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Research Article

Association of hematological inflammatory indices and monocyte/HDL ratio with plaque formation in patients with atherosclerotic heart disease

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Abstract

Objectives: There are insufficient studies on the combined effect of neutrophil-lymphocyte ratio (NLR), systemic immune-inflammation (SII) index and monocyte-to-high-density lipoprotein ratio (MHR) on plaque status and risk of cardiovascular disease (CVD) occurrence. The aim of this study was to demonstrate the feasibility of using NLR, SII index and MHR, which are preferable markers in terms of favorable cost/benefit ratio and easy measurement, to monitor and evaluate the severity of the disease, considering that CVD is an inflammatory disease.

Methods: Two thousand two hundred seventy-three patients presenting with complaints of shortness of breath or chest pain who were followed up in the Cardiovascular Surgery outpatient clinic of Gaziosmanpaşa Training and Research Hospital between January 2024 and October 2024 were retrospectively included in the study.

Results: Lymphocyte levels were significantly higher in the deceased patients (p=0.02). Conversely, the NLR and the SII were higher in the surviving patients compared to the deceased patients (p<0.001; p<0.001). LDL levels and plaque status were statistically significantly different between the groups. Patients in the moderate-risk group had significantly lower LDL levels compared to those in the mild-risk group (p<0.001).

Conclusion: These results suggest that MHR, a novel biomarker derived from the inflammatory marker monocyte and the antiatherogenic HDL, may be associated with CAD. Given that CVD is an inflammatory disease, NLR, SII and MHR may be preferable in terms of favorable cost/benefit ratio and easy measurement. These markers can also be calculated practically and inexpensively from whole blood and HDL values, which are routine tests that can be performed in primary health care centers. It also demonstrates NLR and MHR are associated with plaque formation in patients with atherosclerotic heart disease.

Keywords: Monocyte-to-high-density lipoprotein ratio, neutrophil-lymphocyte ratio, plaque formation, systemic immune-inflammation index

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Cardiovascular diseases (CVD) encompass a range of conditions affecting the heart and blood vessels, with coronary heart disease (CHD) and stroke being the most prevalent and fatal forms. In 2019, CVD accounted for approximately 18.6 million deaths worldwide, underscoring their significant global health burden [1]. At the core of

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many CVDs, particularly CHD, is atherosclerosis, a chronic inflammatory process characterized by the development of plaques within arterial walls. Epidemiology studies show that among many genetic and environmental factors, elevated serum cholesterol levels alone are sufficient for the development of atherosclerosis, even in the absence of other known risk factors. Oxidation of low-density lipoprotein cholesterol (LDL-C) in the endothelial is the initiating factor in the development of atherosclerosis [2].

Atherosclerosis begins with impaired endothelial function. In the final stage of plaque rupture, endothelial dysfunction plays an important role. Lymphocytes and neutrophils, as a subgroup of leukocytes, play a role in the formation of plaque rupture as well as in infarct healing and reperfusion injury [3, 4]. The recently widely used neutrophil to lymphocyte ratio (NLR) is a reliable, accessible, and clinically relevant marker of acute coronary syndrome (ACS). Increased NLR has been proven to be associated with the severity and prevalence of atherosclerosis in ST-elevation heart attack patients [5–8]. Although, the association between NLR and the morbidity of CVD with vulnerable plaque characteristics is not fully understood to date.

The systemic immune-inflammation index (SII), new index is an emerging composite biomarker that reflects the balance between the immune system and inflammatory processes. It combines three key blood parameters: neutrophil count, platelet count, and lymphocyte count. The index is designed to provide a more comprehensive view of systemic inflammation and immune activation, which plays a crucial role in many diseases, including CVD [9].

Recently, the monocyte/ high-density lipoprotein (HDL) ratio (MHR) has been shown to be a predictor of cardiovascular events in patients with chronic renal failure and to be associated with coronary slow flow and stent thrombosis [10]. The association of high monocyte count, and low HDL has emerged as a new prognostic marker of inflammation and oxidative stress associated with adverse outcomes in various cardiovascular diseases [11, 12]. Considering the contribution of monocytes and macrophages to inflammation and oxidative stress and the inhibitory effect of HDL-C on them, the idea that the MHR can be used as a prognostic indicator in inflammation-related diseases has yielded significant results in studies conducted in renal failure and various heart diseases [6, 13–18].

Since CVD is largely driven by inflammation, markers such as NLR, SII and MHR could offer valuable insights into immune system activation and chronic inflammation, which are known to play a key role in the disease's progression. The aim of this study was to demonstrate the feasibility of using NLR, SII and MHR, which are preferable markers in terms of favorable cost/benefit ratio and easy measurement, to monitor and evaluate the correlation of these markers with traditional clinical outcomes (e.g. plaque burden, major adverse cardiovascular events).

Materials and Methods

Study design and population

The study protocol adhered to ethical guidelines and was approved by the Istanbul Atlas University Clinical Research Ethics Committee (Approval Date: 14/05/2022, Approval Number: E-22686390-050.99-42823). All procedures were conducted in compliance with the principles defined in the Declaration of Helsinki. Informed consent was obtained from participant or their relative.

Two thousand two hundred seventy-three patients presenting with complaints of shortness of breath or chest pain who were followed up in the Cardiovascular Surgery outpatient clinic of Gaziosmanpaşa Training and Research Hospital between January 2024 and October 2024 were retrospectively included in the study. All patients were questioned about cardiac risk factors such as smoking, hypertension, diabetes mellitus, hyperlipidaemia, family history of coronary heart disease and medications. All this information was obtained from the patients' medical record.

Inclusion criteria

Patients who underwent previous coronary angiography (CAG) and were found to have ≥50% stenosis in their major coronary arteries, who underwent percutaneous coronary procedure or bypass surgery for CAD, or who were newly diagnosed with CAD by myocardial perfusion sintigraphy (MPS) at outpatient clinic presentation were included.

Exclusion criteria

Active infection, inflammatory disease, acute coronary syndrome clinic, advanced heart failure, history of cancer, GFR<15 mL/minute, chronic obstructive pulmonary disease and liver failure, patients receiving antibiotics, immunosuppressive therapy, and non-steroidal anti-inflammatory drugs were excluded from the study. Patients with known significant valvular heart disease, malignancy, acute or chronic infections, those receiving systemic anti-inflammatory treatment, antihyperlipidemic therapy, or those with severe liver disease and renal failure were excluded from the study.

Electronic health records of patients hospitalized for CAD were retrospectively reviewed using the hospital's electronic database system. The demographic and clinical characteristics, systolic and diastolic blood pressure, complete blood count parameters, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, troponin, creatinine kinase-MB (CK-MB) levels were recorded from the hospital automation system and patient files.

Patients were evaluated according to survival and deceased status and according to plaque status detected at angiography.

The information you've provided is a description of how intra-plaque angiogenesis (IPN) is assessed using contrast-enhanced ultrasound (CEUS) imaging in the context of evaluating plaque stability [19]. The process of scoring involves evaluating the presence and distribution of microbubbles

within the plaque, which is used to infer the degree of angiogenesis (new blood vessel formation) within the plaque. Here's a breakdown of the IPN scoring system:

1. **IPN Score 0**: No microbubbles detected within the plaque, suggesting no angiogenesis is present within the plaque. This is considered a stable plaque.
2. **IPN Score 1:** Microbubbles are confined to the shoulder or adventitial side of the plaque, indicating some degree of angiogenesis, but the plaque remains relatively stable.
3. **IPN Score 2:** Microbubbles are seen throughout the entire plaque, suggesting significant intra-plaque angiogenesis, which is associated with plaque instability.

An IPN score of ≥2 (i.e., microbubbles throughout the plaque) is considered indicative of an unstable plaque, while an IPN score of <2 (i.e., microbubbles are confined to the shoulder or absent) indicates a stable plaque. This scoring system is important for evaluating the risk of plaque rupture or other complications, with unstable plaques generally being at a higher risk for rupture or causing adverse cardiovascular events [20].

Diagnoses of hypertension (HT), type 2 diabetes mellitus (T2DM) were made according to current guidelines [21]. T2DM was defined as fasting blood glucose levels ≥126 mg/dL and/or a previous diagnosis and treatment of diabetes. HT was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, the use of antihypertensive therapy, and/or a known history of HT.

Height and weight measurements were obtained, and body mass index (BMI) was calculated according to the formula body weight (kg)/height (m^2). Obesity was defined as BMI >30 kg/m^2.

Laboratory parameters

Blood samples were collected in tubes, both plain (without anticoagulant) and containing EDTA. The CBC analyses were conducted using an automated hematology analyzer (Sysmex XN-1000, Norderstedt, Germany), ensuring precision and reliability in data acquisition. NLR were calculated from neutrophil/ lymphocyte count. The SII was calculated as (platelet count × neutrophil count) /lymphocyte count. MHR was calculated by taking the ratio of monocytes to HDL in peripheral blood count.

The high-sensitive cTnI (hs-cTnI) levels were assessed by the immunofluorescent method using fluorescent antibody conjugates (ARCHITECTR Abbott assay, USA).

Glucose, albumin, total cholesterol, HDL, LDL, CK-MB, CRP were assessed with an autoanalyzer (COBAS 8000, ROCHE-2007, Tokyo, Japan).

Statistical analysis

Statistical analyses were performed using SPSS v.26 (IBM Corp., Armonk, NY, USA) software. Descriptive data were expressed as frequency (n) and percent (%) for categorical variables, and as mean ± standard deviation or median (25^{th} percentile–75^{th} percentile) for numerical variables. Normality of the distribution was assessed using the Kolmogorov–Smirnov test, as well as Q–Q plots and histograms. Pearson chi-square test or Fisher's exact test was used to compare categorical variables. Mann-Whitney U test was used for comparisons between two independent groups, while Kruskal-Wallis test was used for comparisons between more than two independent groups. Numerical variables were also evaluated by Spearman Correlation test. Laboratory parameters were categorized using Receiver Operating Characteristic (ROC) curve analysis, and the cutoff point where sensitivity and specificity were maximized was selected. Youden index values were used to determine the optimal cutoff points. The area under the curve (AUC) was reported.

Multivariate logistic regression (Enter and Forward: LR) analysis was performed to identify risk factors associated with survival, and plaque formation. The goodness-of-fit of the model was evaluated using the Hosmer–Lemeshow test. The regression model does not include highly correlated variables. The significance level for statistical tests was set at $p<0.05$.

Results

The mean age of the patients was 63.5±13.2 years, and 49.8% were female (Table 1). The age distribution between the survival groups was similar. However, the sex distribution showed a significant difference, with a higher survival rate in males ($p=0.012$). The body mass index (BMI) was higher in the deceased group compared to the survival group ($p=0.001$). Lymphocyte levels were significantly higher in the deceased patients ($p=0.02$). Conversely, the NLR and the SII were higher in the surviving patients compared to the deceased patients ($p<0.001$; $p<0.001$). A statistically significant difference was observed between survival and plaque progression ($p<0.001$). The frequency of no plaque was higher in the survival group.

There was no statistically significant difference in age, sexes, and BMI between the plaque groups (Table 2). However, LDL levels were statistically significantly different between the groups. In pairwise comparisons, significant differences were observed across all groups ($p<0.001$). LDL levels were lower in the stable plaque group compared to the other groups, with the highest LDL levels observed in the without plaque group ($p<0.001$). Mild risk was higher in without plaque group, while moderate risk was higher in patients with stable plaque. Furthermore, all patients with stable plaque were categorized into the moderate-risk group, while all patients without plaque were classified into the mild-risk group.

Clinical and sociodemographic characteristics of the patients were compared across different risk groups (Table 3). Glucose, LDL, Troponin, CK-MB levels and plaque status were statistically significantly different between the groups. Patients in the moderate-risk group had significantly lower LDL levels compared to those in the mild-risk group ($p<0.001$). Additionally, Glocose, Troponin and CK-MB levels were significantly higher in the moderate-risk group compared to the mild-risk group ($p<0.001$).

Table 1. Comparison of demographic and clinical characteristics of the patients

Characteristic	All patients (n=2273)	Deceased group (n=673)	Survival group (n=1600)	p
Age (years)	63.5±13.2	64.0±13.2	63.2±13.2	0.244
	64.0(54.0–73.0)	65.0 (55.0–74.0)	64.0 (54.0–73.0)	
Sex (female)	1133 (49.8)	308 (27.2)	825 (72.8)	**0.012**
BMI (kg/m^2)	28.1 (24.6–32.5)	29.3 (25.4–32.7)	27.7 (24.0–32.4)	**0.001**
Systolic blood pressure (mmHg)	153.0 (143.0–163.0)	153.0 (143.0–163.0)	153.0 (144.0–163.0)	0.295
Diastolic blood pressure (mmHg)	85.0 (79.0–88.0)	84.0 (79.0–88.0)	85.0 (79.0–88.0)	**0.046**
LYMPH (10^{3}cell/µL)	1710.0 (1439.5–2008.5)	1730.0 (1414.0–2360.0)	1700.0 (1447.0–1983.0)	**0.020**
NEU (10^{3}cell/µL)	7812.0 (6687.5–8236.0)	7803.0 (6210.0–8315.0)	7812.0 (7260.0–8205.0)	0.941
MONO (10^{3}cell/µL)	398.0 (386.0–416.0)	399.0 (386.0–416.0)	398.0 (386.0–416.0)	0.880
WBC (10^{3}cell/µL)	9.0 (7.6–10.9)	8.9 (7.7–11.0)	9.0 (7.6–10.9)	0.813
PLT (10^3/uL)	207.2 (164.8–242.4)	208.2161.8–242.1)	206.4 (165.4–242.7)	0.757
Glucose (mg/dL)	120.0 (102.0–145.0)	125.0 (102.0–148.0)	120.0 (102.0–145.0)	**0.020**
Albumin (g/dL)	3.6 (2.7–4.1)	3.8 (3.3–4.1)	3.6 (2.6–4.0)	**<0.001**
HDL (mg/dL)	36.0 (26.0–44.0)	36.0 (26.0–42.0)	36.0 (26.0–46.0)	0.742
LDL (mg/dL)	159.0 (146.0–264.5)	153.0 (141.0–164.0)	186.0 (150.0–297.0)	**<0.001**
CRP (mg/L)	66.4 (33.3–108.8)	82.8 (46.5–134.7)	56.2 (33.3–100.8)	**<0.001**
NLR	4.4 (3.6–5.2)	4.1 (2.5–5.2)	4.5 (3.7–5.2)	**<0.001**
SII	852.0 (586.2–1113.8)	780.0 (449.4–1123.9)	876.0 (622.7–1112.2)	**<0.001**
MHR	11.0 (9.0–15.1)	11.0 (9.0–14.9)	10.9 (8.9–15.2)	0.726
Troponin I (ng/ml)	0.6 (0.1–18.8)	0.1 (0.05–5.4)	1.8 (0.1–21.9)	**<0.001**
CK-MB (ng/ml)	32.4 (15.0–144.0)	20.7 (12.5–100.5)	82.3 (17.2–154.0)	**<0.001**
Hypertension (+)	1758 (77.3)	503 (28.6)	1255 (71.4)	0.055
Diabetes (+)	1072 (47.2)	319 (29.8)	753 (70.2)	0.883
Dyslipidemia (+)	1844 (81.1)	570 (30.9)	1274 (69.1)	**0.005**
Smoking (+)	1310 (57.6)	349 (26.6)	961 (73.4)	**<0.001**
Alcoholism (+)	574 (25.3)	158 (27.5)	416 (72.5)	0.206
Plaque status				
Without plaque	463 (20.4)	80 (17.3)[a]	383 (82.7)[b]	**<0.001**
Unstabil plaque	912 (40.5)	265 (28.8)[a]	656 (71.2)[b]	
Stabil plaque	889 (39.1)	328 (36.9)[a]	561 (63.1)[b]	

Mann Whitney U Testi, Fisher Exact Test, Pearson Chi-Square Test. Comparisons were made between survival and deceased groups. Each superscript letter denotes a subset of survival categories whose column proportions do not differ significantly from each other at the 0.05 level. BMI: Body mass index; LYMPH: Lymphocyte; NEU: Neutrophil; MONO: Monocyte; WBC: White blood count; PLT: Platelet count; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio; SII: Systemic immune-inflammation; MHR: Monocyte-to-high-density lipoprotein ratio; CK-MB: Creatinine kinase-MB.

Correlation between inflammatory indices was evaluated. A statistically significant very high correlation was observed between NRI and BMI (p<0.01; r=0.999). There was a very weak but statistically significant correlation between CRP levels and LDL (p<0.01; r=-0.064). A highly significant correlation was observed between NLR and SII (p<0.01; r=0.784) (Table 4).

When evaluating the risk factors associated with survival, PNI (OR:1.018; 95% CI:1.006–1.031), CRP (OR:1.004; 95% CI:1.003–1.005), Albumin (OR:1.444; 95% CI:1.252–1.665) were considered as risk factors that increased the likelihood of death. Conversely, an increased Troponin (OR:0.992; 95% CI:0.986–0.998) and LDL levels (OR:0.996; 95% CI:0.995–0.997) were found to be a preventive factor, positively associated with survival. NRI and NLR were not independent risk factors for survival (p>0.05) (Table 5).

In Figure 1, the predictive performance of the MHR parameter for plaque formation is illustrated by the ROC curve. MHR parameter was found to be non-predictive for plaque formation (p=0.279).

Discussion

Inflammatory molecules and lipids are two key elements in CVD [22]. Studies with animal models have demonstrated the invasion of neutrophils into atherosclerotic plaques [23]. In the current study, lymphocyte levels were significantly higher in the deceased patients. Conversely, the NLR and the SII were higher in the surviving patients compared to the deceased patients. HDL levels were lower in the stable plaque group compared to the other groups, with the highest HDL levels observed in the non-plaque group. The MHR was higher in the stable plaque

Table 2. Comparison of demographic and clinical characteristics of patients according to plaque status detected at angiography

Characteristic	Without plaque (n=463)	Unstabil plaque (n=921)	Stabil plaque (n=889)	p
Age (years)	63.8±13.7	63.5±13.3	63.5±13.7	0.473
	65.0 (55.0–74.0)	64.0 (55.0–74.0)	64.0 (54.0–72.0)	
Sex (female)	222 (19.6)	455 (40.2)	456 (40.2)	0.476
BMI (kg/m^2)	28.3 (24.7–33.2)	28.1 (24.5–32.4)	28.0 (24.5–32.0)	0.241
Systolic blood pressure (mmHg)	153 (144–163)	153 (144–163)	153 (141–163)	0.487
Diastolic blood pressure (mmHg)	85.0 (79.0–88.0)	85.0 (79.0–88.0)	85.0 (79.0–88.0)	0.673
LYMPH (10^{3}cell/µL)	1698 (6439–8256)	1710 (1444–2016)	1722 (1431–2013)	0.855
NEU (10^{3}cell/µL)	7795 (6439–8256)	7817 (6495–8225)	7817 (7260–8225)	0.944
MONO (10^{3}cell/µL)	396 (386–416)	398 (386–416)	398 (386–416)	0.977
WBC (10^{3}cell/µL)	9.0 (7.7–11.0)	9.0 (7.6–11.0)	8.9 (7.6–10.8)	0.482
PLT (10^3/uL)	211.3 (165.4–247.2)	206.3 (164.6–242.4)	206.3 (164.8–240.8)	0.338
Glucose (mg/dL)	120.0 (100.0–145.0)	120.0 (102.0–145.0)	120.0 (102.0–145.0)	0.159
Albumin (g/dL)	3.6 (2.6–4.0)	3.6 (2.7–4.1)	3.6 (2.7–4.1)	0.076
HDL (mg/dL)	36.0 (26.0–46.0)	36.0 (26.0–44.0)	36.0 (26.0–44.0)	0.528
LDL (mg/dL)	193.0 (149–342)[a]	161.0 (146–243)[b]	156.0 (144–194)c	**<0.001**
CRP (mg/L)	66.4 (33.3–108.8)	66.4 (33.3–108.8)	66.4 (33.3–108.8)	0.682
NLR	4.4 (3.3–5.2)	4.3 (3.6–5.3)	4.4 (3.7–5.2)	0.839
SII	855.1 (575–1120)	837.5 (586–1114)	862.6 (591–1108)	0.862
MHR	10.8 (8.7–15.1)	11.0 (9.1–15.2)	10.9 (9.0–14.8)	0.520
Troponin I (ng/ml)	0.1 (0.04–4.8)	0.7 (0.05–18.6)	1.8 (0.05–23.6)	0.738
CK-MB (ng/ml)	26.6 (14.7–101.2)	28.0 (14.4–142.2)	53.4 (15.2–154.6)	0.640
Hypertension (+)	364 (20.6)	707 (39.6)	687 (39.8)	0.738
Diabetes (+)	221 (20.6)	424 (39.6)	427 (39.8)	0.671
Dyslipidemia (+)	377 (20.4)	740 (40.1)	727 (39.4)	0.727
Smoking (+)	277 (21.1)	529 (40.4)	504 (38.5)	0.536
Alcoholism (+)	112 (19.5)	225 (39.2)	237 (41.3)	0.463
Survival patients	383 (23.9)[a]	656 (41.0)[b]	561 (35.1)[c]	**<0.001**
Risk score				
Mild risk	463 (100.0)[a]	259 (28.1)[b]	0 (0.0)[c]	**<0.001**
Moderate risk	0 (0.0)[a]	662 (71.9)[b]	889 (100.0)[c]	

Kruskall -Wallis Test, Pearson Chi-Square Test. Each superscript letter denotes a subset of plaque categories whose column proportions do not differ significantly from each other at the 0.05 level. BMI: Body mass index; LYMPH: Lymphocyte; NEU: Neutrophil; MONO: Monocyte; WBC: White blood count; PLT: Platelet count; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio; SII: Systemic immune-inflammation; MHR: Monocyte-to-high-density lipoprotein ratio; CK-MB: Creatinine kinase-MB.

group compared to the others, and the without plaque group had the lowest MHR. Additionally, the moderate risk ratio was higher in the stable plaque group than in the other groups. Furthermore, all patients with stable plaque were classified in the moderate-risk group, whereas all patients without plaque were classified in the mild-risk group. Although monocytes and macrophages are the most common white blood cell seen in atherosclerotic plaque, increased MHR may have accelerated monocyte infiltration of neutrophils into atherosclerotic plaques. NLR and MHR are associated with plaque formation in patients with atherosclerotic heart disease.

Chronic inflammation is a key factor in the pathogenesis of atherosclerosis and the development of subsequent CVD. It contributes to the initiation, progression, and destabilization of atherosclerotic plaques. Recent studies have shown that CRP, platelet/lymphocyte and neutrophil/lymphocyte ratios used as inflammatory markers both increased in atherosclerotic CVD and that these markers are independently associated with CAD [24–27]. On the other hand, it has long been known that HDL levels are inversely associated with atherosclerosis [28]. This relationship is largely explained by the reverse cholesterol transport of HDL in the vessel wall. It has been demonstrated that HDL exerts a protective role in atherosclerosis by inhibiting the expression of endothelial adhesion molecules. This action reduces the recruitment and accumulation of monocytes at sites of vascular injury. By preventing monocyte adhesion to the endothelial cells, HDL helps to mitigate the inflammatory processes that contribute to the formation and progression of atherosclerotic plaques [28]. Kahraman et al. [8] found that the ratio of MHR consisting of monocytes, an inflammatory marker, and HDL, an antiatherogenic lipid parameter, was associated with high

Table 3. Evaluation of risk factors in patients

Characteristic	Mild risk (n=722)	Modereta risk (n=1551)	p
Age (years)	65.5 (54.0–74.0)	64.0 (54.0–73.0)	0.593
Sex (female)	340 (30.0)	793 (70.0)	0.073
BMI (kg/m^2)	28.0 (24.7–33.0)	28.1 (24.5–32.2)	0.210
Systolic blood pressure (mmHg)	153.0 (144–163)	153.0 (141–163)	0.199
Diastolic blood pressure (mmHg)	85.0 (79.0–88.0)	85.0 (79.0–88.0)	0.958
LYMPH (10^{3}cell/µL)	1700 (1432–2004)	1710 (1440–2011)	0.707
NEU (10^{3}cell/µL)	7795 (6418–8236)	7818 (7130–8236)	0.236
MONO (10^{3}cell/µL)	398 (386–416)	398 (386–416)	0.541
WBC (10^{3}cell/µL)	9.0 (7.6–11.0)	8.9 (7.6–10.9)	0.492
PLT (10^3/uL)	207.9 (165.5–247.1)	206.9 (164.5–240.9)	0.234
Glucose (mg/dL)	120 (100–145)	125 (102–145)	**0.01**
Albumin (g/dL)	3.6 (2.6–4.0)	3.6 (2.7–4.1)	0.08
HDL (mg/dL)	36.0 (26–46)	36.0 (26–43)	0.173
LDL (mg/dL)	186.0 (149–297)	159.0 (145–195)	**<0.001**
CRP (mg/L)	66.4 (33.3–107.8)	66.4 (33.3–108.8)	0.252
NLR	4.3 (3.4–5.3)	4.4 (3.6–5.2)	0.621
SII	854.5 (578–1119)	849.2 (590–1108)	0.778
MHR	10.9 (8.7–15.1)	11.0 (9.0–15.1)	0.229
Troponin I (ng/ml)	0.2 (0.05–5.1)	11.0 (9.0–15.1)	**<0.001**
CK-MB (ng/ml)	27.9 (14.7–105.3)	38.8 (15.0–154.0)	**<0.001**
Hypertension (+)	564 (32.1)	1194 (67.9)	0.548
Diabetes (+)	344 (32.1)	728 (67.9)	0.753
Dyslipidemia (+)	587 (31.8)	1257 (68.2)	0.884
Smoking (+)	422 (32.2)	888 (67.8)	0.591
Alcoholism (+)	171 (29.8)	403 (70.2)	0.240
Survival patients	570 (35.6)	1030 (64.4)	**<0.001**

Mann Whitney U Test, Fisher Exact Test, Pearson Chi-Square Test. BMI: Body mass index; LYMPH: Lymphocyte; NEU: Neutrophil; MONO: Monocyte; WBC: White Blood Count; PLT: Platelet Count; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-Reactive Protein; NLR: Neutrophil-lymphocyte ratio; SII: Systemic immune-inflammation; MHR: Monocyte-to-high-density lipoprotein ratio; CK-MB: Creatinine kinase-MB.

Table 4. Evaluation of correlation between parameters

	MHR	Troponin I	CK-MB	CRP	NLR	SII	PNI	NRI	Age	BMI	HDL
MHR	.										
Troponin I	0.038	.									
CK-MB	-0.056**	0.798**	.								
CRP	0.013	0.075**	-0.095**	.							
NLR	-0.045*	0.006	0.035	-0.012	.						
SII	-0.036	0.022	0.032	-0.016	0.784**	.					
PNI	0.015	-0.030	0.012	-0.065**	-0.608**	-0.495**	.				
NRI	0.013	-0.060**	-0.074**	0.193**	0.022	0.025	-0.096**	.			
Age	0.001	-0.006	0.006	0.006	-0.014	-0.025	0.029	0.017	.		
BMI	0.013	-0.059**	-0.073**	0.189**	0.022	0.026	-0.095**	0.999**	0.018	.	
HDL	-0.984**	0.031	0.056**	-0.010	0.045*	0.035	-0.015	-0.009	-0.002	-0.010	.
LDL	0.006	0.021	0.028	-0.064**	0.050*	0.072**	0.051*	-0.035	0.029	-0.034	-0.012

<0.25 very weak; 0.26–0.49 weak; 0.50–0.69 moderate; 0.70–0.89 high; 0.90–1.0 very high correlation. *: p<0.05; **: p<0.01. MHR: Monocyte-to-high-density lipoprotein ratio; CK-MB: Creatinine kinase-MB; CRP: C-Reactive Protein; NLR: Neutrophil-lymphocyte ratio; SII; Systemic immune-inflammation; PNI: Prognostic nutritional index; NRI: Net reclassification index; BMI: Body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

Table 5. Evaluation of risk factors associated with survival in patients

Characteristic	Multivariate logistic regression (Multivariate-Enter method)		Multivariate logistic regression (Multivariate-Forward:LR method)	
	OR (95% CI)	p	OR (95% CI)	p
NRI	1.009 (0.999–1.019)	0.091	–	–
NLR	0.974 (0.906–1.048)	0.484	–	–
PNI	1.015 (0.998–1.032)	**0.004**	1.018 (1.006–1.031)	**0.004**
CRP	1.003 (1.002–1.005)	**<0.001**	1.004 (1.003–1.005)	**<0.001**
Troponin I (ng/ml)	0.992 (0.986–0.998)	**0.009**	0.992 (0.986–0.998)	**0.007**
Albumin	1.446 (1.253–1.668)	**<0.001**	1.444 (1.252–1.665)	**<0.001**
LDL	0.996 (0.995–0.997)	**<0.001**	0.996 (0.995–0.997)	**<0.001**

Forward LR and Enter methods were used for logistic regression analysis. Enter Model: Hosmer Lemeshow test p=0.002, Cox & Snell R^2= 0.101, Nagelkerke R^2= 0.143, -2 Log Likelihood= 2520.2. Forward LR Model: Hosmer Lemeshow test p=0.001, Cox & Snell R^2= 0.100 Nagelkerke R^2=0.142, -2 Log Likelihood= 2523.4. OR: Odds ratio; CI: Confidence interval; NRI: Net reclassification index; NLR: Neutrophil-lymphocyte ratio; PNI: Prognostic nutritional index; CRP: C-reactive protein; LDL: Low-density lipoprotein.

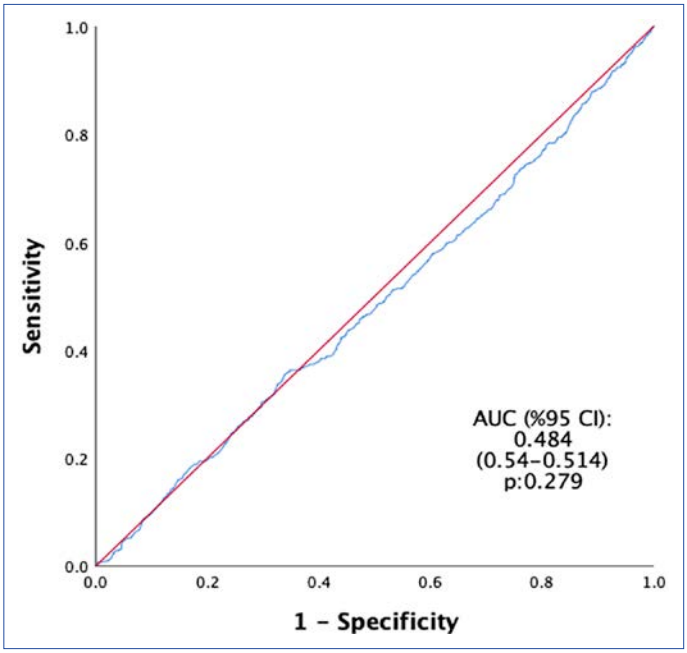

Figure 1. Predictive performance of the MHR parameter for plaque formation.

AUC: Under the curve; CI: Confidence interval.

SYNTAX score in patients with stable CAD. In a study conducted with patients with ACS, high NHR ratio consisting of neutrophils and HDL was found to be associated with long-term mortality [22]. In the same study, it was also shown that the prognostic value of NHR was superior to MHR and LDL/HDL. In another recent study, it was emphasized that high NHR ratio was associated with CAD severity in stable CAD [29]. In our study, like these studies, the NLR and the SII were higher in the surviving patients compared to the deceased patients. But no statistical significance was observed between survival and plaque progression. HDL levels and the MHR were statistically significantly different between the groups. In pairwise comparisons, significant differences were observed across all groups. HDL levels were lower in the stable plaque group compared to the other groups, with the highest HDL levels observed in the without plaque group. Previous studies have shown that HDL also has anti-inflammatory, antithrombotic and antioxidant effects. HDL exerts antiatherogenic effects by preventing macrophages from transporting lipid loads and lipids to the arterial wall. Furthermore, HDL-C inhibits endothelial expression of adhesion molecules through inhibition of CD11b activation and thus prevents monocyte adhesion to the arterial wall [30].

HDL is thought to prevent atherosclerosis primarily through reverse cholesterol transport in the vessel wall. In recent studies, mice with impaired reverse cholesterol transport pathway showed an increase in hematopoietic stem cells, monocytosis, neutrophilia and systemic foam cells and infiltration of many organs with myeloid cell lines. When these mice were infused with reconstituted HDL, the proliferation of hematopoietic stem cells and myeloid cell lines was reversed [31]. In the study by Qin et al. [32], it was shown that monocyte increase was a predictor of plaque development in previously plaque-free arteries. Excess lipids and inflammatory reactions (cellular and humoral) are considered the major contributors to plaque development, and the loss of smooth vascular muscle cells (VSMCs) and increased intraplaque hemorrhage are critical steps in necrotic core destabilization and enlargement [33].

There are also studies showing that HDL is effective in monocyte activation and inflammation in the development of atherosclerosis [34, 35]. Our results confirm this study. The fact that neutrophils, an inflammatory marker, and HDL, which have antiatherogenic properties, are both associated with atherosclerosis and with each other suggests that NHR may be a successful indicator for many diseases with an atherosclerotic background in the clinic. Indeed, in our study, we found that male gender, diabetes, and CAD were independent predictors of high MHR rate. We think that larger randomized prospective studies are needed in this regard.

Study Limitations

There were several limitations in our study. One of them is the retrospective design of the study. Another limitation is that the coronary artery calcium (CAC) test was not performed. Future studies investigating the association between MHR and plaque and cardiovascular events should be prospectively designed in larger patient series.

Conclusion

These results suggest that MHR, a novel biomarker derived from the hematological inflammatory marker monocyte and the antiatherogenic HDL, may be associated with CAD. Given that CVD is an inflammatory disease, NLR, SII and MHR may be preferable in terms of favorable cost/benefit ratio and easy measurement. These markers can also be calculated practically and inexpensively from whole blood and HDL values, which are routine tests that can be performed in primary health care centers. It also demonstrates the usability of NLR, SII and MHR for monitoring and assessing disease severity. Although the predictive performance of the MHR parameter for plaque formation (sensitivity and selectivity 0.59 and 0.53, respectively) was low, it was found to be higher in the stable plaque group compared to the others, while it had the lowest value in the plaque-free group. NLR and MHR are associated with plaque formation in patients with atherosclerotic heart disease.

Ethics Committee Approval: The study was approved by The Istanbul Atlas University Non-interventional Scientific Research Ethics Committee (No: E-22686390-050.99-42823, Date: 14/05/2022).

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