








Predictive value of systemic inflammatory response index (SIRI) for complex coronary artery disease occurrence in patients presenting with angina equivalent symptoms

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Abstract

Background: *Currently, atherosclerotic cardiovascular disease is the major cause of mortality worldwide. Inflammatory processes are postulated to be a major driving force for coronary plaque initiation and progression and can be evaluated by simple inflammatory markers from whole blood count analysis. Among hematological indexes, systemic inflammatory response index (SIRI) is defined as a quotient of neutrophils and monocytes, divided by lymphocyte count. The aim of the present retrospective analysis was to present the predictive role of SIRI for coronary artery disease (CAD) occurrence.*

Methods: *There were 256 patients (174 [68%] men and 82 [32%] women) in the median (Q1–Q3) age of 67 (58–72) years enrolled into retrospective analysis due to angina pectoris equivalent symptoms. A model for predicting CAD was created based on demographic data and blood cell parameters reflecting an inflammatory response.*

Results: *In patients with single/complex coronary disease the logistic regression multivariable analysis revealed predictive value of male gender (odds ratio [OR]: 3.98, 95% confidence interval [CI]: 1.38–11.42, $p = 0.010$), age (OR: 5.57, 95% CI: 0.83–0.98, $p = 0.001$), body mass index (OR: 0.89, 95% CI: 0.81–0.98, $p = 0.012$), and smoking (OR: 3.66, 95% CI: 1.71–18.22, $p = 0.004$). Among laboratory parameters, SIRI (OR: 5.52, 95% CI: 1.89–16.15, $p = 0.029$) and red blood cell distribution width (OR: 3.66, 95% CI: 1.67–8.04, $p = 0.001$) were found significant.*

Conclusions: *Systemic inflammatory response index, a simple hematological index, may be helpful in patients with angina equivalent symptoms to diagnose CAD. Patients presenting with SIRI above 1.22 (area under the curve: 0.725, $p < 0.001$) have a higher probability of single and complex coronary disease. (Cardiol J)*

Key words: coronary artery disease, systemic inflammatory response index (SIRI), angiography

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Introduction

Inflammatory processes are postulated to be a major driving force for coronary plaque initiation and progression [1]. Those occurring within the arterial wall or systemic circulation, driven by modified lipoproteins, have been recognized as the hallmark of the of atherosclerotic disease and its clinical complications [2]. Lately, uprising interest has been noted in novel biomarkers which may predict adverse outcomes in patients with coronary artery disease (CAD) related to the family of inflammatory markers [3] and the possibility of their modification. Systemic inflammatory modification may influence cardiovascular morbidity and mortality according to the results of lipid-lowering and anti-inflammatory [4] therapy trials.

The hematological indices obtained from whole blood count analysis were proven to be easily accessible and reliable prognosis predictors in patients with CAD [5]. Blood monocyte count was related to CAD severity in Arnold et al. [6] analysis. The existence of pro-inflammatory monocytes population as a reflection of more advanced atherosclerotic disease was shown in the SMARTool substudy [7].

Systemic inflammatory response index (SIRI) is one of the easily accessible markers representing the monocytes, neutrophils and lymphocytes count as three distinctive types of cells involved in inflammatory processes and atherosclerosis progression and was presented as an independent major long-term outcome risk factor [8, 9].

The interventional therapy for CAD includes percutaneous and/or surgical revascularization. Currently, surgical revascularization is performed with or without the use of cardiopulmonary bypass. Although still of limited application worldwide [10], the surgical off-pump technique (off-pump coronary artery bypass grafting [OPCAB]) presents low perioperative morbidity and mortality rate [11], with less advanced inflammatory burden compared with the on-pump method.

Clinical symptoms of stable CAD vary from classical chest pain on exertion to fatigue and dyspnea. Evaluation of patients with less typical characteristics is often challenging since symptoms may be subjective and individually dependent. An indication of some objective parameters, which would enable more precise diagnostics, would be beneficial. The aim of the retrospective analysis was to analyze the role of SIRI as a predictor of CAD in patients suffering from angina pectoris equivalent symptoms.

Methods

Patient selection

Three hundred and twenty-two patients were admitted to two departments, cardiological and cardiosurgical, between January and October 2022. From these, 256 patients (174 [68%] men and 82 [32%] women) in the median (Q1–Q3) age of 67 (58–72) years were enrolled in this retrospective analysis. Patients with acute coronary syndromes ($n = 25$) and those with co-existing hematological diseases, rheumatic diseases, and oncological history ($n = 41$) were excluded from the study. A flow chart of the study population is presented in Figure 1.

Patients were hospitalized in the cardiological department and underwent non-invasive and invasive diagnostics of suspected CAD based on symptoms including shortness of breath and fatigue on exertion combined with chest discomfort. Only patients without previous coronary artery computed tomography (CT) were included in the analysis. Patients admitted for surgical intervention had previously been diagnosed with one, two or three vessel disease and underwent revascularization with the OPCAB method. Basic characteristics data were obtained at admission. Blood samples were collected at admission after at least 6 hours of fasting before coronary angiography or cardiac surgery and were analyzed utilizing a routine hematology analyzer (Sysmex Europe GmbH, Norderstedt, Germany). The blood element counts were assessed for calculation of the hematological indices, including neutrophil to lymphocyte ratio (NLR) and SIRI, a quotient of neutrophils and monocytes, divided by lymphocyte count.

A thorough analysis of coronary angiography revealed patients without coronary lesions ($n = 61$) and with various severity of CAD ($n = 132$). Those with previously performed percutaneous intervention, without stent restenosis, were excluded from the analysis. Group 1 consisted of patients without any significant coronary lesions ($n = 61$), group 2 — patients with single vessel CAD ($n = 51$) and group 3 — patients with complex two or three vessel CAD ($n = 81$). Demographic and clinical characteristics of the analyzed groups are presented in Table 1.

A total number of 86 patients were referred for surgical revascularization due to complex chronic CAD. The procedures were performed through median sternotomy with the OPCAB technique. The median (Q1–Q3) number of performed anas-

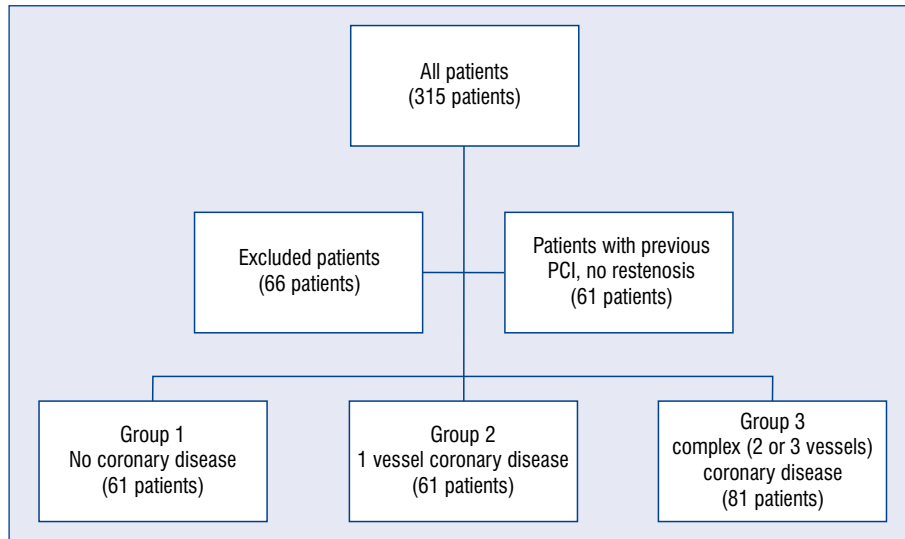


Figure 1. Flow chart of included patients into analysis; PCI — percutaneous coronary intervention.

Table 1. Demographic and clinical characteristics of analyzed groups.

	Group 1 (n = 63)	Group 2 (n = 51)	Group 3 (n = 81)
Demographics:			
Age [years]	70 (63–74)	64 (54–72)	67 (64–72)
Sex (male/female)	33 (52%)/30 (48%)	20 (39%)/31 (61%)	9 (22%)/72 (78%)
Weight [kg]	85 (74–97)	85 (78–92)	85 (69–89)
Height [cm]	164 (159–171)	176 (173–182)	175 (164–176)
BMI	31 (26–35)	28 (25–29)	28 (24–30)
Clinical:			
Arterial hypertension	51 (81%)	37 (73%)	69 (85%)
Diabetes mellitus	22 (34%)	14 (28%)	29 (36%)
COPD	6 (10%)	9 (8%)	5 (6%)
Hypercholesterolemia	49 (78%)	41 (81%)	59 (73%)
PAD	4 (6%)	4 (8%)	6 (8%)
Kidney dysfunction	6 (10%)	5 (10%)	10 (12%)
Atrial fibrillation	3 (5%)	4 (8%)	7 (9%)
Stroke	3 (5%)	4 (8%)	7 (9%)
Family CVD history	25 (41%)	(20%)	6 (10%)
Nicotine:			
Current smoker	8 (13%)	9 (18%)	10 (16%)
Smoking in history	13 (21%)	13 (26%)	25 (40%)
Echocardiography:			
LV [mm]	48 (44–52)	49 (47–56)	46 (42–52)
RV [mm]	29 (27–31)	30 (27–31)	29 (27–32)
LA [mm]	38 (33–43)	42 (38–42)	38 (34–42)
IVS [mm]	11 (10–12)	10 (10–12)	12 (11–14)
LVEF [%]	60 (55–60)	55 (55–65)	60 (55–60)

Data are shown as number (%) and median (Q1–Q3). BMI — body mass index; COPD — chronic obstructive pulmonary disease; CVD — cardiovascular disease; IVS — intraventricular septum; LA — left atrium diameter; LV — left ventricular diameter; LVEF — left ventricular ejection fraction; PAD — peripheral artery disease; RV — right ventricular diameter

tomosis was 2.3 (2.0–2.6) with no perioperative mortality and with uneventful hospitalizations. Among cardiac department group, 51 patients underwent percutaneous intervention including stent implantation into the left descending artery (n = 33 [64%]) circumflex artery (n = 5 [10%]) and right coronary artery (n = 13 [26%]).

Statistical analysis

Since data did not follow normal distribution (the Shapiro-Wilk test), the parameters were presented as medians and interquartile ranges (Q1–Q3). The comparison of parameters between subgroups 1, 2 and 3 was performed with the Skilling-Mack test with the post-hoc Dunn's test. Additionally, patients without CAD were compared to patients with CAD (1 vs. 2+3) (the Mann-Whitney test). A logistic regression analysis was used to reveal predictors of CAD. The analysis was performed twice, as a single logistic regression model, and then as multiple logistic regression. The multiple logistic models were assessed via backward stepwise selection procedure. The results are presented as odds ratio (OR) and its 95% confidence intervals (95% CI). The receiver operating characteristic (ROC) analysis was performed in order to find an optimal cut-off point for continuous predictors. The parameter was considered to have prognostic properties if the area under the ROC curve (AUC) significantly differed from 0.5. The optimal cut-off point was determined by the Youden index (optimal cut-off point = max [sensitivity + specificity - 1]). Statistical analysis was performed with the use of statistical package STATA 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.). All tests were considered significant at $p < 0.05$.

Results

Laboratory tests

The laboratory results including whole blood count analysis, lipid profiles, liver, and kidney function biomarkers were followed by myocardial injury markers and thyroid-stimulating hormone were compared between the subgroups (Table 2).

Significantly higher counts of inflammatory cells were found, including leucocytes, neutrophils, monocytes in more severe stages of CAD (Table 2). Similarly, the monocyte to high density lipoprotein cholesterol ratio was higher in the subgroups 2 and 3 compared to subgroup 1. Moreover, red blood cell count, and red blood cell distribution width (RDW) differed between patients with coronary and without coronary lesions.

In the kidney function analysis, despite significant serum creatinine concentration between subgroups 1 vs. 2 ($p = 0.045$) and 1 vs. 3 ($p = 0.004$), the glomerular filtration rate results were insignificant.

Significant differences between troponin levels were noted between groups 1 vs. 3 ($p = 0.013$), however criteria for acute coronary syndrome were not met (exclusion criterium).

Logistic regression

Logistic regression analysis was performed for the evaluation of study subgroups, initially for analysis of patients without coronary artery involvement and those with one-vessel disease (Table 3) and was followed by the evaluation of patients without coronary artery involvement and surgically treated two- and three-vessels disease (Table 4).

The logistic regression analysis performed in patients presenting with one vessel CAD vs. no coronary disease, revealed predictive properties of demographic and clinical characteristics including male gender (OR: 3.67, 95% CI: 1.63–8.27, $p = 0.002$) and history of smoking (OR: 2.71, 95% CI: 1.19–6.17, $p = 0.018$). In the analysis, the following laboratory parameters presented significant differences: white blood cells (WBC) count (OR: 139, 95% CI: 1.09–1.78, $p = 0.006$), monocyte count (OR: 30.85, 95% CI: 6.27–151, $p = 0.011$), serum hemoglobin concentration (OR: 1.75, 95% CI: 1.03–2.97, $p = 0.039$), SIRI (OR: 3.32, 95% CI: 1.56–7.03, $p = 0.002$) followed by high density lipoprotein (HDL) cholesterol level (OR: 0.01, 95% CI: 0.01–0.11, $p < 0.001$).

Thereafter, the multivariable logistic regression analysis of group 1 vs. 3 (chronic coronary syndrome with complex CAD) was performed (Table 4).

The predictive clinical values of demographic parameters were found when logistic regression analysis was performed between group 1 vs. group 3, including sex (OR: 8.8, 95% CI: 3.76–20.62, $p < 0.001$) and smoking (OR: 2.49, 95% CI: 1.13–5.53, $p = 0.024$). The results of laboratory test presenting predictive values between no coronary and complex coronary disease groups were: WBC (OR: 1.41, 95% CI: 1.14–1.75, $p = 0.002$), neutrophil count (OR: 1.62, 95% CI: 1.22–2.14, $p = 0.001$), NLR (OR: 2.06, 95% CI 1.39–3.05, $p < 0.001$), SIRI (OR: 11.65, 95% CI: 4.22–32.16, $p < 0.001$), total cholesterol (OR: 0.57, 95% CI: 0.4–0.81, $p = 0.002$) and HDL (OR: 0.08, 95% CI: 0.02–0.27, $p < 0.001$).

Table 2. Laboratory results.

Parameters	Group 1 (n = 63)	Group 2 (n = 51)	Group 3 (n = 81)	P 1 vs. 2	P 1 vs. 3	P 1 vs. 2+3
Whole blood count:						
WBC [10^9 /dL]	6.5 (5.6–7.3)	6.8 (5.5–8.1)	7.8 (6.3–8.9)	0.010	0.001	< 0.001
Neutrophils [10^9 /dL]	3.9 (3.3–4.7)	3.9 (3.3–4.6)	4.9 (4–6.1)	0.067	< 0.001	< 0.001
Lymphocytes [10^9 /dL]	1.8 (1.4–2.2)	1.8 (1.6–2.6)	1.7 (1.4–2.0)	0.342	0.403	0.942
Monocytes [10^9 /dL]	0.4 (0.3–0.5)	0.5 (0.4–0.6)	0.4 (0.4–0.5)	< 0.01	< 0.001	< 0.001
RBC [10^{12} /dL]	4.6 (4.4–4.8)	4.8 (4.7–5.6)	4.7 (4.4–4.9)	0.025	0.455	0.109
Hemoglobin [mmol/L]	8.9 (8.6–9.2)	9.3 (9.3–10.3)	9.1 (8.5–9.6)	0.009	0.078	0.014
Hematocrit [%]	41 (40–43)	45 (39–46)	43 (40–45)	0.002	0.028	0.003
RDW [%]	13.4 (13–13.9)	13.5 (13–14.4)	13.6 (13.1–14.1)	0.246	0.079	0.084
Platelets [10^9 /dL]	212 (186–272)	228 (189–242)	236 (200–262)	0.874	0.324	0.469
SIRI	0.82 (0.57–1.06)	0.98 (0.68–1.46)	0.99 (0.76–1.27)	< 0.001	< 0.001	< 0.001
Lipid profile:						
TC [mmol/L]	4.1 (3.7–5.4)	3.5 (3.3–5.6)	3.6 (3.2–4.3)	0.255	< 0.001	0.006
LDL [mmol/L]	2.63 (1.9–3.8)	2.1 (1.8–4.0)	2.1 (1.7–2.5)	0.787	0.002	0.016
HDL [mmol/L]	1.32 (1.19–1.54)	1.2 (1.09–1.28)	1.1 (0.94–1.3)	< 0.001	< 0.001	< 0.001
TG [mmol/L]	1.32 (1.04–1.73)	1.11 (0.91–1.67)	1.21 (0.89–1.61)	0.941	0.379	0.589
LDL/HDL ratio	2.01 (1.37–2.94)	1.63 (1.48–2.69)	1.89 (1.45–2.48)	0.226	0.958	0.565
TG/HDL ratio	0.96 (0.66–1.41)	0.93 (0.5–1.53)	1.19 (0.75–1.56)	0.051	0.034	0.018
TC/HDL ratio	3.1 (2.7–4.3)	3.1 (2.7–3.8)	3.3 (2.7–3.9)	0.051	0.016	0.429
Liver function test:						
ALT [U/L]	25 (20–31)	33 (15–37)	28 (22–35)	0.429	0.211	0.222
AST [U/L]	32 (25–39)	25 (20–31)	26 (23–36)	0.141	0.768	0.098
Kidney function test:						
Creatinine [mmol/L]	78 (68–93)	92 (77–100)	85 (74–101)	0.002	0.009	0.001
GFR [mL/min]	76 (68–88)	76 (67–89)	68 (61–86)	0.418	0.770	< 0.001
Myocardial injury marker:						
Troponin I [ng/mL]	0.004 (0.003–0.005)	0.005 (0.003–0.007)	0.01 (0.005–0.023)	0.056	0.023	0.023
Thyroid:						
TSH [mU/L]	1.43 (0.92–2.35)	1.42 (1.12–2.35)	1.51 (0.89–3.89)	0.148	0.698	0.159

Data are shown as number (%) and median (Q1–Q3). ALT — alanine transaminase; AST — aspartate aminotransferase; GFR — glomerular filtration rate; HDL — high density lipoprotein cholesterol; LDL — low density lipoprotein cholesterol; RBC — red blood cell count; RDW — red blood cell distribution width; SII — systemic immune inflammation index; SIRI — systemic inflammatory response index; TC — total cholesterol; TG — triglycerides; TSH — thyroid stimulating hormone; WBC — white blood cell count

Finally, the analysis was performed between group 1 and combined groups 2 and 3 (Table 5). The logistic regression analysis revealed predictive clinical factors for single or complex CAD including male gender (OR: 5.87, 95% CI: 2.97–11.57, $p < 0.001$), body mass index (BMI) (OR: 0.93, 95% CI: 0.87–0.99, $p = 0.022$), smoking (OR: 2.59, 95% CI: 1.26–5.31, $p = 0.009$) and family history (OR: 0.19, 95% CI: 0.08–0.46, $p < 0.001$). The laboratory results presenting predictive values were

WBC (OR: 1.43, 95% CI: 0.97–2.13, $p = 0.074$), neutrophil counts (OR: 1.52, 95% CI: 1.17–1.98, $p = 0.002$), monocyte counts (OR: 16.43, 95% CI: 1.29–108.14, $p = 0.031$), NLR (OR: 1.62, 95% CI: 1.18–2.24, $p = 0.030$), SIRI (OR: 6.06, 95% CI: 2.69–13.65, $p < 0.001$) and systemic immune inflammation index (SII) (OR: 1.00, 95% CI: 1.00–1.00, $p = 0.032$). Among other laboratory results, the total cholesterol serum concentration (OR: 0.73, 95% CI: 0.56–0.94, $p = 0.015$), low density

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

Parameters	Odds ratio	Standard error	P	95% CI
Group 1 vs. Group 2: No coronary vs. single vessel coronary disease				
Sex	3.67	1.52	0.002	1.63–8.27
Age	0.97	0.02	0.159	0.93–1.01
BMI	0.95	0.03	0.099	0.89–1.01
Clinical:				
Arterial hypertension	0.99	0.47	0.980	0.39–2.51
Diabetes mellitus	0.91	0.36	0.802	0.42–1.97
COPD	0.57	0.42	0.448	0.14–2.42
Hypercholesterolemia	2.19	1.16	0.139	0.78–6.18
PAD	1.57	1.09	0.519	0.39–6.17
Atrial fibrillation	2.61	1.91	0.191	0.62–10.99
History of stroke	0.80	0.75	0.811	0.13–4.98
Active smoking	1.50	1.30	0.588	0.49–3.43
History of smoking	2.71	1.14	0.018	1.19–6.17
Family history	0.36	0.29	0.220	0.07–1.84
Kidney disease	1.22	0.74	0.747	0.37–4.03
Echocardiographic:				
LV	1.12	0.27	0.286	0.92–1.03
RV	1.09	0.12	0.439	0.87–1.36
LVEF	0.93	0.06	0.258	0.83–1.05
Morphology:				
WBC	1.39	0.17	0.006	1.09–1.78
Neutrophils	0.98	0.22	0.937	0.64–1.52
Lymphocytes	2.33	1.15	0.086	0.89–6.12
Monocytes	30.85	9.8	0.011	6.27–151
RBC	6.78	5.25	0.206	0.76–3.54
Hemoglobin	1.75	0.47	0.039	1.03–2.97
Hematocrit	1.04	0.45	0.400	0.95–1.13
RDW	1.40	0.36	0.187	0.85–2.32
Platelets	0.99	0.01	0.574	0.98–6.71
NLR	1.23	0.22	0.253	0.86–1.76
SIRI	3.32	1.27	0.002	1.56–7.03
SII	1.00	< 0.001	0.416	0.99–1.00
Lipidogram:				
TC	0.89	0.14	0.466	0.66–1.21
LDL	0.90	0.13	0.430	0.68–1.18
HDL	0.01	0.01	< 0.001	0.01–0.11
TG	1.08	0.35	0.810	0.57–2.03
LDL/HDL	0.93	0.18	0.726	0.64–1.37
TG/HDL	0.98	0.46	0.959	0.38–2.47
TC/HDL	1.07	0.38	0.859	0.01–1.71
Other laboratory:				
ALT	1.02	0.26	0.413	0.97–1.08
AST	0.99	0.34	0.757	0.92–1.06
Troponin	1.0	1.7	0.142	2.11–4.70
GFR	1.0	0.03	0.770	0.96–1.06
TSH	0.94	0.21	0.789	0.60–1.47

ALT — alanine transaminase; AST — aspartate aminotransferase; BMI — body mass index; CI — confidence interval; COPD — chronic obstructive pulmonary disease; GFR — glomerular filtration rate; HDL — high density lipoprotein cholesterol; LDL — low density lipoprotein cholesterol; LV — left ventricular diameter; LVEF — left ventricular ejection fraction; NLR — neutrophil to lymphocyte ratio; PAD — peripheral artery disease; RV — right ventricular diameter; RBC — red blood cell count; RDW — red cell distribution width; SII — systemic immune inflammation index; SIRI — systemic inflammatory response index; TC — total cholesterol; TG — triglycerides; TSH — thyroid stimulating syndrome; WBC — white blood cell count

Table 4. Logistic regression analysis of patients without coronary artery disease vs. patients with complex coronary artery disease.

Parameters	Odds ratio	Standard error	P	95% CI
Group 1 vs. Group 3: No coronary disease vs. complex coronary disease				
Sex	8.80	3.82	< 0.001	3.76–20.62
Age	0.98	0.02	0.461	0.94–1.03
BMI	0.87	0.05	0.005	0.78–0.96
Clinical:				
Arterial hypertension	1.35	0.60	0.500	0.56–3.26
Diabetes mellitus	1.04	0.37	0.913	0.52– .07
COPD	0.60	0.38	0.423	0.18–2.08
Hypercholesterolemia	0.77	0.31	0.498	0.35–1.65
PAD	1.20	0.80	0.789	0.32–4.43
Atrial fibrillation	1.89	1.34	0.370	0.47–7.63
History of stroke	1.89	1.35	0.370	0.47–7.63
Active smoker	1.27	0.65	0.637	0.47–3.48
History of smoking	2.49	1.01	0.024	1.13–5.53
Family history	0.16	0.08	< 0.001	0.06–0.44
Kidney disease	1.31	0.72	0.184	0.89–1.80
Echocardiographic:				
LV	0.95	0.28	0.096	0.89–1.01
RV	1.04	0.05	0.373	0.95–1.14
LVEF	0.94	0.03	0.092	0.69–1.01
Morphology:				
WBC	1.41	0.16	0.002	1.14–1.75
Neutrophils	1.62	0.23	0.001	1.22–2.14
Lymphocytes	0.89	0.30	0.732	0.47–1.71
Monocytes	11.93	5.70	0.060	0.91–57
Monocyte/HDL	42.74	14.55	0.003	3.50–121
RBC	1.35	0.57	0.478	0.59–3.07
Hemoglobin	1.34	0.31	0.206	0.85–2.11
Hematocrit	1.11	0.06	0.050	1.00–1.22
RDW	1.47	0.33	0.083	0.95–2.27
Platelets	1.00	0.03	0.627	0.99–1.01
NLR	2.06	0.41	< 0.001	1.39–3.05
SIRI	11.65	6.04	< 0.001	4.22–32.16
SII	1.00	0.01	0.011	1.00–1.00
Lipidogram:				
TC	0.57	0.10	0.002	0.40–0.81
LDL	0.62	0.11	0.057	0.45–0.88
HDL	0.08	0.05	< 0.001	0.02–0.27
TG	1.05	0.23	0.838	0.68–1.60
LDL/HDL	0.90	0.10	0.373	0.72–1.13
TG/HDL	1.32	0.27	0.171	0.89–1.97
TC/HDL	1.14	0.44	0.595	0.22–2.39
Other laboratory:				
ALT	1.02	0.13	0.106	0.99–1.05
AST	0.99	0.34	0.757	0.92–1.06
Troponin	1.00	1.70	0.142	2.11–4.70
GFR	1.03	0.01	0.924	0.98–1.03
TSH	1.07	0.19	0.718	0.75–1.52

ALT — alanine transaminase; AST — aspartate aminotransferase; BMI — body mass index; CI — confidence interval; COPD — chronic obstructive pulmonary disease; GFR — glomerular filtration rate; HDL — high density lipoprotein cholesterol; LDL — low density lipoprotein cholesterol; LV — left ventricular diameter; LVEF — left ventricular ejection fraction; NLR — neutrophil to lymphocyte ratio; PAD — peripheral artery disease; RV — right ventricular diameter; RBC — red blood cell count; RDW — red cell distribution width; SII — systemic immune inflammation index; SIRI — systemic inflammatory response index; TC — total cholesterol; TG — triglycerides; TSH — thyroid stimulating syndrome; WBC — white blood cell count

Table 5. Logistic regression analysis of patients without coronary artery disease vs. patients with single or complex coronary artery disease.

Parameters	Odds ratio	Standard error	P	95% CI
Group 1 vs. Group 2+3: No coronary disease vs single or complex coronary disease				
Sex	5.87	2.04	< 0.001	2.97–11.57
Age	0.98	0.02	0.223	0.94–1.02
BMI	0.93	0.03	0.022	0.87–0.99
Clinical:				
Arterial hypertension	1.19	0.47	0.665	0.55–2.58
Diabetes mellitus	0.99	0.32	0.963	0.53–1.85
COPD	0.59	0.33	0.352	0.20–1.79
Hypercholesterolemia	1.07	0.39	0.852	0.52–2.21
PAD	1.34	0.81	0.628	0.41–4.39
Atrial fibrillation	2.17	1.43	0.241	0.59–7.89
History of stroke	1.45	0.99	0.586	0.38–5.56
Active smoker	1.31	0.64	0.588	0.49–3.43
History of smoking	2.59	0.95	0.009	1.26–5.31
Family history	0.19	0.09	< 0.001	0.08–0.46
Kidney disease	1.28	0.65	0.629	0.47–3.44
Echocardiographic:				
LV	0.97	0.27	0.286	0.92–1.03
RV	1.05	0.05	0.335	0.96–1.14
LVEF	0.95	0.03	0.090	0.89–1.01
Morphology:				
WBC	1.43	0.29	0.074	0.97–2.13
Neutrophils	1.52	0.21	0.002	1.17–1.98
Lymphocytes	1.08	0.31	0.782	0.63–1.88
Monocytes	16.43	11.28	0.031	1.29–108.14
RBC	1.64	0.64	0.206	0.76–3.54
Hemoglobin	1.43	0.31	0.103	0.93–2.19
Hematocrit	1.05	0.04	0.172	0.98–1.12
RDW	1.43	0.29	0.080	0.96–2.14
Platelets	1.0	0.03	0.750	0.99–1.01
NLR	1.62	0.27	0.03	1.18–2.24
SIRI	6.06	2.51	< 0.001	2.69–13.65
SII	1.00	< 0.001	0.032	1.00–1.00
Lipidogram:				
TC	0.73	0.09	0.015	0.56–0.94
LDL	0.75	0.10	0.035	0.57–0.98
HDL	0.01	0.01	< 0.001	0.01–0.06
TG	1.06	0.22	0.813	0.69–1.59
LDL/HDL	0.91	0.09	0.315	0.73–1.12
TG/HDL	1.29	0.26	0.315	0.87–1.90
TC/HDL	1.13	0.19	0.467	0.81–1.57
Other laboratory:				
ALT	1.02	0.12	0.107	0.99–1.04
AST	0.99	0.34	0.757	0.92–1.06
Troponin	1.0	1.7	0.142	2.11–4.70
GFR	1.0	0.1	0.882	0.97–1.02
TSH	1.0	0.15	0.970	0.72–1.36

ALT — alanine transaminase; AST — aspartate aminotransferase; BMI — body mass index; CI — confidence interval; COPD — chronic obstructive pulmonary disease; GFR — glomerular filtration rate; HDL — high density lipoprotein cholesterol; LDL — low density lipoprotein cholesterol; LV — left ventricular diameter; LVEF — left ventricular ejection fraction; NLR — neutrophil to lymphocyte ratio; PAD — peripheral artery disease; RV — right ventricular diameter; RBC — red blood cell count; RDW — red cell distribution width; SII — systemic immune inflammation index; SIRI — systemic inflammatory response index; TC — total cholesterol; TG — triglycerides; TSH — thyroid stimulating syndrome; WBC — white blood cell count

Table 6. Logistic multiple regression analysis of patients without coronary artery disease vs. patients with single or complex coronary artery diseases.

Parameters	Odds ratio	Standard error	P	95% CI
Group 1 vs. Group 2: No coronary vs. single vessel disease				
RDW	2.79	1.21	0.017	1.20–6.51
Sex	4.67	2.62	0.006	1.56–14.01
BMI	0.89	0.04	0.027	0.82–0.99
Age	0.91	0.03	0.06	0.85–0.97
Smoking history	8.16	5.15	0.001	2.37–28.13
WBC	1.89	0.33	< 0.001	1.34–2.67
Group 1 vs. Group 3: No coronary vs. complex coronary disease				
RDW	4.06	2.56	0.026	1.18–13.99
Group 1 vs. Group 2 + 3: No coronary vs. single/complex coronary disease				
SIRI	5.52	3.03	0.002	1.89–16.15
Sex	3.98	2.14	0.010	1.38–11.42
BMI	0.89	0.41	0.012	0.81–0.98
Age	5.57	0.03	0.001	0.83–0.98
Smoking history	3.66	3.36	0.004	1.71–18.22
RDW	3.66	1.47	0.001	1.67–8.04

BMI — body mass index; CI — confidence interval; RDW — red blood cell distribution width; SIRI — systemic inflammatory response index; WBC — white blood cell count

lipoprotein (LDL) (OR: 0.75, 95% CI: 0.57–0.98, $p = 0.035$), HDL (OR: 0.01, 95% CI: 0.01–0.06, $p < 0.00$) were found to be significant.

Logistic multiple regression analysis

A multiple analysis between patients without CAD (group 1) vs. single (group 2) or complex CAD (group 2) and combined groups (2+3) was performed (Table 6).

The logistic regression multivariable analysis revealed predictive values of clinical factors for single vessel coronary disease including male gender (OR: 2.79, 95% CI: 1.20–6.51, $p < 0.017$), age (OR: 0.91, 95% CI: 0.85–0.97, $p = 0.060$), lower BMI (OR: 0.89, 95% CI: 0.82–0.99, $p = 0.027$) and smoking (OR: 8.16, 95% CI: 2.37–28.13, $p = 0.001$). The parameters of laboratory test presenting predictive values were WBC (OR: 1.89, 95% CI: 1.34–2.67, $p < 0.001$) and RDW (OR: 2.79, 95% CI: 1.20–6.51, $p = 0.017$).

Red blood cell distribution width was revealed as an independent predictor of complex CAD (OR: 4.06, 95% CI: 1.18–13.99, $p = 0.026$).

For combined single and complex coronary disease male gender (OR: 3.98, 95% CI: 1.38–11.42, $p = 0.010$), age (OR: 5.57, 95% CI: 0.83–0.98, $p = 0.001$), lower BMI (OR: 0.89, 95% CI: 0.81–0.98, $p = 0.012$), and smoking (OR: 3.66, 95%

CI: 1.71–18.22, $p = 0.004$), and among laboratory results SIRI (OR: 5.52, 95% CI: 1.89–16.15, $p = 0.029$) and RDW (OR: 3.66, 95% CI: 1.67–8.04, $p = 0.001$) were found significant.

Receiver operator curves for single vessel atherosclerosis prediction

Among multivariable analysis results, the RDW was presented as significant. The ROC analysis was performed, however presented low significance for group 2 (AUC = 0.563, $p = 0.247$), group 2+3 (AUC = 0.588, $p = 0.074$) and for group 3 (AUC = 0.578, $p = 0.075$).

Moreover, the predictive values of SIRI between groups 1, 2+3 were estimated. The ROC analysis comparing SIRI between group 1 and 2 revealed an optimal cut-off value > 1.95 (AUC = 0.630, $p = 0.014$) with sensitivity of 23.53% and specificity of 100%. The ROC curve analysis comparing SIRI between group 1 and 3 showed an optimal cut-off value > 1.03 (AUC = 0.792, $p < 0.001$) with sensitivity of 71.23% and specificity of 75%. The ROC curves analysis comparing SIRI between group 1 and combined groups 2+3 revealed optimal cut-off value > 1.21 (AUC = 0.725, $p < 0.001$) with sensitivity of 49.19% and specificity of 85% (Fig. 2A–C).

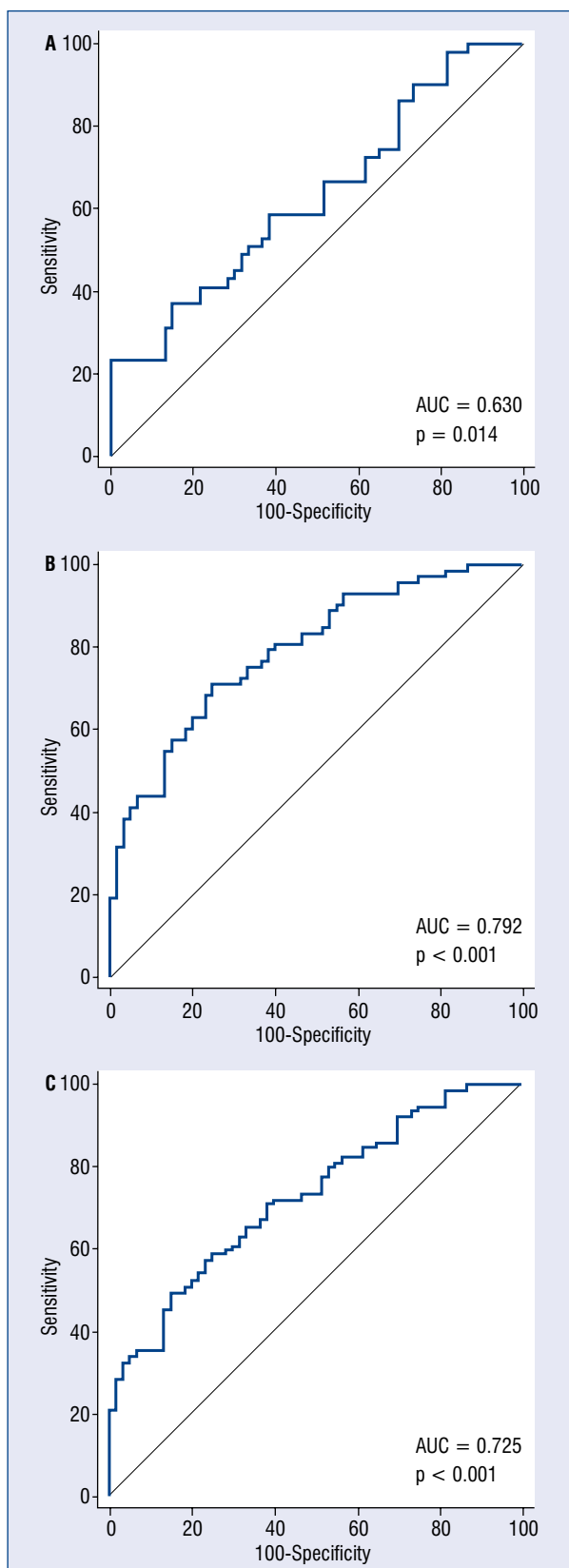


Figure 2. Receiver operator curves analysis for preoperative systemic inflammatory response index (SIRI) comparison between group 1 vs. 2 (A), 1 vs. 3 (B) and 1 vs. 2 + 3 (C); AUC — area under the curve.

Discussion

The study presented herein, shows SIRI as an easily accessible marker for CAD in patients with angina pectoris equivalent symptoms in the form of dyspnea and fatigue and secondary chest discomfort on exertion. Coronary artery revascularization is the optimal therapy to improve clinical outcomes in chronic CAD [12–14]. The diagnostics in patients with less typical symptoms are difficult [15, 16]. Some patients may undergo unnecessary invasive procedures, and others, with anginal equivalent, may be declined from beneficial treatment. The results indicate patients who should be considered for invasive diagnostics though classical chest pain symptoms are expressed as mild.

According to the current study, SIRI may be regarded as a simple predictive marker for CAD. Patients admitted for coronary angiography, irrespective of family history or co-existing diseases, should be evaluated by SIRI to improve clinical prediction of CAD. The possible explanation of clinical symptom occurrence in patients with non-atherosclerotic coronary arteries may be related to intracoronary pressure gradient differences irrespective to the presence of minor atherosclerotic plaques and related to the amount of supplied myocardium mass [14]. The prevalence of non-atherosclerotic coronary arteries in patients presenting with stable CAD at coronary angiography is as high as 42% [15]. Another possible explanation of clinical symptoms in patients with non-atherosclerotic coronary arteries may be related to coronary microcirculation dysfunction [16]. SIRI may allow more adequate patient diagnosis when combined with clinical symptoms.

The present study results confirm the significant value of SIRI as an indicator of inflammatory response in atherosclerotic disease. The index comprises neutrophil and monocyte together with lymphocyte counts. Neutrophil and monocyte activation has been reported in atherosclerotic plaques, with the release of proinflammatory cytokines, chemokines, enzymes, and reactive oxidative species. Activated monocytes transform into foam cells and promote dysfunctional lipoproteins accumulation. The role of lymphocytes is even more combined and includes a plaque destabilization process [13]. Xia et al. [17] study showed that higher SIRI and SII levels are linked with increased cardiovascular and all-cause mortality in the general population. SII include calculation of platelets, neutrophil and lymphocytes, and may therefore reflect inflammatory and immunothrombotic risk

of cardiovascular events. Yasar et al. [18] presented a significant association between increased SII and angiographically proved impaired microcirculation in patients with cardiac syndrome X. In Candemir et al. [19] analysis SII revealed predictive value in evaluating the extent of CAD. Despite several reports in the literature, no markers reflecting neutrophil/monocyte/lymphocyte/platelet counts are currently used in coronary risk stratification according to guidelines, although these simple parameters are easily obtained in each patient's peripheral blood morphology.

The results of the current analysis point out the well-known risk factors, such as sex, age, smoking and BMI. Moreover, RDW was found as a possible predictor, however its usefulness was considered worse due to low sensitivity and specificity.

The reported high prevalence of non-atherosclerotic angiograms in patients with stable angina [20] points out the necessity for more adequate patient identification. According to current guidelines, CT or magnetic resonance imaging are recommended as a following diagnostic step [21]. The accuracy of CT in CAD is excellent for the left descending artery atherosclerosis [22], but not for complex CAD [23]. Moreover, heavy calcifications and heart rhythm abnormalities are other possible limitations of this method and should be taken into consideration [24]. Magnetic resonance imaging accuracy for CAD diagnosis is believed superior to other non-invasive tools [25] but with limited accessibility in clinical practice. These issues indicate that a combination of noninvasive tools and laboratory indexes might be valuable in diagnostics.

The overall results are convincing and confirm increased risk for CAD in males. The genetic backgrounds suggesting high risk for CAD in men was presented by Huang et al. [26]. Atypical syndromes including shortness of breath and back pain are more frequently reported in women [27, 28].

Although the survival rates in cardiovascular diseases have improved in recent years [29], the onset of prompt diagnosis has declined [30]. The modifiable parameters should be taken into consideration to improve patient outcomes [31]. The findings in the TCGS study, disease onset was related to age and gender differences [32]. The present results indicate age-related risk for CAD.

Despite obesity being claimed as an independent risk factor for cardiovascular diseases, its association is claimed with improved survival [33]. In patients with metabolic syndrome, a severe endothelial dysfunction is observed [34]. However, the present results point out that in patients with

higher BMI, presented symptoms are more often atypical, including shortness of breath and fatigue that are not related to CAD.

The current study indicates a certain group of patients who may be referred for coronary angiography based on simple blood parameter for single or complex coronary atherosclerosis disease prediction. It is believed herein, that simple inflammatory markers obtained from whole blood count analysis can help in patient evaluations, especially those presenting with chest pain symptom equivalents, such as fatigue and shortness of breath on exertion. According to the results from recent ISCHEMIA study [35], a conservative therapy shall be considered in patients who present non-chest pain symptoms. Based on initial results, it was convincing that the simple indices from blood analysis may advocate for invasive diagnostics to indicate those patients, who may benefit from either percutaneous or surgical revascularization.

The simple indices from whole blood count analysis may be regarded as predictive for long-term results following either angioplasty [36] or surgical revascularization [9]. They were found predictive for long-term outcomes following surgical revascularization [37]. This is the first analysis, according to available research, proposing identification of those patients presenting with angina pectoris equivalent symptoms who may require coronary angiography. Fatigue is a symptom which is often reported as secondary to diagnosed CAD and is related to distress syndrome [38].

Shortness of breath, as a secondary non-chest pain symptom, is believed to require additional diagnostics [39]. Echocardiographic parameters [40] have been proposed to improve diagnosis. It can be suggested that adding a simple parameter from whole blood analysis be utilized for prompt assessment. Previously, the prognostic values of calcium scores were postulated for evaluation of patients presenting typical chest pain [41].

Limitations of the study

Lack of non-invasive imaging including coronary CT is the major limitation. Angiography was performed based on referring practitioner diagnosis. Generally, clinicians at the hemodynamics labs rarely disqualify the patients previously accepted for invasive diagnostics by the referring physician. No analysis based on the extent of atherosclerosis was performed, and probably Gensini Score would be more appropriate than dividing patients into one- vs. two-vessel disease. The analysis did not include other inflammation parameters. A consid-

erable group of patients had a stress test before coronary angiography, though its limited value is well known. The strength of the present study reflects good predictive value of easily available and repetitive SIRI for CAD assessment.

Conclusions

Systemic inflammatory response index is a simple hematological index, which may be a helpful tool in CAD diagnostic in patients with anginal equivalent. Patients presenting with SIRI above 1.22 have a higher probability of single and complex CAD and should be considered for coronary angiography.

Conflict of interest: None declared

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