p>0.05) (Figure 2). The results of the ROC analysis (diagnostic value) performed to distinguish the healthy and severe coronary stenosis groups according to the inflammatory biomarkers (diagnostic value) were not significant (p>0.05) (Table 2). The diagnostic value of inflammatory biomarkers in distinguishing the healthy and coronary plaques was not significant (p>0.05) (Table 2).

Discussion

In the present study, we investigated the inflammation-related index including NLR, PLR, MHR, and RDW that have a possible diagnostic potential in CAD, with their prognostic significance in patients who were presented with stable chest pain and underwent CTCA. In all these indexes, NLR positively differentiated in patients with coronary stenosis on angiography.

Besides conventional coronary angiography, new modalities showing CAD have been developed with high sensitivity and specificity. CTCA stands out as an investigation method with high sensitivity and high negative predictive value [11]. In the last two decades, the radiation dose has dropped to 2 mSv owing to the technological advancements in CTCA. On the other hand, the exercise stress test shows CAD by 64%, the negative predictive value of CTCA is 100% [12]. Studies have shown that CTCA is more cost-effective and has begun to replace myocardial perfusion scintigraphy in low-to-moderate risk patients presented with chest pain. It has also been included in international guides [13, 14]. Hence, we analyzed patients who underwent CTCA because of the increasing importance of this technique.

Two decades ago, we knew that CAD can be easily improved with the treatment of hypertension and hyperlipidemia. However, deaths from CAD are continuing to increase, and cardiovascular disease will remain the leading cause of mortality in the next few decades [15]. All these reasons show the necessity of new risk categorizations and treatment approaches for CAD. Numerous biomarkers have been studied to reduce CAD-related mortality and morbidity. As inflammation plays a major role in atherosclerosis, studies have focused on this area. Atherosclerosis begins with intimal proliferation and inflammation [16]. Among numerous inflammatory biomarkers, a significant association has been found between white blood cells, their subtypes, and CAD [17]. NLR stands out among

these inflammatory biomarkers. Furthermore, NLR has been associated with many cardiovascular diseases. The association of NLR with cardiac arrhythmia, CAD, chronic renal failure, and acute coronary syndrome has been well-defined [18].

Some studies have shown the presence of polymorphonuclear (PMN) cells in the coronary thrombus area in patients undergoing coronary intervention. PMNs secrete neutrophil extracellular traps (NTEs) in the lesion site. NETs have a high level of proinflammatory and prothrombotic properties. They are positively correlated with the infarction area. Again, a high level of NTEs causes ST-segment resolution to be more difficult [19]. Unlike neutrophils, lymphocytes adjust the adaptive mechanisms of the immune system, with helper T cells specifically reducing and limiting inflammation. Low lymphocyte count is associated with poor outcomes in patients with acute coronary syndrome. Studies have identified an association between low lymphocyte count and increased atherosclerosis [20]. In our study, a significantly higher NLR ratio in groups with coronary stenosis indicates the importance of this ratio in the development and progression of atherosclerosis. Wikananda et al. compared the GRACE risk score and NLR in patients with acute myocardial infarction. NLR was significantly higher in patients with a high GRACE score [21]. Acet et al. found that NLR was significant in STEMI patients with a high TIMI risk score [22]. All of these studies have been conducted in patients who had severe coronary stenosis and myocardial infarction. Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a heterogeneous entity in which the inflammatory process plays a role in etiopathogenesis. MINOCA was included in the 2017 guidelines by the European Society of Cardiology. Interestingly, this group of patients with myocardial infarction has no significant coronary stenosis [23]. It is thought that inflammation plays a critical role in this group of CAD. In a study by Gürdal et al., NLR was found to be significantly higher in patients who presented with ST-elevation MI (STEMI) and were grouped as MINOCA [24]. All these findings suggest that NLR can provide important information in patients with acute coronary syndrome.

In a recent study, Monocyte count and MHR were reported as potential bio indexes in adverse clinical events occurring in acute coronary syndrome [25]. In contrast, we found no correlation between MHR and CAD. This may be attributed to much more intense inflammation and decreased HDL in acute coronary syndrome. In our study, a lower MHR compared to acute coronary syndrome could be expected because the patients in our study group were with stable CAD.

Detecting coronary artery disease much earlier will be cost-effective and will reduce patient mortality and morbidity. Therefore, we included patients with stable chest pain who were taken into the low-to-moderate risk group and who underwent CTCA. Thus, reducing risk factors with inexpensive biomarkers with a prognostic value in the very early stage of coronary artery disease will positively contribute to cardiovascular mortality and morbidity. Another objective of our study was that inflammatory biomarkers are not included in cardiovascular risk scoring systems such as GRACE and SYNTAX. An increase in the number of such studies in the literature will facilitate the inclusion of these inexpensive and readily calculated biomarkers in risk scorings and the definition of their cut-off values.

The study had some limitations. The retrospective nature of the study design and the relatively small number of patients may be considered as the main limitation. The lack of possible long-term follow-up and limited pairwise comparison can also be considered as another important limitation.

Conclusion

In the present study, we investigated the inflammation-related index including NLR, PLR, MHR, and RDW that have a possible diagnostic potential in CAD, with their prognostic significance in patients who were presented with stable chest pain and underwent CTCA. Although we did not identify a parameter to be defined as a diagnostic value among these indexes, NLR appears to be stronger than others in the low-to-moderate risk group.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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