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Monocyte Count/HDL Cholesterol Ratio Is Associated With the Severity of Coronary Artery Disease

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Abstract

Objective: To examine the association between complete blood count parameters and severity of Coronary Artery Disease (CAD) in patients who underwent coronary angiography.

Methods: From October 2018 to February 2019, a total of 437 patients who had anginal symptoms and underwent coronary angiography were included in this study. Patients were divided into two groups according to their angiography findings; as significant CAD group (n=243) and non-significant CAD group (n=194). Patients' baseline clinical characteristics and laboratory data including complete blood count parameters were recorded and compared between the groups.

Results: According to univariate analysis; White Blood Cell (WBC) count, neutrophil (NEU) count, Monocyte/Lymphocyte Ratio (MLR), Neutrophil/Lymphocyte Ratio (NLR) and monocyte count/HDL cholesterol ratio (MHR) were detected to be significantly higher in significant CAD group as compared with non-significant CAD group. Multivariate logistic regresion analysis revealed that among laboratory parameters only MHR was found to be a significant and independent predictor of severity of CAD.

Conclusion: Our study demonstrated that MHR could be used as a novel biomarker for the prediction of the severity of CAD.

Keywords: Monocyte count/HDL cholesterol ratio; Complete blood count; Severity; Coronary artery disease

Introduction

Coronary artery disease (CAD), known to develop on the basis of atherosclerosis, is the leading cause of death worldwide. Atherosclerosis is a disease with major clinical outcomes such as CAD after a very long asymptomatic period. Well known atherosclerotic risk factors such as hypertension (HT), hyperlipidemia (HL), diabetes mellitus (DM) and smoking play an important role in the development and progression of CAD [1].

Atherosclerosis involves a wide spectrum of factors like inflammation. Inflammation occurring in the vascular walls leads to changes in the levels of some cytokines in the blood (acute phase reactants and proinflammatory proteins etc.), blood cells and some complete blood count (CBC) parameters [2,3]. The severity of inflammation can be detected with the increase of some cytokines in patients with CAD and Peripheral Artery Disease (PAD). Studies have found an association between atherosclerosis and systemic inflammation markers such as C-reactive protein (CRP), serum amyloid A (SAA), IL-6, TGF-beta, neopterin and procalcitonin in patients with CAD and PAD [4-8].

Recent studies have focused on simple, inexpensive and promising parameters of CBC that can provide important diagnostic and prognostic information about diseases associated with chronic inflammation. Today CBC parameters are in general recognized as inflammatory markers and prognostic determinants in a wide spectrum of diseases. These parameters include red blood cell distribution width (RDW), Mean Platelet Volume (MPV), White Blood Cell (WBC) count; leukocyte subtypes (neutrophil, monocyte and lymphocyte counts, monocyte/lymphocyte ratio (MLR) and Neutrophil/Lymphocyte Ratio (NLR)). Recent studies have found a significant association between chronic inflammatory markers and CAD. In addition, a novel marker, monocyte count/HDL cholesterol ratio (MHR) was shown to be associated with CAD in recent studies.

The objective of this study was to search difference of CBC parameters in patients with angiographically proven significant and non-siginificant CAD.

Methods

Study design and patients

This retrospective cohort study was performed in the department of cardiology of a tertiary referral hospital in Turkey after approval by local ethics committee. Patients who underwent coronary angiography (CAG) with the diagnosis of stable angina pectoris or acute coronary syndrome between October 2018 and February 2019 were included in the study. Exclusion criteria included recent previous acute coronary syndrome, history of previous coronary intervention or coronary artery bypass graft, severe valvular heart disease, decompensated heart

failure, cerebrovascular disease, renal or hepatic disease, acute or chronic infection and/or inflammation, malignancy, malnutrition, hematologic diseases, thrombocytopenia, symptomatic peripheral arterial disease, autoimmune diseases, cancer, pregnancy and chronic obstructive pulmonary disease.

Patients were divided into two groups according to CAG findings. Significant CAD group (Group 1) consisted of the patients with ≥ 70% in at least one major coronary artery (LAD, Cx, RCA and major branches), while non-significant CAD group (Group 2) included the other patients. All patients' demographic information and laboratory parameters were obtained by file screening. The studied laboratory parameters included basic biochemical tests as well as CBC parameters such as WBC, neutrophil (NEU), lymphocytes (LYM), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), RDW, platelet count (PLT), platelet distribution width (PDW), MPV, plateletcrit (PCT), NLR, platelet/lymphocyte ratio (PLR), RDW/platelet ratio (RPR), mean platelet volume/platelet ratio (MPR), MLR and MHR. These recorded data were compared between the groups.

Blood sample analysis

Peripheral venous blood samples of 5 ml were collected from all patients and put into the standard sterile tubes. In order to determine CBC parameter values, the blood samples were analyzed in the Beckman Coulter Device (Beckman Coulter In.; Bre CA) within 15 minutes. These analyses were performed using the original kits of the manufacturer.

Statistical analysis

Data were evaluated using SPSS version 15.0 (SPSS 15.0; SPSS Inc., Chicago, IL, USA). Normality of the variables was tested with Kolmogorov-Smirnov method. Student t test was used for the comparison of normally distributed variables and these data were expressed as mean ± SD. Mann-Whitney test was used for the comparison of non-normally distributed variables and these data were expressed as median (min-max). Chi-square test was used for the comparison of categorical variables. In addition to univariate analyses, multivariate logistic regression analysis was performed for the determination of independent predictors of significant CAD after other variables were adjusted. $p<0.05$ values were considered as statistically significant.

Results

A total of 437 patients were included in the study. Significant CAD group (Group 1) included 243 patients while non-significant CAD group (Group 2) included 194 patients. There was significant difference between the groups in terms of gender ($p<0.001$). Of the patients in Group 1 74% were male and 26% were female. Whereas in Group 2 57% of the patients were male and 43% female. The difference was significant in terms of age (65 ± 11 vs 61 ± 12 years $p<0.001$). Forty percent of the patients in Group 1 and 29% of the patients in group 2 were smokers, and the difference was statistically significant ($p=0.03$). Group 1 had significantly more hypertensive patients than Group 2 (60% vs. 50%, $p=0.03$). HL was found in 31% of the patients in Group 1 and 23% of the patients in group 2, but the difference between the groups was not significant ($p=0.06$). DM was found in 57% of the patients in Group 1 and 38% of the patients in Group 2 ($p<0.001$) (Table 1).

	Severe CAD (+) n=243	**Severe CAD (-) n=194**	**p value**
Age (years)	65 ± 10	61 ± 11	p<0.001
Gender (F/M), n	63/180	84/110	p<0.001
HT, n	145	96	p=0.03
DM, n	139	74	p<0.001
HL, n	76	45	p=0.06
Family History, n	32	28	p=0.69
Smoking, n	86	53	p=0.03
BMI, kg/m2	29.06 ± 5.1	29.35 ± 5.5	p=0.66
Waist Circumference, cm	105.9 ± 13.8	104.56 ± 15.2	p=0.36

Table 1: Baseline characteristics of the groups

There was no statistically significant difference between the groups in terms of other data of the study including height ($p=0.052$), weight ($p=0.47$), body mass index (BMI) ($p=0.66$), waist circumference ($p=0.36$), family history ($p=0.69$), LDL-cholesterol ($p=0.15$), total-cholesterol ($p=0.65$), triglyceride (TG) ($p=0.40$), Lym ($p=0.89$), Hgb ($p=0.69$), MCV ($p=0.45$), RDW ($p=0.94$), PLT ($p=0.59$), PDW ($p=0.94$), MPV ($p=0.27$), PCT ($p=0.73$), PLR ($p=0.76$), RPR ($p=0.94$), MPR ($p=0.28$).

Glucose, hba1c, urea, creatinine, AST, ALT, K, WBC, NEU, NLR, MLR, and MHR levels were significantly higher in Group 1 compared to Group 2 (All values $p<0.05$). GFR, TSH and HDL levels were significantly lower in Group 1 than in Group 2 (All values $p<0.05$) (Table 2).

	CAD (+) n=243	**CAD (-) n=194**	**p Value**
HbA1c	7.04 ± 1.7	6.48 ± 1.3	p<0.001
Urea	39.41 ± 21.26	34.51 ± 15.15	p=0.002
Creatinine	1.08 ± 0.99	0.94 ± 0.83	p<0.001
GFR	80.09 ± 21.18	86.10 ± 18.19	p=0.007
Glucose	147.50 ± 72	116.45 ± 53.88	p<0.001

AST	42.27 ± 50	27.10 ± 12.73	p<0.001
ALT	25.05 ± 21.88	21.29 ± 14.68	p=0.048
TSH	1.16 ± 1.05	2.32 ± 6.31	p=0.007
Sodium	135.98 ± 3.85	136.35 ± 3.60	p=0.103
Potasium	4.47 ± 0.52	4.36 ± 0.50	p=0.025
HDL, mg/dl	42.15 ± 9.75	46.41 ± 11.10	p<0.001
LDL, mg/dl	117.19 ± 38.87	112.24 ± 37.13	p=0.145
TC, mg/dl	187.67 ± 44.98	186.97 ± 45.70	p=0.654
TG	153.95 ± 109.50	152.34 ± 158	p=0.397
WBC	9.12 ± 3.29	7,67 ± 2.25	p<0.001
NEU	6.12 ± 3.11	4.81 ± 1.99	p<0.001
LYM	2.22 ± 1.17	2.16 ± 0.97	p=0.891
HGB	13.75 ± 1.8	13.73 ± 1.67	p=0.690
HTC	41.67 ± 5.25	41.71 ± 4.64	p=0.813
MCV	85.92 ± 5.71	85.69 ± 5.56	p=0.449
RDW	15.72 ± 1.48	15.64 ± 1.42	p=0.437
PLT	255.49 ± 69.02	251.8 ± 69.12	p=0.594
PDW	17.86 ± 1.21	17.82 ± 1.08	p=0.943
MPV	7.94 ± 1.33	8.08 ± 1.22	p=0.265
PCT	0.20 ± 0.06	0.20 ± 0.05	p=0.725
NLR	3.62 ± 3.23	3.06 ± 3.77	p=0.005
PLR	140.66 ± 83.44	162.60 ± 244.43	p=0.763
RPR	0.07 ± 0.02	0.07 ± 0.02	p=0.938
MPR	0.03 ± 0.01	0.03 ± 0.01	p=0.279
MLR	0.29 ± 0.19	0.28 ± 0.30	p=0.013
MHR	0.0138 ± 0.0077	0.0111 ± 0.0059	p<0.001

Table 2: Laboratory findings of the groups

In the logistic regression analysis; considering well known CAD risk factors such as age, gender, DM, HT and smoking, among laboratory data only MHR was detected to be a significant and independent indicator of significant CAD (Table 3).

Variables	p value*	Odds ratio (95% CI)
Age (years)	<0.001	1.042 (1.021, 1.064)
Gender (F/M)	<0.001	2.544 (1.533, 4.222)
HT	0.092	1.514 (0.935, 2.452)
DM	<0.001	2.850 (1.808, 4.491)
HL	0.843	1.053 (0.631, 1.758)
Smoking	0.009	1.986 (1.186, 3.326)
MHR	0.001	1.059 (1.024, 1.095)

CI: Confidence Interval; DM: Diabetes Mellitus; HL: Hyperlipidemia; MHR: monocyte count/HDL cholesterol ratio

*Results of multivariate logistic regression analysis of significant coronary artery disease as the dependent variable Bold values indicate p<0.05.

Table 3: Independent predictors of coronary artery disease by logistic regression analysis.

Discussion

The main finding of our study was that traditional risk factors of CAD such as advanced age, male gender, HT and DM were more

common and some CBC parameters (WBC, NEU, NLR and MLR) were significantly higher in patients with severe CAD than those without severe CAD. However, logistic regression analysis including those CAD risk factors and CBC parameters revealed that only MHR was detected to be a significant and independent indicator of significant CAD, hereby it was considered as an independent indicator of the severity of CAD.

Today subclinical inflammation is known to play an important role in the pathogenesis and progression of CAD [9-10]. Agents responsible for inflammation include various growth factors (platelet-derived growth factor (PDGF) epidermal growth factor (EGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) etc.), cytokines (interleukins, tumor necrosis factor (TNF), interferon (IFN), colony stimulating factors (CSF), transforming growth factors (TGF), and chemokines) and adhesion molecules (intercellular adhesion molecule (ICAM)-1, vascular adhesion molecule (VCAM)-1, E- and P-selectin etc.) [10,11]. These agents are expensive and not widely available. Parameters obtained from CBC, which is a simple, inexpensive and a readily accessible test, have gained popularity and been studied more commonly in recent years.

NLR, one of the CBC parameters, has been accepted as an inflammatory marker recently and have been commonly emphasized in studies about CAD and its severity. Uysal et al. studied CBC parameters in a cohort consisting of 194 patients who underwent coronary angiography, and found NLR and MPV as predictors of severe CAD [12]. They stated that these parameters can be used in the prediction of cardiac risk in CAD patients. Arbel et al. investigated predictive effect of NLR on the severity of CAD in 3005 consecutive patients who underwent coronary angiography. In this study, patients were divided into three groups as patients with a NLR<2, patients with a NLR between 2-3 and those with a NLR>3. A NLR value of>3 was demonstrated to be associated with more advanced CAD and poor prognosis [13]. In a meta-analysis of eight studies including 4339 participants, Wang et al. reported that NLR was a predictor of cardiovascular events and all-cause mortality [14]. Kalay et al. included 394 patients requiring repeat CAG in their study and they categorized patients into two groups as with and without progressive athesosclerosis [15]. NLR value was found to be significantly higher in the groups with progressive atherosclerosis. Similar to the studies in the literature, in our study NLR was also significantly higher in the significant CAD group compared with the non-significant CAD group, but it was not able to indicate significant CAD in the multivariate regression analysis.

In recent years, MLR has drawn attention as a popular CBC parameter. In their study including 542 patients who underwent CAG, Ji et al. divided the patients into three groups according to Syntax score, while patients with normal CAG were assigned as controls. MLR was found to be an independent risk factor predicting presence and severity of CAD [16]. Fan et al. has investigated the association between MLR and fragility of the coronary plaque in patients with stable angina pectoris, and found that MLR level has a potential to determine fragile plaques in patients with stable angina [17]. In addition, Gong et al. retrospectively examined 199 patients who underwent CAG, and they showed that lymphocyte/monocyte ratio (LMR) was independently and positively associated with the severity of atherosclerosis measured with Gensini score. They reported that LMR may be a useful determinant of future cardiac events in CAD patients. Accordingly, in our study MLR was also higher in the significant CAD group compared to the non-significant CAD group [18].

MHR, which is obtained by dividing monocyte count among the CBC parameters by HDL cholesterol, is another laboratory data which has been stated to be a novel and striking indicator of cardiovascular diseases in recent years [19-21]. In their study including 428 patients with stable coronary disease who underwent CAG, Kundi et al. divided patients into two groups according to Syntax scores as high Syntax score (≥ 23) and low Syntax score (<23) groups. The authors found that MHR was significantly higher in the high Syntax score group [22]. Akboga et al. has also demonstrated a significant correlation between MHR and Syntax score in 1229 patients [23]. Again in a recent study, Kızıltunç et al. divided 760 patients who underwent CAG as low (<20) and high (>20) Gensini score groups [24]. They found a positive, but weak correlation between MHR and high Gensini score. Therefore, MHR may be independently associated with coronary atherosclerosis burden. In our study, MHR was also significantly higher in the significant CAD group compared to the non-significant CAD group. In addition, according to the multivariate logistic regression analysis, MHR was found to be the only laboratory parameter that could be accepted as a significant and independent indicator of significant CAD. A limitation of this study was its retrospective design and relatively small number of patients. However, it supports the other studies in the literature.

Conclusion

High NLR, MLR, and especially MHR values that are obtained from simple hemogram samples may be associated with the severity of CAD. We believe that, besides traditional atherosclerotic risk factors, these parameters may have additional benefit in cardiovascular risk evaluation.

Declaration of Conflicting Interests

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Author contributions

MC initiated the concept and design of the paper, performed and analysed all the angiographic data and drafted the manuscript. GA, IS, YG analysed patient's clinical data. MC, IS, YG contributed to the interpretation of data and manuscript. All authors revised it critically for important intellectual content and approved the final version of the manuscript.

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