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ORIGINAL RESEARCH

Correlations Between Acute Coronary Syndrome and Novel Inflammatory Markers (Systemic Immune-Inflammation Index, Systemic Inflammation Response Index, and Aggregate Index of Systemic Inflammation) in Patients with and without Diabetes or Prediabetes

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Purpose: Type 2 diabetes mellitus (DM) is a recognized independent risk factor for both chronic coronary syndrome (CCS) and its complication, acute coronary syndrome (ACS). Patients with DM and prediabetes (preDM) face an increased ACS risk. Inflammation plays a significant role in the pathogenesis of both CCS and ACS. This study delves into novel inflammatory markers, such as the systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI, also known as SIIRI or PIV), to explore their relationship with ACS and CCS in patients that have been or have not been diagnosed with DM or preDM.

Patients and Methods: This study included data of 493 patients with chest pain undergoing coronary angiography. They were categorized into four groups: 1) without DM/preDM and with CCS; 2) with both DM/preDM and CCS; 3) without DM/preDM and with ACS, 4) with both DM/preDM and ACS. Standard methods of statistical analysis were used to reveal possible differences between groups and to find the most influential ACS risk factors in groups with DM/preDM and without DM/preDM.

Results: The analysis showed no significant differences in SII, SIRI, or AISI between the respective patient groups. A logistic regression analysis generated a model incorporating SII, high-density lipoprotein, and low-density lipoprotein levels as the influential ACS risk factors for patients with DM/preDM. The model demonstrated 71.0% accuracy, 37.0% sensitivity, and 89.4% specificity.

Conclusion: The findings suggest that the aforementioned inflammatory markers may have potential for distinguishing DM/preDM patients at higher risk of ACS at a low financial cost. However, further comprehensive and well-designed research is required to validate their clinical utility.

Plain Language Summary: People with type 2 diabetes (DM) and prediabetes (preDM) have a higher risk of heart problems. These include chronic coronary syndrome (CCS) and acute coronary syndrome (ACS). Inflammation is a key element in these issues. We looked at 493 patients with chest pain. We divided them into groups based on diabetes status (DM/preDM vs no diabetes) and heart conditions (ACS and CCS). We explored new markers related to inflammation. These include the systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) that all can be calculated from simple blood tests. We found no differences in these markers between groups. To understand ACS risk factors better, we used statistical analysis. The model found key factors for patients with DM/preDM: SII, LDL, and low-density lipoprotein levels. It was accurate (71.0%), but sensitivity was 37.0%, and specificity was 89.4%. These markers could be helpful in identifying DM/preDM patients at risk of ACS with low cost tests. We need more research to confirm their use in real-life medical settings.

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Introduction

Type 2 diabetes mellitus (DM) is an independent risk factor for chronic coronary syndrome (CCS) and its complication, acute coronary syndrome (ACS).[1] Epidemiological data revealed that almost a third of DM patients are concurrently affected with cardiovascular disease, and approximately one in ten suffered from ACS.[2]

Inflammation is a pivotal factor in the pathogenesis of both DM and atherosclerosis, one of the underlying causes of CCS.[3] Inflammatory processes influence various mechanisms involved in atherosclerotic plaque formation and rupture, ultimately culminating in the onset of ACS.[4]

Recently, the degree of inflammation has been characterized in terms of the ratios of various leukocyte subtypes in the complete blood count: the systemic immune-inflammation index (SII) the systemic inflammation response index (SIRI), and the aggregate index of systemic inflammation (AISI), which is also referred to as systemic immune-inflammation response index (SIIRI) or pan-immune-inflammation value (PIV). These markers have previously demonstrated their utility in predicting clinical outcomes in cardiovascular diseases. SII was established as a risk factor for the occurrence and severity of CSS,[5–7] and was independently associated with cardiovascular[8] and all-cause mortality,[9,10] as well as hospital readmission due to heart failure,[11,12] or major adverse cardiovascular events (MACE)[13,14] in patients with ACS. SIRI was described to correlate with the occurrence of ACS in patients with CCS,[6,7] and was recognized as an independent risk factor for MACE in patients with ACS who underwent PCI.[15,16] AISI was identified as an independent predictor of adverse outcomes in patients with ACS who underwent PCI.[17] Considering their cost-effectiveness, accessibility, and potential clinical significance, this study aims to investigate the relationship between these inflammatory markers and the diagnosis of ACS or CCS in patients with and without DM or preDM (DM/preDM).

Patients and Methods

Population

The data for this study comprised a total of 699 cases of patients who presented with chest pain and subsequently underwent coronary angiography. These data were collected between 2013 and 2017 at Bielanski Hospital in Warsaw, Poland. All patients included in the study had received diagnoses of CCS or ACS and provided written consent for their data to be included. The study was approved by the Medical University of Warsaw bioethics committee (KB/124/2014) and was carried out in accordance with the Declaration of Helsinki. The grouping of patients with preDM and DM into a single DM/preDM category was based on a recent meta-analysis that indicated no significant differences in all-cause mortality, recurrent MACE, or cardiovascular death between patients with DM and those in the preDM group.[18] However, these groups were notably distinct from patients without DM. Cases involving patients with viral or bacterial infections, active neoplasia, or paraneoplastic syndromes were not incorporated into the database. Furthermore, nine cases were excluded due to incomplete data, and an additional 197 cases were excluded because they exhibited elevated inflammatory markers (defined as elevated erythrocyte sedimentation rate (ESR) and/or white blood cell (WBC) count exceeding 10,000 cells/μL, and/or C-reactive protein (CRP) levels exceeding 5 mg/L). Consequently, the final analysis encompassed 493 cases.

Clinical and Laboratory Data

Sex, age, comorbidities (DM or preDM, dyslipidemia, hypertension), smoking, and statin therapy status were obtained during the admission process. Standing height and weight were measured with a standard electronic scale with a telescopic measuring rod (Bielskie Wagi, Zywiec, Poland). Smoking status was separated into three categories: smokers (*yes* category in the tables), ex-smokers, and never-smokers (*no* category in the tables). To qualify as a smoker, a patient had to claim that they had smoked daily or less frequently up to their current age, and that they had smoked more than 100 cigarettes

throughout their lifetime. Ex-smokers were defined as having smoked more than 100 cigarettes and not smoking for at least a year. Never-smokers had never smoked or had smoked no more than 100 cigarettes in their lifetime.[19]

Laboratory tests were carried out on blood samples from the cephalic vein and examined with standard clinical chemical analysis in hospital laboratory using SYSMEX XT2000i analyzer (up to 10 April 2014) or SYSMEX XN1000 analyzer (since 11 April 2014; SYSMEX, Kobe, Japan) for total blood count and Cobas Integra 400 Plus (Roche Diagnostics, Rotkreuz, Switzerland) for lipid profile. Body mass index (BMI) was calculated as body mass/height^2 (kg/m^2). PreDM was used as an umbrella term for impaired fasting glycaemia (diagnosed if fasting plasma glucose (FPG) was between 100 and 125 mg/dL twice) and impaired glucose tolerance (diagnosed if oral glucose tolerance test (OGTT) resulted with glucose concentrations between 140 and 199 mg/dL); DM was diagnosed if FPG ≥ 126 mg/dL twice or random plasma glucose measurement ≥200 mg/dL with symptoms of hyperglycemia or OGTT ≥ 200 mg/dL.[20] Hypertension (HTN) was diagnosed if systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) ≥ 140 mmHg and ≥ 90 mmHg, respectively, in at least two office measurements; or average SBP and/or DBP ≥ 135 mmHg and ≥ 85 mmHg, respectively, in multiple measurements outside the office.[21] Diagnostic criteria of dyslipidemia were used to assess total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels in each patient independently of statin intake.[22] SII was calculated as (neutrophil count) · (platelet count)/(lymphocyte count), SIRI as (neutrophil count) · (monocyte count)/(lymphocyte count), and AISI as (neutrophil count) · (monocyte count) · (platelet count)/(lymphocyte count).

All patients included in this study underwent coronary angiography, which was performed using either radial or femoral access, in order to evaluate the presence of significant stenoses and to carry out percutaneous coronary intervention (PCI) when necessary.[23] The diagnosis of ACS followed the criteria outlined in the European Society of Cardiology guidelines for the management of acute coronary syndromes.[24] This diagnosis required that increased myocardial necrosis markers, particularly troponin, be present in conjunction with at least one of the following criteria: symptoms indicative of myocardial ischemia, recent signs of ischemia or the presence of pathological Q waves on the electrocardiogram, evidence of new loss of viable myocardium in imaging studies, detection of a fresh segmental disturbance in heart wall movement, or the observation of a coronary artery thrombus during angiography.

Statistical Analysis

The dataset was divided into four groups: patients without DM or preDM (DM/preDM) and with CCS, with DM/preDM and CCS, without DM/preDM and with ACS, with DM/preDM and ACS. The normality of continuous data was analyzed with the Kolmogorov–Smirnov test. Continuous variables were shown as medians with interquartile range (IQR 25–75) and compared using Mann–Whitney *U*-test or Kruskal–Wallis *H*-test with post-hoc Dunn test, where applicable. Categorical variables were presented as numbers (%) and compared with chi-square test. A binomial logistic regression analysis was used to assess the impact of variables, including BMI, age, sex, smoking, previous myocardial infarction (MI), diagnosis of hypertension and dyslipidemia, TC, HDL, LDL, TG concentrations, SII, SIRI, and AISI values. A stepwise backward multivariate logistic regression was used to identify risk factors contributing to ACS from the abovementioned variables in the groups. At each step, the variables were eliminated using the likelihood ratio to set a limit on the total number of variables included in the final models. The Hosmer–Lemeshow goodness of fit test was used to assess the generated models. Receiver-operating characteristic curves were calculated to assess the cutoff values for generated models, and the area under the curve (AUC) with 95% confidence interval was calculated to compare their differentiating capability. The correlations between those indices were evaluated with Spearman's rank correlation coefficient. The two-sided level of P-value ≤0.05 was considered significant. Analyses were performed using IBM SPSS Statistics for Windows, version 29.0.0.0 (241) software (IBM Corp., Armonk, N.Y., USA).

Results

Characteristics of the Population. Differences in Selected Biomarkers Between Groups of Patients

The final analysis included data of 493 patients – 300 (60.9%) males and 193 (39.1%) females, with a median age of 66.74 (IQR 59.99–75.37). The median BMI value (N = 468) was 27.68 (IQR 24.86–30.97). DM/preDM group consisted

158 (32.0%) patients with DM and 23 (4.7%) with pre-DM, and the remaining patients were classified as no DM/preDM group. Active smoking was declared by 122 (26.2%) patients, 56 (12.0%) smoked in the past, and 288 (61.8%) never smoked (N = 466). During the hospitalization, ACS was diagnosed in 220 (44.6%) patients, and CSS was diagnosed in 273 (55.4%) patients. 167 (33.9%) patients had MI diagnosed before the hospitalization. Lipid profile (medians and IQR of: TC 170.08 mg/dL (IQR 143.65–202.05), HDL 47.76 mg/dL (IQR 39.71–57.93), LDL 94.60 mg/dL (IQR 71.62–122.90), TG 113.77 mg/dL (IQR 85.64–157.04) was assessed in 452 patients, and 257 (56.9%) of those patients were diagnosed with hyperlipidemia. The median and IQRs of WBC and platelet counts were as follows: leukocytes 7.40 k/μL (IQR 6.20–8.50), neutrophils 4.37 k/μL (IQR 3.50–5.26), lymphocytes 1.91 k/μL (IQR 1.55–2.36), monocytes 0.67 k/μL (IQR 0.54–0.82), platelets 211.00 k/μL (IQR 179.00–248.00). The median and IQR values of markers were assessed as follows: SII 469.88 (IQR 353.98–641.38), SIRI 1.50 (IQR 1.01–2.12), AISI 343.54 (IQR 226.75–543.26). When comparing the abovementioned parameters between males and females, significant differences with small effect size were found in age, TC, HDL and platelet count (Mann–Whitney U). Women were older ($z = -5.78$, $p \leq 0.001$), had higher concentration of TG ($z = -3.07$, $p = 0.002$), HDL ($z = -4.58$, $p < 0.001$), and platelet count ($z = -3.62$, $p < 0.001$). Table 1 depicts an analysis of the differences between four groups of patients: without DM/preDM and with CCS, with DM/preDM and CCS, without DM/preDM and with ACS, and with DM/preDM and ACS.

Factors Associated with ACS in Patients with and without DM/preDM

Table 2 presents the results of the logistic regression analysis of all possible factors associated with the probability of ACS in subgroups with and without DM/preDM. For patients with DM/preDM, the accuracy, sensitivity, and specificity were estimated at 71.0%, 39.1%, and 88.2%, respectively (Nagelkerke $R^2 = 0.22$; $\chi^2 = 22.65$, $p = 0.046$; Hosmer–Lemeshow goodness of fit $\chi^2 = 15.36$, $p = 0.052$; AUC = 0.726). For patients without DM/preDM, the accuracy, sensitivity, and specificity were estimated at 72.2%, 72.5%, and 71.9%, respectively (Nagelkerke $R^2 = 0.31$; $\chi^2 = 59.84$, $p < 0.001$; Hosmer–Lemeshow goodness of fit $\chi^2 = 5.88$, $p = 0.661$; AUC = 0.783). Total cholesterol, WBC subtypes count, and platelet count were omitted due to collinearity (variance inflation factor > 5).

To distinguish the factors contributing to the risk of ACS, models were generated using stepwise backward elimination (Table 3). For patients with DM/preDM, the model includes HDL, LDL, and SII as its constituents. The model's performance metrics were as follows: accuracy was estimated at 71.0%, sensitivity at 37.0%, and specificity at 89.4%.

Conversely, for patients without DM/preDM, the model excluded the new inflammatory markers. The model's performance metrics in this context were as follows: accuracy was calculated at 70.4%, sensitivity at 71.6%, and specificity at 69.4%.

Discussion

In our study, we examined the levels of SII, SIRI, and AISI in four patient groups: those 1) without DM/preDM and with CCS; 2) with both DM/preDM and CCS; 3) without DM/preDM and with ACS, 4) with both DM/preDM and ACS. Our findings indicate no statistically significant differences in these inflammatory markers across these groups. However, further investigation suggests that combining SII with LDL and HDL could potentially serve as an indicator of possible ACS in patients with chest pain and DM/preDM during hospital admission. This novel approach to risk assessment warrants additional investigation to elucidate its clinical significance.

It is noteworthy that our results may not be easily comparable to existing studies, as most investigations analyzing inflammatory biomarkers adopt a prospective design with endpoints, such as hospital readmission, MACE occurrence, or mortality. Notably, SII has previously been established as a risk factor for the occurrence and severity of CCS,[5–7] demonstrating its utility in cardiovascular risk stratification,[13] thrombus burden prediction[25,26] and the no-reflow phenomenon in ACS patients.[27,28] Additionally, SII has shown independent associations with cardiovascular[8] and all-cause mortality,[9,10] as well as hospital readmission due to severe heart failure[11] or MACE[13,14] in patients with ACS. In patients with DM, SII has displayed strong associations between all-cause and cardiovascular mortality.[10]

Similarly, SIRI has been associated with various cardiovascular outcomes, including correlation of this marker with 10-year cardiovascular risk in the rural population[29] and the occurrence of ACS in patients with CCS.[6,7] SIRI was also closely associated with cardiovascular and all-cause mortality in the entire population,[8,30] as well as with long-term

Table 1 Differences in Variables Between Groups of Patients. Values are Presented as Numbers (%) or Medians (IQR). P-values Were Calculated Using Pearson's Chi-Square (Dichotomous Data) or Kruskal–Wallis *H*-Test (Non-Parametric Continuous Data); Subsets of Groups That Do Not Differ Significantly from Each Other For a Particular Variable at the $p = 0.05$ Level are Denoted with Consecutive Letters (a, b, …). For All Tests $Df = 3$

Total N = 493	**No IGM, CCS, N = 166**	**IGM, CCS, N = 107**	**No IGM, ACS, N = 146**	**IGM, ACS, N = 74**	**X^2 (3)**	**H (3)**	***p*-value**
N of cases [♂/♀]	93 (18.9) / 73 (14.8) a	68 (13.8) / 39 (7.9) a	96 (19.5) / 50 (10.1) a	43 (8.7) / 31 (6.3) a	3.66	–	0.301
Age, [years]	68.63 (61.37–76.09) a	68.43 (61.45–75.11) a	63.99 (55.82–73.27) b	67.96 (60.67–76.37) a, b		13.50	0.004
BMI, [kg/m^2], N = 468	27.05 (26.61–30.48) a	28.72 (25.86–32.05) b	26.23 (24.22–29.39) a	29.39 (26.03–33.25) b		27.50	<0.001
Hyperlipidemia† [yes/no]	85 (18.8) / 65 (14.4) a	48 (10.6) / 52 (11.5) a	86 (19.0) / 50 (11.1) a	38 (8.4) / 28 (6.2) a	5.47	–	0.140
Total cholesterol† [mg/dL]	178.98 (148.57–217.15) a	160.16 (129.59–191.54) b	173.22 (145.14–205.55) a	162.71 (144.09–201.73) a, b	–	14.67	0.002
HDL† [mg/dL]	56.26 (44.21–63.04)	46.52 (40.21–55.43) a	46.45 (38.23–52.39) a	42.78 (36.26–50.08) a	–	39.93	<0.001
LDL† [mg/dL]	93.59 (71.68–128.56) a	78.68 (59.11–98.14)	101.81 (78.24–131.70) a	101.21 (71.84–121.31) a	–	24.67	<0.001
TG† [mg/dL]	115.7 (81.52–158.12)	118.39 (90.49–172.11)	105.94 (85.03–139.00)	119.82 (84.68–163.26)	–	6.80	0.079
HTN [yes/no]	121 (24.5) / 45 (9.1) a	102 (20.7) / 5 (1.01) b	123 (25.0) / 23 (4.7) a, c	71 (14.4) / 3 (0.6) b, c	34.214	–	<0.001
Previous MI [yes/no]	40 (8.1) / 126 (25.6) a	34 (6.9) / 73 (14.8) a, b	58 (11.8) / 88 (17.9) b	35 (7.1) / 39 (7.9) b	15.48	–	0.001
Smoking [yes or in the past / no], N = 466	56 (12.0) / 99 (21.2) a, b	30 (6.4) / 72 (15.5) b	66 (14.2) / 74 (15.9) a	26 (5.6) / 43 (9.2) a, b	8.37	–	0.039
Leukocytes [k/μL]	7.3 (5.80–8.38)	7.50 (6.18–8.48)	7.20 (6.23–8.40)	7.80 (6.38–8.73)	–	4.49	0.213
Neutrophils [k/μL]	4.33 (3.37–5.14)	4.37 (3.48–5.49)	4.26 (3.51–5.10)	4.69 (3.72–5.61)	–	4.29	0.231
Lymphocytes [k/μL]	1.85 (1.49–2.40)	1.92 (1.55–2.39)	1.91 (1.55–2.36)	1.92 (1.58–2.22)	–	0.18	0.981
Monocytes [k/μL]	0.67 (0.54–0.83)	0.66 (0.51–0.80)	0.66 (0.53–0.79)	0.69 (0.57–0.86)	–	4.37	0.224
Platelets [k/μL]	209.00 (179.50–249.00)	200.00 (177.00–236.50)	214.50 (180.00–251.25)	220.00 (179.50–252.75)	–	3.24	0.356
SII	467.55 (354.09–610.32)	439.06 (338.79–640.84)	470.06 (357.69–623.73)	564.88 (370.28–747.78)	–	6.22	0.101
SIRI	1.53 (1.02–2.11)	1.40 (0.93–2.13)	1.43 (1.02–2.08)	1.68 (1.11–2.48)	–	4.81	0.186
AISI	340.28 (238.97–538.66)	352.82 (224.09–573.71)	353.86 (209.13–542.41)	307.50 (196.33–520.76)	–	2.20	0.533

Note: † N = 452.

Abbreviations: ACS, acute coronary syndrome; CCS, chronic coronary syndrome; TG, triglycerides; HTN, hypertension; MI, myocardial infarction; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; AISI, aggregate index of systemic inflammation.

Table 2 Binomial Logistic Regression Analysis of Factors Associated with ACS Diagnosis in Patients with and without DM/preDM

		Category	B	S.E. B	Wald	*p*-value	Odds Ratio (95% CI)
No DM/preDM	BMI	–	−0.113	0.04	7.798	0.005	0.893 (0.825–0.967)
	Age	–	−0.021	0.016	1.841	0.175	0.979 (0.949–1.01)
	Smoking	Yes or in the past	0.227	0.329	0.479	0.489	1.255 (0.659–2.391)
	Previous MI	Yes	0.7	0.333	4.424	0.035	2.013 (1.049–3.864)
	Sex	Men	−0.528	0.342	2.384	0.123	0.59 (0.302–1.153)
	HTN	–	0.695	0.393	3.132	0.077	2.004 (0.928–4.327)
	HDL	–	−0.077	0.015	26.302	<0.001	0.926 (0.899–0.954)
	LDL	–	0.004	0.006	0.465	0.495	1.004 (0.992–1.016)
	TG	–	−0.012	0.004	9.395	0.002	0.988 (0.98–0.996)
	Hyperlipidemia	Yes	0.284	0.468	0.369	0.544	1.329 (0.531–3.324)
	SII	–	0.002	0.001	2.643	0.104	1.002 (1–1.004)
	SIRI	–	−0.456	0.278	2.692	0.101	0.634 (0.368–1.093)
	AISI	–	−0.001	0.001	1.686	0.194	0.999 (0.998–1)
	Const.	–	9.018	2.125	18.016	<0.001	8253.235
DM/preDM	BMI	–	−0.031	0.045	0.485	0.486	0.969 (0.888–1.058)
	Age	–	−0.017	0.027	0.388	0.533	0.983 (0.932–1.037)
	Smoking	Yes or in the past	−0.142	0.501	0.081	0.776	0.867 (0.325–2.317)
	Previous MI	Yes	0.359	0.436	0.678	0.41	1.432 (0.609–3.363)
	Sex	Men	−0.412	0.486	0.72	0.396	0.662 (0.256–1.716)
	HTN	–	−0.351	1.07	0.108	0.743	0.704 (0.086–5.73)
	HDL	–	−0.061	0.022	7.707	0.005	0.941 (0.902–0.982)
	LDL	–	0.016	0.007	4.867	0.027	1.016 (1.002–1.031)
	TG	–	−0.006	0.005	1.926	0.165	0.994 (0.985–1.003)
	Hyperlipidemia	Yes	0.298	0.621	0.23	0.631	1.347 (0.399–4.547)
	SII	–	0.001	0.001	1.361	0.243	1.001 (0.999–1.004)
	SIRI	–	0.102	0.282	0.131	0.717	1.108 (0.637–1.925)
	AISI	–	0	0.001	0.001	0.98	1 (0.999–1.001)
	Const.	–	3.185	3.141	1.028	0.311	24.162

Abbreviations: ACS, acute coronary syndrome; CCS, chronic coronary syndrome; TG, triglycerides; HTN, hypertension; MI, myocardial infarction; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; AISI, aggregate index of systemic inflammation.

survival of patients after off-pump coronary artery bypass surgery.[31] Our own findings do not reveal significant differences in SIRI among the investigated patient groups, emphasizing the need for well-designed investigations to further explore its potential utility as a predictor or marker in cardiovascular and related health outcomes.

Table 3 The Regression Model for the Prediction of ACS in Patients with and without DM/preDM

	Variable	Category	B	S.E. B	Wald	*p*-value	Odds Ratio (95% CI)
No DM/preDM	BMI	–	−0.100	0.038	6.875	0.009	0.905 (0.840–0.975)
	Previous MI	Yes	0.648	0.309	4.405	0.036	1.913 (1.044–3.504)
	HDL	–	−0.066	0.013	24.627	<0.001	0.936 (0.912–0.961)
	TG	–	−0.009	0.003	8.227	0.004	0.991 (0.985–0.997)
	Const.	–	6.856	1.463	21.968	<0.001	949.815
	Nagelkerke R^2 = 0.23; χ^2 = 43.3, p < 0.001; Hosmer–Lemeshow goodness of fit χ^2 = 6.823, p = 0.556; AUC = 0.728; YI = 0.390 for cut-off value = 0.484.						
DM/preDM	HDL	–	−0.052	0.019	7.259	0.007	0.949 (0.914–0.986)
	LDL	–	0.016	0.006	8.371	0.004	1.016 (1.005–1.028)
	SII	–	0.002	0.001	5.352	0.021	1.002 (1.000−1.003)
	Const.	–	−0.660	0.924	0.510	0.475	0.517
	Nagelkerke R^2 = 0.18; χ^2 = 17.9, p < 0.001; Hosmer–Lemeshow goodness of fit χ^2 = 15.221, p = 0.055; AUC = 0.688; YI = 0.383 for cut-off value = 0.395.						

In the case of AISI, despite its demonstrated superior predictive value for mortality and the severity of CCS when compared to other markers derived from the total blood count,[32,33] our study did not identify statistically significant differences among the patient groups. Nonetheless, previous research supports AISI as an independent predictor of adverse outcomes in patients with ACS who underwent PCI,[17] and in those with post-cardiotomy vasoplegia syndrome in patients following cardiopulmonary bypass.[34]

Our multivariate logistic regression analysis reveals that SII employed in a model with HDL and LDL may serve as an indicator for potential ACS in patients experiencing chest pain and having DM or preDM. While this model is a novel concept, it bears similarities to models found in the literature. Notably, recent research has identified the synergistic effect of SII and SIRI in enhancing a predictive model for in-hospital death in elderly ACS patients. This model incorporated age, BMI, previous stroke, and DM.[35] Additionally, SII demonstrated its ability to significantly enhance the concordance index for predicting all-cause and cardiovascular mortality in a prospective investigation involving a substantial cohort of individuals with CCS, incorporating glucose metabolism status as a variable.[10]

Furthermore, in the context of CCS, the addition of SII to a baseline model that included traditional risk factors (age, gender, chest pain, DM, hypertension, hyperlipidemia, and smoking) resulted in an improved correlation with the Coronary Artery Disease-Reporting and Data System score.[36] These findings, along with our own results, underscore the potential significance of SII and, potentially, SIRI as valuable predictive factors in the field of cardiology, particularly for groups of patients with increased cardiovascular risk.

Our study has revealed a noteworthy inverse relationship between TG levels and the diagnosis of ACS in patients without DM/preDM. This finding adds complexity to the existing discourse on TG management, particularly in individuals at high cardiovascular risk. Current recommendations advocate for lowering TG levels in patients with elevated cardiovascular risk.[22] However, our results align with reports suggesting a potential "TG paradox".[37] Lower TG levels (≤150 mg/dl) have been correlated with increased all-cause mortality in patients with cardiovascular diseases,[37,38] as well as identified as a risk factor for in-hospital and late major adverse events in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention.[39] Furthermore, a U-shaped association between non-fasting TG and fatal cardiovascular events has been described in the general Japanese population. In individuals aged ≥65 years, lower non-fasting TG levels were associated with an increased risk of cardiovascular mortality, while higher levels had a stronger impact in those aged <65 years.[40] The underlying mechanisms of this

"TG paradox" remain unclear and may involve factors such as nutritional status, heparin use, sympathetic activity during the acute phase of myocardial injury, and potential protective roles in plaque buildup.[37] The complexity of TG levels in cardiovascular outcomes underscores the need for comprehensive research. Our findings, along with the existing literature, suggest that further investigations into the relationship between TG levels and cardiovascular events should consider additional factors, including aforementioned inflammatory indices and other biochemical factors like the triglyceride-glucose index, which has been shown to predict MACE in patients with high cardiovascular risk and long-term mortality in heart failure patients.[41,42]

This study exhibits certain limitations that need to be considered. First, its retrospective, cross-sectional, and observational design precludes the formulation of causal relationships among the variables investigated. Second, the study was conducted on a relatively small number of patients, lacking the requisite demographic diversity to provide a comprehensive representation of the population. The potential influence of statin usage and the metabolic control of DM could not be fully assessed due to the inadequacy of available data concerning medication dosages, therapy duration, and glycated hemoglobin levels. Furthermore, the assessment of smoking habits lacked more precise quantification (e.g. pack-years). While patients with elevated ESR, CRP and WBC count were excluded from the study, other markers of inflammation, such as tumor necrosis factor-alpha, interleukin-6, and ferritin, were not measured. The proposed models were not validated due to the limited number of cases available. These limitations should be taken into account when interpreting the study's findings, as they emphasize the need for more comprehensive research in the future.

The heightened prevalence of cardiovascular diseases in individuals with DM or preDM, coupled with their increased susceptibility to ACS, underscores the urgency of identifying new risk factors and enhancing preventive measures. The advent of artificial intelligence and machine learning introduces promising avenues for achieving these goals, as highlighted in recent research.[43]

Although our studies did not reveal a significant association between ACS and the systemic SII, SIRI, and AISI in the cohort of cardiovascular patients that have or have not been diagnosed with DM or preDM, our regression analysis, coupled with insights from other research, suggest that novel inflammatory markers based on leukocyte subtypes could potentially emerge as valuable tools. These markers may aid in distinguishing DM/preDM patients with a higher likelihood of ACS when presenting with chest pain. Considering the aforementioned results that underscore the complexity of inflammatory markers in the context of cardiovascular risk assessment, there is a compelling need for further comprehensive and well-designed investigations. Therefore, expanding research efforts to encompass demographically diverse patient groups is crucial for our understanding and establishing the potential utility of these novel inflammatory markers.

Conclusion

Within our cohort of patients presenting with chest pain, no statistically significant differences were discerned in SII, SIRI, and AISI across the defined groups: those without DM or preDM and with CCS, those with DM/preDM and CCS, those without DM/preDM and with ACS, and those with DM/preDM and ACS. Our findings suggest the potential utility of SII in combination with LDL and HDL as a predictive tool for identifying ACS in patients with chest pain and DM or preDM. However, this model remains at a need to be validated through further in-depth and well-designed research.

Abbreviations

ACS, acute coronary syndrome; AISI, aggregate index of systemic inflammation; AUC, area under the curve; CCS, chronic coronary syndrome; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, type 2 diabetes mellitus; ESR, erythrocyte sedimentation rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HTN, hypertension; IQR, interquartile range; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; MI, myocardial infarction; OGTT, oral glucose tolerance test; PCI, percutaneous coronary intervention; preDM, prediabetes; SBP, systolic blood pressure; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; TC, total cholesterol; TG, triglycerides; WBC, white blood cells.

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Disclosure

All authors report no conflicts of interest in this work.

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