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Systemic Immune-Inflammation Index vs Metabolic Indices for the Prediction of Chronic Coronary Artery Disease Severity

Índice de inmunidad-inflamación sistémica vs índices metabólicos en la predicción de severidad de enfermedad arterial coronaria crónica

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Abstract

Introduction. Inflammation, insulin resistance, and dyslipidemia are key pathophysiological mechanisms involved in atherosclerotic cardiovascular disease which may be quantified by the systemic immune-inflammation index (SII), the triglyceride-glucose index (TyG), and the lipid accumulation product (LAP), respectively.

Objective. To compare the predictive capacity of the SII, TyG and LAP for coronary artery disease (CAD) severity.

Methodology. A cross-sectional study was conducted on 73 patients with chronic CAD; cardiovascular risk factors, statin use and laboratory values were evaluated. CAD severity was determined through assessment of angiographic features for the application of the SYNTAX score. The SII was calculated as absolute platelet count × (absolute neutrophil count / absolute lymphocyte count); while the TyG index was calculated using the formula: ln [triglycerides × fasting glucose] / 2, on a logarithmic scale; and LAP was calculated as waist circumference (cm) − 65 × triglycerides (mmol/L) for men; and waist circumference − 58 × triglycerides for women.

Results. The average age was 59.5±7.7 years, with a predominance of men in the sample (50.7%; n = 37). Of the indices evaluated, SII showed the greatest area under the curve (AUC) for the prediction of moderate to severe CAD (AUC: 0.73 CI95%: 0.61-0.85), a cut-off point off 378.4 with a sensitivity of 71.4% and specificity of 66.6%. In the multivariate analysis, subjects with an SII value ≥378.4 displayed an increased risk for higher CAD severity (OR: 7.56; CI95%: 1.62-35.28; P = 0.01).

Conclusions. SII had a greater predictive capacity for moderate to severe CAD in comparison to TyG and LAP, demonstrating the importance of inflammation in chronic atherosclerotic disease.

Data availability
All data supporting the findings of this study are available within the article. For additional details, please contact the corresponding author.

Author Contributions
Juan Salazar: conceptualization, methodology, writing – original draft.
Soledad Briceño: conceptualization, methodology, writing – review & editing.
Mayela Bracho: formal analysis, writing – original draft.
Carlos Esis: data curation, formal analysis.
Egle Silva: investigation, methodology, writing – review & editing.
Roberto Añez: data curation, writing – original draft.

Generative AI declaration
The authors declare that no generative AI tools were used in the writing, editing, data analysis, or any other part of the preparation of this manuscript.

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Keywords

Coronary artery disease; inflammation; insulin resistance; dyslipidemia; severity.

Resumen

Introducción. La inflamación, la resistencia a la insulina y la dislipidemia son mecanismos fisiopatológicos implicados en la enfermedad cardiovascular aterosclerótica, que podrían cuantificarse mediante el índice de inmunidad-inflamación sistémica (IIIS), el índice triglicéridos-glucosa (ITG), y el producto de acumulación lipídica (LAP), respectivamente.

Objetivo. Comparar la capacidad predictiva del IIIS, ITG y LAP para la severidad de la enfermedad arterial coronaria (EAC).

Metodología. Se realizó un estudio transversal en 73 pacientes con EAC crónica, en quienes se evaluaron factores de riesgo cardiovascular, consumo de estatinas y valores de laboratorio. La severidad de la EAC se determinó mediante características angiográficas empleadas para calcular el puntaje SYNTAX. La fórmula para calcular el IIIS fue: contaje de plaquetas * (contaje de neutrófilos / contaje de linfocitos), para el ITG: Ln (Triglicéridos * Glucemia / 2) y para LAP: circunferencia de cintura – 65 * triglicéridos para hombres, circunferencia de cintura – 58 * triglicéridos para mujeres.

Resultados. El promedio de edad fue 59,5±7,7 años, predominó el sexo masculino (50,7%; n = 37). De los índices evaluados, el IIIS mostró una mayor área bajo la curva (AUC) para predicción de EAC moderada o severa (AUC: 0,73 IC95%: 0.61-0.85), un punto de corte de 378,4 ofrece una sensibilidad de 71,4% y especificidad de 55,6%. En el análisis multivariante, aquellos con valores ≥378,4 mostraron un riesgo superior para mayor severidad de EAC (OR: 7,56; IC95%: 1,62-35,28; P = 0,01).

Conclusiones. El IIIS tuvo una mayor capacidad predictiva de EAC moderada o severa en comparación con el ITG y el LAP, lo que resalta la importancia de la inflamación en la enfermedad aterosclerótica crónica.

Palabras clave

Enfermedad coronaria; inflamación; resistencia a la insulina; dislipidemia; severidad.

Introduction

Cardiovascular diseases (CVD) are the leading cause of death in developed countries. In 2019, they accounted for over 17.9 million deaths, representing 32% of total global mortality, according to the World Health Organization (WHO). More than 75% of these deaths occur in low- or middle-income countries, with an increasing trend in recent decades [1,2]. The region of the Americas is no exception: According to the Pan American Health Organization (PAHO), CVD are responsible for more than 2 million deaths annually in this geographic delimitation [3]. In Venezuela, current data are almost nonexistent; however, the last official reports from 2014 identify heart diseases as the leading cause of death [4].

From a pathophysiological standpoint, coronary artery disease (CAD) is mediated by atherosclerosis, which is a chronic, progressive, and silent process that involves inflammatory, hemodynamic and metabolic mechanisms. Lipid accumulation and infiltration, platelet aggregation, and smooth muscle cell proliferation in vascular walls are key elements, among others [5,6]. Some studies suggest that inflammation can drive vascular hyperplasia without traditional cardiovascular risk factors and involves aspects of plaque biology that lead to the complications of advanced atherosclerosis [7].

However, there is no consensus on which of these mechanisms (inflammation, insulin resistance, or excessive fat accumulation) is the most clinically relevant to quantify during the development or progression of the disease. Currently several modalities are highly useful in evaluating chronic CAD, including non-invasive test as ECG, echocardiography, serum markers, stress testing, coronary artery calcium scoring, coronary computed tomography angiography and finally cardiac catheterization [8]. To bridge the gap between pathophysiology and clinical assessment in a simple way, several indices based on cellular biomarkers of inflammation, mostly derived from bloodwork values, have been proposed. Recently, combinations of these parameters have been suggested to increase predictive value. Based on this, the systemic immune-inflammation index (SII) was developed, calculated using neutrophil, lymphocyte, and platelet counts in a mathematical expression [9]. On the other hand, the lipid accumulation product (LAP) index is a biomarker that indicates central lipid accumulation and has been proposed as an accurate and independent indicator of risk for various cardiometabolic conditions [10]. Lastly, the triglyceride-glucose index (TyG) is a biomarker of insulin resistance (IR) and has also been previously linked to cardiovascular risk and events [11].

Although these pathophysiological phenomena may coexist in these patients, determining which of these indices best correlates with CAD severity could be useful from a clinical perspective, especially in low-resource settings. In this context, the objective of this study was to compare the predictive capacity of the SII, TyG, and LAP indices for chronic CAD severity in patients undergoing cardiac catheterization at the Cardiovascular Disease Research Institute of the University of Zulia.

Methods

Study Design and Sample Selection

A descriptive, cross-sectional, correlational, and non-experimental study was conducted on all male and female patients diagnosed with chronic coronary syndrome (CCS) who underwent cardiac catheterization at the Hemodynamics Unit of the Cardiovascular Disease Research Institute of the University of Zulia, located in Maracaibo, Venezuela, between October 2022 and October 2023. The institutional ethics committee approved the investigation under code IECLUZ-2022-5, and all the analysis was conducted in accordance with the Declaration of Helsinki.

Subjects were selected via non-probabilistic convenience sampling, including all patients of both genders over 18 years of age with a diagnosis of CCS. Subjects with disorders that could affect laboratory test results were excluded, such as those with acute or chronic infections, autoimmune or systemic inflammatory diseases, glucocorticoid use in the preceding two months, active neoplasms, hematologic disorders, liver or kidney failure, thyroid disorders, recent trauma or surgery, acute coronary syndrome, previous revascularization (percutaneous coronary intervention or coronary artery bypass grafting), decompensated heart failure, and clinically significant valvulopathies. Patients who were unwilling or unable to participate were also excluded. The final sample included 73 patients.

Patient Evaluation

Each patient included in the study provided informed consent. A structured interview was conducted to collect data including sex, age, educational level (categorized as primary, secondary, or university), and urban or rural origin. Psychobiological habits and personal medical history were also recorded. Patients were considered sedentary if they reported performing no regular physical activity. Patients were classified as smokers if they were actively smoking during the study, and as former smokers if they had stopped smoking for more than one year. A family history of CAD was recorded only if it occurred prematurely in first- or second-degree relatives. The presence of hypertension, diabetes, and dyslipidemia was also recorded if a previous diagnosis had been established, or if patients were taking medication for these disorders.

Weight and height were measured using a Health o meter scale and a stadiometer; and body mass index was calculated as weight/height^2. Abdominal circumference was measured using a calibrated tape, as guided by the standard anatomical landmarks.

Laboratory Analyses

Peripheral blood samples (5 ml) were collected after at least 8 hours of fasting and prior to the angiographic procedure. Complete blood counts were performed using a Mindray BC-2600 analyzer (China). Glucose, urea, creatinine, total cholesterol, HDL-C, triglycerides, and high-sensitivity C-reactive protein (hsCRP) were enzymatically analyzed using commercial kits (Pars Azmun, Karaj, Iran) with a BT-3000 autoanalyzer (Biotechnica, Rome, Italy). LDL-C levels were calculated using the Friedewald formula when triglyceride levels were under 400 mg/dL. The samples were taken in standardized EDTA tubes for the cell counts, and serum measurements were performed immediately after sample drawing.

Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) were calculated as absolute neutrophil count / absolute lymphocyte count and absolute platelet count / absolute lymphocyte count, respectively. SII was calculated as absolute platelet count × (absolute neutrophil count / absolute lymphocyte count) [12]. The LAP was calculated as waist circumference (cm) − 65 × triglycerides (mmol/L) for men; and waist circumference − 58 × triglycerides for women [13]. The TyG index was calculated using the formula: ln [triglycerides × fasting glucose] / 2, on a logarithmic scale [14].

Angiographic Analyses

Coronary angiography was performed using the standard Judkins technique. At least two projections of each coronary artery were obtained. Anatomical severity was assessed by two interventional cardiologists through qualitative and quantitative methods, and the SYNTAX I score was calculated using the online platform (www.syntaxscore.com). Results were grouped into three categories according Syntax study cutoffs: SYNTAX <23, SYNTAX 23–32, and SYNTAX ≥33 [15].

Statistical Analyses

The data were organized using a specifically designed tabulation sheet. Normal distribution of continuous variables was evaluated by using Kolmogorov-Smirnov test. Results were expressed as descriptive measures of central tendency (means) and dispersion (standard deviations) for variables with normal distribution and medians (P25-P75) for variables without normal distribution; as well as absolute and relative frequencies. The chi-square test was used for qualitative variable comparisons; whereas the Student's t-test was used for quantitative

comparisons. Pearson's correlation coefficient was used to evaluate correlation between variables. The variables without normal distribution were logarithmically transformed for comparison and correlation. ROC curves were used to determine the area under the curve (AUC) for each index. Cut-off points were selected using the Youden index and distance to the point (0,1). AUCs were compared using the Delong test. A logistic regression analysis was also performed, with moderate to severe CAD (based on the SYNTAX score) as the dependent variable. The model was adjusted for sex, age, LDL, CRP, statin use, previous acute coronary syndrome (ACS), and each of the indices in study. The alpha level was set at 0.05. Analyses were conducted using SPSS version 20 for Windows (Chicago, IL).

Results

Of the 73 subjects, 50.7% (n = 37) were men, and the average age was 59.5±7.7 years. The most prominent sociodemographic groups were secondary education (41.1%; n = 30), urban origin (93.2%; n = 68), sedentary (83.6%; n = 61), and former smokers (41.1%; n = 30). Hypertension was the most common comorbidity (83.6%; n = 61), followed by previous ACS (68.5%; n = 50), which was more frequent in men (83.3% vs. 54.1%; p<0.01). Regarding drug use, ACEI/ARB were the most common (74%; n = 54), followed by statins and nitrates (54.8%; n = 40), with higher usage among men (Table 1).

Table 1. General characteristics of the sample by sex.

	Female n (%)	Male n (%)	Total n (%)	*P**
Clinical characteristics				
Secondary education	12 (32.4)	18 (50)	30 (41.1)	NS
Urban origin	34 (91.9)	34 (94.4)	68 (93.2)	NS
Sedentary	33 (89.2)	28 (77.8)	61 (83.6)	NS
Current smokers	3 (8.1)	6 (16.7)	9 (12.3)	NS
Former smokers	17 (45.9)	13 (36.1)	30 (41.1)	NS
Family history of CVD	21 (56.8)	14 (38.9)	35 (47.9)	NS
Hypertension	32 (86.5)	29 (80.6)	61 (83.6)	NS
Diabetes	11 (29.7)	12 (33.3)	23 (31.5)	NS
Dyslipidemia	12 (32.4)	17 (47.2)	29 (39.7)	NS
Personal history of ACS	20 (54.1)	30 (83.3)	50 (68.5)	<0,01
Drug consumption				
Nitrates*	15 (40.5)	25 (69.4)	40 (54.8)	<0,01
ACEI or ARB	27 (73)	27 (75)	54 (74)	NS
Single antiplatelet therapy	13 (35.1)	11 (30.6)	24 (32.9)	NS
Dual antiplatelet therapy	16 (43.2)	21 (58.3)	37 (50.7)	NS
Statins*	13 (35.1)	27 (75)	40 (54.8)	<0,01
Antidiabetics	9 (24.3)	9 (25)	18 (24.7)	NS
SGLT2i	4 (10.8)	3 (8.3)	7 (9.6)	NS
Age (years) Mean±SD	60.4±7.1	58.7±8.3	59.5±7.7	NS
Total	37 (50.7)	36 (49.3)	73 (100)	

Notes. ACEI: Angiotensin-converting enzyme inhibitors; ACS: Acute coronary syndrome; ARB; Angiotensin Receptor Blockers; CVD: Cardiovascular disease; SGLT2: Sodium-glucose co-transporter-2 inhibitors; SD: Standard deviation. *Chi Squared Test between sex.

Table 2 shows clinical and laboratory characteristics by sex. Men had higher hemoglobin, hematocrit, creatinine, and SYNTAX scores, while women had higher averages of total cholesterol, LDL, and LAP.

Table 2. Clinical and laboratory characteristics of the sample by sex.

	Female (n=37)	Male (n=36)	Total (n=73)	*P*
	Mean±SD	Mean±SD	Mean±SD	
BMI (Kg/m^2)	28.9 ± 5.3	29.1 ± 7.5	29.0 ± 6.7	NS
Abdominal Circumference (cm)	101.7 ± 8.2	100.3 ± 10.1	101.0 ± 9.1	NS
Systolic Blood Pressure (mmHg)	144.2 ± 19.4	139.8 ± 16.8	142.0 ± 18.2	NS
Diastolic Blood Pressure (mmHg)	79.5 ± 10	82.2 ± 8.8	80.8 ± 9.5	NS
Leukocytes (x10^3/mm^3)	7.8 ± 1.9	7.5 ± 2.3	7.7 ± 2.1	NS
Neutrophils (x10^3/mm^3)	4.8 ± 1.4	4.6 ± 1.8	4.7 ± 1.6	NS
Lymphocytes (x10^3/mm^3)	3.0 ± 0.7	2.9 ± 0.8	2.9 ± 0.8	NS
Platelets (x10^3/mm^3)	256.6 ± 85.5	306.7 ± 95.6	281.3 ± 93.4	NS
NLR (Neutrophil-to-Lymphocyte Ratio)	1.64 ± 0.46	1.63 ± 0.61	1.63 ± 0.53	NS
PLR (Platelet-to-Lymphocyte Ratio)	91.31 ± 44.7	112.8 ± 46.5	101.9 ± 46.6	NS
SII (Systemic Immunity-Inflammation Index)	425.0 ± 206.3	515.2 ± 298.7	469.5 ± 258.3	NS
Hemoglobin (g/dL)	12.1 ± 1.1	13.3 ± 1.2	12.7 ± 1.3	<0,05*
Hematocrit (%)	37.4 ± 4.3	40.4 ± 4.6	38.9 ± 4.7	<0,05*
Glucose (mg/dL)	114.6 ± 39.3	117.7 ± 55.5	116.1 ± 47.7	NS
Creatinine (mg/dL)	0.9 ± 0.2	1.0 ± 0.1	1.0 ± 0.2	<0,05*
Urea (mg/dL)	37.4 ± 13.7	37.7 ± 9.2	37.6 ± 11.6	NS
Total Cholesterol (mg/dL)	186.2 ± 56.3	158.4 ± 44	172.5 ± 52.2	<0,05*
LDL-C (mg/dL)	114.5 ± 52.4	91.6 ± 40.7	103.2 ± 48.1	<0,05*
HDL-C (mg/dL)	45.2 ± 7.0	44 ± 6	44.6 ± 6.5	NS
Triglycerides (mg/dL)	157.9 ± 108.3	123.5 ± 60	140.9 ± 89	NS
VLDL-C (mg/dL)	31.1 ± 21.2	24.4 ± 12.6	27.8 ± 17.7	NS
C-Reactive Protein (mg/L) Median (P25-P75)	5 (3-10.2)	3.4 (3-5)	4 (3-7.1)	NS
LAP* (Lipid Accumulation Product)	78.6 ± 62.2	49.1 ± 33	64 ± 51.8	NS
TyG (Triglyceride-Glucose Index)	4.8 ± 0.4	4.7 ± 0.3	4.8 ± 0.3	NS
SYNTAX Score Median (P25-P75)	8 (1-22)	22 (11-39.3)	14 (1-35)	<0,05**
Total	37 (50,7)	36 (49,3)	73 (100)	

Notes. BMI: Body Mass Index; LAP: Lipid Accumulation Product; NLR: Neutrophil-Lymphocyte Ratio; PLR: Platelet-Lymphocyte Ratio; SII: Systemic Immunity-Inflammation Index; TyG: Triglyceride-Glucose Index. *t-Student's Test. **Mann-Whitney's U Test

When evaluating inflammatory and metabolic indices according to the SYNTAX score, only SII was significantly higher in the group with moderate/severe CAD (376.7±140.8 vs. 618.7±328.9; p<0.01) (Table 3). Figure 1 displays the correlation between SII, metabolic indices and log-SYNTAX score and Figure 2 shows the ROC curves and cut-off points for each index. For the SII, the cut-off was 378.4 [AUC: 0.73 (0.61–0.85); sensitivity: 71.4%; specificity: 55.6%]. The TyG and the LAP had lower AUCs (0.61 and 0.52, respectively). Evaluation of the subjects' distribution according to these indices revealed those with SII ≥378.4 had higher rates of moderate/severe CAD (no/mild CAD: 44.4% vs. moderate/severe: 71.4%; p = 0.02; OR: 7.56; 95% CI: 1.62–35.28; p = 0.01) (Table 4).

Table 3. Inflammatory and metabolic indices according to SYNTAX scores.

	No CAD / Mild CAD Mean±SD	Moderate CAD / Severe CAD Mean±SD	*P**
Indices			
SII	376.7±140.7	618.7±328.9	<0.01
LAP	62.1±44	67.2±53.1	0.68
TyG	4.7±0.3	4.8±0.4	0.13
Total n (%)	45 (61.6)	28 (38.4)	73; 100

Notes. CAD: Coronary Artery Disease; LAP: Lipid Accumulation Product; SD: Standard Deviation; SII: Systemic Immune-Inflammation Index; TyG: Triglyceride-Glucose Index. *t-Student's Test.

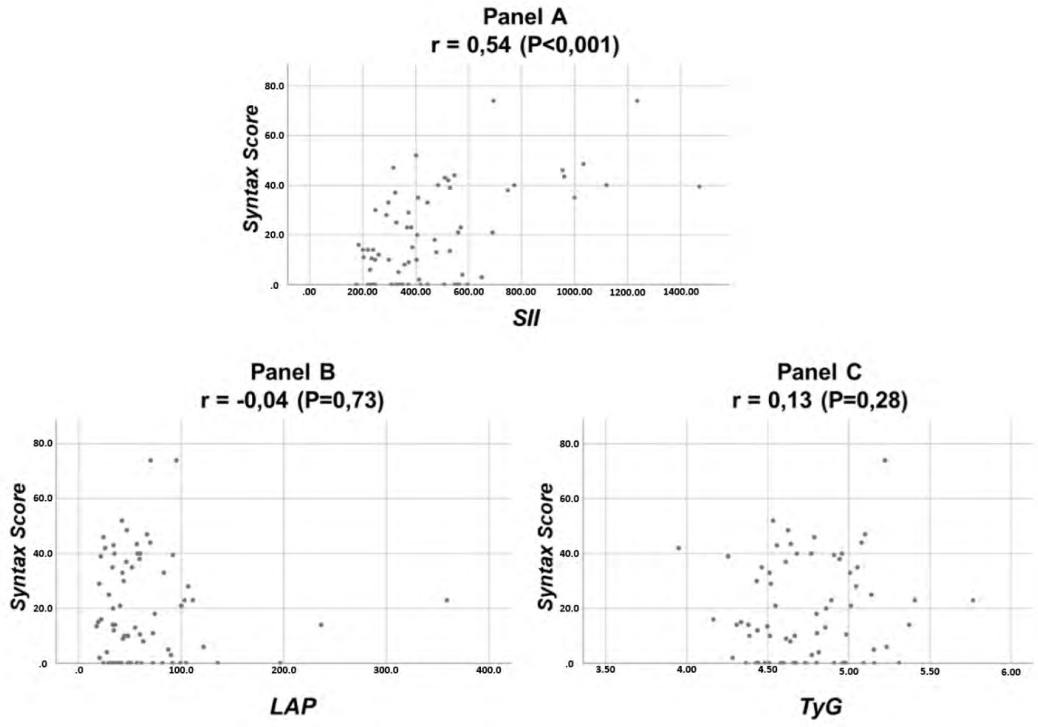
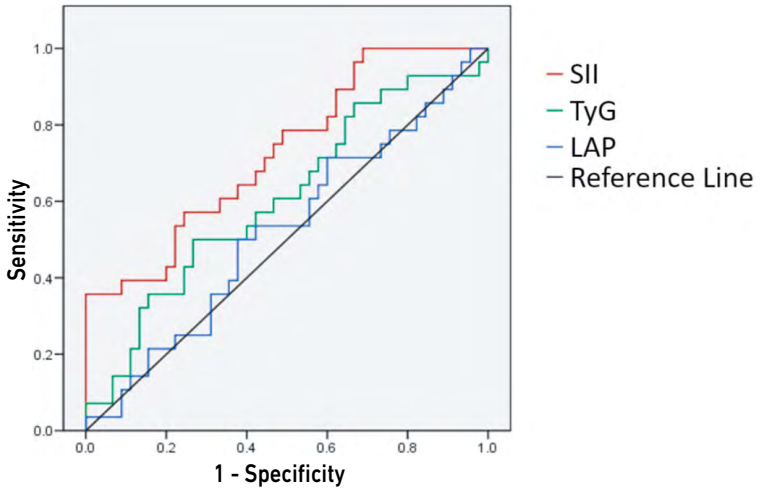


Figure 1. Correlation between SII, metabolic indices and log-SYNTAX score.



	AUC (CI95%)	Cut-off point	Sensitivity	Specificity	Youden's index	PPV	NPV
			%	%		%	%
Indices							
SII	0.73 (0.61-0.85)	378.4	71.4	55.6	0.27	62	67
TyG	0.61 (0.47-0.74)	4.7	60.7	53.3	0.14	55	56
LAP	0.52 (0.38-0.66)	47.7	53.6	46.7	0.1	51	51

AUC: Area Under Curve; LAP: Lipid Accumulation Product; NPV: Negative Predictive Value; PPV: Positive Predictive Value; SII: Systemic Immune-Inflammatory Index; TyG: Triglyceride-Glucose Index.

Figure 2. ROC curves and cut-off points of SII, TyG and LAP for moderate to severe coronary artery disease.

Table 4. Association between SII, TyG and LAP and moderate to severe coronary artery disease.

	No CAD Mild CAD (n=45) n (%)	Moderate CAD Severe CAD (n=28) n (%)	Chi Squared Test (p)	OR (CI95%) *p**
Systemic Immune-Inflammation Index			0.02	
<378.4	25 (55.6)	8 (28.6)		1.00
≥378.4	20 (44.4)	20 (71.4)		7.56 (1.62-35.28); 0.01
Triglyceride-Glucose Index			0.38	
<4.7	24 (53.3)	12 (42.9)		1.00
≥4.7	21 (46.7)	16 (57.1)		0.52 (0.07-3.93); 0.52
Lipid Accumulation Product			0.98	
<47.7	21 (46.7)	13 (46.4)		1.00
≥47.7	24 (53.3)	15 (53.6)		1.89 (0.26-14.01); 0.53

Notes. CAD: Coronary Artery Disease. *Model adjusted for: Sex, age, LDL, CRP, statin use, previous acute coronary syndrome and each of the indices in study. Hosmer–Lemeshow test: Chi-square 10.84 (P=0.21).

Discussion

Low-grade inflammation, abdominal adiposity, and insulin resistance (IR) are some of the main factors underlying atherosclerosis, contributing to the continuum of cardiometabolic disorder and its associated diseases [16,17]. Regarding CAD, the SYNTAX score was developed originally to quantify the anatomical extent and its complexity on conventional invasive coronary angiography. The SYNTAX trial demonstrated its prognostic impact on mid and long-term outcomes of patients undergoing percutaneous coronary intervention or coronary artery bypass grafting. Since then, the Syntax score has been endorsed in international guidelines for the assessment of lesion complexity before revascularization; European (Class 1, Level B), North American (Class 2b, Level B),4 and Japanese (Class 1, Level B) [18]. This study aimed to compare the predictive capacity of various inflammatory and metabolic indices for CAD severity in patients undergoing cardiac catheterization at a specialized cardiovascular institute in Maracaibo, Venezuela.

Our key finding is that SII demonstrated greater predictive capacity (AUC) and a stronger association with CAD severity, independent of other risk factors and superior to LAP and TyG. This demonstrates the greater importance of the inflammatory marker in CAD severity in our population compared to metabolic markers. Indeed, various other inflammatory biomarkers, such as hsCRP, interleukins, TNF-α and interferon-γ, have been reported to be elevated in prior studies [19,20]. In this sense, different therapeutic strategies have been proposed for modulation of inflammation in the treatment of atherosclerosis, including inhibiting pro-inflammatory cytokines, blocking key inflammatory signaling pathways, and promoting inflammatory resolution; these anti-inflammation interventions can prevent the complications of atherosclerosis and merely scratch the surface of their potential as novel therapeutic approaches [7,21].

It should be noted that few studies have compared these indices for CAD severity. Xiao et al. [22] showed a strong correlation between higher SII values, estimated pulse wave velocity, and TyG. Likewise, they ascertained a U-shaped curved between SII values and cardiovascular events in over 17,000 subjects from the NHANES. On the other hand, Dong et al. [23] found SII, TyG, and the systemic inflammation response index (SIRI) were risk factors for CAD in 407 patients with non-alcoholic fatty liver disease (NAFLD); and they were all associated with prediction of CAD severity as well. Meanwhile, in a retrospective analysis with 518 diabetic subjects, Li et al. [24] reported TyG and NLR were significantly associated with CAD presence, and their combination offered better diagnostic accuracy.

Several novel CVD inflammatory markers based on immune circulatory cells have been proposed, including not only the SII but also neutrophil–lymphocyte ratio (NLR), and platelet–lymphocyte ratio (PLR). NLR and PLR; all associated with CAD severity and clinical outcome. Likewise, SII is associated with coronary severity and provides a better prediction of major cardiovascular events and mortality than conventional risk factors do in patients with CAD, this due SII integrates peripheral platelet, neutrophil, and lymphocyte counts to better reflect the balance between the host inflammation and immune situation. Thus, low-grade inflammatory markers and inflammatory indices based on immune cells play a pivotal role in CAD development. [25,26].

In light of this panorama, routine measurement of these hematological parameters should be considered in chronic CAD patients—especially in low-resource settings, given the ease of access—as a means of assessing inflammatory status in patients with CCS in the primary care or outpatient settings. The association between SII and CAD severity, independent of LDL-C

and hsCRP, supports the need for further clinical trials testing anti-inflammatory therapies like monoclonal antibodies, enzyme regulators, or colchicine, and their potential effects at both medium and long term for primary and secondary prevention [27,28].

Notoriously, in our study, drug adherence was inadequate. In particular, no anti-ischemic drug class reached 80% usage, indirectly indicating poor treatment adherence and reflecting suboptimal management of risk factors. This suggests a need for improved cardiovascular prevention strategies, especially centering on pharmacological adherence, as a tool to seek early mitigation of inflammation and, by extension, reduction of CAD severity [29]. Specifically, identifying the underlying causes of these low adherence rates—an area currently under active investigation in our population—and providing systematic counseling on the importance of medication adherence for all patients with CAD—are key steps to address this issue.

Limitations

Limitations of this report include our small sample size, limiting generalizability to large-scale populations, and can lead to low statistical power, making it harder to detect real effects and increasing the risk of false negatives. Additionally, the cross-sectional design precludes establishing causal relationships between variables. The study also lacked more specific inflammatory and metabolic mediators like interleukins, tumor necrosis factor, and insulin, mainly due to their high cost and limited availability in our community.

Conclusions

The SII demonstrated superior predictive capacity and was significantly associated with greater CAD severity (as measured by the SYNTAX score) compared to metabolic indices like LAP and TyG, independently of other inflammatory and lipid variables in a Venezuelan cohort of patients with CCS. These findings highlight the potential role and relevance of inflammation in the atherosclerotic CAD severity and support the routine assessment of inflammatory indices like the SII in patients with this profile.

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