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The High-Grade Oxidative Profile (OXpr), Aortic Stiffness Parameters, and Hemogram-Derived Indices (HDI) as Predictors of Long-Term Major Adverse Cardiovascular Events (MACEs) Following Percutaneous Coronary Intervention (PCI) in Patients with Non-ST-Elevation Acute Coronary Syndrome (NSTE-ACS) and Chronic Coronary Syndrome (CCS)

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ABSTRACT

BACKGROUND.

Despite the achievements in the management of coronary heart disease (CHD), there is a need to appropriately tailor the long-term management strategies and risk stratification, particularly after percutaneous coronary intervention (PCI) because of a non-ST-elevation acute coronary syndrome (NSTE-ACS) or chronic coronary syndrome (CCS).

OBJECTIVES

The Present study aimed to (i) evaluate the long-term cardiovascular prognostic value of oxidative stress markers, arterial stiffness parameters, and hemogram-derived inflammatory indices and (ii) compare the long-term predictive performance of the abovementioned markers with the periprocedural SYNTAX score II (SS-II) in Georgian patients following PCI.

METHODS

After PCI because of NSTE-ACS or CCS, the annual incidence of 6-component MACEs, and values of the oxidative profile, arterial stiffness measurements, and hemogram-derived indices (HDI) were measured during the 36-month follow-up period in the development (100 patients with NSTE-ACS) and validation cohorts (91 patients with CCS), respectively.

RESULTS

By the multiple regression analysis NLR (0.505±0.069, p<0.0001), OXpr (0.181±0.076, p=0.018), SBPao (0.174±0.076, p=0.023), and PLR (0.164±0.056, p=0.004) are positively correlated with 36-month MACEs.

CONCLUSIONS

The oxidative stress profile, central systolic blood pressure, and hemogram-derived indices such as neutrophil-lymphocyte and monocyte-lymphocyte ratios may be novel independent predictors of long-term major adverse cardiovascular events.

KEYWORDS

Central systolic blood pressure (SBPao); chronic coronary syndrome (CCS); major adverse cardiovascular events (MACEs); neutrophil-to-lymphocyte ratio (NLR); non-ST-elevation acute coronary syndrome (NSTE-ACS); oxidative profile (OXpr); platelet-to-lymphocyte ratio (PLR).

BACKGROUND

Despite the latest achievements in managing coronary heart disease (CHD), there is a residual risk of subsequent major cardiovascular events (MACEs).[1] The risk of future dramatic events is highly heterogeneous, and patients may differ in the degree of benefit received from existing treatment.[2-4] Therefore, there is a need to appropriately tailor the long-term management strategies and risk stratification in patients after percutaneous coronary intervention (PCI) because of a non-ST-elevation acute coronary syndrome (NSTE-ACS) or chronic coronary syndrome (CCS).

A recent index, the SYNTAX score II (SS-II), is the most potent tool to predict a long-term major cardiovascular event in patients undergoing coronary revascularization.[5-8] However, this predictive index was not validated in a Georgian acute coronary syndrome (ACS) patient.

The accumulated evidence of the recent decades provides deeper insights into the pathophysiology of cardiovascular diseases and accentuates the prognostic significance of new markers related to arterial stiffness, oxidative stress, and low-grade systemic inflammation.[9-37]

In our previous comparative studies of periprocedural systemic oxidative stress markers, arterial stiffness parameters, and hemogram-derived inflammatory indices in patients undergoing percutaneous coronary intervention (PCI) because of a non-ST-elevation acute coronary syndrome (NSTE-ACS) or chronic coronary syndrome (CCS), we found a strong positive correlation between advanced oxidative stress, aortic pulse wave velocity (PWVao), augmentation index (AIx), central systolic blood pressure (SBPao), and neutrophil-to-lymphocyte ratio (NLR) with high clinical/angiographic risk of the non-ST-elevation acute coronary syndrome (NSTE-ACS).[16,38,39]

The present study aimed to (i) evaluate the long-term cardiovascular prognostic value of oxidative stress markers, arterial stiffness parameters, and hemogram-derived inflammatory indices and (ii) compare the long-term predictive performance of the markers mentioned above with the periprocedural SYNTAX score II (SS-II) in Georgian patients following PCI.

METHODS

Patient population

Overall, 191 of 938 patients admitted to the LTD LJ Clinic Coronary Care Unit (Kutaisi, Georgia) were included in the study after a successful primary PCI between April 2018 and June 2019. The study population of 100 patients with NSTE-ACS and 91 patients with CCS was distributed among the development and validation cohorts, respectively.

Patients with a history of coronary revascularization or with hemodynamically compromised severe myocardial infarction; those recovering from cardiopulmonary arrest, decompensated heart failure; and those with valvular heart disease, cardiomyopathy, severe supraventricular/ventricular arrhythmias (including atrial fibrillation) and conductivity disturbances, end-stage renal disease (ESRD), chronic inflammatory conditions, active cancer, type 1 diabetes mellitus (DM) or decompensated type 2 diabetes mellitus (DM); pregnancy; those on hormone replacement therapy (HRT) or oral contraceptive assumption were excluded from the study.[16]

The study protocol was reviewed and approved by the Ethic Committees of Tbilisi State Medical University and LTD LJ Clinic (Kutaisi, Georgia), and written informed consent was provided by each study participant.

Angiographic examination

The standard radial approach with the sheathless guiding catheters was used for percutaneous coronary intervention.

In CCS patients, coronary revascularization was performed in case of the high clinical likelihood of obstructive coronary artery disease (OCAD), severe symptoms refractory to optimal medical treatment, typical angina at a low level of exercise, and clinical prediction of high-risk of events or left ventricular dysfunction suggestive of coronary artery disease (CAD).[16]

Basic measurements

A demographic characteristic, all basic laboratory tests, oxidative stress markers, arterial stiffness parameters, and calculation of hemogram-derived inflammatory indices were performed during the first hour of admission before PCI.

Calculation of SYNTAX score II (SS-II)

The complexity of coronary artery disease was determined retrospectively, reevaluating the digital angiographic and medical records by the SYNTAX score II (SS-II) angiographic grading tool with incorporated anatomical SYNTAX score I (SS-I) with the following variables: dominance coronary system, number of lesions, segments involved per lesion, and presence of chronic total occlusions, trifurcation/bifurcation, aorto-ostial lesion, tortuosity, length of lesion >20 mm, heavy calcification, and presence of thrombus; diffuse disease and/or lesion of small vessels; age and gender of the patient, creatinine clearance (CrCl, ml/min), left ventricle ejection fraction (LVEF,%), and comorbidities, such as chronic obstructive pulmonary disease (COPD) and peripheral vascular disease (PVD).[40] According to these variables, a separate angiographic risk score and PCI/CABG 4-year mortality risks were calculated for each lesion.

Follow-up measurements

In patients of both cohorts, 36-month follow-up was used to determine six-point MACEs as a composite of total death, myocardial infarction, stroke, coronary revascularization (PCI or CABG), hospitalization because of heart failure, and atrial fibrillation (AF).

During the follow-up period, in addition to registration of MACEs, the following annual measurements were taken: Free Oxygen Radical Test (FORT), Free Oxygen Radicals Defense (FORD), and Oxidative-reductive balance (REDOX index); Central et al. (SBPao), Aortic Pulse Wave Velocity (PWVao), Aortic Pulse Pressure (PPao), Augmentation Index (AIx), and Return Time (RT) of the aortic pulse wave; and neutrophil-to-lymphocyte ratio (NLR).

Statistical analysis

IBM SPSS Statistics software version 26.0 (IBM et al., USA) was used for analyzing data. The differences between development and validation cohorts had assessed by the nonparametric Mann-Whitney U test for independent samples. Descriptive statistics, linear and quantile regression analysis, Pearson correlation, ANOVA test, Z-scores, and unstandardized/standardized B coefficients with zero-order, partial, and part correlations were also used to assess relations between dependent variables and predictors. The Kaplan-Meier survival analysis with Log Rank (Mantel-Cox) test statistics was used to assess survival and hazard functions. A statistical significance was taken as a 2-tailed $p<0.05$.

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RESULTS

Patient characteristics

There were no significant differences in terms of age, male gender, body mass index, hypertension, dyslipidemia, smoking status, type 2 diabetes mellitus, creatinine clearance (CrCl), left ventricular ejection fraction (LVEF), and comorbidities such as chronic pulmonary obstructive disease (COPD), peripheral artery disease (PAD), and baseline treatment (except nitrates consumption) between the development and validation cohorts (Tab.S1).

Baseline oxidative stress, arterial stiffness, and hemogram-derived indices

Baseline oxidative stress parameters (FORT and FORD), oscillometric arterial stiffness measurements (SBPao, PWVao, and Aix), and hemogram-derived indices (neutrophil-to-lymphocyte ratio [NLR], the monocyte-to-lymphocyte ratio [MLR], the platelet-to-lymphocyte ratio [PLR], and mean platelet volume [MPV]) were significantly higher in the development cohort comparing to the validation cohort (Tab.1).

PCI SYNTAX II score

The mean PCI SYNTAX score II (SS-II) and PCI 4-year mortality were significantly higher in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) patients (development cohort) compared to chronic coronary syndrome (CCS) patients (validation cohort) (Tab.1).

Follow-up measurements

Table 2 and Table 3 present the annual and overall incidence of 6-component MACEs and values of the oxidative profile, arterial stiffness measurements, and hemogram-derived indices (HDI) during the 36-month follow-up period in the development and validation cohorts, respectively.

The results of the nonparametric independent test revealed that all overall MACEs of the development cohort were significantly higher than in the validation cohort (p<0.0001). There was no difference in the frequency of the first- and second-year total death, myocardial infarction, and stroke (p=0.211 and p=0.912; p=0.134 and p=0.071; p=0.305 and p=0.165, respectively); the first-year incidence of heart failure hospitalization, percutaneous coronary intervention (PCI), and atrial fibrillation (p=0.073, p=0.052, and p=0.257, respectively) between cohorts. However, at the end of the 36-month follow-up period, overall frequencies of total death, myocardial infarction, stroke, hospitalization because of heart failure, PCI, CABG, and atrial fibrillation were significantly higher in the development cohort (p=0.004, p=0.001, p=0.001, p<0.0001, p<0.0001, p<0.0001, and p=0.002, respectively).

The mean OXPr (4.40±0.77 vs. 2.66±1.33, p<0.0001), SBPao (126.9±15.5 mmHg vs. 117.7±19.4 mmHg, p=0.013), PWVao (10.4±1.87 m/s vs. 8.56±1.38 m/s, p<0.0001), PPao (47.6±8.2 mmHg vs. 40.77±9.6 mmHg, p<0.0001), and Aix (34.4±11.9 % vs. 24.2±12.3 %, p<0.0001); NLR (9.39±5.82 vs. 4.24±2.80, p<0.0001), MLR (0.80±0.58 vs. 0.36±0.19, p<0.0001), and PLR (262±166.1 vs. 141.0±65.2, p<0.0001) were statistically higher in the development cohort comparing to the validation cohort. The overall mean RT (115.5±19.2 ms vs. 128.9±19.3 ms, p<0.0001) was higher in the validation cohort. There was no difference in the mean MPV (9.52±1.16 vs. 9.43±1.29, p=0.721) between the development and validation cohorts.

TABLE 1. Baseline oxidative stress parameters, arterial stiffness measurements, hemogram-derived indices and PCI SYNTAX score II of study patients

	NSTE-ACS N=100	*CCS N=90*	*p-value*
FORT, units/2.36 mmol/l H2O2 eq, M±SD	404.37±9.83	282.34±9.83	**<0.0001**
FORD, mmol/l Trolox eq	1.37±0.035	1.5±0.045	**0.03**
REDOX index, M±SD	69.2±1.47	1.5±0.45	**<0.0001**
Oxidative profile, M±SD	4.56±1.01	1.92±1.26	**<0.0001**
SBPao (mmHg), M±SD	122.1±13.96	111.5±14.17	**<0.0001**
PWVao (m/s), M±SD	10.25±1.92	8.30±1.38	**<0.0001**
PPao (mmHg), M±SD	45.65±9.8	42.41±11.5	**0.01**
AIx (%), M±SD	31.13±14.51	21.84 ± 11.66	**<0.0001**
RT (ms), M±SD	117.5±19.73	132.3±20.2	**<0.0001**
NLR, M±SD	9.79±6.33	2.61±1.39	**<0.0001**
MLR, M±SD	1.83±10.3	0.36±0.19	**<0.0001**
PLR, M±SD	262.2±166.2	141.0 ± 66.8	**<0.0001**
MPV, M±SD	9.52±1.16	9.48±1.20	0.941
PCI SYNTAX score II, M±SD	25.98±11.93	20.81±8.78	**0.002**
PCI 4-year mortality (%), M±SD	8.10±10.07	4.74±7.98	**0.002**

Abbreviations: Aix: augmentation index; CCS: chronic coronary syndrome; FORD: free oxygen radicals defense test; FORT: free oxygen radical test; M±SD: mean ± standard deviation; MLR: monocyte-to-lymphocyte ratio; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; NSTE-ACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; PLR: platelet-to-lymphocyte ratio; PPao: aortic (central) pulse pressure; PWVao: aortic pulse wave velocity; RT: return time of the aortic pulse wave; SBPao: central systolic blood pressure.

TABLE 2. MACEs annual and overall frequency during the 36-month follow-up period

	Development cohort (NSTE-ACS)				*Validation cohort (CCS)*				
	1st year	2nd year	3rd year	Overall	1st year	2nd year	3rd year	Overall	p-value[a]
Death, n	4	7	12	**23**	1	6	0	**7**	**0.004**
Miocardial infarction, n	16	22	17	**55**	8	11	1	**20**	**0.001**
Stroke, n	5	8	16	**29**	2	3	1	**6**	**0.001**
Heart failure hospitalization (HF), n	8	17	12	**37**	2	2	0	**4**	**<0.0001**
Percutaneous coronary intervention (PCI), n	20	25	14	**59**	9	12	1	**22**	**<0.0001**
Coronary artery bypass graft (CABG), n	9	16	9	**34**	1	1	0	**2**	**<0.0001**
Atrial fibrillation (AF), n	18	10	4	**32**	11	0	1	**12**	**0.002**
All major adverse cardiac events (MACEs), n	80	105	84	**269**	34	35	4	**73**	**<0.0001**

[a] *probability value for overall frequencies.*

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TABLE 3. The baseline and annual measures during the 36-month follow-up period

	Development cohort (NSTE-ACS)					*Validation cohort (CCS)*					
	Baseline	**1st year**	**2nd year**	**3rd year**	**Mean**	**Baseline**	**1st year**	**2nd year**	**3rd year**	**Mean**	**p-value[a]**
OXPr, M±SD	4.56±1.01	4.44±0.81	4.1±1.32	3.64±1.78	**4.40±0.77**	1.92±1.26	2.97±1.62	2.89±1.75	2.60±1.89	**2.66±1.33**	**<0.0001**
SBPao, M±SD	122.1±14.0	127.1±15.0	120.7±30.1	108.9±45.5	**126.9±15.5**	111.5±14.2	118.1±19.2	116.9±20.6	109.8±31.6	**117.7±19.4**	**0.013**
PWVao, M±SD	10.3±1.92	10.4±1.96	10.1±2.99	9.01±3.77	**10.4±1.87**	8.30±1.38	8.55±1.42	8.67±1.43	8.21±2.26	**8.56±1.38**	**<0.0001**
PPao, M±SD	45.65±9.8	47.5±8.43	46.1±12.6	41.6±17.5	**47.6±8.2**	42.41±11.5	40.33±9.60	38.06±12.7	38.06±12.4	**40.77±9.6**	**<0.0001**
Aix, M±SD	31.1±14.5	34.7±12.0	32.7±13.7	29.8±15.8	**34.4±11.9**	21.8±11.7	24.1±12.5	24.5±12.7	22.7±13.2	**24.2±12.3**	**<0.0001**
RT, M±SD	117.5±19.7	115.6±19.4	110.8±29.3	102.5±41.1	**115.5±19.2**	132.3±20.2	129.1±19.6	128.6±19.7	124.5±29.9	**128.9±19.3**	**<0.0001**
NLR, M±SD	9.79±3.33	10.2±6.14	8.82±6.75	7.06±6.13	**9.39±5.82**	2.61±1.39	4.30±3.14	5.10±4.10	4.61±4.19	**4.24±2.80**	**<0.0001**
MLR, M±SD	1.83±10.3	0.80±0.57	0.76±0.58	0.69±0.60	**0.80±0.58**	0.36±0.19	0.36±0.19	0.36±0.19	0.33±0.20	**0.36±0.19**	**<0.0001**
PLR, M±SD	262±166.2	262±165.5	248±158.2	232±165.6	**262±166.1**	140.7±64.9	141.1±64.9	134.0±69.8	141.0±65.2	**141.0±65.2**	**<0.0001**
MPV, M±SD	9.52±1.16	9.52±1.16	9.12±2.19	8.43±3.19	**9.52±1.16**	9.48±1.20	9.44±1.29	9.42±1.30	9.01±2.33	**9.43±1.29**	0.721

Abbreviations: Aix: augmentation index, %; CCS: chronic coronary syndrome; M±SD: mean ± standard deviation; MLR: monocyte-to-lymphocyte ratio; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; NSTE-ACS: non-ST-elevation acute coronary syndrome; PLR: platelet-to-lymphocyte ratio; PPao: aortic (central) pulse pressure, mmHg; PWVao: aortic pulse wave velocity, m/s; RT: return time of the aortic pulse wave, ms; SBPao: central systolic blood pressure, mmHg.
[a] probability value for overall frequencies.

The association of the oxidative profile, aortic stiffness parameters, and hemogram-derived indices with long-term MACEs

The multivariate regression analysis assessed the unique contribution of the abovementioned variables in predicting long-term MACEs following PCI in patients with NSTE-ACS and CCS.

Table 4 presents a multiple linear regression analysis investigating the independent association between OXpr, arterial stiffness parameters, HDIs, and 36-month cumulative MACEs. For the comparison of variables measured in different values, we used Z-scores.

TABLE 4. Multiple linear regression analysis coefficients of correlation between Z-scores of average values of oxidative profile (OXpr), arterial stiffness parameters, hemogram-derived indices (HDI), PCI SYNTAX score II, and 36-month MACEs

Model	***Unstandardized/Standardized Coefficients Beta ± SE***	***95% Confidencial Interval***	***p-value***
Zscore(OXpr)	0.181±0.076	0.031, 0.330	**0.018**
Zscore(SBPao)	0.174±0.076	0.025, 0.323	**0.023**
Zscore(Ppao)	0.026±0.061	-0.093, 0.145	0.667
Zscore(Aix)	0.001±0.064	-0.124, 0.127	0.984
Zscore(PWV)	0.063±0.077	-0.090, 0,215	0.420
Zscore(RT)	0.071±0.067	-0.062, 0.203	0.292
Zscore(NLR)	0.505±0.069	0.369, 0.640	**<0.0001**
Zscore(MLR)	-0.053±0.059	-0.170, 0.064	0.368
Zscore(PLR)	0.164±0.056	0.053, 0.276	**0.004**
Zscore(MPV)	0.093±0.048	-0.002, 0.187	0.055
Zscore(SYNTAX II)	-0.077±0.051	-0.178, 0.024	0.136

Abbreviations: Aix: augmentation index; MACEs: major adverse cardiovascular events; MLR: monocyte-to-lymphocyte ratio; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; OXpr: oxidative profile; PLR: platelet-to-lymphocyte ratio; PPao: aortic (central) pulse pressure; PWVao: aortic pulse wave velocity; RT: return time of the aortic pulse wave; SBPao: central systolic blood pressure; SE: standard error.

By the analysis, 4 of 10 variables significantly contributed to predicting long-term MACEs (with R=0.802):

- NLR (coefficient beta=0.505±0.069, p<0.0001);
- OXpr (coefficient beta=0.181±0.076, p=0.018);
- SBPao (coefficient beta=0.174±0.076, p=0.023);
- MLR (coefficient beta=0.174±0.076, p=0.023).

Supplementary materials (Tab.S6-S11) represent multiple linear regression analysis of the correlation between Z-scores of average values of OXpr, arterial stiffness parameters, HDIs, baseline PCI SYNTAX score II, and each constituent of MACEs.

The mean estimated survival time for MACE was 21.68±0.596, 95%CI (20.52, 22.85) months in the development cohort versus 24.77±1.012, 95%CI (22.78, 26.75) months in the validation cohort with OR=3.40, 95%CI (1.87, 6.17) (p=0.05) (Fig.1A).

The all-cause mortality odds ratio for the patients with NSTE-ACS was 3.58, 95%CI (1.46, 8.82), and the mean estimated survival was 32.99±0.67, 95%CI (31.68, 34.30) months versus 34.615±0.433, 95%CI (32.92, 35.64) months in the survival and validation cohorts, respectively (Fig.1B).

FIGURE 1A. Kaplan–Meier survival curves for MACEs in the development and validation cohorts

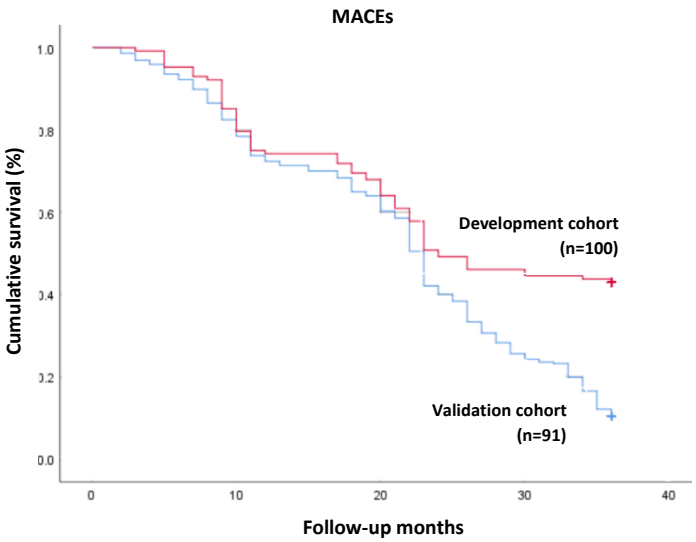
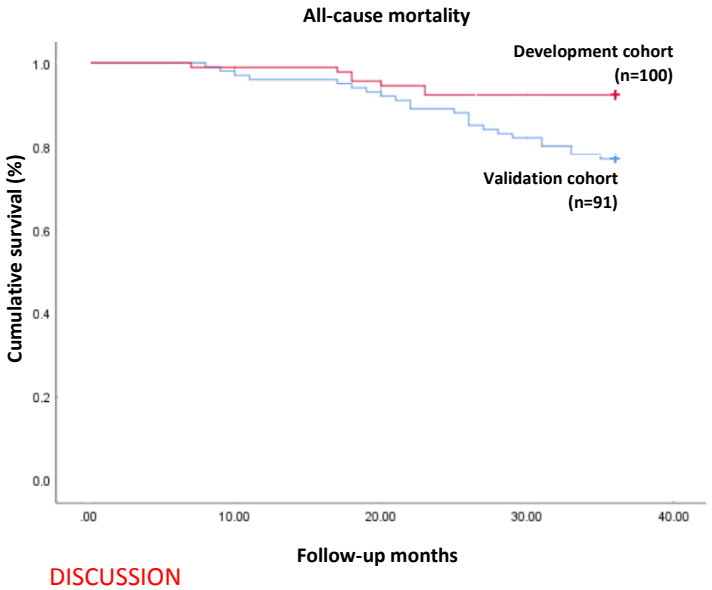


FIGURE 1B. Kaplan–Meier survival curves for all-cause mortality in the development and validation cohorts



DISCUSSION

Despite the achievements of pharmacological and non-pharmacological management of cardiovascular diseases, there is a lack of adequate primary, secondary, tertiary, and quaternary prevention strategies; that is why coronary heart disease (CHD) has remained the leading cause of mortality, representing 32% of all global deaths.[38,41-43]

In recent years, there has been growing evidence regarding the role of oxidative stress,[12-16] arterial stiffness,[17-23,27,28,38,44] and nonspecific inflammation[36,39,45-60] in the pathogenesis of the cardiovascular disease as well as prognosis of long-term cardiovascular events.

The present study evaluated the long-term cardiovascular prognostic value of the novel biomarkers above. We compared their predictive performance with the SYNTAX score II (SS-II) in 191 Georgian patients following PCI because of the non-ST-elevation acute coronary syndrome (NSTE-ACS) or chronic coronary syndrome (CCS).

Recently developed SS-II is a tool that predicts post-procedural outcomes.[5] As we found in our study, in NSTE-ACS patients' postprocedural PCI SS-II and PCI 4-year mortality, as well as periprocedural oxidative profile, arterial stiffness parameters (SBPao, PPao, Aix, PWVao, and RT) and 3 of 4 hemogram-derived indices (NLR, MLR, and PLR) were statistically higher, compared to CCS patients (Tab.1).

Considering the lack of evidence, the particular interest deserves assessment of the correlation between the mentioned novel markers and SS-II. We found a positive correlation between periprocedural OXpr, SBPao, PPao, Aix, PWVao, NLR, PLR, and postprocedural SS-II using univariate linear regression analysis. RT negatively correlated with SS-II (Tab.S2). However, by the multiple regression model, only periprocedural SBPao appeared positively correlated with postprocedural SS-II (Tab.S3).

This result coincides with the pattern of favorability of central blood pressure to predict cardiovascular disease occurrence and complications.[61]

According to the systematic review and meta-analysis made by Hua Yang et al. shown that a high SS-II (> 17) was associated with significantly higher mortality risk (RR: 2.65, 95% CI: 1.05–6.73; P= 0.04) than low SS-II (<17).[62] In our case, there was a strong positive correlation between postprocedural SS-II and 36-month cumulative mortality (Tab.S4)

The results of several studies emphasize the predictive role of the SYNTAX score of a long-term MACE.[63-65] A strong positive correlation was found in our case by the univariate regression model (Tab.S5). However, the multiple linear regression analysis revealed that NLR (0.505±0.069, p<0.0001), OXpr (0.181±0.076, p=0.018), SBPao (0.174±0.076, p=0.023) and PLR (0.164±0.056, p=0.004), but not PCI SS-II (-0.077±0.051, p=0.136) strongly correlate with 36-month MACEs following PCI because of NSTE-ACS or CCS.

By the multivariate analysis of the unique contribution of all the mentioned measures in the prediction of each long-term adverse cardiovascular event, we found positive correlations between:

- SS-II, NLR, PLR, and cumulative mortality (Tab.S6);
- NLR, OXpr, SBPao, PLR, and cumulative incidence of myocardial infarction (Tab.S7);
- NLR and cumulative incidence of stroke (Tab.S8);
- NLR, PLR, and incidence of hospitalization because of heart failure (Tab.S9);
- NLR and cumulative incidence of revascularization procedures (Tab.S10);
- NLR, PLR, MPV, and cumulative incidence of atrial fibrillation (Tab.S11).

Our results suggest that the oxidative stress profile, central systolic blood pressure, and hemogram-derived indices such as neutrophil-lymphocyte and monocyte-lymphocyte ratios may be used as novel independent predictors of long-term major adverse cardiovascular events.

There are some limitations to this study. First, our study was single-center observational research with a limited sample size, which might have affected obtained results. Another limitation is the analysis of different types of coronary artery disease (NSTE-ACS and CCS) and the extent/complexity of coronary artery involvement. Nevertheless, using SYNTAX score II, which quantifies the magnitude of coronary involvement, this limitation might not affect the results to a significant extent.

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SUPPLEMENTARY MATERIALS

Supplementary materials represent demographic characteristics (Tab.S1) and medical history of study patients, uni- and multivariate analysis of baseline (Tab.S2-S5), and 36-month follow-up measurements (Tab.S6-S11).

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