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Short communication

Monocyte-to-high density lipoprotein ratio (MHR) can predict the significance of angiographically intermediate coronary lesions☆

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ABSTRACT

Purpose: Monocyte-high density lipoprotein ratio (MHR) has recently emerged as a marker of inflammation and oxidative stress in the cardiovascular disease. We aimed to investigate whether baseline MHR is associated with functional significance of intermediate coronary artery lesions.
Methods: Three hundred and one consecutive patients, 215 males and 86 females, who underwent fractional flow reserve (FFR) measurement for angiographically intermediate coronary stenosis (40–70% in quantitative coronary analysis) in the left anterior descending coronary artery were enrolled into the study. An FFR value of ≤0.80 was accepted for hemodynamic significance.
Results: Of the 301 patients, 115 (38.2%) exhibited significant functional stenosis (FFR ≤ 0.80) in the FFR measurement. Patients with hemodynamically significant lesions had higher MHR values (11.6 ± 3.3 vs. 12.6 ± 2.5 p = 0.003).In stepwise multivariate logistic regression analysis, total cholesterol (OR = 1.008, 95% CI = 1.002–1.013, p < 0.010), plateletcrit (OR = 1.310, 95% CI = 1.097–1.564, p = 0.013) and MHR (OR = 2.993, 95% CI = 1.365–6.561, p = 0.008) were independent predictors of significant functional stenosis. An MHR value of 12.1 had 65% sensitivity and 55% specificity for prediction of hemodynamically significant coronary artery stenosis.
Conclusions: Increased MHR values were associated with functional significance of angiographically intermediate coronary artery stenosis.

Introduction

Coronary angiography is one of the principal methods used for diagnosing and assessing coronary artery lesions.[1] However, qualitative evaluation of coronary artery stenosis with coronary angiography is not always reliable and the visible anatomic stenosis may not be hemodynamically significant. FFR measurement is a well-established method for functional assessment of lesion severity, which involves the measurement of a coronary artery lesion's hemodynamic significance when the coronary artery stenosis is particularly between 40 and 70% (i.e. at an intermediate level).[2]

Inflammation, oxidative stress, platelet activation and endothelial dysfunction assume an important role in both the development and progression of atherosclerosis.[3,4] Monocytes and macrophages are the main types of cells that secrete proinflammatory cytokines, which play a central role in in the pathogenesis of atherosclerosis.[4] Studies have shown that the adverse effects of low-density lipoproteins (LDLs) on endothelial cells can be limited by high-density lipoprotein cholesterol (HDL-C), which prevents the oxidation of LDL.[5–7] HDL-C is believed to have both antioxidant and anti-inflammatory properties. A new cardiovascular disease marker that has appeared in recent times is the monocyte to HDL-C ratio (MHR), which combines the prognostic and predictive effectiveness of two widely used and accessible laboratory parameters.[8–10] The aim of the present study was to examine the relationship between MHR and the functional significance of intermediate level coronary artery stenosis evaluated with FFR measurement.

Subjects and methods

This retrospective study was conducted between January 2012 and March 2016 with a total of 301 consecutive patients, including 86 female and 215 male patients, diagnosed with single intermediate-grade coronary stenosis (40–70%, based on quantitative coronary analysis) on their left anterior descending coronary artery who were examined with fractional flow reverse (FFR) measurement. Patients who had

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undergone coronary angiography with an indication of stable angina pectoris involved in the present study. Patients with the following conditions were excluded from the study: acute coronary syndrome; moderate or severe valvular heart disease; significant arrhythmia; hemodynamic instability; second lesion at the index coronary artery; another coronary artery with a ≥40% luminal narrowing (determined by coronary angiography); a history of previous surgical or percutaneous coronary artery intervention; acute or chronic inflammatory or infectious diseases; anemia, chronic renal failure, and malignancy.

Hospital files and records were examined to determine the patients' demographic, clinical and angiographic data. Blood samples were collected from veins within 24 h after hospital admission. Measurements included lipid profile, serum creatinine and complete blood count. The patients' baseline MHR was determined by dividing their monocyte count with their HDL cholesterol level. The institutional local ethics committee approved the study protocol.

FFR measurements for intermediate-grade lesions with a 40–70% stenosis rate were performed based on the cardiologists' decision and discretion. Following the intra-arterial administration of a 5000 unit heparin bolus, the coronary artery was examined by employing a guiding catheter without side holes. A 0.014 in. pressure monitoring guidewire (PrimeWire, Volcano, San Diego, Calif., USA) was positioned distally to the stenosis after calibration. A 200 μg bolus of nitroglycerin was administered intracoronarily prior to FFR measurements. The patients' distal intracoronary pressure was recorded at baseline, and hyperemia was triggered by applying intracoronary adenosine at gradually increasing doses until the FFR value ceased to decrease any further. FFR was determined as the ratio between the mean distal intracoronary pressure and the mean aortic pressure, at the moment the highest level of hyperemia is observed.

An FFR value of ≤0.80 was defined as functionally significant. Patients with an FFR value of >0.80 formed group I and patients with an FFR value of ≤0.80 formed group II.

Statistical analysis

Statistical analysis was performed using the SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA) package software. Whether the data exhibited normal distribution was determined using the Kolmogorov–Smirnov test. The chi-square test was used for comparing categorical variables, while the Mann–Whitney *U* test or Student's *t*-test were used for comparing continuous variables. Percentages were used for presenting categorical variables, while mean ± standard deviation or median (interquartile range) were used for presenting continuous variables. Possible confounding factors for the coronary artery lesions' severity were determined using the univariate and multiple logistic regression analysis. The multiple regression model was used to test variables in the univariate regression analysis that has p values below 0.10. To determine optimum MHR cut-off value for predicting the hemodynamic significance of the coronary artery stenosis, the receiver-operating characteristic (ROC) curve was employed. Statistical significance level was set at <0.05.

Results

The baseline characteristics of the patients are shown in Table 1. Among the 301 patients included into the study, 115 (38.2%) were found to have significant functional stenosis. Group II has a lower mean age than group I (58 ± 12 vs. 61 ± 11 years, p = 0.007). While group II had a higher ratio of male patients, the difference between the two groups was not significant (68% vs. 77%, p = 0.072). There were also no statistically significant differences with regards to the coronary risk factors, including smoking, hyperlipidemia, hypertension and diabetes mellitus (Table 1).

The laboratory parameters of two groups are reported in Table 2. Group II had higher level of total cholesterol (203 ± 46 vs. 188 ± 42 mg/dL, p = 0.004). LDL-C level was also higher in group II, although the difference was not statistically significant (125 ± 39 vs. 117 ± 38 mg/dL, p = 0.078). Group II exhibited higher monocyte count (50 (40–56) vs. 55 (45–58), p = 0.004), plateletcrit (0.21 ± 0.01 vs. 0.20 ± 0.01, p = 0.002) and MHR (12.67 ± 2.59 vs. 11.65 ± 3.33, p = 0.003). Group I had a higher lymphocyte-to-monocyte ratio (LMR), although this difference was not statistically significant (0.044 (0.034–0.057) vs. 0.042 (0.030–0.054), p = 0.227). Other laboratory data did not differ significantly between the two groups (Table 2).

Univariate and multiple logistic regression analysis indicated that MHR (OR = 3.401, 95% CI = 1.378–8.391, p = 0.008), plateletcrit (OR = 1.276, 95% CI = 1.052–1.549, p = 0.013) and total cholesterol (OR = 1.025, 95% CI = 1.006–1.044, p = 0.010) are independent predictors of significant functional stenosis (Table 3). ROC analysis revealed that an MHR value of 12.1 had a specificity of 55% and a sensitivity of 65% in predicting hemodynamically significant coronary artery stenosis (Fig. 1).

Table 1
Basal characteristics of the study groups.

Variable	Insignificant FFR (n = 186)	Significant FFR (n = 115)	p value
Age, year	61 ± 11	58 ± 12	**0.007**
Basal FFR	0.93 ± 0.03	0.86 ± 0.08	<**0.001**
Smoking, n (%)	91 (49)	55 (48)	0.853
Male gender, n (%)	126 (68)	89 (77)	0.072
Diabetes mellitus, n, %	56 (30)	30 (26)	0.453
Hypertension, n, %	69 (37)	42 (37)	0.920
Hyperlipidemia, n, %	51 (28)	24 (21)	0.198

FFR - fractional flow reserve. Data are expressed as mean ± standard deviation for normally distributed parametric variables, median (interquartile range) for non-parametric variables and percentage for categorical variables.

Discussion

In this study, MHR levels were independently associated with functionally significant coronary artery lesions assessed with FFR

Table 2
Comparison of laboratory parameters between patients with hemodynamically significant coronary artery lesions and patients with hemodynamically non-significant coronary artery lesions.

Variable	Insignificant FFR (n = 186)	Significant FFR (n = 115)	p value
Glucose, mg/dL	110 (94–153)	112 (94–147)	0.838
Urea, mg/dL	34 (28–39)	34 (27–40)	0.951
Creatinine, mg/dL	0.91 (0.79–1.04)	0.93 (0.80–1.03)	0.678
Total cholesterol, mg/dL	188 ± 42	203 ± 46	**0.004**
Trygliceride, mg/dL	146 (107–195)	154 (112–242)	0.122
HDL-C, mg/dL	42 (35–50)	41 (37–45)	0.495
LDL-C, mg/dL	117 ± 38	125 ± 39	0.078
WBC count, $\times 10^9$/L	8.5 ± 2.7	8.9 ± 2.3	0.233
Neutrophile count, $\times 10^9$/L	5.46 ± 2.41	5.81 ± 2.03	0.199
Lymphocyte count, $\times 10^9$/L	2.22 ± 0.84	2.25 ± 0.83	0.709
Monocyte count, $\times 10^{12}$/L	50 (40–56)	55 (45–58)	**0.004**
Eosinophile count, $\times 10^{12}$/L	23 (11–38)	30 (20–40)	0.054
Hb, gr/dL	14.2 (13.0–15.4)	14.5 (13.3–15.4)	0.241
RDW	13.7 (13.0–14.6)	13.5 (13.1–14.3)	0.212
Platelet count, $\times 10^9$/L	254 ± 62	247 ± 65	0.369
MPV, fL	8.4 ± 0.6	8.4 ± 1.4	0.641
Platecrit (PCT)	0.20 ± 0.01	0.21 ± 0.01	**0.002**
PDW	16.9 (16.3–18.0)	16.8 (16.2–17.5)	0.338
NLR	2.39 (1.75–3.19)	2.56 (1.74–3.54)	0.196
PLR	121 (93–151)	117 (91–155)	0.369
LMR	0.044 (0.034–0.057)	0.042 (0.030–0.050)	0.227
MHR	11.65 ± 3.33	12.67 ± 2.59	**0.003**

FFR - fractional flow reserve; HDL - high-density lipoprotein; LDL - low-density lipoprotein; MPV - mean platelet volume; NLR - neutrophil-to-lymphocyte ratio; PLR - platelet-to-lymphocyte ratio; RDW - red cell distribution width; WBC - white blood cell; LMR - lymphocyte-to-monocyte ratio; MHR - monocyte count -to -HDL-C ratio. Data are expressed as mean ± standard deviation for normally distributed parametric variables and median (interquartile range) for non-parametric variables.
Bold values indicate significance at p < 0.05.

Table 3
Univariate and multiple logistic regression analyses performed to find out possible confounding factors of hemodynamically significant coronary artery stenosis.

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
T chol	1.008	1.002–1.013	0.005	1.025	1.006–1.044	**0.010**
Age	0.971	0.950–0.992	0.008	0.984	0.961–1.008	0.193
LDL-C	1.006	0.999–1.012	0.079	0.984	0.967–1.000	0.053
PCT	1.310	1.097–1.564	0.003	1.276	1.052–1.549	**0.013**
MHR	2.993	1.365–6.561	0.006	3.401	1.378–8.391	**0.008**
Male gender	1.603	0.939–2.738	0.084	1.436	0.788–2.615	0.237

T chol - total cholesterol; LDL-C - low-density lipoprotein cholesterol; PCT -plateletcrit; MHR - monocyte count -to -HDL-C ratio.
Bold values indicate significance at $p < 0.05$.

measurement. In addition, total cholesterol and plateletcrit remained independent predictors of functional significance on multivariate analysis in the current study.

Oxidative stress and inflammation are central mechanisms in the development and progress of atherosclerosis.[3,4,9] Monocytes play a particularly important role in these processes.[4,5] The interaction of activated monocytes with activated or damaged endothelium leads to the overexpression of adhesion molecules and proinflammatory cytokines, such as the intercellular adhesion molecule-1, the vascular cell adhesion molecule-1, and the monocyte chemotactic protein-1 ligand.[4,11,12] Monocytes then differentiate into the macrophage cells, which absorb oxidized LDL cholesterol molecules, forming harmful foamy cells in the process.[12] On the contrary, HDL-cholesterol molecules reduce macrophage accumulation and promote removal of oxidized cholesterol from arterial wall.[13–15] Recent studies also showed that HDL-cholesterol can inhibit monocyte activation, adhesiveness, and inflammation.[5–7] In addition to its antioxidative and antiinflammatory effects, HDL also increases the expression of nitric oxide synthase in endothelial tissues and promotes vasorelaxation.[16] Higher HDL levels are known to provide protection against atherosclerosis, and are associated with better prognosis among patients with atherosclerosis.[17] Therefore, HDL-C counteracts the predominantly prooxidant and proinflammatory effects of monocytes.

MHR is a new and promising marker that indicates the inflammatory state of the patient. Based on the current literature, we assumed that higher MHR values might serve as an effective predictor of functional significance of coronary artery stenosis.

Qualitative evaluation of coronary artery stenosis with coronary angiography is not always reliable and the visible anatomic stenosis may not be hemodynamically significant.[2,18] FFR measurement is a well-established method for functional assessment of lesion severity. FFR technique is based on pressure decline between proximal and distal parts of the stenosis after obtaining maximal hyperemia and linearly related to maximum blood flow to the myocardium supplied by the respective coronary artery. Thus, in this study FFR measurement was utilized to determine the functional significance of coronary lesion severity and its relationship with the MHR level.

MHR is a newly discovered marker for oxidative stress and inflammation. Kanbay et al. previously suggested that in patients with chronic kidney disease, high MHR values are linked with worse cardiovascular prognosis.[8] Another study reported that high MHR values are correlated with a greater severity and occurrence of isolated coronary artery ectasia.[10] Kundi et al. demonstrated, based on SYNTAX score assessments, a relationship between higher MHR and greater coronary atherosclerosis severity.[19] Cetin et al. demonstrated that in patients with acute coronary syndrome MHR was an independent predictor of stent thrombosis and severity of coronary artery disease as well as future cardiovascular events.[20,21] Also in a study of Cicek et al., MHR was found to be significantly associated with both short- and long term mortality in patients with ST elevation myocardial infarction who underwent primary percutaneous coronary intervention.[22]

In our study, we found that MHR is significantly higher in patients with hemodynamically significant lesions assessed by FFR (FFR ≤ 0.80). There are some possible explanations of our findings. First of all, it was clearly shown that patients with hemodynamically significant coronary lesions have a poor prognosis and increased MHR has been closely linked with worse outcomes.[8,20–22] Secondly, higher MHR can

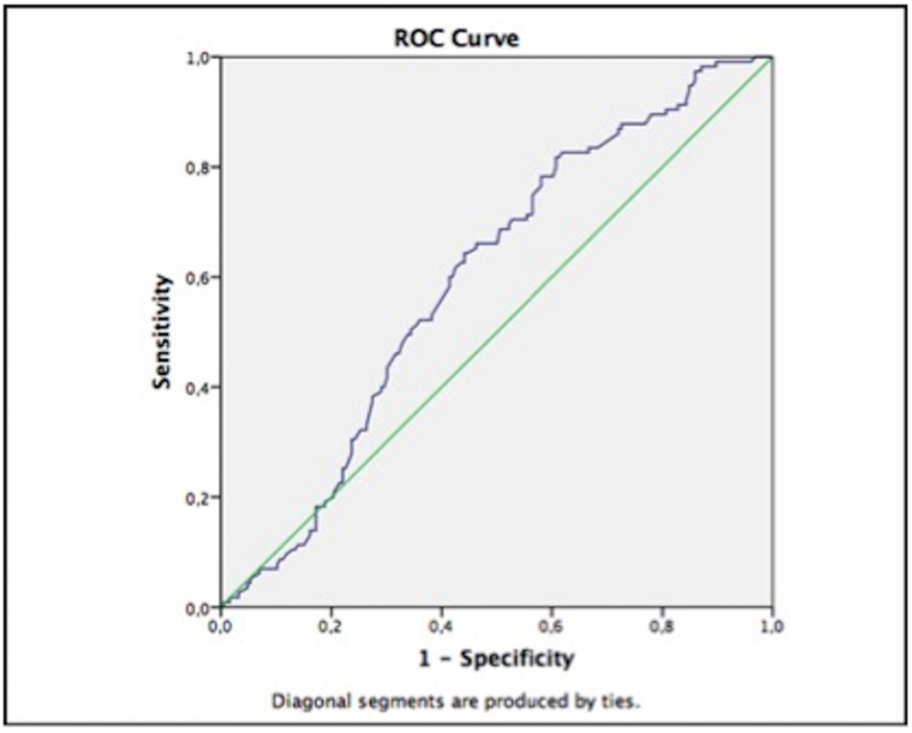

Fig. 1. The receiver-operating characteristic curve analysis for MHR in predicting functionally significant coronary stenosis in FFR measurements. MHR (monocyte count -to -HDL-C ratio) value of 12.1 had 65% sensitivity and 55% specificity for prediction of hemodynamically significant coronary artery stenosis. AUC: 0.598, 95% CI = 0.534–0.662, p = 0.004.

be viewed as a reaction to coronary artery lesions of greater severity. Based on this view, we consider that ischemias can lead to various inflammatory responses that alter WBC distribution and count. There is evidence suggesting that higher monocyte levels are linked with the development of proinflammatory and atherosclerotic responses.[3,4,9,11–12] It is known that HDL-C molecules can inhibit the activation and movement of monocytes.[13–15] The observation that coronary artery disease patients with high SYNTAX levels (≥23) tend to have with increased MHR values is in line with the present study's findings that increased MHR may serve as a predictor of functional significance in patient with intermediate-grade coronary artery stenoses.[19,23] In addition, previous studies indicate that severe CAD with good collaterals tend to have high monocyte counts, while those which poorer collaterals have lower HDL levels. This finding is also in agreement with the results of our study.[24–26] Considering that the degree and duration of coronary stenosis is the one of the most important determinants of coronary collateral development, it can be said that MHR values can help predict significant coronary stenosis that leads to myocardial ischemia.

In contrast to other studies, we determined during the multivariate analysis that plateletcrit and total cholesterol are both independent predictors for significant functional stenosis. These findings are in line with the known pathogenesis of coronary atherosclerosis. But there is insignificant correlation between functional stenosis, MHR and LDL-Cholesterol. Previous similar studies showed that there was not statistically significant difference between lipid biomarkers and functional coronary stenosis severity in stable coronary artery disease.[27–29] The difference in results between our work and other studies, can be explained by the he effects of antihyperlipidemic treatment; and genetic, environmental (including obesity, physical inactivity, and cigarette smoking), and unmeasured variables.

Studies have demonstrated that the platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR) are both significant markers of inflammation, and that they are linked with a variety of cardiovascular diseases.[30–32] In two studies similar to our own on the FFR, red cell distribution width (RDW) and NLR showed close relationship with the functional significance of intermediate-grade coronary artery stenoses.[28–29] However, in our study, it was observed that PLR, NLR and RDW did not function as independent predictors hemodynamically severe coronary artery stenosis. Similarly, Sels et al.'s study failed to demonstrate any relationship of FFR with inflammatory markers – such as the tumor necrosis factor, interleukin-6, interleukin-8 and WBC count.[33] These different results might be explained with differences in patient characteristics and numbers in different studies. Also, these differences might also be accounted by the different approaches of researchers towards coronary stenotic lesions (e.g. percutaneous, medical and sintigraphy approaches).

The evaluation of platelet indices such as platelet counts, mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT) is easy and practical and can play a role in the onset and progression of atherosclerosis.[34] İn our study, only higher PCT is independent predictors for significant functional stenosis but there is weak correlation. There are few studies investigating the relationship between PCT and coronary artery disease in the literature. Previous studies suggested that high PCT values on admission are independently associated with long-term adverse outcomes in patients with ST-segment elevation myocardial infarction (STEMI), non STEMI (NSTEMI), coronary slow flow phenomenon and saphenous vein grafting disease.[35–38] In the light of these findings PCT may show correlation with significant functional stenosis of angiographically intermediate coronary lesions, but this may be a coincidence arising from the coexistence of atherosclerosis severity and not a causal relationship.

Study limitations

The present study had a number of limitations. First of all, the study has a retrospective design with limited number of patients. Secondly, many other important markers of inflammation – such as the hs-CRP – were not used in this study (although it is certainly unfeasible to conduct a study that can include and examine all types of inflammatory markers). Thirdly, our study analyses were based on a single MHR values; in other words, we did not follow temporal changes and variations in MHR. Finally our study does not provide a mechanistic explanation for the effect of specific monocyte subsets on the severity of CAD and MHR.

Conclusion

The present study demonstrated that in FFR assessments, MHR values exhibit an independent relationship with the functional significance of angiographically intermediate coronary artery stenosis. As they are based on commonly used and low cost parameter found in lipid panels and complete blood counts, MHR values can be readily determined to predict the likelihood of hemodynamically significant coronary artery stenosis in clinical settings. Nevertheless, the results of this study should be further expanded and confirmed through studies involving larger samples and prospective designs.

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