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Predictive role of monocyte count for significant coronary artery disease identification in patients with stable coronary artery disease

Tomasz Urbanowicz et al., Monocyte count as significant coronary disease predictor

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Abstract

Background: The coronary artery disease (CAD) remains the leading cause of morbidity that is characterized by broad spectrum of symptoms. Up to 30% of performed angiographies reveal normal coronary arteries. The aim of the study was to find simple predictor for significant epicardial artery stenosis among patients with chronic coronary syndrome.

Methods: There were 187 patients (131 (709%) men and 56 (30%) women) in the median (Q1–Q3) age of 67 [58–72] presenting with stable CAD symptoms enrolled into the present retrospective analysis. The demographical, clinical and laboratory characteristics between patients with normal and significant coronary artery stenosis were compared.

Results: The multivariable analysis revealed coexistence of hypercholesterolemia as significant differentiation factor (odds ratio [OR]: 4.38, 95% confidence interval [CI]: 1.78–

10.80, $p = 0.001$) for significant CAD and inverse relation to serum high density lipoprotein (OR: 0.19, 95% CI: 0.05–0.72, $p = 0.015$) and relation to creatinine concentration (OR: 1.03, 95% CI: 1.00–1.05, $p = 0.012$). Among whole peripheral blood count analysis, the significant relation was noticed to be hemoglobin concentration (OR: 1.09, 95% CI: 1.10–1.18, $p = 0.022$) and monocyte count (OR: 32.3, 95% CI: 1.09–653.6, $p = 0.017$). Receiver operator curve revealed (AUC: 0.641, $p = 0.001$) with the optimal cut-off value above 0.45 K/uL for monocyte, yielding sensitivity of 81.82% and specificity of 58.06%.

Conclusions: The peripheral monocyte count above 0.45 k/uL may be considered as a predictor of significant coronary artery disease in symptomatic patients with chronic coronary syndrome.

Keywords: coronary artery disease, monocyte, significant stenosis, atherosclerosis, angina

INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of morbidity [1, 2], and its probability can be estimated based on patient characteristics and symptoms [3]. If there is a clinical suspicion of CAD, non-invasive or invasive tests should be performed depending on the likelihood stratification [4]. According to recent reports, patients should be meticulously evaluated before being referred to an invasive strategy, unless the tests indicate a high likelihood of obstructive CAD [5, 6].

Among the non-invasive functional tests in patients with clinical likelihood of obstructive CAD, stress echocardiography [7], coronary computed tomography angiography [8, 9], single-photon emission computed tomography [10], positron emission tomography [11] and cardiac magnetic resonance [12] are proposed as reasonable diagnostic approaches.

One of the driving forces for coronary plaque initiation and progression is inflammatory cascade activation [13]. There is growing evidence that inflammatory processes modification may influence morbidity and mortality [14, 15]. Among simple inflammatory markers, hematological indices obtained from the whole blood count analysis were proven to be an easily accessible and reliable predictors of prognosis in patients with CAD [16–18]. Monocytes were presented in Arnold et al. [19] analysis as related to the severity of CAD. Among inflammatory cellular components, monocytes are postulated as a major source of proinflammatory background of atherogenesis [20].

The aim of the present retrospective analysis was to evaluate the predictive role of monocyte count in patients presenting with stable CAD admitted for coronary angiography.

METHODS

One hundred eighty-seven consecutive patients who were admitted to cardiac-internal profile department in 2022 due to the stable CAD symptoms composed the analyzed population. They were assessed using Canadian Cardiovascular Society (CCS) grading system as mean (standard deviation) CCS class 2.1 (0.4). The study group was divided regarding coronary angiography results into patients with normal coronary arteries, which refers to atherosclerotic lesions of less than 30% of lumen narrowing, and significant culprit lesions regarded as hemodynamically significant coronary artery lumen stenosis. Patients with acute coronary syndrome (ACS), advanced chronic or acutely decompensated heart failure, rheumatic, oncological and hematological diseases were excluded from the study.

Patients underwent non-invasive and invasive diagnostics including angiography due to suspected CAD based on symptoms including chest pain and/or to shortness of breath and fatigue on exertion. Demographical and clinical data, followed by laboratory and echocardiography results, were collected, as presented in Table 1. The significant stenosis of culprit lesion was estimated as at least 70%, except for left main disease that was regarded as at least 50%.

The informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Bioethics Committee of Poznan University of Medical Sciences No 55/20 from 16 January 2020.

RESULTS

There were 187 patients (131 [70%] men and 56 [30%] women) in the median (Q1–Q3) age of 67 (58–72) years who were enrolled into retrospective analysis. They were divided into two subgroups based on the coronary angiography results. Although both groups were characterized by similar anginal symptoms estimated in CCS class with mean values of 2.0 (0.23) vs. 2.0 (0.49), respectively ($p = 0.076$), they differed in CAD occurrence. Group 1 consisted of 69 symptomatic patients (35 males and 34 females) in the mean age of 68 (63–73) with normal coronary arteries, while group 2–118 symptomatic patients (96 males and 22 females) in the mean age of 67 (63–72) with significant CAD, requiring either percutaneous coronary intervention (51 [74%] patients) or coronary artery bypass grafting (18 [26%]

patients). The patients varied regarding sex ($p < 0.001$) and body mass index ($p = 0.026$). There were no statistically significant differences concerning co-morbidities nor family history ($p = 0.054$) as presented in Table 1.

Laboratory test results

The laboratory results collected on admission included whole blood count analysis, lipid profiles, thyroid-stimulating hormone and kidney function analysis and is presented in Table 2. The patients were screened for myocardial injury markers on admission.

There were significant differences in peripheral whole blood count analysis between both groups regarding: white blood cell count ($p = 0.004$), neutrophil count ($p = 0.002$), monocyte ($p < 0.001$), hemoglobin ($p = 0.001$), hematocrit ($p = 0.004$), mean corpuscular volume ($p = 0.029$) and mean corpuscular hemoglobin concentration ($p = 0.025$).

The statistically significant differences between inflammatory indexes were found between both groups including neutrophil-to-lymphocyte ratio ($p = 0.046$), monocyte-to-lymphocyte ratio ($p = 0.001$) and systemic inflammatory response index ($p \leq 0.001$).

The lipid profile's results on admission were significantly different between both groups, including total serum cholesterol ($p < 0.001$), low-density lipoprotein fraction (LDL; $p = 0.007$) and high-density lipoprotein fraction (HDL; $p < 0.001$).

Significant differences were found in serum creatinine between groups ($p < 0.001$), but not in the glomerular filtration rate ($p = 0.340$).

Logistic regression

The logistic regression analysis was performed for the evaluation of prognostic parameters of CAD occurrence in the study subgroups (normal angiography vs. significant CAD) and is presented in Table 3.

The multivariable analysis revealed coexistence of hypercholesterolemia as a significant differentiation factor (odds ratio [OR]: 4.38, 95% confidence interval [CI]: 1.78–10.80, $p = 0.001$) for significant CAD and inverse relation to serum HDL (OR: 0.19, 95% CI: 0.05–0.72, $p = 0.015$) and relation to creatinine concentration (OR: 1.03, 95% CI: 1.00–1.05, $p = 0.012$). Among whole peripheral blood count analysis, the significant relation was noticed to be hemoglobin concentration (OR: 1.09, 95% CI: 1.10–1.18, $p = 0.022$) and monocyte count (OR: 32.3, 95% CI: 1.09–653.6, $p = 0.017$) as presented in Table 3.

Receiver operating characteristic curves for predicting significant coronary atherosclerosis

In the multivariable analysis, the creatinine, serum HDL cholesterol fraction, hematocrit and monocyte count were found significant. The receiver operator curves for mentioned parameters were performed.

The multivariate analysis and receiver operating characteristic (ROC) analysis revealed predictive values for best prediction of significant coronary artery stenosis occurrence, of the following indicators: serum creatinine (area under the curve [AUC]: 0.647, $p = 0.001$) which presented the optimal cut-off value above 78 mg/dL yielding sensitivity of 69.57% and specificity of 54.55%; serum HDL below 1.22 mmol/L (AUC: 0.641, $p = 0.002$) yielding sensitivity of 69.64% and specificity of 56.72%; hematocrit above 41% (AUC: 0.618, $p = 0.007$) yielding sensitivity of 64.76% and specificity of 59.42%; and monocyte count (AUC: 0.641, $p = 0.001$) with the optimal cut-off value above 0.45 K/uL yielding sensitivity of 81.82% and specificity of 58.06% as presented in Figure 1.

Following the current results presenting the value of monocyte count for significance of culprit lesions in coronary artery bed, the assessment of the peripheral blood analysis and clinical symptoms was performed. In the logistic regression analysis CCS classification of 2 or higher grade was used. Exactly the same parameters were included as in the primary analysis, and multivariable analysis found significance of co-existence of arterial hypertension (OR: 0.01, 95% CI: -9.21-0.07, $p = 0.021$), echocardiographic results including left ventricle diameter (OR: 0.78, 95% CI: 0.08-0.90, $p = 0.042$) and right ventricle diameter (OR: 1.75, 95% CI: 1.37-9.76, $p = 0.009$). The laboratory results presented the following parameters as significant in the multivariable model: neutrophil count (OR: 5.26, 95% CI: 1.02-11.52, $p = 0.019$), monocyte count (OR: 3.72, 95% CI: 0.708-12.08, $p = 0.049$), and hematocrit (OR: 0.603, 95% CI: 0.063-0.947, $p = 0.025$).

DISCUSSION

Results presented in this retrospective analysis indicate possible predictive factors of significant coronary artery stenosis on coronary angiography among patients with stable angina.

The novelty of the performed study is the possible relation between significant CAD and the peripheral monocyte count in symptomatic patients. The more possible implication of the present results in clinical practice regarding patients with stable coronary disease, rely on a more accurate diagnosis of the subgroup who should undergo coronary catheterization due

to the significance of the disease. According to recent results, patients presenting with chronic coronary syndrome can be treated pharmacologically [21], however simple parameters available from the whole blood count analysis may point out the subgroup in which invasive strategy is justified.

The relation between elevated concentration of monocytes-related cytokines and ACS risk was already postulated by Hojo et al. [22] and presented in a histopathological examination by Sato et al. [23]. The subendothelial infiltration of monocyte type cells with edematous change, increased endothelial permeability and damage caused by coronary vasospasm [23]. Standard risk factors include lipid profiles. Moreover, significant CAD has been associated with infections [24], that were found related to infarct size and hemodynamic instability in ST-segment elevation myocardial infarction (STEMI) patients.

The possible relation between inflammatory activation measured by lymphocyte to monocyte ratio in non-obstructive CAD was reported by Akil et al. [25]. Microvascular angina refers to anginal symptoms relieved by nitroglycerine and beta/calcium-blockers use in non-obstructive CAD [26]. The monocyte-to-HDL-cholesterol ratio is another marker associated with inflammation, which was presented in Dogan et al. [27] analysis as significant for microcirculatory dysfunction in patients with non-obstructive disease and anginal symptoms. The correlation between surrogate marker of inflammation, which is the neutrophil-to-lymphocyte ratio and anginal symptoms in female population, was shown by Okyay et al. [28]. The results of the present analysis indicate a relation between myocardial hypoperfusion related to significant CAD and inflammatory activation measured by peripheral monocyte count. The monocyte role in patients with defined epicardial atherosclerosis was presented in the Schirmer et al. study [29].

The prevalence of anginal patients with no obstructive coronary arteries is estimated to be as high as 40%, whereas coronary spasm or microvascular diseases are reported as mechanistic explanation in nearly half of the patients [30]. Inducible myocardial ischemia due to microvascular dysfunction is an important finding in symptomatic patients regardless of sex according to Murthy et al. analysis [31].

The relation between inflammatory activation and non-obstructive coronary angina was presented [32], as well as in ACSs requiring percutaneous interventions [33]. The present study reflects the association between inflammatory activation and coronary atherosclerosis likelihood in symptomatic patients.

Among other possible indicators, the multivariable analysis revealed the predictive value of serum HDL in accordance with previous reports [34]. In the current study, the

hypercholesterolemia was found in majority of patients and though significant differences regarding lipid profiles were found, only HDL was pointed out to be predictive in the multivariable analysis. Recently, the new, large-scale data were published suggesting inflammatory profile is much more important than lipid profile in patients with stable angina. According to this study, residual inflammatory risk is a stronger determinant risk of future cardiovascular events than residual cholesterol risk [35]. In the analysis of the present group, LDL-cholesterol levels were even slightly, but significantly, higher in the “no disease” population when compared to the “significant coronary artery disease” population. Moreover, the sex differences in clinical scenario of chronic coronary syndrome were postulated [36]. Addiction to smoking is still an epidemiological problem [37].

An association between hematocrit values and anginal symptoms was found, although the results were within the normal range in both groups. The relation between the mentioned parameters and anginal symptoms has been already reported [38], and there was a tendency for variable results in individual patients [39].

Moreover, the relation between serum creatinine concentration and significant coronary disease are presented, consistent with previous reports [40]. However, the glomerular filtration rate results did not confirm this finding.

Limitations of the study

Present results were based on a single center retrospective analysis with a limited group of patients. The monocyte count was estimated by the concentration in peripheral blood, but monocytes' activation was not measured. Patients' drug panel list nor history of previous viral infection episodes was not analyzed. Further, more sophisticated research is required, in larger populations. However, in the contemporary “post-COVID health debt” era, new methods are expected to optimize and shorten the non-invasive algorithms in patients with a clinical likelihood of obstructive CAD.

Finally, the AUC of 0.641 may be considered as relatively low. However, it should be pointed out, that there are still several clinical and laboratory parameters which indicate the significance of CAD. Thus, monocyte count is one of them and not the only one, though observations herein lead to the conclusion that this parameter is substantially considerable.

CONCLUSIONS

The peripheral monocyte count above 0.45 k/uL may be considered as a predictor of significant CAD in symptomatic patients with chronic coronary syndrome.

Conflict of interest: None declared

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Table 1. Demographic and clinical characteristics of the analyzed groups.

	Group 1; No disease (n = 69)	Group 2; Significant coronary disease (n = 118)	P
Demographic:			
Age [years]	68 (63–73)	67 (63–72)	0.444
Sex: male/female	35 (51%)/34 (49%)	96 (81%)/22 (19%)	< 0.001*
BMI	29 (26–35)	28 (25–30)	0.026*
CCS class	2 (0.23)	2 (0.49)	0.073
Clinical:			
Arterial hypertension	54 (78%)	102 (86%)	0.179
Diabetes mellitus	23 (33%)	40 (34%)	0.614
Smoking	27 (39%)	59 (50%)	0.274
COPD	6 (9%)	9 (8%)	0.557
Hypercholesterolemia	54 (78%)	100 (85%)	0.798
PAD	4 (6%)	12 (10%)	0.282
Kidney dysfunction	6 (9%)	18 (15%)	0.054
Atrial fibrillation	5 (7%)	11 (9%)	0.996
Stroke	3 (4%)	7 (6%)	0.189
Family history of CVD	25 (36%)	24 (20%)	0.056
Echocardiography:			
LV [mm]	49 (45–53)	47 (45–54)	0.466
RV [mm]	29 (27–31)	29 (27–31)	0.973
IVs [mm]	11 (10–12)	11 (10–13)	0.091
PWd [mm]	10 (9–11)	11 (10–13)	0.001*
LVEF [%]	60 (55–60)	60 (55–60)	0.647

Continuous variables are expressed as the medians (Q1–Q3) whereas categorical variables are expressed as the numbers (n) with percent (%);* statistically significant. BMI — body mass index; COPD — chronic obstructive pulmonary disease; CVD — cardiovascular disease; IV — interventricular; LV — left ventricular diameter; LVEF — left ventricular ejection fraction; RV — right ventricular diameter

Table 2. Laboratory results in group 1 (normal angiography) vs. group 2 (significant coronary disease).

	Group 1 (n = 69)	Group 2 (n = 118)	P
Whole blood count:			
WBC [K/uL]	6.5 (5.5–7.3)	7.4 (6.1–8.9)	0.004*
Neutrophils [K/uL]	3.9 (3.3–4.6)	4.6 (3.8–5.8)	0.002*
Lymphocytes [K/uL]	1.8 (1.5–2.2)	1.8 (1.5–2.1)	0.851
Monocytes [K/uL]	0.38 (0.30–0.47)	0.46 (0.36–0.54)	< 0.001*
NLR	2.2 (1.7–2.8)	0.31 (0.24–0.44)	0.046*
MLR	0.21 (0.16–2.8)	4.7 (4.5–4.9)	0.001*
SIRI	0.82 (0.63–1.15)	9.3 (8.8–9.7)	< 0.001*
SII	501 (374–616)	43 (43–46)	0.079
Eo [K/uL]	0.14 (0.08–0.23)	13.4 (13–13.8)	0.386

Baso [K/uL]	0.04 (0.03–0.06)	235 (209–256)	0.056
LUC [K/uL]	0.13 (0.11–0.16)	0.14 (0.11–0.17)	0.407
RBC [M/uL]	4.6 (4.4–4.9)	4.7 (4.4–5.0)	0.243
Hemoglobin [mmol/L]	8.9 (8.6–9.4)	9.3 (8.5–9.6)	0.015*
Hematocrit [%]	41 (40–43)	43 (40–45)	0.004*
MCV [K/uL]	90 (88–93)	92 (88–95)	0.029*
MCHC [K/uL]	21.5 (21.1–21.8)	21.3 (20.9–21.7)	0.025*
RDW [fL]	13.4 (13.0–13.9)	13.6 (13.1–14.1)	0.070
Platelets [K/uL]	216 (194–270)	231 (188–265)	0.832
MPV [fL]	8.4 (8.0–9.4)	8.8 (8.0–9.6)	0.095
Lipid profile:			
TC [mmol/L]	4.1 (3.6–4.5)	3.5 (3.3–4.4)	< 0.001*
LDL [mmol/L]	2.5 (1.9–3.8)	2.0 (1.7–2.8)	0.007*
HDL [mmol/L]	1.3 (1.2–1.6)	1.2 (1.0–1.3)	< 0.001*
Triglycerides [mmol/L]	1.3 (1.0–1.7)	1.3 (0.9–1.6)	0.909
Uric acid [umol/L]	351 (284–403)	389 (310–403)	0.339
Kidney function test:			
Creatinine [mmol/L]	80 (70–93)	85 (78–103)	<0.001*
GFR [mL/min]	75 (68–87)	74 (56–90)	0.340
Myocardial injury marker:			
CK-MB [ug/L]	1.88 (1.07–2.73)	1.56 (1.24–2.45)	< 0.001*
Troponin-I [ug/L]	0.004 (0.003–0.005)	0.005 (0.004–0.006)	0.010*
Thyroid:			
TSH [uU/mL]	1.41 (0.92–2.34)	1.21 (1.06–2.17)	0.365

Continuous variables are expressed as the medians (Q1–Q3); *statistically significant; ALT — alanine transaminase; AST — aspartate aminotransferase; CK-MB — creatine phosphokinase myocardial band; GFR — glomerular filtration rate; HDL — high density lipoprotein cholesterol; LDL — low density lipoprotein cholesterol; NLR — neutrophil-to-lymphocyte ratio; MLR — monocyte-to-lymphocyte ratio; MCHC — mean corpuscular hemoglobin concentration; MCV — mean corpuscular volume; RBC — red blood cells; RDW — red cell distribution width; SIRI — systemic inflammatory response index; TC — total cholesterol; TSH — thyroid stimulating hormone; WBC — white blood cells

Table 3. Logistic regression analysis of patients without coronary artery disease vs patients with single coronary artery atherosclerosis.

Parameters	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
Sex	3.24	1.67–6.42	0.001	–	–	–
Age	1.01	0.97–1.05	0.538	–	–	–
BMI	0.94	0.87–1.02	0.240	–	–	–
Clinical:						
HA	1.33	0.58–3.01	0.494	–	–	–
DM	0.73	0.40–1.36	0.321	–	–	–
COPD	0.73	0.26–2.07	0.557	–	–	–
Hypercholesterolemia	2.41	1.17–4.93	0.016	4.38	1.78–	0.001

a	1.88	0.58–6.06	0.003	–	10.80	–
PAD	0.83	0.30–2.29	0.715	–	–	–
AF	0.81	0.25–2.67	0.735	–	–	–
Stroke in history	1.44	0.79–2.63	0.236	–	–	–
Smoking	0.69	0.35–1.39	0.302	–	–	–
Family history	1.16	0.59–2.30	0.338	–	–	–
CCS syndromes					–	
Echocardiographic:						
LV	1.12	0.92–1.03	0.286	–	–	–
RV	1.09	0.92–1.08	0.439	–	–	–
IVs	1.03	0.90–1.16	0.689	–	–	–
PWd	0.98	0.93–5.16	0.378	–	–	–
LVEF	0.98	0.93–1.03	0.331	–	–	–
Morphology:						
WBC	1.11	0.94–1.32	0.225	–	–	–
Neutrophils	1.19	0.96–1.48	0.106	–	–	–
Lymphocytes	0.85	0.52–1.40	0.525	–	–	–
Monocytes	53.2	6.32–653.6	0.002	32.3	1.09–	0.017
NLR	1.17	0.92–1.48	0.193	–	653.6	–
MLR	1.52	1.10–2.11	0.012	–	–	–
SIRI	1.60	1.05–2.44	0.028	–	–	–
SII	1.00	1.00–1.00	0.141	–	–	–
Eo	1.40	0.25–7.97	0.704	–	–	–
LUC	2.76	0.01–1692	0.756	–	–	–
RBC	1.31	0.69–2.47	0.410	–	–	–
Hemoglobin	1.23	0.86–1.77	0.264	–	–	–
Hematocrit	1.09	1.00–1.18	0.033	1.09	–	0.022
MCV	1.02	0.99–1.05	0.185	–	1.01–1.18	–
MCH	0.70	0.08–6.38	0.750	–	–	–
MCHC	0.66	0.39–1.10	0.112	–	–	–
RDW	1.16	0.84–1.59	0.362	–	–	–
Platelets	1.00	1.00–1.00	0.331	–	–	–
					–	
Lipidogram:						
TC	0.84	0.64–1.11	0.216	–	–	–
LDL	0.86	0.65–1.13	0.275	–	–	–
HDL	0.13	0.04–0.42	0.001	0.19	0.05–0.72	0.015
Triglycerides	0.93	0.63–1.38	0.724	–	–	–
Another laboratory:						
Uremic acid	1.00	1.00–1.00	0.468	–	–	–
CK-MB	1.05	1.00–1.11	0.070	–	–	–

Troponin	879	0.00–5.28	0.318	–	–	–
Creatinine	1.03	E10	0.001	1.03	1.00–1.05	0.012
GFR	0.98	1.01–1.05 0.97–1.00	0.127	–	–	–

AF — atrial fibrillation; BMI — body mass index; CI — confidence interval; CCS — Canadian cardiovascular Society; CK-MB — creatine kinase myocardial band; COPD — chronic obstructive pulmonary disease; DM — diabetes mellitus; GFR — glomerular filtration rate; HA — arterial hypertension; HDL — high density lipoprotein cholesterol; IVs — intraventricular septum diameter; LDL — low-density lipoprotein cholesterol; LV — left ventricular diameter; LVEF — left ventricular ejection fraction; MCHC — mean corpuscular hemoglobin concentration; MCV — mean corpuscular volume; MLR — monocyte to lymphocyte ratio; NLR — neutrophil to lymphocyte ratio; OR — odds ratio; PAD — peripheral artery disease; PWd — posterior wall diameter; RBC — red blood cells; RDW — red cells distribution width; RV — right ventricular diameter; SIRI — systemic inflammatory response index; TC — total cholesterol; WBC — white blood count

Monocytes

