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The Utility of Systemic Immune-Inflammation Index for Predicting Contrast-Induced Nephropathy in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Keywords
Primary percutaneous coronary intervention · Acute coronary syndrome · Nephropathy

Abstract
Objective: The systemic immune-inflammation index (SII), derived from counts of neutrophils, platelets, and lymphocytes, has been developed to predict clinical outcomes in several cancers and cardiovascular diseases. The aim of this study was to evaluate the utility of SII to predict contrast-induced nephropathy (CIN) in patients with ST-segment elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (PCI). ***Methods:*** A total of 632 patients with STEMI who underwent primary PCI were retrospectively included. The patients were divided into two groups based on the presence or absence of CIN. Baseline demographic, laboratory, and clinic characteristics were evaluated between the two groups. Logistic regression analysis was used to identify independent predictors of CIN. ***Results:*** The receiver operating characteristic curve analysis demonstrated that the optimal cutoff value of SII for predicting CIN was 1,282 with a sensitivity of 76.1% and specificity of 86.7% (AUC: 0.834; 95% CI: 0.803–0.863; $p < 0.001$). Multivariate analysis performed in two models (SII; as separate continuous and categorical variables) showed age, estimated glomerular filtration rate (eGFR), diabetes, left ventricular ejection fraction (LVEF), Killip class ≥2, use of an intravenous diuretic, troponin I, and SII as independent predictors of CIN in model 1. In model 2, age, eGFR, diabetes, LVEF, Killip class ≥2, use of an intravenous diuretic, troponin I, and a value of SII >1,282 ($p < 0.001$, OR 6.205, 95% CI: 2.301–12.552) remained as independent predictors of CIN. ***Conclusion:*** SII may be a useful and reliable indicator to predict the development of CIN in patients with STEMI undergoing primary PCI than NLR and PLR.

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Introduction

Contrast-induced nephropathy (CIN) is one of the most important and serious complications of angiographic procedures [1, 2]. CIN is characterized by the development of acute kidney injury (AKI) after iodine contrast medium exposure [1, 2]. The incidence of CIN ranges from 1% to 6% in the general population, and it increases to more than 50% in high-risk patients, such as

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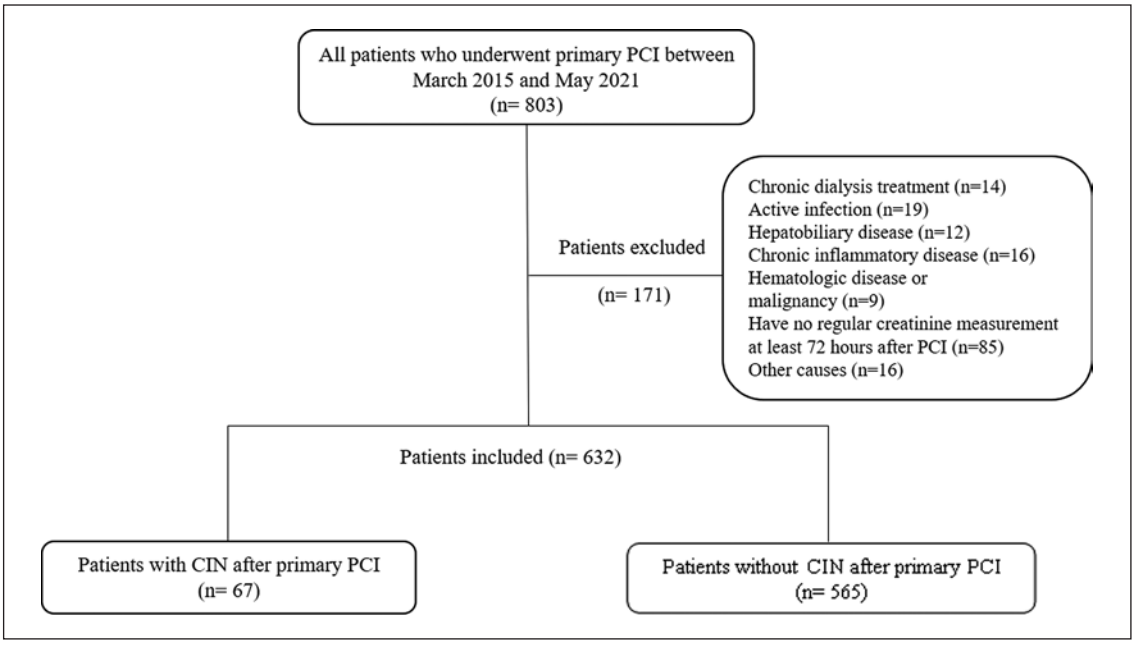


Fig. 1. The flowchart algorithm of study patients enrollment. CIN, contrast-induced nephropathy; PCI, percutaneous coronary intervention.

those with older age, diabetes, heart failure (HF), or chronic kidney disease [3, 4]. CIN is associated with an increased risk for renal replacement therapy, longer length of stay in the hospital, recurrent revascularization procedures, and higher mortality [4, 5].

Although the underlying mechanisms of CIN are not fully understood, it has been suggested that inflammation has a key role in the development of CIN [6, 7]. Therefore, inflammation-related biomarkers are being studied intensively in this area. These biomarkers are usually derived from hematologic indices, such as red cell distribution width, and counts of neutrophils, monocytes, platelets, and lymphocytes [8, 9]. In particular, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been associated with poor clinical outcomes in many cardiovascular diseases, and they are also predictors of CIN in patients undergoing primary or elective percutaneous coronary intervention (PCI) [10–15].

As CIN is associated with worse clinical outcomes, early and accurate prediction of CIN is crucial for applying preventive strategies before PCI procedure. Therefore, useful and reliable indicators will help the clinicians in identifying high-risk patients for development of CIN. The systemic immune-inflammation index (SII), which is derived from a combination of circulating neutrophils, platelets, and lymphocytes, has been developed to predict clinical outcomes and prognosis in many malignancies [16–18]. The relationship between SII and cardiovascular diseases such as coronary artery disease (CAD), HF, pulmonary embolism, acute myocardial infarction, and calcific aortic stenosis has been demonstrated subsequently [19–23]. Recently, SII has been shown to be a predictive indicator of CIN in patients with different ACS manifestations undergoing PCI [24, 25]. Our study sought to evaluate the utility of SII to predict CIN in patients with ST-segment elevation myocardial infarction (STEMI) who underwent primary PCI.

Materials and Methods

Study Population

A total of 803 consecutive patients with STEMI who underwent primary PCI, between March 2015 and May 2021, at our cardiology department were retrospectively enrolled into the study. Exclusion criteria included, thrombolytic therapy before PCI (n = 3), chronic dependence on renal replacement therapy (n = 14), active infection (n = 19), chronic hepatobiliary disease (n = 12), primary hematologic disease or active malignancy (n = 9), chronic inflammatory conditions (n = 16), use of chronic steroid or nonsteroidal anti-inflammatory drug therapy (n = 11), history of organ transplantation (n = 2), and absence of creatinine measurement in the first 72 h after primary PCI (n = 85). After excluding 171 patients,

a total of 632 patients were included in the final study population (shown in Fig. 1). The study protocol was approved by Institutional Review Board.

Study Protocol

Demographic information and medical history, such as gender, age, body mass index, smoking status, diabetes, hypertension, dyslipidemia, use of statin therapy on admission, use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy on admission, and previous history of CAD were collected. Data regarding vital signs on admission, including heart rate, and systolic and diastolic blood pressures, were recorded for the study.

At presentation, the diagnosis of STEMI was defined as the presence of new-onset left bundle branch block or at least 1-mm ST elevation in two or more contiguous leads on electrocardiogram, based on symptoms consistent with myocardial ischemia and/or elevated cardiac necrosis biomarkers according to the recommendations of the current practical guidelines [26]. All patients received aspirin (loading dose of 300 mg) and a P2Y12 antagonist (loading dose of 600 mg for clopidogrel or 60 mg for prasugrel or 180 mg for ticagrelor) before the procedure.

Hemodynamic status of study patients on admission was evaluated according to the Killip classification. According to Killip classification, with no evidence of HF in Killip class 1, the presence of the findings consistent with mild to moderate HF (i.e., S3 gallop and lung rales less than one-half way up the posterior lung fields) in Killip class 2, the presence of pulmonary edema in Killip class 3, and the presence of cardiogenic shock in Killip class 4 were described [27]. The patients who used intravenous diuretics and/or inotropes were recorded for the study. Coronary angiography was performed using femoral or radial access according to the interventional cardiologists' preference. Primary PCI was performed using standard techniques following international guidelines. During primary PCI unfractionated heparin was applied intravenously at a dose of 70–100 units/kg to maintain an activated clotting time of 250–300 s, and 200–250 s when tirofiban was used. The use of tirofiban was left to the decision of the operators. Nonionic, low-osmolar contrast medium (iohexol, Omnipol 300 mg I/mL; Polifarma, Istanbul, Turkey) was used in all procedures. The main vessel CAD was defined in the presence of ≥50% luminal obstruction. Other medical treatments recommended by the current practical guidelines were given to all patients, unless contraindicated. Intravenous hydration (0.9% sodium hydrochloride) at a dose of 1 mL/kg/h (at a reduced dose of 0.5 mL/kg/h in patients with left ventricular ejection fraction [LVEF] < 40%) were given to the patients for 12 h after primary PCI [28]. Hydration was not applied to the patients with cardiogenic shock and/or acute HF.

All venous blood samples for measurements were drawn before primary PCI procedure. These samples were taken into standard tubes containing EDTA for full blood count and were analyzed using an automated blood cell counter within 30 min (Symex K-1000, Kobe, Japan). Biochemical analysis, including serum creatinine, albumin, lipid profile, and glucose levels were measured using standard laboratory techniques (Roche Diagnostic Modular Systems, Tokyo, Japan). The peak values of troponin I were examined at 18–24 h from biochemical analysis. SII was calculated using the formula: (neutrophil count × platelet count)/lymphocyte count. The NLR and PLR were calculated from neutrophil count/lymphocyte count and platelet count/lymphocyte count, respectively. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula [29]. Transthoracic echocardiography was performed within 24–48 h after the procedure and LVEF assessment was made using the modified Simpson method according to the recommendations of the current guidelines [30].

CIN was defined as an increase in the serum creatinine level of ≥0.5 mg/dL or ≥25% above baseline within 72 h after contrast medium exposure [31]. Patients were classified into two groups: a CIN (+) group and a CIN (−) group, based on this definition. All data used in the study were obtained from hospital records and patient files.

Statistical Analysis

SPSS, version 20.0 software (IBM Inc., Chicago, IL, USA) was used for all analyses. Kolmogorov-Smirnov test was used to assess the normality of the distribution of the continuous variables. Continuous variables were presented as mean ± standard deviation or medians and interquartile according to the distribution pattern. Categorical variables were presented as numbers, percentages, or proportions. The χ^2 test was performed to compare the proportions of the groups and categorical variables. The comparison of continuous variables with normal distributions were performed with an independent sample *t*-test and the comparison of continuous variables with nonnormal distributions were performed with the Mann-Whitney U test. The independent predictors of CIN were determined using the logistic regression analysis. The variables, which could possibly predict the development of CIN, such as age, eGFR, diabetes, hypertension, use of an intravenous diuretic, Killip class ≥2, LVEF, serum albumin, troponin I, glucose level on admission, and SII were included in the univariate analysis. To avoid a multicollinearity problem, NLR, PLR, and other indices including neutrophils, lymphocytes, and platelets were not added to the logistic regression models. The variables that were associated with CIN in the univariate analysis (p value <0.05) were included in the multivariate analysis. Multivariate analysis was performed as two separate models which were: model 1 (SII was a continuous variable) and model 2 (SII was a categorical variable). The receiver operating characteristics (ROC) curve analysis was used to identify optimal cutoff values of SII, NLR, and PLR in predicting CIN. The area under the ROC curves (AUC) of these indicators is shown with 95% confidence interval (CI) with the highest sensitivity and specificity. A two-sided p value <0.05 was considered statistically significant.

Results

A total of 632 patients (mean age 59.2 ± 12.1 years, male 71.8%) who underwent primary PCI for STEMI were included in the study. CIN was identified in 67 (10.6%) patients. Baseline demographic and clinical characteristics of the study patients with and without CIN are presented in Table 1. Patients with CIN were older than patients without CIN (67.1 ± 10.1 vs. 58.3 ± 10.9, p < 0.001). There was no difference between the groups in terms of gender, body mass index, systolic and diastolic blood pressure, heart rate, and smoking status. Com-

Table 1. Baseline demographic and clinical characteristics of the study patients with and without CIN

Variables	All (n = 632)	CIN (+) (n = 67)	CIN (–) (n = 565)	p value
Age, years	59.2±12.1	67.1±10.1	58.3±10.9	<0.001
Male, n (%)	454 (71.8)	43 (64.2)	411 (72.7)	0.141
BMI, kg/m^2	27.9±9.1	30.7±5.2	27.6±4.1	0.922
Systolic blood pressure, mm Hg	126.4±25.4	124.1±36.7	126.6±23.7	0.113
Diastolic blood pressure, mm Hg	77.5±14.5	74.6±20.2	77.8±13.6	0.139
Heart rate on admission, bpm	79.1±17.9	81.1±20.3	78.9±17.7	0.204
Comorbidities, n (%)				
Hypertension	225 (35.6)	31 (46.3)	194 (34.3)	0.054
Diabetes	200 (31.6)	30 (44.8)	170 (30.1)	0.015
Dyslipidemia	124 (19.6)	16 (23.9)	108 (19.1)	0.353
Current smoker	264 (41.8)	25 (37.3)	239 (42.3)	0.434
Previous CAD	44 (7)	2 (3)	42 (7.4)	0.176
LVEF (at discharge), %	41.7±13.9	36.9±12.2	42.4±13.9	0.003
Medical therapy on admission, n (%)				
Statin	105 (16.6)	14 (20.9)	91 (16.1)	0.319
ACEi or ARB	188 (29.7)	26 (38.8)	162 (28.7)	0.086

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CIN, contrast-induced nephropathy; LVEF, left ventricular ejection fraction.

Table 2. Laboratory results on admission of the study population

Variables	CIN (+) (n = 67)	CIN (–) (n = 565)	p value
Baseline creatinine, mg/dL	1.12±0.47	1.01±0.42	0.081
eGFR, mL/min/1.73 m^2	59.7±24.4	75.3±25.5	<0.001
Glucose level on admission, mg/dL	183.2±107.7	133.2±72.6	<0.001
Hemoglobin, g/dL	13.1±2.3	13.7±1.9	0.134
Total cholesterol, mg/dL	179.3±43.6	182.9±39.7	224
Triglyceride, mg/dL	147.9±86.6	152.9±82.9	0.569
HDL cholesterol, mg/dL	37.6±9.1	38.1±9.1	0.641
LDL cholesterol, mg/dL	112.5±30.2	113.7±31.9	0.784
Serum albumin, g/dL	3.88±0.30	3.98±0.34	0.031
Troponin I, ng/mL	6.72±2.71	4.22±2.35	<0.001
Lymphocyte count (×10^3/mL), median (IQR)	1.34 (1.01–1.92)	1.78 (1.27–2.37)	<0.001
Neutrophil count (×10^3/mL), median (IQR)	7.09 (4.26–10.70)	4.35 (3.10–6.68)	<0.001
Platelet count (×10^3/mL), median (IQR)	266 (217–313)	223 (187–272)	0.005
NLR, median (IQR)	4.89 (2.97–8.49)	2.54 (1.55–4.06)	<0.001
PLR, median (IQR)	173.9 (114.4–257.1)	128.4 (91.3–185.1)	<0.001
SII (×10^3/mL), median (IQR)	1,715 (1,017–2,538)	628 (359–951)	<0.001

CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

pared to the patients without CIN, patients with CIN had a higher prevalence of diabetes (30 [44.8%] versus 170 [30.1%], respectively; p = 0.015). The frequency of hypertension approached significance in patients with CIN (31 [46.3%] versus 194 [34.3%]; p = 0.054). The frequency of hyperlipidemia and previous CAD were similar between the groups (p = 0.353 and p = 0.176, respectively). LVEF was significantly lower in patients with CIN than in those without CIN (36.9 ± 12.2 vs. 42.4 ± 13.9; p = 0.003). Additionally, the use of statin therapy and use of angioten-

Table 3. Angiographic and hemodynamic characteristics of the study patients

Variables	CIN (+) (*n* = 67)	CIN (–) (*n* = 565)	*p* value
Total volume of contrast medium, mL	171.9±31.5	165.7±31.2	0.616
Vascular access, *n* (%)			
Transfemoral	51 (76.1)	457 (80.9)	0.353
Transradial	16 (23.9)	108 (19.1)	
Vessel breakdown, *n* (%)			
One-vessel disease	43 (64.2)	433 (76.6)	
Two-vessel disease	16 (23.9)	88 (15.6)	0.082
Three-vessel disease	8 (11.9)	44 (7.8)	
Use of tirofiban during PCI, *n* (%)	18 (26.9)	129 (22.8)	0.460
Killip class, *n* (%)			
Class 1	44 (65.7)	500 (88.5)	
Class 2	7 (10.4)	26 (4.6)	<0.001
Class 3	11 (16.4)	22 (3.9)	
Class 4	5 (7.5)	17 (3.0)	
Intravenous diuretic, *n* (%)	20 (29.9)	58 (10.3)	<0.001
Intravenous inotropes, *n* (%)	5 (7.5)	18 (3.2)	0.077
Culprit vessel, *n* (%)			
Left main coronary artery	2 (3)	5 (0.9)	
Left anterior descending artery	21 (31.3)	247 (43.7)	
Right coronary artery	23 (34.3)	174 (30.8)	0.159
Left circumflex artery	20 (29.9)	125 (22.1)	
Bypass graft	1 (1.5)	14 (2.5)	
Door-to-balloon time, min	56.4±29.6	52.5±25.6	0.744
Stent implantation, *n* (%)	63 (94.0)	529 (93.6)	0.898
Stents implanted, *n*	1.36±0.59	1.19±0.61	0.065
Postprocedural TIMI-3 flow, *n* (%)	60 (89.6)	524 (92.7)	0.351

CIN, contrast-induced nephropathy; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

sin-converting enzyme inhibitor or angiotensin receptor blocker therapy on admission were not different between the two groups.

Laboratory results of the study population are shown in Table 2. The patients in the CIN group had lower eGFR and higher glucose level on admission compared with the non-CIN group (59.7 ± 24.4 vs. 75.3 ± 25.5, $p < 0.001$ and 183.2 ± 107.7 vs. 133.2 ± 72.6, $p < 0.001$, respectively). Baseline serum creatinine, hemoglobin, and lipid profile levels were similar between the groups. Serum albumin was significantly higher in patients with CIN than those without CIN (3.88 ± 0.30 vs. 3.98 ± 0.34, $p = 0.031$). The patients with CIN had markedly elevated troponin I values compared with non-CIN patients (6.72 ± 2.71 vs. 4.22 ± 2.35, $p < 0.001$). While lymphocyte count was lower (1.34 [1.01–1.92] versus 1.78 [1.27–2.37], $p < 0.001$), neutrophil count (7.09 [4.26–10.70] versus 4.35 [3.10–6.68], $p < 0.001$), platelet count (266 [217–313] versus 223 [187–272], $p = 0.005$), NLR (4.89 [2.97–8.49] versus 2.54 [1.55–4.06], $p < 0.001$), PLR (173.9 [114.4–257.1] versus 128.4 [91.3–185.1], $p < 0.001$) and SII (1,715 [1,017–2,538] versus 628 [359–951], $p < 0.001$) were higher in patients who developed CIN.

The angiographic and hemodynamic characteristics of the study patients with and without CIN are summarized in Table 3. The total volume of contrast medium and the percentage of patients receiving tirofiban were similar between the two groups. The patients with CIN had worse Killip class than the patients without CIN ($p < 0.001$). The use of intravenous diuretics was more frequent in patients with CIN than the patients who did not develop CIN (29.9% vs. %10.3, $p < 0.001$). The patients with CIN needed intravenous inotropes therapy nearly significant more than the patients without CIN (7.5% vs. 3.2%, $p = 0.077$). The number of vessel breakdowns and the number of stents implanted were slightly more in patients with CSF than in those without CIN, but statistically not significant ($p = 0.082$ and $p = 0.065$, respectively). Additionally, there was no difference in terms of vascular access, door-to-balloon time, stent implantation, and postprocedural

Table 4. Logistic regression analysis for predicting CIN in the study patients

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Model 1: SII value as a continuous variable				
Age	1.065 (1.041–1.090)	<0.001	1.100 (1.010–1.198)	**0.029**
Diabetes	1.884 (1.127–3.150)	0.016	1.363 (1.089–1.636)	**0.037**
eGFR	0.975 (0.965–0.986)	<0.001	0.979 (0.969–0.990)	**0.024**
Admission glucose	1.006 (1.003–1.009)	<0.001	1.010 (0.997–1.033)	0.059
LVEF	0.973 (0.949–0.997)	0.030	0.989 (0.978–0.998)	**0.048**
Killip class ≥2	1.814 (1.198–2.355)	<0.001	1.928 (1.225–2.630)	**0.009**
Use of intravenous diuretic	2.720 (1.063–5.708)	<0.001	1.386 (1.192–1.579)	**0.008**
Serum albumin	0.892 (0.783–1.016)	0.084		
Troponin I	1.456 (1.181–1.796)	<0.001	1.702 (1.236–2.345)	**0.001**
Hypertension	1.647 (0.988–2.744)	0.056		
SII (cont)	1.001 (1.001–1.002)	<0.001	1.007 (1.004–1.011)	<0.001
Model 2: SII value as a categorical variable				
Age	1.065 (1.041–1.090)	<0.001	1.096 (1.004–1.197)	**0.041**
Diabetes	1.884 (1.127–3.150)	0.016	1.270 (1.068–1.467)	**0.043**
eGFR	0.975 (0.965–0.986)	<0.001	0.980 (0.971–0.988)	**0.019**
Admission glucose	1.006 (1.003–1.009)	<0.001	1.014 (0.996–1.031)	0.067
LVEF	0.973 (0.949–0.997)	0.030	0.979 (0.968–0.990)	**0.038**
Killip class ≥2	1.814 (1.198–2.355)	<0.001	1.633 (1.191–2.075)	**0.007**
Use of intravenous diuretic	2.720 (1.063–5.708)	<0.001	1.696 (1.271–2.064)	**0.006**
Serum albumin	0.892 (0.783–1.016)	0.084		
Troponin I	1.456 (1.181–1.796)	<0.001	1.514 (1.123–2.043)	**0.007**
Hypertension	1.647 (0.988–2.744)	0.056		
SII (cat)	10.327 (5.639–18.912)	<0.001	6.205 (2.301–12.552)	**<0.001**

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker CI, confidence interval; CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; OR, odds ratio; SII, systemic immune-inflammatory index.

thrombolysis in myocardial infarction-3 flow ratios between the study groups.

Logistic regression analysis, performed with the two different models (continuous values of SII in model 1 and categorical values of SII in model 2) is presented in Table 4. In univariate analysis; age, diabetes, admission glucose level, LVEF, Killip class ≥2, eGFR, use of intravenous diuretic, troponin I, and SII (in both models) were associated with the development of CIN. In multivariate analysis with model 1; age (p = 0.029, odds ratio [OR] 1.100, 95% CI: 1.010–1.198), eGFR (p = 0.024, OR 0.979, 95% CI: 0.969–0.990), diabetes (p = 0.037, OR 1.363, 95% CI: 1.089–1.636), LVEF (p = 0.048, OR 0.989, 95% CI: 0.978–0.998), Killip class ≥2 (p = 0.009, OR 1.928, 95% CI: 1.225–2.630), intravenous diuretic (p = 0.008, OR 1.386, 95% CI: 1.192–1.579), troponin I (p = 0.001, OR 1.702, 95% CI: 1.236–2.345), and SII (p < 0.001, OR 1.007, 95% CI: 1.004–1.011) and with model 2; age (p = 0.041, OR 1.096, 95% CI: 1.004–1.197), eGFR (p = 0.019, OR 0.980, 95% CI: 0.971–0.988), diabetes (p = 0.043, OR 1.270, 95% CI: 1.068–1.467), LVEF (p = 0.038, OR 0.979, 95% CI: 0.968–0.990), Killip class ≥2 (p = 0.007, OR 1.633, 95% CI: 1.191–2.075), use of intravenous diuretic (p = 0.006, OR 1.696, 95% CI: 1.271–2.064), troponin I (p = 0.007, OR 1.514, 95% CI: 1.123–2.043) and SII >1,282 (p < 0.001, OR 6.205, 95% CI: 2.301–12.552) were found to be independent predictors of CIN.

The optimal cutoff value of SII in predicting of CIN was 1,282 in the ROC curve analysis (p < 0.001, AUC = 0.834, 95% CI: 0.803–0.863). This cutoff value of SII >1,282 predicted the development of CIN with a sensitivity of 76.1% and specificity of 86.7% (Fig. 2). Additionally, the optimal cutoff value of NLR was 3.47 (p < 0.001, AUC = 0.742, 95% CI: 0.679–0.806) and optimal cutoff value of PLR was 150 (p < 0.001, AUC = 0.651, 95% CI: 0.582–0.719) (shown in Fig. 2).

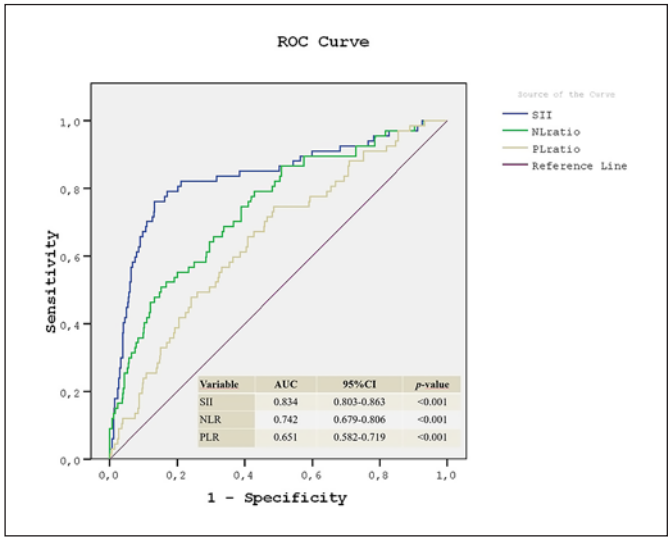


Fig. 2. The ROC curves of SII, NLR, and PLR in predicting CIN. AUC, area under the curve; CI, confidence interval.

Discussion

We sought to evaluate the relationship between SII and CIN in patients with STEMI undergoing primary PCI. Our study demonstrated that SII was an independent predictor of CIN in these patients. Additionally, age, eGFR, LVEF, Killip class ≥2, diabetes, use of an intravenous diuretic, and troponin I were shown to be associated with the development of CIN in the multivariate analysis.

Many risk factors for the development of CIN have been well-recognized in the literature [3, 4]. However, the prediction of CIN occasionally can be difficult in clinical practice due to the interindividual variability of nephrotoxic effects of contrast medium [32, 33]. CIN occurs at significantly higher rates in patients with STEMI than in patients with a stable clinical presentation due to the higher complexity of primary PCI, the use of more contrast medium, hemodynamic instability, and inadequate precautions [34, 35]. The identification of high-risk patients for the development of CIN is crucial to improve worse clinical outcomes, as initiation and progression of the CIN can be reduced by applying preventive strategies [36]. Although prophylactic hydration has not been yet routinely recommended in patients with normal renal function during PCI by current guidelines [26], a few studies have been conducted to investigate the role of prophylactic hydration in the development of CIN in patients with STEMI undergoing primary PCI [37, 38]. They concluded that prophylactic hydration was significantly reduced rates of CIN in patients with normal renal function [37, 38]. In this regard, if there is no contraindication (i.e., acute HF and congestion findings), we give prophylactic hydration at recommended doses in chronic kidney disease to the patients with STEMI undergoing primary PCI. On the other hand, the incidence of CIN was reported to be more frequent in patients who could not be hydrated in the setting of congestive HF or pulmonary edema [39, 40]. Killip class ≥2 was shown to be associated with CIN in many studies as well as our study [40–42]. In light of these data, easy, widely available, and accurate indicators are needed to predict CIN in patients with STEMI undergoing primary PCI.

Although the exact pathophysiology of CIN has not been clearly elucidated yet, possible underlying mechanisms such as direct tubular epithelial injury, intrarenal vasoconstriction, medullary hypoxia, and increased reactive oxygen species have been demonstrated in previous studies [6, 7]. Besides, chronic inflammation has been suggested to play a major role in the etiopathogenesis of CIN [6, 7]. An important theory is that contrast medium causes to AKI by stimulation of the inflammatory pathway [43]. Supporting this mechanism, experimental animal studies have demonstrated that inflammatory cytokines, including IL-1, IL-6, and TNF-α significantly increase immediately after contrast administration, which leads to acute tubular damage [44, 45]. These studies also showed that antithrombin and renalase improved kidney damage by suppressing inflammation [44, 45]. Additionally, NOD-like receptor pyrin containing 3, a receptor in phagocytes is activated by increased reactive oxygen species, oxidative stress, and tubular epithelial injury resulting from direct contrast injection [46]. This activation of NOD-like receptor pyrin containing 3 induces caspase-1 enzyme and caspase-1 activates inflammatory cascades, followed by migration of inflammatory cells, particularly macrophages, lymphocytes, platelets, and neutrophils, to damaged kidney tissue [46, 47]. Recently, Kwasa et al. [6] conducted a prospective study that enrolled patients who examined contrast-enhanced computed tomography in the absence of any risk factors for CIN. They reported that the patients who developed CIN had increased CRP levels compared to the patients who did not develop CIN [6]. All of these data proposed that renal inflammatory response might be responsible for the pathophysiology of CIN.

CBC is a routine, cheap, and quick examination that provides detailed information regarding white blood cells, red blood cells, platelets, and others [48]. In recent years,

various indices that are derived from neutrophils, lymphocytes, monocytes, and platelets have been developed to investigate the relationship between cardiovascular diseases and inflammation [10–15]. The NLR and PLR, which are two of the most widely used of these, have been demonstrated to be associated with many clinical outcomes and CIN in patients undergoing primary PCI [13–15, 49]. SII as a relatively novel inflammation-based biomarker has been described based on counts of circulating neutrophils, platelets, and lymphocytes [16]. The authors have suggested that since SII includes three different cells, it may better reflect the inflammatory status than NLR and PLR which are typically developed from two cells [16]. Indeed, several studies have been conducted to support this hypothesis [17, 18]. The relationship between SII and development of CIN in patients with non-STEMI who underwent PCI was first shown by the study of Kelesoglu and colleagues [24]. They revealed that higher SII was an independent predictor of CIN with a relatively low specificity and they also suggested that SII may be a better indicator than NLR and PLR in predicting CIN [24]. Subsequently, Ertem et al. [50] investigated the whether SII was associated with CIN in patients undergoing transcatheter aortic valve replacement for severe aortic stenosis. Their study demonstrated that white blood cells, NLR, and SII were higher in patients with CIN than in those without CIN and SII was a good index to predict CIN in patients undergoing transcatheter aortic valve replacement [49]. Yilmaz et al. [51] evaluated the role of SII on the development of CIN in patients who performed carotid artery disease angioplasty. They reported that the patients with CIN had increased hsCRP, glucose, total cholesterol, NLR, and SII levels compared with the patients without CIN and SII was an independent predictor of CIN [51]. Recently, Ozturk et al. [25] have concluded that SII was markedly elevated in patients with STEMI undergoing primary PCI and independently predicted CIN. Also, CRP, eGFR, and baseline creatinine were associated with CIN in their study [25]. In addition, Bagcı et al. [52] conducted a novel study to assess the relationship between SII and development of CIN in patients with STEMI who underwent primary PCI. Uric acid, female gender, hsCRP, CK-MB, and SII were found to be associated with development of CIN [52].

In the present study, we demonstrated that SII, both as a continuous and categorical variable, was associated with development of CIN in patients with STEMI who underwent primary PCI as well as the studies mentioned above. However, our study has critical differences that should be emphasized. First, as known multicollinearity is an important issue while analyzing study data. We avoided this multicollinearity problem, which may cause confusion in the reliability of results. Second, ROC curve analysis of our study showed better values of sensitivity, specificity, and AUC than in other studies. Third, both of the two logistic regression models of the present study showed that well-known risk factors for the development of CIN such as age, eGFR, LVEF, Killip class ≥2, diabetes, use of an intravenous diuretic, and troponin I were independent predictors of CIN. These results of our models are consistent with the literature. However, future studies are needed to confirm all of these results.

Overall, CIN is more frequent in patients with STEMI than in stable patients due to the challenging procedural and clinical features [34, 35]. Since the development of CIN causes to significant morbidity and mortality, useful biomarkers are needed for applying preventive strategies to reduce the incidence of CIN in these patients [4, 5, 36]. SII may be a practice and reliable indicator, which can be easily calculated from a CBC, in predicting CIN. Some preventive strategies such as the use of low-dose iso-osmolar contrast medium and/or prophylactic hydration administration pre- and post-procedure regardless of renal function can be applied easily in patients with higher SII values undergoing primary PCI.

Study Limitations

The present study has some limitations. This study was a retrospective, single-center study, and the number of study patients was relatively small. We could not perform internal and external validations for our results. In addition, patients who developed CIN after 72 h may have been missed from our study. The cutoff values of SII calculated by ROC may be variable due to the different designs of the studies. We did not evaluate the correlation of transient changes of study variables and the development of CIN during hospitalization. It has been known that many studies have evaluated acute HF and CIN together. However, the relationship between cardiorenal syndrome and CIN may be controversial regarding etiology of AKI. Therefore, the inclusion of patients with Killip class 2–4 may have affected the results of the present study. Long-term clinical outcomes were not evaluated in the study. Future studies are needed to confirm these results.

Conclusion

CIN is an important complication of PCI and it is associated with poor clinical outcomes [1–5]. Inflammation has been shown to play a key role in the pathophysi-

ology of CIN and many inflammation-based markers have been reported to be associated with CIN [6, 7]. In this regard, this study showed the relationship between SII, a relatively novel inflammatory marker combining platelet, neutrophil, and lymphocyte counts, and development of CIN in patients with STEMI undergoing primary PCI. SII may be a more useful and reliable indicator of CIN than NLR and PLR in these patients. SII, as a good indicator of CIN, may help clinicians in identifying high-risk patients who need preventive strategies before and after primary PCI procedure.

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Statement of Ethics

This study was conducted in accordance with ethical standards and approved by the Ethics Committee of the Kocaeli University (K.U. GOKAEK/2021/286).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Irem Karauzum and Prof. Ertan Ural contributed to the conception. Dr. Irem Karauzum, Dr. Kurtulus Karauzum, and Prof. Ertan Ural contributed to the design. Dr. Irem Karauzum and Prof. Ertan Ural contributed to supervision. Dr. Irem Karauzum, Dr. Kurtulus Karauzum, Dr. Kaan Hanci, Dr. Dogus Gokcek, Dr. Beyza Kalas and Prof. Ertan Ural contributed to the data collection. Dr. Irem Karauzum and Dr. Kurtulus Karauzum contributed to data analysis and manuscript drafting. All the authors contributed to critical review and the final draft.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author, upon reasonable request.

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