Northwestern Med J.2022;2(1):32-39
doi: 10.54307/NWMJ.2022.32932

Original Article

The diagnostic value of monocyte/high-density lipoprotein ratio (MHR) in patients with unstable angina pectoris

Unstabil angina pektoralisli olgularda monosit/high density lipoprotein (HDL) oranının tanısal değeri

Kaan Çelik

Atıf/Cite as: Çelik K. The diagnostic value of monocyte/high-density lipoprotein ratio (MHR) in patients with unstable angina pectoris. Northwestern Med J.2022;2(1):32-39.

ABSTRACT

Objective: The present study aimed to review the association of Monocyte/High-Density Lipoprotein (HDL) ratio (MHR) in patients with and without stenosis who had angiography due to preliminary diagnosis of unstable angina pectoris (USAP) and evaluate the diagnostic value of MHR for diagnosis of USAP with stenosis. (stenosis requiring intervention (≥50%) and stenosis not requiring intervention (<50%).
Methods: The patients admitted due to USAP diagnosis and presented stenosis above 50% in the angiography (Group 1), and the patients who presented stenosis below 50% (Group 2) were compared. Age, gender, co-morbidity, smoking habits, hemogram parameters, cholesterol levels before angiography, MHR, and mortality states were reviewed.
Results: The median age of the patients in Group 1 was 61 (IQR:20), and 71.6% of the patients were male. The median MHR in Group 1 and Group 2 were 0.02 (IQR:0.01) and 0.01 (IQR:0.0), respectively. MHR of the patients with stenosis above 50% was significantly higher ($p<0.05$). Sensitivity and specificity were detected at 83.2% and 82.6%, respectively, for a cut-off value of 0.014 for determination of stenosis above 50% in the present study (EAA 0.879; 95% CI 0.817-0.941).
Conclusion: We believe that MHR may be a parameter to determine mine the degree of stenosis in patients with a preliminary diagnosis of USAP. The intervention requirement of the opinion that MHR has a high predictability power for indicating of degree of stenosis has arisen in our mind with this study.

Keywords: monocyte, high-density lipoprotein, monocyte to high-density lipoprotein ratio, unstable angina pectoris

ÖZ

Giriş ve Amaç: Çalışmamızda unstabil angına pektoris (USAP) ön tanısı ile angiografi yapılan olgularda stenozu % 50'nin üstünde ve altında saptanan hastaların monosit/yüksek yoğunluklu lipoprotein (HDL) oranı (MHR) ile olan ilişkisini değerlendirerek, USAP'ı olup stenozu % 50'nin üstünde saptanan hastaların tanısında MHR'nin tanısallığını değerlendirmeyi amaçladık.
Yöntem ve Gereçeler: USAP tanısı ile yatırılan ve yapılan angiografilerinde %50'den fazla darlığı olan hastalar (Grup 1) ile %50'den az darlığı olan hastalar (Grup 2) karşılaştırıldı. Olguların yaş, cinsiyet, komorbidite, sigara alışkanlıkları, angiografi öncesi hemogram parametreleri ve kolesterol düzeyleri monosit/HDL oranı (MHR) ve mortalite durumları incelendi.
Bulgular: Çalışmamızda Grup 1 deki hastaların yaş ortancası 61 (IQR: 20) ve hastaların %71,6'sının erkek olduğu saptandı. Çalışmamızda Grup 1 deki hastaların MHR ortancası 0.02 (IQR: 0.01) ve Grup 2 deki hastaların MHR ortancası 0.01 (IQR: 0.0) olarak saptandı. Stenozu %50'den fazla olan hastaların MHR'si anlamlı olarak yüksek saptandı ($p<0.05$). Çalışmamızda %50'den fazla stenozu belirlemede 0,014 cut-off değeri için sensitivite %83.2, spesifite %82,6 olarak saptandı (EAA 0,879; %95 CI 0.817-0.941).
Tartışma ve Sonuç: MHR'nin klinik değerlendirmede USAP tanısı konan hastalarda, stenozun derecesini belirlemede kullanılabilecek bir parametre olabileceği kanısındayız.

Anahtar kelimeler: monosit, high density lipoprotein, monosit high density lipoprotein oranı, unstabil anjina pektoris

Received: 01.28.2022
Accepted: 01.28.2022
Publication date: 02.14.2022

Corresponding Author:
K. Çelik
ORCID: 0000-0002-9664-6732
Bolu Abant İzzet Baysal University, Faculty of Medicine, Department of Emergency Medicine, Bolu, Turkey
✉ drkaancelik@yahoo.com

INTRODUCTION

Deaths due to ischemic heart disease are responsible for 12.7% of all-cause mortality cases today (1). Chest pain is an important sign among referrals to the emergency department, and approximately 15% of these patients are observed due to the diagnosis of an acute coronary syndrome (ACS) (2). ACS is classified into three groups: ST-segment elevation MI (STMI), Non-ST-segment elevation MI (NSTMI), and unstable angina pectoris. It was suggested that inflammatory mediators are involved in the development of ACS, and the mechanisms in this process are similar in the clinical presentation of all ACS cases (3).

Although electrocardiogram (ECG) and cardiac markers such as creatine kinase MB (CKMB) and troponin provide significant prognostic information by contributing to the differential diagnosis of the patients with chest pain, they remain insufficient in the patients with USAP. Therefore, variable risk factors, insufficient medical history, different chest pain characteristics, or unclear expression of the chest pain due to sociocultural causes may cause misdiagnosis or unnecessary interventional procedures (angiography) (4).

Monocytes are one of the most important components of the plaques and act in immunity by releasing some pro-inflammatory and pro-oxidant cytokines. Various studies indicated that monocyte count is an independent risk factor for coronary artery disease (CAD) and is associated with plaque progression during the acute phase of ACS (5-7). A stenosis with a diameter by 50% in coronary arteries after angiography in the patients with ACS is used as a threshold for the treatment (8). Along with the pro-inflammatory effect of monocytes, the protective effect of high-density lipoprotein (HDL) cholesterol due to anti-inflammatory and antioxidant effects were suggested. HDL inhibits endothelial expression of adhesion molecules through inhibition of CD11b activation and prevents adhesion of monocytes onto the arterial wall (7, 9).

Previous studies reported that cholesterol levels are closely associated with atherosclerosis resulting from ACS. Such studies suggest the protective effects of HDL and atherosclerosis-aggravating effects of low-density lipoprotein (LDL) (7, 10). Furthermore, it was also stated that HDL has a protective effect against LDL oxidation and monocyte activation (11).

Monocyte/HDL ratio (MHR) is recently considered a new marker for inflammation and oxidative stress (7, 9).

We aimed to review the association between MHR and the patients with stenosis requiring intervention (>50%), and stenosis not requiring intervention (<50%) who had angiography due to preliminary diagnosis of USAP and assess the diagnostic value of MHR in the present study.

MATERIALS AND METHODS

Study design

The study was performed retrospectively on 421 patients diagnosed with USAP in the emergency department of Abant Izzet Baysal University, Faculty of Medicine, between June 2016 and June 2019.

The patients who presented stenosis above 50% (Group 1) and those who presented stenosis below 50% (Group 2) detected by angiography were compared in the present study. A thousand and fourteen patients with STMI and NSTMI were excluded.

Age, gender, co-morbidity, smoking habits, hemogram parameters before angiography (white blood cell count and sub-parameters, hemoglobin, platelet), cholesterol levels before angiography (total cholesterol, HDL, LDL and triglyceride), Monocyte/HDL ratio (MHR), and mortality rates were compared.

Exclusion criteria

The patients with unknown monocyte and HDL levels and deficient clinical data were excluded. The patients with hematological disease that causes

monocytosis (i.e. acute or chronic myeloblastic leukemia, polycythemia vera, myelodysplastic syndromes, idiopathic thrombocytopenic purpura, Non-Hodgkin and Hodgkin lymphoma etc.), those with active infections (i.e. cytomegalovirus, varicella-zoster), those with non-hematopoietic diseases (malignant diseases, glucocorticoid use), those using exogenous corticoids, and pregnant and breastfeeding women were excluded. Furthermore, patients treated with anti-hyperlipidemic agents because of hyperlipidemia, metabolic syndrome, etc., were also excluded.

Statistical analysis

The data were analyzed via the Statistical Package for the SocialSciences® (SPSS, IBM-Illinois, USA) for Windows Ver. 23.0 program. Categoric variables were expressed in numbers and percentages. The Chi-square test was used for data analysis. The distribution of continuous data was tested by Kolmogorov-Smirnov. Since the data were non-parametric, median and interquartile range (IQR) were used for data presentation; double comparisons were performed. The ROC curve was utilized for the area under the curve (AUC), cut-off value, sensitivity, and specificity. P-values below 0.05 were accepted as statistically significant.

RESULTS

The median of MHR of Group 1 was significantly higher than Group 2 in the present study ($p<0.05$). The rate of male gender in Group 1 was significantly higher than Group 2 ($p<0.05$). There was no association between co-morbidity and the groups. Comorbidity prevalence of the patients enrolled in the groups was comparable ($p>0.05$). The active smoking state was higher in Group 1, whereas the smoking cessation rate was significantly higher in Group 2 ($p<0.05$). There was no difference between the groups for hemoglobin, white blood cell, lymphocyte, basophile, eosinophile, platelet, urea, and creatinine values ($p>0.05$). In this study, monocyte count was higher, and neutrophil count was lower in Group 1 than Group 2 ($p<0.05$). Total cholesterol and LDL levels were significantly higher, whereas HDL level was significantly lower in Group 1 ($p<0.05$). There were no significant differences between the groups for triglycerides ($p>0.05$) (Table 1).

Median MHR was 0.02 (IQR: 0.01) and 0.01 (IQR: 0.0) in Group 1 and Group 2, respectively. MHR level of the patients in Group 1 was statistically higher ($p<0.05$) (Figure 1).

The mortality rate of the patients in present study was 1.3% (n:5); all cases were in Group 1. The median MHR of the patients who have died was 0.03 (IQR:0.01), and the median MHR of alive patients was 0.02 (0.01). The MHR of deceased patients was significantly higher (p:0.010) (Figure 2).

In the present study, the following statistical values were detected for MHR to determine the degree of stenosis; AUC 0.879 (95% CI 0.817-0.941), 83.2% sensitivity, and 82.6% specificity for a cut-off value of 0.014 (Figure 3).

DISCUSSION

The MHR of the patients with stenosis above 50% was significantly higher in the patients with stenosis than those without. The MHR level was detected higher in the patients with stenosis requiring intervention (≥50%) than those with stenosis that do not require intervention (<50%).

Arisoy et al. compared patients with higher and lower thrombus load and reported sensitivity by 60.5% and specificity by 69.6% (7). Sercelik et al. reported the sensitivity and specificity rates for MHR as 43% and 87%, respectively in patients with ST elevation (9). A study conducted on patients with nephropathy detected sensitivity and specificity of MHR for AMI as 65.7% and 64.0%, respectively (12). In the present study, sensitivity and specificity of MHR were detected as 83.2% and 82.6%, respectively. Higher sensitivity and specificity levels were considered that MHR might be used for diagnosis of the stenosis at and over 50% in the coronary arteries.

Table 1. Comparison of demographic data and laboratory findings between the groups.

		Group 1(n:398)	Group 2 (n:23)	
Age (years); Median (IQR)		61 (20)	52 (9)	<0.001*
Gender, n (%)	Male	285 (71.6)	12 (52.2)	0.047*
	Female	113 (28.4)	11 (47.8)	
Co-morbidity, n (%)	Diabetes mellitus	226 (56.8)	9 (39.1)	0.097
	Hypertension	194 (48.7)	13 (56.5)	0.468
	Cardiac failure	65 (16.3)	3 (13)	0.677
	Stroke	74 (18.6)	5 (21.7)	0.707
	COPD	48 (12.1)	3 (13)	0.888
	Renal failure	16 (9)	2 (8.7)	0.541
	Other	10 (2.5)	0	0.442
	None	154 (38.7)	5 (21.7)	0.029*
Smoking, n (%)	Quit	134 (33.7)	14 (60.9)	
	Smoker	110 (27.6)	4 (17.4)	
Hb (g/dl); Median (IQR)		15.2 (3.6)	14.1 (2.2)	0.064
White blood cell (x10^3 /mm^3); Median (IQR)		7.4 (2.1)	7.9 (2.2)	0.347
Neutrophil (x10^3 /mm^3); Median (IQR)		4.0 (1.7)	4.5 (0.7)	0.013*
Lymphocyte (x10^3 /mm^3); Median (IQR)		2.10 (1.0)	2.30 (0.6)	0.357
Monocyte (x10^3 /mm^3); Median (IQR)		0.7 (0.2)	0.5 (0.1)	<0.001*
Basophile (x10^3 /mm^3); Median (IQR)		0.09 (0.08)	0.08 (0.07)	0.106
Eosinophile (x10^3 /mm^3); Median (IQR)		0.18 (0.17)	0.20 (0.11)	0.632
Platelet (x10^3 /mm^3); Median (IQR)		249 (93)	227 (132)	0.476
Urea (mg/dl); Median (IQR)		34 (15)	31 (11)	0.420
Creatinine (mg/dl); Median (IQR)		0.98 (0.25)	0.90 (0.3)	0.080
Total cholesterol (mg/dl); Median (IQR)		202 (62)	185 (57)	0.003*
Triglyceride (mg/dl); Median (IQR)		195 (88)	173 (73)	0.756
HDL (mg/dl); Median (IQR)		38 (9)	44 (17)	0.014*
LDL (mg/dl); Median (IQR)		149 (41)	117 (33)	0.023*

IQR: Interquartile range, COPD: Chronic obstructive pulmonary disease, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

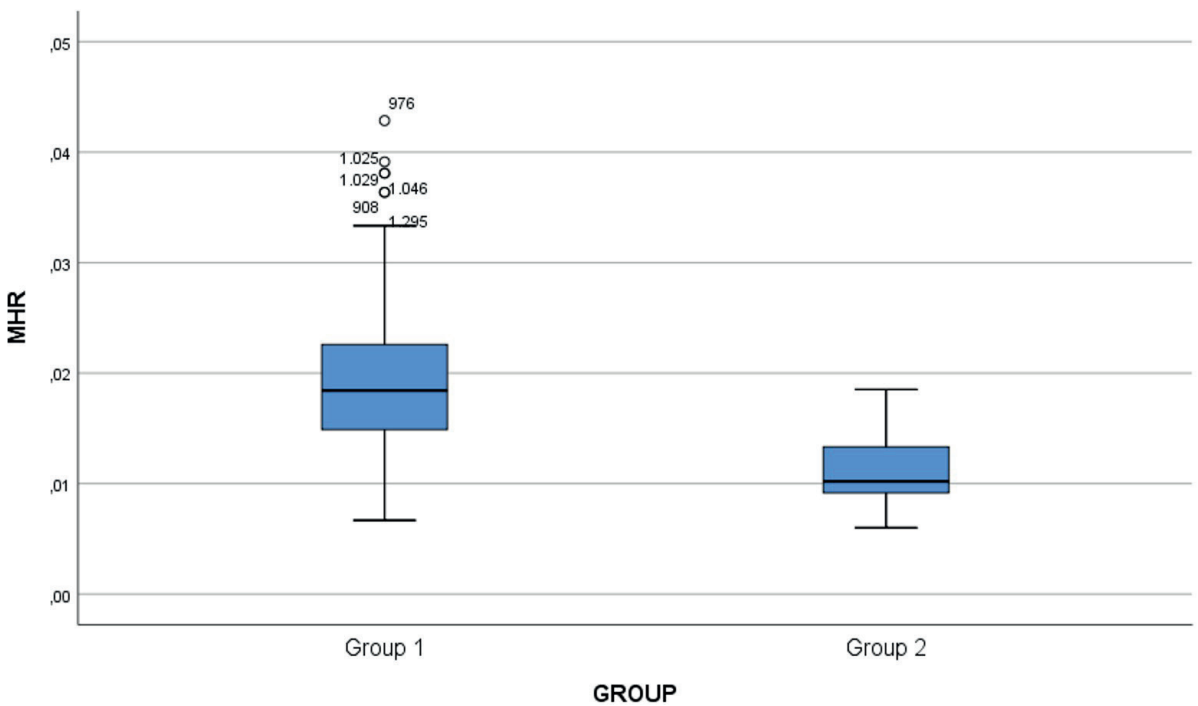

Figure 1. MHR comparison of the groups.

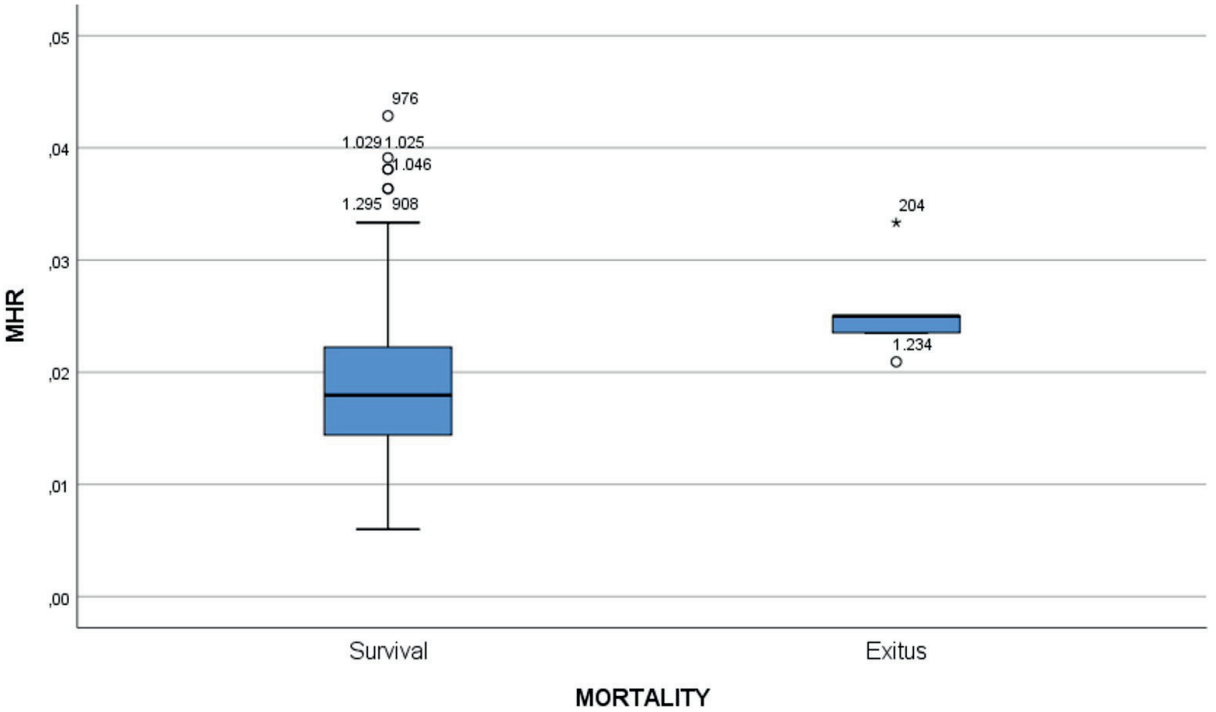

Figure 2. The association between mortality and MHR.

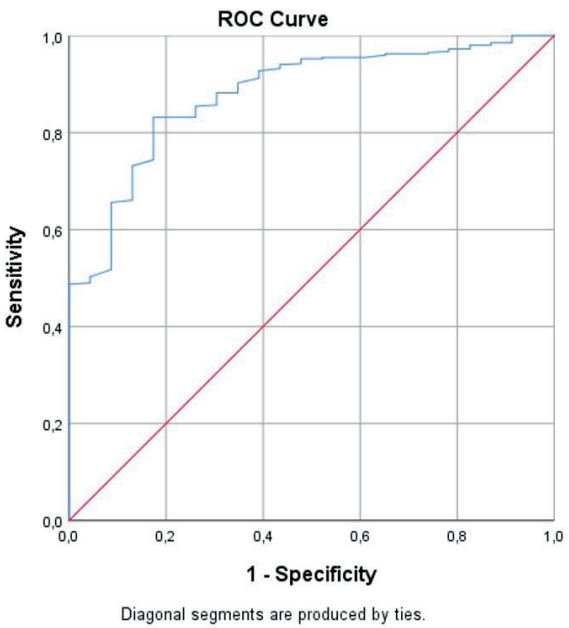

Figure 3. ROC analysis for MHR.

Multiple studies indicated that ACS prevalence increases by age, and it is common in the male gender (13, 14). It was stated that the risk of ACS increases after 45 years of age in male patients and after 55 years of age in female patients (15). In the present study, the patients in Group 1 were older and male dominant. The increase in co-morbidities, including the catabolic process, atherosclerosis, and the decrease in prevalence of vascular impairment may increase the incidence of stenosis in older ages. The protective effect of estrogen in females and risk factors such as hyperlipidemia due to the higher prevalence of smoking and unhealthy nutrition habits in male patients might have caused higher rates.

Many risk factors were identified in patients with ACS, and the most common risk factor was smoking. The most common co-morbidity factors were hypertension (HT) and diabetes mellitus (DM) in the literature (16, 17). Yılmaz et al. reported the most common risk factors as HT, hyperlipidemia, and DM (13). Eligini et al. detected that 66% of the cases smoke, and the most common risk factors were DM, family history of coronary artery disease, and HT (14). It was mentioned that smoking is an independent and serious risk factor for ACS (15). In line with the literature, the prevalence of HT and DM were higher in this study. We also detected no difference for co-morbidity between the groups, and the number of smokers was more in Group 1. We believe that the incidence of ACS might have increased due to the older patient population, higher prevalence

of co-morbidities, microvascular complications of DM, and cardiac failure caused by HT.

Eligini et al. expressed that the blood cell count and white blood cell sub-groups of the patients with AMI are similar to the control group. However, monocyte morphologies were different in the AMI group. It was stated that monocytes in the AMI group present two morphological patterns including round and fusiform; round pattern was more than fusiform pattern (14). Sercelik et al. compared STMI and control groups in their study and detected no difference between platelet and Hb levels (9). However, white blood cells, monocyte, and neutrophil levels were higher in the STMI groups. Numerous studies indicated monocyte count as a predictive factor in ischemic heart diseases to indicate the risk of cardiovascular diseases (5-7, 17). It was reported that monocytes play a role in atherosclerosis, and the monocyte count in the circulation affects the macrophage count and macrophage content in the plaque (18). Kucuk and Recep stated that the monocyte level was higher in patients with NSTMI than in the control group. However, this was not statistically significant (16). In the present study, we detected a higher monocyte count and neutrophil count in Group 1 than in Group 2. This may be associated with the rapid increase of monocyte count in the acute phase after formation and rupture of the plaque that causes USAP. In the present study, the cause for the higher neutrophil count in Group 2 may be infectious pathologies that cause chest pain.

Previous studies stated that the creatinine levels of patients with AMI were similar to the control groups (9, 14, 16). In line with the literature, urea and creatinine levels were similar between the groups in our study. This may be associated with similar demographic characteristics of the patient groups.

Pirazzi et al. (19) stated that the risk of ACS increased 15-fold in patients with higher total cholesterol and LDL levels. Eligini et al. stated that the HDL, triglycerides and total cholesterol levels were lower in patients with AMI (14). A previous study detected no difference in total cholesterol levels between NSTMI and the control groups (16). Lower HDL levels were addressed as a risk factor for AMI; higher HDL levels were considered protective against AMI and other cardiovascular diseases (20). In this study, the total cholesterol and LDL levels of the patients were significantly higher, whereas HDL levels were significantly lower in Group 1. Although the triglyceride level was higher in Group 1 no significant difference was detected. We believe that descending levels of HDL and ascending levels of total cholesterol and LDL caused atherosclerosis and thereby stenosis. Furthermore, regarding the younger population in Group 2, co-morbidities might have developed less, and since the patients have more physical exercise, HDL might have been slightly higher whereas other cholesterol sub-groups were lower.

Although the prognostic and predictive role of MHR in ischemic heart diseases were shown in many studies (21-24), Zhang et al. expressed that MHR is more important than isolated monocyte and HDL elevation (25). Furthermore, multiple studies showed that MHR increases in those with more thrombus load (7, 26). Kucuk and Recep found MHR significantly higher in NSTMI patients than in the control group (16). Sercelik et al. reported the MHR level as an independent risk factor, which was significantly higher in STMI patients (9). A previous study suggested that troponin may be deceptive in patients with nephropathy. However, MHR may be useful to diagnose AMI (12). There is a mutual interaction between monocyte and HDL in ACS cases. HDL inhibits CD11b and prevents monocyte activation, diffusion, and activated monocytes (27). In addition, monocyte suppresses multipotent progenitor cell proliferation in the hematopoietic system (28). Kuvin et al. reported that HDL causes nitric oxide synthase (eNOS) expression and contributes to vasodilatation in the coronary arteries (29). Furthermore, it was mentioned

that atherosclerosis enables the migration of the monocytes into the intima layer to create foam cells (20). In the present study, MHR was detected higher in Group 1 than in Group 2. We believe that the ratios were higher due to monocyte elevation and lower HDL levels. Moreover, the vicious cycle effect of HDL on monocyte might have caused the increase of MHR.

It is well-known that thrombus load effectively demonstrates the amount of coronary flow, re-flow, and restenosis after angiography (22, 24). Cicek et al. indicated MHR as an independent variable to show short- and long-term mortality (24). Arisoy et al. suggested MHR as an indicator for thrombus load and higher mortality prevalence of patients (7). Ucar et al. expressed that MHR may show stenosis in cases with a bare stent (23). MHR was higher in patients who died. It was reported in the literature that MHR might be an indicator for postoperative complications and flow quantities (22, 24). We believe that poor protective effects of low HDL and excessive thrombus load in patients who died may increase the risk of restenosis, high myocardial damage, and risk of complications.

In this study, MHR was detected in association with higher sensitivity and specificity in patients with high coronary stenosis rates (> 50%). This finding may make it a parameter to determine the degree of stenosis in patients with a preliminary diagnosis of USAP for determination of the patients without any indication for intervention.

Ethics Committee Approval: The study protocol was approved by the Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee on November 7, 2019 (Ethics committee registration number: 2019/249).

Conflict of Interest: The authors have declared that they have no conflict of interest.

Funding: The authors have declared that they have not received any financial support.

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