ORIGINAL ARTICLE

NEUTROPHIL-LYMPHOCYTE RATIO AND PLATELET-LYMPHOCYTE RATIO AS PREDICTORS OF CORONARY MICROCIRCULATORY DISEASE OCCURRENCE AND OUTCOME IN PATIENTS WITH CHRONIC CORONARY SYNDROME AND NO SIGNIFICANT CORONARY ARTERY STENOSIS

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ABSTRACT

Introduction: Index of microcirculatory resistance assessment is an invasive method of measuring coronary microcirculation function. Association between impaired microcirculatory function and higher rate of cardiovascular events was proven. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio seem to be a promising parameters to predict coronary microcirculatory disease in patients with chronic coronary syndrome.

The aim: To determine neutrophil-lymphocyte ratio and platelet-lymphocyte ratio levels in patients with coronary microcirculatory disease and potential association with clinical outcome.

Material and methods: 82 consecutive patients with mean age of 67 years, 67% male, were tested for presence of coronary microcirculatory disease using index of microcirculatory resistance. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were calculated based on admission full blood count. Follow-up with major adverse cardiac and cardiovascular events registration was performed (median 24 months).

Results: The study showed significantly higher neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in patients with coronary microcirculatory disease compared to control group (3.58±2.61 vs 2.54±1.09 and 164±87.9 vs 124±36.6 respectively). Higher level of platelet-lymphocyte ratio in patients with coronary microcirculatory disease results in worse MACCE-free survival. Optimal cut-off values of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio to detect coronary microcirculatory disease were 3.2 and 181.3, respectively.

Conclusions: Higher neutrophil-lymphocyte ratio and platelet-lymphocyte ratio are associated with increased index of microcirculatory resistance value. Platelet-lymphocyte ratio may be used as a predictor of worse outcome in patients with coronary microcirculatory disease.

KEY WORDS: inflammation, coronary artery disease, functional assessment, microcirculation, index of microcirculatory resistance, coronary microcirculatory disease

ABBREVIATIONS:

CAD – coronary artery disease
CCS – Canadian Cardiovascular Society
CMD – coronary microcirculatory disease
CVD – cardiovascular disease
ETT – exercise treadmill test
PLR – platelet-lymphocyte ratio
NLR – neutrophil-lymphocyte ratio
NA – not applicable
FFR – fractional flow reserve
CFR – coronary flow reserve
IMR – index of microcirculatory resistance
SPECT – single photon emission computed tomography
PCI – percutaneous coronary intervention

CABG – coronary artery bypass grafting
SD – standard deviation
LVEF – left ventricle ejection fraction
LAD – left anterior descending
LCX – left circumflex branch
RCA – right coronary artery
MACCE – major adverse cardiac and cardiovascular event

INTRODUCTION

Cardiovascular diseases are leading cause of morbidity and mortality throughout the world. According to the literature about 30% all deaths worldwide are a result of CVD [1, 2]. Heart ischemic disease is the most common diagnosis in this wide,

heterogenic group [3, 4]. Cardiac ischemic disease may affect both epicardial arteries and coronary microcirculation which consists of small vessels arterioles and capillaries [5]. Dysfunction of coronary microcirculation is associated with increased risk of major adverse cardiovascular events including cardiac death, stroke, and heart failure [6,7]. Chronic inflammation is considered as an important factor in pathophysiology of atherosclerosis [8-10]. Elevated level of inflammatory markers is observed in disease of epicardial arteries [11, 12]. Pathogenesis of coronary microcirculatory dysfunction is still understudied and it remains an interesting clinical issue. Some inflammatory indicators are considered to take a part in coronary microcirculation pathology [12, 13]. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been investigated as new markers for cardiovascular prognosis [14-16]. Elevated levels of both, NLR and PLR ratio were observed in patients with acute coronary syndrome as predictors of worse outcome [17]. Neutrophil-to-lymphocyte ratio measured in patients with chronic coronary syndrome is connected with higher severity of coronary artery disease [18]. To our best knowledge there is no data available on NLR and PLR levels according to coronary microcirculatory dysfunction in chronic coronary syndrome. It was shown that microcirculatory dysfunction is connected with higher risk of the cardiovascular events [5, 6]. The index of microcirculatory resistance (IMR) measurement is an invasive method of coronary microcirculation assessment [19-21].

THE AIM

The aim of our study is to investigate if the levels of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are associated with coronary microcirculation impairment in patients with chronic coronary syndrome.

We hypothesize that:
- levels of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are elevated in patients with

Table 1. Baseline characteristics.

	All patients	CMD (IMR<25)	Control group (IMR<25)	P-value
	N=82	N=30	N=52	
Age, mean (SD) [year]	67.0 (8.74)	69.1 (9.74)	65.8 (7.97)	0.128
Sex male, n (%)	54 (66.7)	20 (69.0)	34 (65.4)	0.935
SBP, mean (SD) [mmHg]	130 (12.5)	131 (11.1)	129 (13.3)	0.656
LVEF, mean (SD) [%]	55.1 (11.2)	53.8 (15.1)	55.9 (8.08)	0.582
Vessel				0.027 *
LAD, n (%)	39 (47.6)	16 (53.3)	23 (44.2)	
LCx, n (%)	27 (32.9)	5 (16.7)	22 (42.3)	
RCA, n (%)	16 (19.5)	9 (30.0)	7 (13.5)	
Diabetes, n (%)	29 (35.4)	9 (30.0)	20 (38.5)	0.595
Arterial hypertension, n (%)	79 (96.3)	30 (100)	49 (94.2)	0.295
Smoking, n (%)	12 (16.2)	5 (18.5)	7 (14.9)	0.749
Medications:				
ASA, n (%)	73 (89.0)	24 (80.0)	49 (94.2)	0.068
B-blocker, n (%)	65 (79.3)	23 (76.7)	42 (80.8)	0.874
ACEI/ARB, n (%)	72 (88.9)	25 (86.2)	47 (90.4)	0.715
Dihydropyridine calcium blocker, n (%)	26 (31.7)	14 (46.7)	12 (23.1)	0.049 *
Loop diuretics, n (%)	11 (13.6)	6 (20.7)	5 (9.62)	0.189
Statin, n (%)	82 (100)	30 (100)	52 (100)	NA

SBP – systolic blood pressure; LVEF – left ventricle ejection fraction; LAD – left anterior descending artery; LCx – left circumflex artery; RCA – right coronary artery; ASA – acetylsalicylic acid; b-bloker – beta-adrenolitic drug; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensyn receptor blocker; * statistical significance (p<0,05)

Table 2. Coronary physiology assessment.

	All patients	CMD (IMR≥25)	Control group (IMR<25)	P-value
	N=82	N=30	N=52	
FFR, mean (SD)	0.88 (0.05)	0.87 (0.05)	0.88 (0.05)	0.281
CFR, mean (SD)	2.22 (1.13)	1.82 (0.78)	2.47 (1.25)	0.007 *
IMR, mean (SD)	24.8 (15.4)	39.3 (15.8)	16.0 (5.05)	<0.001*

FFR – fractional flow reserve; CFR – coronary flow reserve; IMR – index of microcirculatory resistance; * statistical significance (p<0,05)

Table 3. Laboratory results

	All patients	CMD (IMR≥25)	Control group (IMR<25)	P-value
	N=82	N=30	N=52	
NLR, mean (SD)	2.92 (1.86)	3.58 (2.61)	2.54 (1.09)	0.045 *
PLR, mean (SD)	139 (63.1)	164 (87.9)	124 (36.6)	0.023 *
RBC, mean (SD) [*10^6/uL]	4.70 (0.40)	4.70 (0.43)	4.70 (0.38)	0.974
HGB, mean (SD) [g/dL]	14.2 (1.42)	14.1 (1.56)	14.2 (1.36)	0.841
WBC, mean (SD) [*10^6/uL]	7.01 (1.58)	6.84 (1.42)	7.11 (1.67)	0.439
PLT, mean (SD) [*10^6/uL]	222 (50.3)	224 (63.0)	221 (41.8)	0.834
Creatinine, mean (SD) [umol/L]	83.5 (18.9)	88.7 (23.7)	80.6 (15.0)	0.099
Glucose, mean (SD) [mmol/L]	6.50 (1.85)	6.50 (1.77)	6.50 (1.92)	0.994
HbA1c, mean (SD) [%]	6.03 (0.93)	5.69 (0.40)	6.20 (1.08)	0.031 *
LDL, mean (SD) [mmol/L]	2.77 (1.20)	2.84 (1.29)	2.73 (1.16)	0.697
HDL, mean (SD) [mmol/L]	1.33 (0.34)	1.33 (0.34)	1.33 (0.35)	0.999
Total cholesterol, mean (SD) [mmol/L]	4.38 (1.31)	4.51 (1.32)	4.31 (1.31)	0.493
TG, mean (SD) [mmol/L]	1.54 (0.85)	1.53 (0.98)	1.55 (0.77)	0.934

LDL – low density lipoprotein; HDL – high density lipoprotein; TG – triglycerides; NLR – neutrophil-lymphocyte ratio; PLR – platelet-lymphocyte ratio; CMD coronary microcirculatory disease; IMR – index of microcirculatory resistance; RBC – red blood count; HGB – haemoglobin; WBC – white blood count; PLT – platelets; HbA1c – glycated haemoglobin;
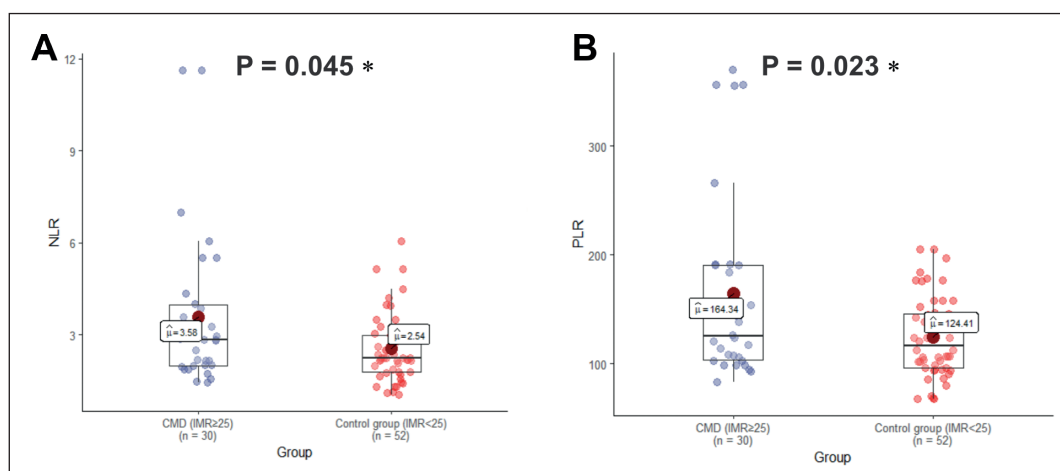* statistical significance (p<0,05)

Fig. 1. Comparison of neutrophile-lymphocyte ratio (NLR) (A) and platelet-lymphocyte (PLR) (B) value in CMD and control group. NLR – neutrophil-lymphocyte ratio; PLR – platelet-lymphocyte ratio; CMD coronary microcirculatory disease; IMR – index of microcirculatory resistance; • statistical significance (p<0,05)
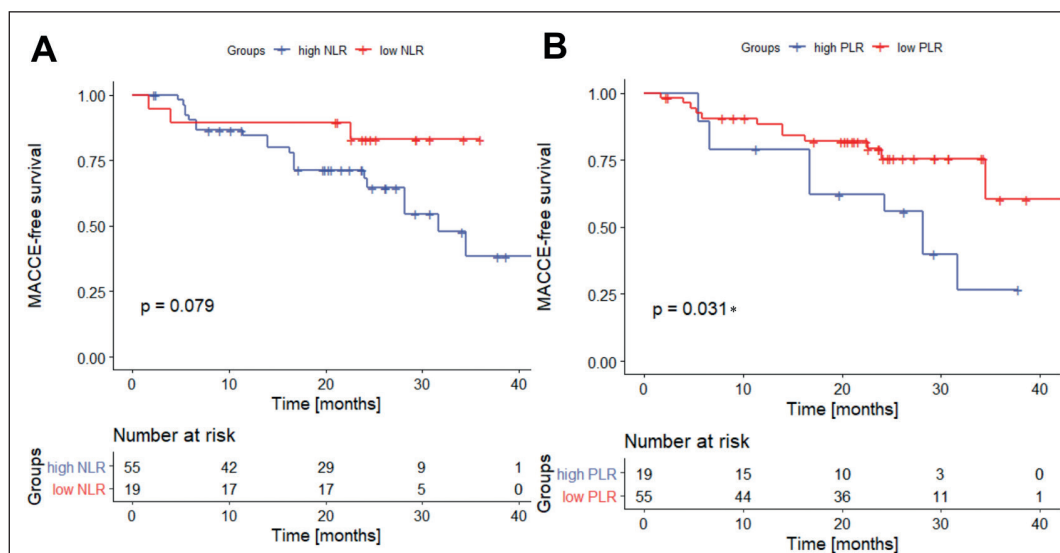

Fig. 2. MACCE free survival in patients with CMD and low/high NLR (A) and PLR (B) levels (Kaplan-Meier estimator). PLR – platelet-lymphocyte ratio; NLR – neutrophil-lymphocyte ratio; * statistical significance (p<0,05)
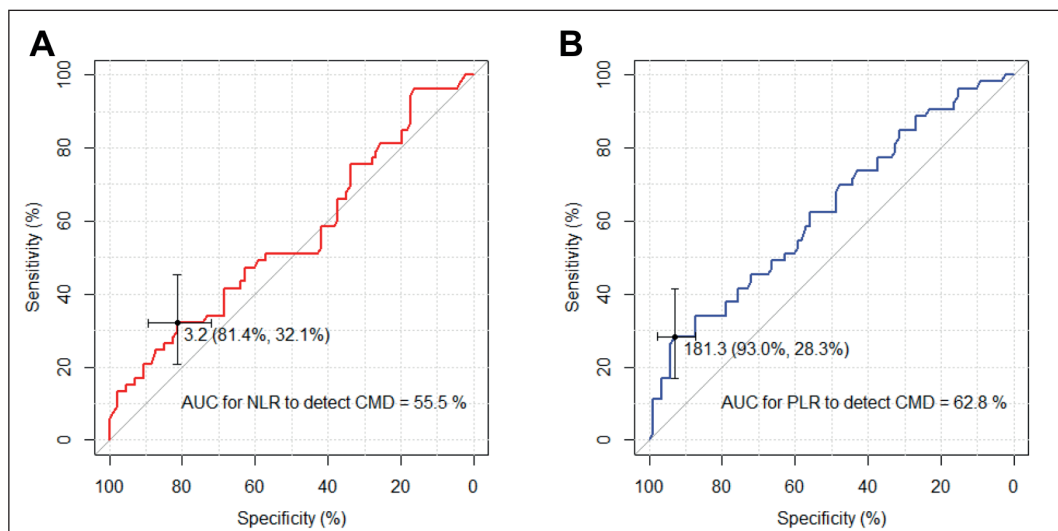
Fig. 3. ROC curves for NLR (A) and PLR (B) to detect CMD. ROC – receiver operating characterisrtic; PLR – platelet-lymphocyte ratio; NLR – neutrophil-lymphocyte ratio; CMD coronary microcirculatory disease.

chronic coronary syndrome and coronary microcirculatory impairment compared to patients with chronic coronary syndrome and normal microcirculatory function - patients with higher level of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have worse survival probability compared to patients with lower NLR and PLR level in group of coronary microcirculatory disease

MATERIAL AND METHODS

This was a prospective study. We enrolled 82 consecutive, adult patients admitted to The Department of Interventional Cardiology in The John Paul II Hospital, Cracow, Poland. Patients had symptoms of stable angina, grade I – III according to the Canadian Cardiovascular Scale (CCS). Evidence of ischemia was proved with non invasive stress tests: exercise treadmill test (ETT), stress echocardiography or single photon emission computed tomography (SPECT). We excluded patients with diagnosed malignant neoplasm, history of prior percutaneous coronary angioplasty or coronary artery bypass grafting, history of chronic inflammatory disease, infectious disease or active bleeding, expected survival less then 1 year.

Vital sings such as arterial blood pressure, heart rate were collected. Risk factors including arterial hypertension, diabetes, smoking were recorded. We gathered information about current medical treatment. Blood samples (2 ml) were taken to test-tubes with EDTA (full blood count measurement) and test-tubes with no anticoagulant (chemistry tests). Peripheral full blood count was analyzed Coulter optical measurement system (Beckman Coulter, United States). Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were counted. In cardiac ultrasound (Philips XC50, Holland) left ventricle ejection fraction was measured with Simpson's biplane method.

The patients were screened for presence of intermediate stenosis of epicardial arteries. We considered coronary artery stenosis of 50-90% as a borderline lesion [22]. If present, we performed full coronary physiology assessment using Pressure Wire X (Abbott Vascular, Santa Clara, California, US) connected to computer by Wi-Fi. Measurements of mean transit time were initially made in resting conditions. Than we induced maximal hyperemia with continuous intravenous infusion of adenosine (140 ug/kg/min) and repeated transit mean time registration. FFR was calculated as a ratio between blood pressure in distal part of examined coronary artery and blood pressure in aorta at maximal hyperemia. Result of ratio between resting and hyperemic transit mean time was CFR. IMR value was calculated by multiplying mean transit time of room temperature saline through coronary artery and distal coronary artery pressure. All measurements registered during procedure were automatically sent to Coroflow software (Coroventis AB, Uppsala, Sweden) which performed calculations of fractional flow reserve (FFR), coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) [23]. Patients with positive result of fractional flow reserve (FFR 0.8) underwent coronary revascularization and were excluded from this study. If more than one vessel was examined in one patient, results from all vessels were analyzed. The study protocol received positive opinion from Jagiellonian University Ethical Committee (nr 122.6120.262.2015).

FOLLOW-UP

Clinical follow was made at 24 months. Major adverse cardiac and cardiovascular event (MACCE) as a primary composite end point was assessed, which was defined as myocardial infarction, percutaneous coronary angioplasty, stroke, all cause-death.

STATISTICAL METHODS

Statistical analysis was performed using IBM SPSS Statistics (version 25) and R language (R-Studio, version 8.9) packages for Windows. Categorical data were described as percentages, while continuous data were described as mean (± SD). Normal distribution was tested by Kolmogorov-Smirnov test. Categorical variables were compared using chi-squared test. Continuous

Table 4. Logistic regression models.

	NLR			PLR		
Predictors	Odds Ratios	CI	p	Odds Ratios	CI	p
(Intercept)	0.16	0.03 – 0.78	0.023 *	0.05	0.01 – 0.48	0.010 *
NLR increase of 1 unit	1.50	1.05 – 2.13	0.026 *			
Present smoker	1.54	0.35 – 6.70	0.563	2.07	0.47 – 9.12	0.338
Diabetes	0.84	0.27 – 2.59	0.762	0.84	0.27 – 2.57	0.756
Male sex	1.03	0.32 – 3.35	0.959	1.57	0.47 – 5.26	0.461
PLR increase of 10 units				1.16	1.03 – 1.31	**0.016 ***

NLR – neutrophil-lymphocyte ratio; PLR – platelet-lymphocyte ratio;
* statistical significance (p<0,05)

Table 5. Supplementary table. Baseline characteristics.

	All patients	IMR- CFR-	IMR- CFR+	IMR+ CFR-	IMR+ CFR +	P-value
	N=76	N=32	N=15	N=7	N=22	
Age, mean (SD) [year]	67.4 (8.65)	66.6 (8.06)	66.6 (7.76)	67.6 (9.57)	69.1 (10.0)	0.738
Sex male, n (%)	49 (65.3)	16 (50.0)	13 (86.7)	6 (85.7)	14 (66.7)	0.055
SBP, mean (SD) [mmHg]	130 (12.1)	128 (12.9)	134 (13.1)	132 (10.5)	131 (10.8)	0.500
LVEF, mean (SD) [%]	54.8 (11.5)	55.8 (8.05)	54.8 (9.74)	60.0 (15.4)	51.6 (14.9)	0.540
Vessel:						0.023
LAD, n (%)	36 (47.4)	17 (53.1)	5 (33.3)	5 (71.4)	9 (40.9)	
LCx, n (%)	24 (31.6)	10 (31.2)	9 (60.0)	0 (0.00)	5 (22.7)	
RCA, n (%)	15 (19.7)	5 (15.6)	1 (6.67)	1 (14.3)	8 (36.4)	
Diabetes, n (%)	27 (35.5)	11 (34.4)	8 (53.3)	2 (28.6)	6 (27.3)	0.419
Arterial hypertension, n (%)	74 (97.4)	30 (93.8)	15 (100)	7 (100)	22 (100)	0.753
Smoking, n (%)	12 (17.1)	4 (13.3)	3 (21.4)	1 (14.3)	4 (21.1)	0.899
Medications:						
ASA, n (%)	68 (89.5)	29 (90.6)	15 (100)	6 (85.7)	18 (81.8)	0.311
B-blocker, n (%)	61 (80.3)	28 (87.5)	11 (73.3)	5 (71.4)	17 (77.3)	0.521
ACEI/ARB, n (%)	66 (88.0)	28 (87.5)	14 (93.3)	5 (71.4)	19 (90.5)	0.515
Dihydropyridine calcium blocker, n (%)	26 (34.2)	9 (28.1)	3 (20.0)	2 (28.6)	12 (54.5)	0.126
Loop diuretics, n (%)	10 (13.3)	3 (9.38)	2 (13.3)	1 (14.3)	4 (19.0)	0.769
Statin, n (%)	76 (100)	32 (100)	15 (100)	7 (100)	22 (100)	NA

SBP – systolic blood pressure; LVEF – left ventricle ejection fraction; LAD – left anterior descending artery; LCx – left circumflex artery; RCA – right coronary artery; ASA – acetylsalicylic acid; b-bloker – beta-adrenolitic drug; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensyn receptor blocker; * statistical significance (p<0,05)

Table 6. Supplementary table. Coronary physiology assessment.

	All patients	IMR- CFR-	IMR- CFR+	IMR+ CFR-	IMR+ CFR +	P-value
	N=76	N=32	N=15	N=7	N=22	
FFR, mean (SD)	0.88 (0.05)	0.89 (0.05)	0.88 (0.05)	0.86 (0.04)	0.87 (0.05)	0.474
CFR, mean (SD)	2.22 (1.13)	3.02 (1.14)	1.30 (0.28)	2.99 (0.55)	1.45 (0.36)	<0.001*
IMR, mean (SD)	25.1 (15.4)	16.2 (4.95)	16.3 (5.07)	31.5 (2.99)	41.9 (17.5)	<0.001*

FFR – fractional flow reserve; CFR – coronary flow reserve; IMR – index of microcirculatory resistance; * statistical significance (p<0,05)

variables were compared by Mann-Whitney or t-student tests. The optimal cut off point for multiple continuous variables was determined using the maximally selected rank statistics from the 'maxstat' R package. Survival probability was evaluated using Kaplan-Meier survival estimators. A value of P < 0.05 was established as statistical significant. Logistic mixed effects regression models were built, using NLR, PLR and common atherosclerosis risk factors (i.e. diabetes, smoking status, sex)

Table 7. Supplementary table. Laboratory results.

	All patients	IMR- CFR-	IMR- CFR+	IMR+ CFR-	IMR+ CFR +	P-value
	N=76	N=32	N=15	N=7	N=22	
NLR, mean (SD)	2.28	2.34	2.14	2.02	2.82	0.220
PLR, mean (SD)	119	112	107	117	132	0.161
RBC, mean (SD) [*10^6/uL]	4.69 (0.39)	4.64 (0.41)	4.74 (0.29)	4.52 (0.46)	4.78 (0.40)	0.352
HGB, mean (SD) [d/dL]	14.2 (1.44)	14.0 (1.47)	14.4 (1.19)	13.9 (1.20)	14.3 (1.64)	0.704
WBC, mean (SD) [*10^6/uL]	6.95 (1.60)	7.31 (1.85)	6.34 (1.16)	6.98 (1.27)	6.83 (1.51)	0.273
PLT, mean (SD) [*10^6/uL]	222 (51.0)	224 (42.1)	214 (42.9)	222 (56.9)	226 (66.7)	0.907
Creatinine, mean (SD) [umol/L]	83.9 (19.4)	82.4 (16.7)	78.4 (12.9)	86.9 (11.2)	88.8 (27.1)	0.407
Glucose, mean (SD) [mmol/l]	6.58 (1.89)	6.39 (1.89)	7.21 (2.08)	6.63 (1.51)	6.43 (1.90)	0.578
HbA1c, mean (SD) [%]	6.06 (0.95)	6.27 (0.91)	6.25 (1.41)	5.77 (0.42)	5.65 (0.42)	0.316
LDL, mean (SD) [mmol/L]	2.72 (1.19)	2.75 (1.28)	2.47 (0.69)	2.17 (0.83)	3.02 (1.38)	0.307
HDL, mean (SD) [mmol/L]	1.31 (0.32)	1.28 (0.32)	1.31 (0.30)	1.26 (0.37)	1.36 (0.34)	0.841
Tchol, mean (SD) [mmol/L]	4.32 (1.27)	4.27 (1.39)	4.06 (0.78)	3.77 (0.94)	4.73 (1.39)	0.234
TG, mean (SD) [mmol/L]	1.57 (0.87)	1.68 (0.82)	1.41 (0.72)	1.43 (0.37)	1.58 (1.13)	0.766

LDL – low density lipoprotein; HDL – high density lipoprotein; TG – triglycerides; NLR – neutrophil-lymphocyte ratio; PLR – platelet-lymphocyte ratio; CMD coronary microcirculatory disease; IMR – index of microcirculatory resistance; RBC – red blood count; HGB – haemoglobin; WBC – white blood count; PLT – platelets; HbA1c – glycated haemoglobin;
* statistical significance (p<0,05)

Table 8. Supplementary table. Follow-up endpoints.

	All patients	CMD (IMR<U+2265>25)	Control group (IMR<25)	p-value
	N=80	N=30	N=50	
Hospitalization, n (%)	25 (31.2)	8 (26.7)	17 (34.0)	0.663
CVD hospitalization, n (%)	19 (23.8)	5 (16.7)	14 (28.0)	0.378
AMI, n (%)	6 (8.45)	2 (6.90)	4 (9.52)	1.000
TVR, n (%)	6 (10.3)	2 (8.33)	4 (11.8)	1.000
MACCE, n (%)	24 (30.0)	8 (26.7)	16 (32.0)	0.801

CVD hospitalization - cardiovascular disease hospitalization; AMI - acute myocardial infarction; TVR - target vessel revascularization; MACCE - major adverse cardiac and cardiovascular event

as fixed factors and type of tested vessel as random factor. This approach was used as flow in coronary arteries varies according to type of vessel (i.e. right vs left coronary artery) and the area of myocardium supplied by particular vessel [24].

RESULTS

The study population consists of 82 consecutive patients who underwent elective coronary angiography in chronic coronary syndrome and did not meet exclusion criteria. Whole population was divided into 2 groups according to result of the index of microcirculatory resistance. Patients included to group of normal coronary microcirculatory function (control group, 52 objects) had IMR < 25. Patients in coronary microcirculatory dysfunction group (CMD group, 30 objects) had IMR ≥ 25. Baseline characteristics was shown in table 1. Age distribution in both groups was similar (69.1 ± 9.74 vs 65.8 ± 7.97 years). Number of male patients did not differ in both groups (69% vs 65%). There was no significant difference in systolic blood pressure

(131 ± 11.1mmHg vs 129 ± 13.3mmHg) and left ventricle ejection fraction (53.8 ± 15.1% vs 55.9 ± 8%) between both groups. 52 main coronary vessels in control group and 30 vessels in CMD group were assessed, while the left anterior descending artery was the most often examined vessel. Both groups did not differ significantly in risk factors of coronary artery disease and taken medications despite dihydropyridine calcium channel blockers which were used more often in CMD group (46.7% vs 23.1%) (Table 1).

Fractional flow reserve (FFR) result was similar in both groups (0.87±0.05 vs 0.88±0.05). Coronary flow reserve (CFR) was significantly higher in control group compared to CMD group (2.47 ± 1.25 vs 1.82 ± 0.78; P = 0.007). The result of index of microcirculatory resistance was criterion of groups distinction as we mentioned previously and it was significantly higher in CMD group (39.3 ± 15.8 vs 16.0 ± 5.05; P<0.001) (Table 2).

Level of serum low-density-lipoprotein (LDL) was lower in control group (2.84 ± 1.29 vs 2.73 ± 1.16 mmol/l) however difference was not statistically significant (P > 0.05). The results of neutrophil-lymphocyte ratio (NLR) and

platelet-lymphocyte ratio (PLR) were significantly higher in CMD group (respectively 3.58 ± 2.61 vs 2.54 ± 1.09; P = 0.045 for NLR and 164 ± 87.9 vs 124 ± 36.6; P = 0.023 for PLR) (Table 3, Fig. 1).

Median length of follow-up in whole studied population was 24 months, 22.9 months in CMD group and 24.6 months in control group.

Based on mixed effects logistic regression the increased NLR or PLR values were associated with increased probability od microcirculatory dysfunction, with OR 1.5 (95% CI: 1.05 – 2.13; P < 0.05) and 1.16 (95% CI 1.03 – 1.31; P < 0.05), respectively (Table 4) [25].

Kaplan-Meier estimation showed that MACCE-free survival in patient with high PLR level is worse compared to patients with low PLR level in group of coronary microcirculatory disease (P = 0.031) (Fig. 2A). There is no significant difference in MACCE-free survival between patients with high and low level of NLR in group of coronary microcirculatory disease (P = 0.079), however trend is visible (Fig. 2B).

Study population was divided into 4 groups based on IMR and CFR normal and abnormal results: IMR-CFR-, IMR-CFR+, IMR+CFR-, IMR+CFR+. No significant differences between those groups was founded (Table 5-7.)

Area under curve (AUC) for NLR to detect coronary microcirculatory disease is 55.5% with cut-off 3.2 and specificity of 81.4% (Fig. 3A).

Similarly AUC for PLR to detect coronary microcirculatory disease is 62.8% with cut-off 181.3 and specificity of 93% (Fig. 3B).

DISCUSSION

Epicardial coronary arteries visible in angiography are just about 1% of whole coronary circulation. Nearly 99% is coronary microcirculation which is not visible in standard angiography, as it consists of vessels with lumen diameter less than 500μm [5]. Epicardial coronary disease as well as disease of coronary microcirculation may be a cause of angina symptoms and a relevant impact on adverse cardiovascular events including cardiac death, stroke, and heart failure [5, 6]. Prevalence of coronary microcirculatory disease (CMD) is estimated in literature for up to 40% in patients with suspected coronary artery disease [26]. Guidelines of The European Society of Cardiology for chronic coronary syndrome recommend functional assessment in patients with intermediate coronary artery stenosis (50-90%) [22]. In case of insignificant fractional flow reserve result (i.e. FFR > 0.8), coronary flow reserve and index of microcirculatory resistance should be measured [22]. Abnormal CFR and IMR results are a basis for diagnosis of coronary microcirculatory disease [20, 21, 27]. Management of CMD differs from treatment of typical epicardial coronary artery disease [22]. In CMD treatment more emphasis is put on vasodilator medications such as calcium channel blockers and long acting nitrates [27, 28]. On the other hand specific treatment for CMD is still underdeveloped and this topic requires further investigation. According to CORMICA trial detailed diagnostics in patient with coronary artery disease led to better treatment results, as in that study an invasive diagnostics in patients with chronic coronary syndrome did not stop on coronary angiography only. Patients have also undergone complex functional assessment of coronary circulation including provocative test with acetylcholine to detect artery overreactivity. Using this approach coronary microvascular angina or vasospastic angina were diagnosed and appropriate medications were advised. As a result significant reduction of angina symptoms, increase of exertion tolerance and improvement of quality of life were observed as compared with control group, in which only coronary angiography was performed [29].

In our study we propose evaluation of novel inflammatory markers, the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) as a tool useful in process of qualification of patients with coronary artery disease to complex invasive diagnostics of coronary circulation. NLR and PLR have good specificity to exclude coronary microcirculatory disease, however sensitivity to detect CMD remains low. Even though, utilization of those parameters might help clinicians to select a group of patients with indications for complex coronary circulation assessment, functional examination and provocative testing.

Further investigation is needed to explore possible correlation between NLR and PLR with other, more specific inflammatory markers assessed in patients with coronary microvascular disease.

STUDY LIMITATIONS

This is single-centre study, whole population was enrolled in one cardiology department. We make an effort so as patients were referred to our department by different physicians. Despite patients were diagnosed and treated by few separate teams, whole group followed the same protocol described in methodology chapter. The population finally included and analyzed was not large. We considered different clinical situations and diseases that may affect result of full blood count. Possible fluctuations of lymphocyte and neutrophil counts may be result of asymptomatic infections. Numerous disorders might be a reason for thrombocytopenia. Decreased thrombocyte production, i.e. ferrum/folic acid/ vitamin B12 deficiency, bone marrow diseases, congenital thrombocytopenia or increased thrombocyte destruction, i.e. hemolysis and side effects of medications. Active bleeding, alcohol addiction, chronic inflammatory diseases may result in thrombocytosis. Every patient with diagnosis that may affect result of white count or platelet count was excluded from this study. In our study correlation between PLR, NLR and other more specific inflammatory indicators was not tested.

CONCLUSIONS

In this study we observed higher level of inflammatory markers: neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in patients with chronic coronary syndrome and elevated index of microcirculatory resistance, as com-

pared to patients with normal IMR. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) might be concerned as predictors of coronary microcirculatory disease in chronic coronary syndrome and no significant epicardial stenosis. Assessment of NLR and PLR may be used to select patients who particularly demands complex coronary functional examination during invasive diagnostics.

What is more, higher levels of NLR and PLR are associated with worse MACCE-free survival in this group. Further investigation is needed in aim to compare neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) with other, more specific inflammatory markers of CMD.

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Conflict of interest

Authors declare no conflict of interest.

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