Association of monocyte to high-density lipoprotein ratio with bare-metal stent restenosis in STEMI patients treated with primary PCI

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ABSTRACT

OBJECTIVE: Monocyte to high-density lipoprotein ratio (MHR) has recently been postulated as a novel parameter related to adverse cardiovascular outcomes. In this study, we aimed to investigate the correlation of MHR with stent restenosis (SR) rates after the primary percutaneous coronary intervention (PCI) and bare-metal stent (BMS) implantation.

METHODS: In this study, patients who had undergone primary PCI for STEMI and had a control angiogram during follow-up were retrospectively recruited. Patients were categorized according to admission MHR tertiles, clinical and angiographic data were compared. In addition, predictors of SR were evaluated with logistic regression analysis.

RESULTS: A total number of 448 patients (240 patients with SR and 208 patients without SR) were included in this study. Patients were categorized into three groups according to tertiles of admission MHR. During a follow-up period of median 12 months, the rate of SR was significantly higher in patients with higher MHR levels (45% in tertile 1, 54% in tertile 2 and 62% in tertile 3, p<0.01). In multivariate Cox regression analysis, male gender, stent length, admission NLR levels and MHR levels (HR 1.03, 95% CI 1.02–1.06, p<0.01) remained as the independent predictors of SR in the study population.

CONCLUSION: Gender, stent length, higher MHR and NLR levels are correlated to SR after primary PCI.

Keywords: Bare-metal stent; monocyte to HDL ratio; stent restenosis.

Primary percutaneous coronary intervention (PCI) is the most widely used treatment modality for ST-segment elevation myocardial infarction (STEMI) [1]. The rate of stent restenosis (SR) is approximately 10% and is the leading cause of recurrence of symptoms and re-intervention [2]. Although the patho-physiology of SR is multifactorial, inflammation is the cornerstone of this process [2–4]. The inflammatory response due to barotrauma, plaque disruption, hypersensitivity to stent platform and/or polymer coating is correlated with neointimal hyperplasia leading to lumen loss and SR [2].

The role of inflammation has been shown in cardio-vascular diseases, including STEMI [5]. Higher mono-cyte to high-density lipoprotein ratio (MHR) has been postulated as a negative prognostic marker for cardio-vascular events in patients with chronic kidney disease [6]. In recent studies, MHR has been found to be cor-related with the slow coronary flow and a higher risk of recurrence after atrial fibrillation cryoablation [7, 8]. The present study aims to investigate the association of ad-mission laboratory parameters and especially MHR lev-els with the rate of SR in STEMI patients treated with bare-metal stent (BMS) implantation.

MATERIALS AND METHODS

Patient Population

Medical records of patients, who were admitted to the emergency department of our hospital with the diag-nosis of STEMI, and who underwent primary PCI and stent implantation between January 2008 and October 2013 were retrospectively collected. Initially, 3425 pa-tients were recruited. In 669 patients, a control CAG was performed during the follow-up period (Fig. 1). Patients who had undergone surgical revascularization procedures or had undergone drug-eluting stent (DES) implantation were excluded from this study. In addi-tion, patients with a prior diagnosis of coronary artery disease, peripheral arterial disease, heart failure, acute/chronic inflammatory disease or cancer and patients using lipid-lowering drugs on admission were excluded from this study.

Data regarding clinical and demographic properties and laboratory parameters were collected from medical records. Hypertension was defined as a systolic pressure >140 mmHg and/or a diastolic pressure >90 mmHg or if the individual was taking antihypertensive medica-tions. Diabetes mellitus was defined as a fasting glucose level >126 mg/dl and/or if the patient was taking anti-diabetic medication. Individuals who reported smoking of at least one cigarette per day during the year before ex-amination were classified as smokers. The study protocol was approved by the local ethics committee.

Coronary Angiography, Primary Angioplasty, and Stenting and Control Angiograms

Angiographic data regarding primary PCI was obtained from the cardiac catheterization laboratory records and was examined by two independent observers. All pa-
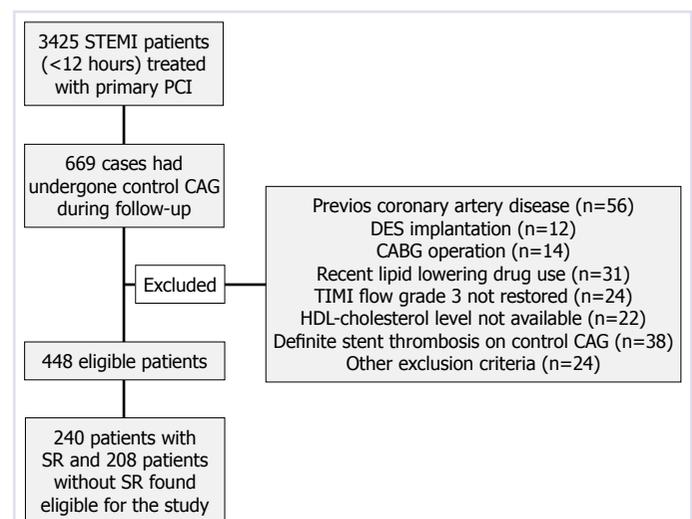

FIGURE 1. Flow-chart showing the recruitment of study cases.

tients were administered chewable aspirin (300mg, un-less contraindicated) and clopidogrel (600 mg, loading dose) before a primary PCI. Coronary artery stenosis of more than 50% was considered clinically significant. Primary coronary interventions, including balloon an-gioplasty and/or stent implantation, pre/post-dilation, were performed only for infarct- related artery (IRA) ac-cording to lesion anatomy and were left to the discretion of the operator. For each procedure, angiographic success at the acute phase was defined as an obstruction/stenosis of the IRA having been reduced to less than 10% stenosis with TIMI of 2 or 3 flows after primary PCI and stent implantation.

Second coronary angiographies were performed be-cause of the clinical indications, including symptoms of angina (stable or unstable) and abnormal non-invasive test results (treadmill exercise tests or myocardial perfu-sion scintigraphy). Data of control coronary angiograms were interpreted by an independent interventional car-diologist who was blinded to patients' characteristics. Stent restenosis was defined as greater than 50% steno-sis within or immediately adjacent (within 5 mm) to the implanted stent(s) according to the control angiographic data. Patients who had definite or probable stent throm-bosis according to the Academic Research Consortium definitions were also excluded from this study [12]. In the control CAGs, development of new coronary lesions with significant stenosis or progression of a non-signif-icant lesion to >50% stenosis was accepted as the pro-gression of CAD. We carried out a subgroup analysis in patients with and without CAD progression.

Laboratory Analysis

The results of laboratory parameters were collected using the electronic database of the hospital. Blood samples were drawn by antecubital venipuncture into EDTA-treated or plain tubes according to hospital protocol. Patients whose lipoprotein levels were not measured within the 24-hours of hospitalization were excluded from this study. Complete blood count (CBC) testing utilized clinical laboratory methods (Coulter LH 780 Hematology Analyzer, Beckman Coulter Ireland Inc, Mervue, Galway, Ireland) for hemoglobin, total white blood cell count (WBC), monocyte, neutrophil and lymphocyte counts. Total cholesterol, HDL-C and triglyceride levels were measured enzymatically (Architec c-Systems, Abbott, USA) and LDL-C levels were measured from these lipid parameters with Friedewald formula. Hs-CRP measurements were conducted on Cobas Integra analyzer (Roche Diagnostics, Turkey) using the turbidimetric method. Neutrophil to lymphocyte ratio (NLR) was measured by dividing neutrophil count to lymphocyte count. Monocyte to HDL-C ratio was calculated by dividing monocyte count ($10^3/\mu L$) to HDL-C level (mg/dL) and reported as 10^6/mg.

Statistical Analysis

All of the data are presented as a mean $\pm$ SD or a median [interquantile range] for continuous variables and as percentages for categorical variables. Continuous variables were checked for the normal distribution assumption using Kolmogorov-Smirnov statistics. Categorical variables were tested by Pearson's χ^2. Differences between the groups were evaluated using the Kolmogorov-Smirnov test, Kruskal-Wallis test, Student's t-test and ANOVA with the Tukey's post hoc test as appropriate. The relation between numerical variables was identified using Pearson or Spearman's rho test. Cox regression analyses were used to investigate the univariable and multivariable predictors of SR during the follow-up. Kaplan-Meier estimates and curves were generated, and comparisons were made using Log-Rank tests. A p-value <0.05 was considered statistically significant. All statistical studies were carried out using Statistical Package for Social Sciences software (SPSS 16.0 for Windows, SPSS Inc., Chicago, Illinois).

RESULTS

A total number of 448 patients (240 patients with SR and 208 patients without SR) were included in this study. Patients were categorized in three groups according to tertiles of admission MHR; MHR was ≤1.33 10^6/mg in tertile 1 (n=150), MHR was between 1.33 and 2.07 10^6/mg in tertile 2 (n=149), and MHR was ≥20.7 10^6/mg in tertile 3 (n=149). When the parameters were checked for the normal distribution with Kolmogorov-Smirnov test, only CRP (D(448)=0.155, p<0.01), MHR (D(448)=0.107, p<0.01), NLR (D(448)=0.095, p<0.01), triglycerides (D(448)=0.099, p<0.01), peak CK-MB (D(448)=0.151, p<0.01) were found to deviate significantly from normality.

The demographic, clinical properties and angiographic data of the study groups are summarized in Table 1. Three groups were comparable regarding age, gender, HT, DM, smoking status, admission systolic blood pressure and left ventricular ejection fraction. The distribution of culprit arteries, the frequency of the patients treated with direct stenting, Gp2b3a antagonist infusion, post-PCI TIMI 3 flow rates were similar between three groups. The mean diameter and length of the implanted stents were not different between the groups (p=0.78 and p=0.48, respectively).

The duration of follow-up was 12 [17] months (minimum 4 – maximum 60 months) and was not different between the three groups ($\chi^2(2)$=4.562, p=0.11). Stent restenosis was observed in 68 (45%) cases in tertile 1, in 80 (54%) cases in tertile 2 and in 92 (62%) cases in tertile 3 which was significantly different (χ^2=7.65, p<0.01). When patients with SR (n=240) were compared to patients without SR (n=208), the demographic and angiographic parameters were similar except for the frequency of male gender (73% vs. 57%), the presence of severe thrombus formation (26% vs. 16%) and mean length of implanted stents (19.7±6.3 vs. 18.1±6.1 mm), which were higher in SR group.

Comparison of the laboratory parameters between the tertiles of MHR is shown in Table 2. Most of the laboratory parameters were significantly different between the groups except for glucose, creatinine, peak-CKMB levels, RDW and NLR. In addition, MHR level was not different between male and female patients (median (1.62 [0.12] vs. 1.55 [0.95] 10^6/mg; U=20910, p=0.32). In univariate correlation analysis, CRP was significantly correlated with MHR (r=0.18, p<0.01) and NLR (r=0.19, p<0.01). Whereas, MHR and NLR was not correlated (p=-0.02, p=0.66).

When SR group was compared to patients without SR, only WBC (12.2±3.8 vs. 11.3±3.9 $10^3/\mu L$,

TABLE 1. Demographic, clinical and angiographic properties of the groups according to the tertiles of MHR

Characteristics	Tertile 1 MHR ≤1.33 (n=150)	Tertile 2 MHR =1.33–2.07 (n=149)	Tertile 3 MHR ≥2.07 (n=149)	P_1*	P_2**
Age, years	56.9±9.8	55.9±9.3	54.5±9.6	0.10	0.09
Male, n (%)	99 (66)	90 (60)	106 (71)	0.17	0.34
HT, (%)	74 (49)	54 (36)	60 (40)	0.12	0.12
DM, n (%)	42 (28)	32 (21)	40 (26)	0.42	0.82
Smoking, n (%)	65 (43)	60 (40)	81 (54)	0.08	0.06
SBP, mmHg	135±25	130±23	137±22	0.67	0.92
LV EF, %	46±9	47±9	48±10	0.62	0.59
Culprit artery					
LAD, n (%)	85 (56)	72 (48)	76 (51)		
CX, n (%)	16 (10)	30 (20)	25 (16)	0.23	0.29
RCA, n (%)	49 (32)	41 (27)	48 (32)		
Severe thrombus, n (%)	40 (26)	22 (14)	35 (23)	0.04	0.53
Direct stenting, n (%)	55(36)	56 (37)	69 (46)	0.17	0.09
Stent diameter, mm	3.1±0.6	2.9±0.6	3.0±0.6	0.78	0.94
Stent length, mm	19.5±6.7	18.6±6.4	18.8±5.9	0.48	0.72
Postprocedural TIMI 3, n (%)	136 (90)	126 (84)	128 (85)	0.51	0.20
Gp2b3a antagonist infusion n (%)	49 (32)	47 (31)	59 (39)	0.25	0.22
Control CAG, months	13 (19)	12 (17)	12 (16)	0.11†	0.47††
Stent restenosis, n (%)	68 (45)	80 (54)	92 (62)	<0.01	<0.01

CAG: Coronary angiography; CX: Circumflex artery; DM: Diabetes mellitus; Gp2b3a: Glycoprotein 2b-3a receptor antagonist; HT: Hypertension; LAD: Left anterior descending artery; LV EF: Left ventricular ejection fraction; RCA: Right coronary artery; SBP: Systolic blood pressure; *p_1 is the p value obtained from comparison of three groups using ANOVA test; **p_2 is the p value obtained from the comparison of Tertile 1 with Tertile 3 using Student's t test. ANOVA test or Student's t test were used for comparisons except for † (Kruskal- Wallis test) and †† (Mann-Whitney U test).

t(446)=1.96, p=0.04), neutrophil count (9.5±3.6 vs. 8.3±3.7 10^3/µL; t(446)=3.19, p<0.01), CRP (median 6.7 [5.6] vs. 4.5 [4.2] mg/L; U=18447, p<0.01), NLR (median 5.1 [4.9] vs. 3.9 [2.6]; U=19616, p <0.01), HDL-C levels (37.6±9.1 vs. 40.5±10.9 mg/dL; t(446)=-3.09, p<0.01) and MHR (median 1.67 [1.27] vs. 1.47 [0.98] 10^6/mg; U=21351, p<0.01) were significantly different between the groups. Total cholesterol, LDL-C, triglyceride levels and lymphocyte counts were not different between SR and no-SR groups.

Univariate and multivariate Cox regression analysis was performed to investigate the possible predictors of SR in the study population (Table 3). In univariate regression analysis, male gender, stent length, presence of severe thrombus, Gp2b3a therapy, WBC, NLR, HDL, MHR and CRP levels were correlated with SR. White blood cell counts, HDL cholesterol and MHR were analyzed separately in the multivariable regression model to prevent multicollinearity. In multivariate Cox regres-
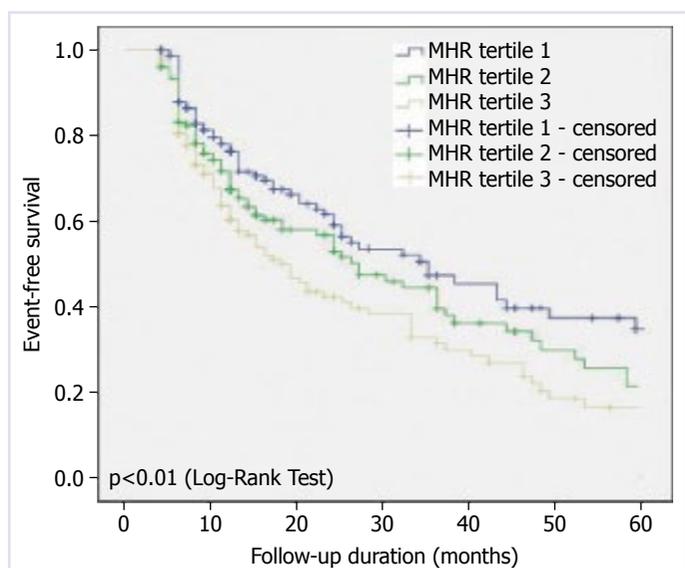

FIGURE 2. Kaplan–Meier curve showing the correlation between tertiles of the monocyte to HDL-C ratio (MHR) and stent restenosis in the study population.

TABLE 2. Laboratory parameters of the groups according to the tertiles of MHR

	Tertile 1 MHR ≤1.33 (n=150)	Tertile 2 MHR =1.33–2.07 (n=149)	Tertile 3 MHR ≥2.07 (n=149)	P_1*	P_2**
Glucose, mg/dL	119±52	113±37	124±49	0.12	0.65
Creatinine, mg/dL	0.88±0.26	0.87±0.2	0.86±0.26	0.86	0.85
Peak CK-MB, IU/L	143 (186)	113 (173)	119 (166)	0.58†	0.39
CRP, mg/L	5 (4.9)	5.2 (4.7)	7.1 (6.8)	0.04†	0.02
Total cholesterol, mg/dL	194±43	187±48	174±41	<0.01	<0.01
LDL, mg/dL	119±38	115±37	108±35	0.03	0.02
Triglyceride, mg/dL	128 (104)	150 (102)	151 (114)	0.03†	0.08††
HDL, mg/dL	45.1±11.4	38.6±7.4	33.1±6.6	<0.01	<0.01
Hemoglobin, g/dL	14.1±1.3	14.4±1.2	14.8±1.3	<0.01	<0.01
WBC, 10^3/µL	10.8±4.3	11.6±3.8	12.9±3.5	<0.01	<0.01
Neutrophil, 10^3/µL	8.2±3.9	8.9±3.7	9.6±3.3	<0.01	<0.01
Lymphocyte, 10^3/µL	1.8±0.7	2.0±0.8	2.2±0.8	<0.01	<0.01
RDW, %	13.6±1.1	13.5±1.6	13.7±1.9	0.63	0.67
Monocyte, 10^3/µL	0.4 (0.16)	0.6 (0.2)	0.9 (0.23)	<0.01†	<0.01††
NLR	4.94 (4.66)	4.52 (4.92)	4.29 (3.53)	0.75†	0.40††
MHR, 10^6/mg	1.03 (0.34)	1.62 (0.34)	2.62 (1.19)	<0.01†	<0.01††

CK: Creatine kinase; CRP: C reactive protein; HDL: High density lipoprotein; LDL: Low density lipoprotein; MHR: Monocyte to HDL ratio; NLR: Neutrophil to lymphocyte ratio; RDW: Red cell distribution width; WBC: white blood cell; *p1 is the p value obtained from comparison of three groups using ANOVA test; **p2 is the p value obtained from comparison of Tertile 1 with Tertile 3 using Student's t test. ANOVA test or Student's t test were used for comparisons except for † (Kruskal- Wallis test) and †† (Mann-Whitney U test).

sion analysis, using model adjusted for parameters with p values <0.10 in univariate analysis, increased MHR levels (HR 1.03, 95% CI 1.02−1.06, p<0.01), increased NLR levels (HR 1.12, 95% CI 1.07−1.16, p<0.01), stent length and gender independently predicted SR. The patients in MHR tertile 3 had 1.65 times higher risk for SR compared to patients in MHR tertile 1. The Kaplan-Meier curve showed a significant difference in the SR rates between the MHR tertile groups (Fig. 1).

DISCUSSION

The main findings of the present study are as follows: male gender, stent length, elevated levels of MHR and NLR were independent predictors of SR in STEMI patients treated with primary PCI with BMS implantation. Patients in the highest MHR tertile had a 1.65 times higher risk for SR compared to patients with the lowest MHR tertile. Stent length but not stent diameter was also correlated with SR in our study.

The role of inflammation in the progression of atherosclerotic plaques, rupture of the necrotic core and thrombus formation has been well established [10]. Mononuclear cells, such as monocytes and T lymphocytes, transform into macrophages in the subendothelial space, take up oxidized LDL-C and become foam cells which form fatty streaks. Foam cells secrete proinflammatory cytokines, matrix metalloproteinases, tissue factor and growth factors that contribute to the maturation of the atherosclerotic plaques. The correlation of inflammation with cardiovascular diseases has also been shown in clinical trials [11–13].

Primary PCI and stent implantation are the current treatment modality in patients with STEMI. However, stent thrombosis and SR, which lead to the recurrence of symptoms and re-intervention, are the major complications of these interventions. Factors related with the patient (such as smoking status, DM), the anatomical properties of the coronary arteries (such as small vessel diameter, long lesions) and the type of the stents have been defined as predictors of SR.

The studies investigating the correlation of CRP with SR are heterogeneous, and the results are controversial; the patient population (stable/unstable CAD),

Table 3. Univariate and multivariate Cox regression analysis for the possible predictors of stent restenosis in the study population

Variables	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)*	P
Age	0.99 (0.97–1.01)	0.16	–	–
Male gender	1.65 (1.24–2.21)	<0.01	1.86 (1.37–2.54)	<0.01
Hypertension	0.89 (0.61–1.31)	0.58	–	–
Smoking	1.37 (0.94–2.1)	0.09	–	–
DM	0.86 (0.56–1.32)	0.51	–	–
Direct stenting	0.91 (0.69–1.18)	0.47	–	–
Severe thrombus	1.51 (1.13–2.1)	<0.01	1.28 (0.81–2.03)	0.28
Gp2b3a antagonist infusion	1.37 (1.05–1.81)	0.02	0.92 (0.59–1.41)	0.69
Stent diameter	1.17 (0.92–1.49)	0.21	–	–
Stent length	1.04 (1.01–1.06)	<0.01	1.03 (1.01–1.05)	0.02
WBC	1.05 (1.02–1.08)	<0.01	–	–
Glucose	1.01 (0.99–1.02)	0.79	–	–
Creatinine	0.67 (0.41–1.13)	0.13	–	–
Total cholesterol	1.01 (0.98–1.03)	0.78	–	–
LDL cholesterol	1.01 (0.99–1.02)	0.61	–	–
HDL cholesterol	0.98 (0.96–0.99)	<0.01	–	–
Triglyceride	1.01 (0.99–1.02)	0.29	–	–
CRP	1.03 (1.01–1.06)	<0.01	1.01 (0.98–1.03)	0.51
NLR	1.11 (1.07–1.15)	<0.01	1.12 (1.07–1.16)	<0.01
MHR[†]	1.03 (1.02–1.05)	<0.01	1.03 (1.02–1.06)	<0.01
MHR tertiles[†]				
Tertile 1	Reference	–	Reference	–
Tertile 2	1.31 (1.09–1.80)	0.03	1.21 (1.05–1.59)	0.04
Tertile 3	1.62 (1.19–2.23)	<0.01	1.65 (1.19–2.30)	<0.01

CRP: C reactive protein; DM: Diabetes mellitus; HDL: High density lipoprotein; LDL: Low density lipoprotein; LV EF: Left ventricular ejection fraction; MHR: Monocyte to HDL ratio; NLR: Neutrophil to lymphocyte ratio; WBC: White blood cell; * Parameters with p<0.10 in univariate model were entered to the multivariate regression analysis.†Monocyte to HDL ratio (tertiles and as a continuous variable) were entered to the multivariable model separately in order to prevent multicollinearity.

the type of stents (DES / BMS), the timing of the laboratory examination (preprocedural/post-procedural/serial measurements), definition of adverse events (angiographic SR or adverse cardiovascular events) are different among the studies. In addition, the number of cases is low in most of the studies. Higher CRP levels have been shown to predict SR after BMS implantation [14], whereas the results are controversial for patients treated with DESs [15, 16]. In our study, we have measured CRP levels within 24-hours of intervention. We have found that higher CRP levels were correlated using SR in univariate analysis, whereas this correlation was not significant in multivariate analysis. As the pharmacological agents used in DESs have anti-inflammatory and immunosuppressant functions, it is hard to investigate the correlation of inflammatory markers with SR in patients treated with DESs. Thus, we excluded patients with DES implantation from this study.

Neutrophil to lymphocyte ratio is a marker of systemic inflammation which has been shown to predict adverse cardiovascular events in various diseases. Higher NLR levels were found to be associated with SR of BMS in patients with stable/unstable angina pectoris and STEMI [4, 17]. In our study, we have found that NLR level measured within 24-hours of intervention is a predictor of SR in STEMI patients.

Monocyte activation is an important step at the beginning of the atherosclerotic process. Monocyte activation yields production of several cytokines, such as interleukin (IL)-1, IL-6, platelet-derived endothelial cell growth factor, transforming growth factor (TGF)-a

and-b, macrophage colony-stimulating factor and insulin-like growth factor that induce atherosclerotic lesion growth and plaque rupture [8]. The count of circulating monocytes, as the source of tissue macrophages and foam cells, was found to be a predictor for new plaque development [18].

It has been evidenced that HDL cholesterol exerts anti-inflammatory, anti-oxidant and anti-thrombotic effects. Karabacak et al. reported that in patients with HDL-C<35 mg/dL, monocyte chemoattractant protein-1 levels were higher [19]. Also, lower levels of HDL cholesterol were reported as independent predictors of mortality in patients with acute coronary syndrome and critical illnesses [20, 21]. Thus, lower levels of HDL-C may theoretically be associated with inadequate limitation of inflammatory response.

Monocyte to HDL ratio was defined as a novel potential marker to determine inflammation and was used to predict clinical outcome in a few trials. The first study indicated the relation of increased MHR levels with adverse cardiovascular outcomes patients with chronic kidney disease [6]. MHR level was found to be associated with coronary slow flow and systemic inflammation [7]. In another study, increased MHR level (especially MHR >11.48) was found to be a predictor of AF recurrence after cryoballoon-based catheter ablation [8]. In our study, we have found that increased levels of MHR are associated with a higher risk of SR in patients with STEMI treated with BMS. Patients in the highest tertile group had a 1.65 fold increased risk of SR compared to lowest tertile group.

Limitations

Our study has several limitations. This study was conducted on a retrospective basis and represented a single center experience. Definition of SR was based on visual inspections, not on quantitative measurements. Use of a single blood sample does not anticipate the persistence of MHR over time, and we could not investigate the impact of medications on MHR levels. In addition, our findings may not be generalized to STEMI patients treated with DES implantation.

Conclusions

High MHR level is a predictor of SR in patients treated with BMS implantation after STEMI. Further prospective studies are needed to confirm and to reveal clinical implications of our findings.

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