Original Paper

Association between Platelet-to-Lymphocyte Ratio and Contrast-Induced Nephropathy in Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndrome

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Abstract

Objective: Contrast-induced nephropathy (CIN) is associated with significantly increased morbidity and mortality after percutaneous coronary intervention (PCI). Patients with acute coronary syndrome (ACS) are at higher risk of CIN. The platelet-to-lymphocyte ratio (PLR) is closely linked to inflammatory conditions. We hypothesized that PLR levels on admission can predict the development of CIN after PCI for ACS. **Subjects and Methods:** A total of 426 patients (mean age 63.17 ± 13.01 years, 61.2% males) with ACS undergoing PCI were enrolled in this study. Admission PLR levels were measured before PCI. Serum creatinine values were measured before and within 72 h after the administration of contrast agents. Patients were divided into 2 groups: the CIN group and the no-CIN group. CIN was defined as an increase in serum creatinine level of ≥0.5 mg/dl or 25% above baseline within 72 h after contrast administration. **Results:** CIN developed in 53 patients (15.9%). Baseline PLR was significantly higher in patients who developed CIN compared to those who did not (160.8 ± 29.7 and 135.1 ± 26.1, respectively; p < 0.001). Multivariate analyses found that PLR [odds ratio (OR) 3.453, 95% confidence interval (CI) 1.453–8.543; p = 0.004] and admission creatinine (OR 6.511, 95% CI 1.759–11.095; p = 0.002) were independent predictors of CIN. **Conclusions:** The admission PLR level is an independent predictor of the development of CIN after PCI in ACS.

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Introduction

Contrast-induced nephropathy (CIN) is a serious complication of invasive cardiovascular procedures. The incidence of CIN is 2% for the general population. However, patients undergoing percutaneous coronary intervention (PCI) are at greater risk, and patients with diabetes or previous renal impairment have a risk of almost 50% [1, 2].

The development of CIN after PCI is associated with poor clinical outcomes including prolonged hospitalization, increased costs, increased rates of end-stage renal failure, myocardial infarction, repeat revascularization, and short- and long-term mortality [3–6]. Furthermore, patients with acute coronary syndrome (ACS) have a 3-fold higher risk of developing CIN [7, 8]. Because CIN occurs more frequently after urgent PCI in patients with ST-segment elevation myocardial infarction (STEMI) and non-STEMI [9], objective, rapidly available and reliable markers may be useful for the identification of patients at risk of developing CIN.

Platelet-to-lymphocyte ratios (PLRs) have recently been introduced as markers of several inflammatory conditions not only in malignancies but also in other pathologies involving the heart, thyroid, kidney and liver, and even diabetes mellitus, metabolic syndrome, and essential hypertension [10].

In the present study, we investigated whether PLR on admission is an independent risk factor that predicts the development of CIN in patients with ACS with ST-segment elevation (STE-ACS) and unstable angina/non-ST-segment elevation (NSTE-ACS) to undergo interventional therapy.

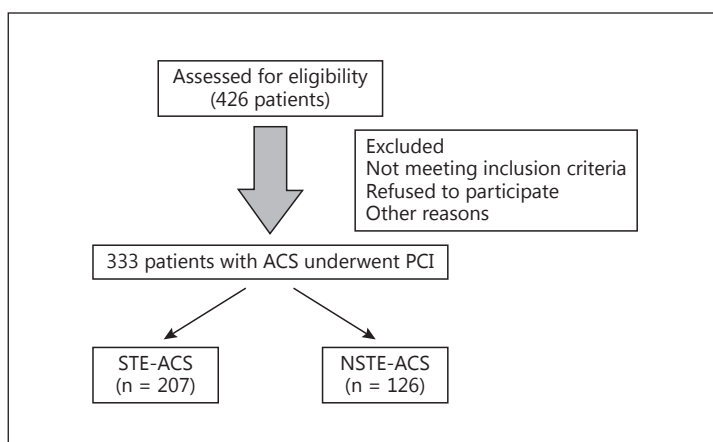## Subjects and Methods

Study Population

Between November 2009 and December 2012, a total of 426 consecutive patients (mean age 63.17 ± 13.01 years, 61.2% males) were identified with acute STE-ACS or NSTE-ACS undergoing emergency PCI. After an evaluation according to inclusion and exclusion criteria, 333 patients were enrolled in our study (fig. 1).

Patients with STE at the J point in 2 or more consecutive leads (with the cutoff point being >0.2 mV in leads V1, V2, or V3, and >0.1 mV in the other leads) and an elevation of the cardiac troponin T level greater than the upper limit of normal were defined as having STE-ACS [11]. Patients with ST-segment depression, T-wave inversion, or no electrocardiographic abnormalities and/or elevation of the cardiac troponin T level greater than the upper limit of normal were defined as having NSTE-ACS [12]. We excluded patients receiving long-term peritoneal or hemodialysis treatment, or those who underwent a renal transplantation or received administration of metformin, nonsteroidal anti-inflammatory drugs, aminoglycosides, or acetylcysteine 1 week before or after PCI. Patients were also excluded if they had intra-aortic balloon pump support before PCI because of cardiogenic shock, cardiac surgery for coronary revascularization, severe chronic heart failure (New York Heart Association class ≥3), and contrast exposure 2 weeks before PCI or died during PCI. Patients with an active infection and a history of collagen vascular disease were excluded from the study. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all participants.

Study Protocol and Laboratory Analysis

In all patients, antecubital venous blood samples for the laboratory analysis were drawn on admission in the emergency room before angiography. Common blood count parameters stored in citrate-based anti-coagulated tubes were measured by the Sysmex K-1000 auto-analyzer (Bohemia, N.Y., USA) within 5 min of sampling. Glucose, creatinine, blood urea nitrogen, lipid profile [total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein cholesterol], and triglyceride were determined by standard methods. High-sensitivity C-reactive protein (hs-CRP) levels were also measured. Immediately after intervention, all patients underwent hydration with intravenous isotonic saline (0.9%) at a rate of 1 ml/kg/h for 12 h (or 0.5 ml/kg/h for 12 h in cases of overt heart failure, including 5 patients from the CIN group and 3 patients from

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Fig. 1. Diagram of the 436 patients who were enrolled in the study after inclusion and exclusion criteria evaluation.

the no-CIN group). Any nephrotoxic medications (i.e., metformin and nonsteroidal anti-inflammatory drugs) were suspended on admission. Serum creatinine was also measured at 24, 48, and 72 h after contrast medium administration. Patients were divided into 2 groups: the CIN group and the no-CIN group. CIN was defined as an increase in serum creatinine level of ≥0.5 mg/dl or ≥25% above baseline within 72 h after contrast administration [13]. High-contrast volume was defined as the administration of a contrast volume of >140 ml [4]. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) equation [5]. Left ventricular ejection fraction (LVEF) was measured using the Simpson method according to the recommendations of the American Society of Echocardiography [14].

Coronary Intervention Procedures and Medications

Coronary angiography (CA) (Siemens Axiom Artis zee 2008; Siemens Healthcare, Erlangen, Germany) was performed using the femoral approach according to standard clinical practice. On admission, all patients in the emergency department received a bolus of 5,000 units of intravenous unfractionated heparin, followed by additional intraprocedural boluses to maintain an activated clotting time of 200–250 s (>300 s when tirofiban was not used), acetylsalicylic acid (300 mg orally), and a clopidogrel loading dose of 600 mg orally. Nonionic, iso-osmolar contrast medium (iodixanol, Visipaque 320 mg/100 ml; GE Healthcare, Cork, Ireland) was used to visualize the coronary arteries. PCI was performed immediately after diagnostic CA when appropriate.

Coronary stenting was performed using standard techniques. Thrombolysis in myocardial infarction grade 3 coronary flow in the treated vessel with a residual stenosis <50% was considered a successful PCI. The use of a glycoprotein IIb/IIIa inhibitor as well as of bare-metal or drug-eluting stents was left to the discretion of the interventional cardiologist. Additional use of thrombectomy was recommended depending on thrombus in the infarct-related artery. After CA, all patients continued to take aspirin (100 mg/day orally) indefinitely and clopidogrel (75 mg/day) for at least 12 months.

Statistical Analysis

We decided on the sample size of the study by using a program named 'Power and Sample Size Calculator' (Statistical Solutions, Cottage Grove, Wisc., USA; www.statisticalsolutions.net/pss_calc.php). Statistical analysis was performed with the Statistical Package for Social Sciences for Windows, version 18.0 (SPSS Inc., Chicago, Ill., USA). Continuous variables were compared using the Student t test. In case of non-normal distribution, nonparametric methods were used (Mann-Whitney U test). All values are expressed as the mean ± standard deviation or the median and interquartile range. Models were developed with stepwise techniques and on account of potential confounding factors as well as of variables that are shown to be statistically significant at univariate analysis. The results of this model were presented as odds ratios (ORs) and 95% confidence intervals (CIs). To identify the independent parameters associated with CIN, multivariable logistic regression analysis was used. According to the results of the univariate analysis, age, smoking, LVEF, hemoglobin, creatinine, PLR, total cholesterol, LDL cholesterol, hs-CRP, uric acid, troponin T, SYNTAX (SYNergy between PCI with TAXus and cardiac surgery) score, the presence of multivessel disease (MVD), and the presence of chronic total occlusion (CTO) were analyzed with the multivariate logistic regression model. The

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Table 1. Baseline characteristics of the study patients

Variable	No-CIN group (n = 280, 84.1%)	CIN group (n = 53, 15.9%)	p value
Age, years	60.2±12.3	68.2±12.6	<0.001
Males	190 (67.8)	35 (66.0)	0.765
BMI	26.83±3.53	27.65±5.53	0.445
Systolic blood pressure, mm Hg	129±12.1	126±11.7	0.675
Diastolic blood pressure, mm Hg	79±10	77± 12	0.876
Hypertension	135 (48.2)	32 (60.3)	0.210
Diabetes mellitus	105 (37.5)	17 (32.0)	0.365
Smoking	120 (42.8)	28 (52.8)	0.432
Hyperlipidemia	88 (31.4)	20 (37.7)	0.345
Prior CABG	20 (7.1)	5 (9.4)	0.543
Prior myocardial infarction	30 (10.7)	4 (7.5)	0.798
LVEF, %	45±10.0	39±9	<0.001
LVEF <40%, %	21.1	40	0.02
Type of ACS			
STE-ACS	175 (62.5)	32 (60.3)	0.698
NSTE-ACS	105 (37.5)	21 (39.7)	0.765
Treatment before admission, %			
ACEI or ARB	28.3	26.1	0.756
Statins	24.4	25.4	0.876

Figures in parentheses are percentages. ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft.

receiver operating characteristic (ROC) analysis was performed to determine the best cutoff value of PLR, and the sensitivity and specificity at that point were obtained for predicting the development of CIN. p values <0.05 were considered statistically significant.

Results

The study population consisted of 426 patients (mean age 63.17 ± 13.01 years, 61.2% males) who had measurements of baseline PLR and creatinine, followed by additional daily measures of creatinine up to 72 h. A total of 53 patients (15.9%) developed CIN. The baseline clinical characteristics of the patient population stratified by CIN are summarized in table 1. Patients in the CIN group were significantly older than those in the no-CIN group (68.2 ± 12.6 vs. 60.2 ± 12.3 years, respectively; p < 0.001) and had a significantly lower proportion of smoking (p < 0.001) compared with patients in the no-CIN group. LVEF was also lower in the CIN group (p < 0.001). There were no significant differences between the groups regarding gender, hypertension, diabetes mellitus, hyperlipidemia, prior myocardial infarction, prior stroke, prior medications, in-hospital medications, and type of ACS.

The baseline laboratory measurements of the study patients are shown in table 2. PLR at baseline was significantly higher in patients who developed CIN compared to those who did not (160.8 ± 29.7 and 135.1 ± 26.1, respectively; p < 0.001). PLR according to risk of developing CIN are shown in table 2. In addition to having elevated PLR, patients who developed CIN had significantly higher baseline serum creatinine, peak troponin T, and uric acid levels, but significantly lower baseline hemoglobin, total cholesterol, LDL, and estimated glomerular filtration rate than those in whom CIN did not occur. Patients with CIN had a higher preva-

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Table 2. Common blood count parameters of patients

Variables	CIN group (n = 53)	No-CIN group (n = 280)	p value
Hemoglobin, g/dl	13.4±1.6	13.0±1.8	0.48
White blood cell count, $\times 10^3/mm^3$	12.0±3.5	12.6±3.9	0.58
Platelet count, $\times 10^3/mm^3$	248±70.8	250.3±66.3	0.82
Hematocrit, %	41±6.6	41±5.3	0.67
Red blood cell distribution width, %	13.0±2.1	13.5±1.4	0.62
Red blood cell count, $\times 10^6/ml$	4.2±0.6	4.1±0.3	0.71
Mean corpuscular volume, fl	82.0±5.1	84.0±5.6	0.59
Mean platelet volume, fl	8.3±1.2	8.4±1.4	0.60
PLR	160.8±29.7	135.1±26.1	<0.001
Serum creatinine, mg/dl	1.40±0.37	1.06±0.26	<0.001
eGFR, ml/min/1.73 m^2	51.3±17.4	71.1±20.1	<0.001
HbA$_{1c}$, %	7.1±1.83	7.0±1.78	0.697
Serum glucose on admission, mg/dl	157±76	155±77	0.777
Total cholesterol, mg/dl	188±48	167±55	0.567
Triglyceride, mg/dl	131±54	140±53	0.438
LDL, mg/dl	123±44	120±39	0.543
High-density lipoprotein, mg/dl	44±12	41±11	0.876
hs-CRP, mg/l	8.44±1.43	7.08±0.9	0.02
Peak CK-MB, ng/ml	50.3 (2.55–426)	33.4 (0.8–435)	0.199
Peak troponin T, ng/ml	1,800 (44.1–10,000)	1,040 (4.8–10,000)	0.003
Serum uric acid, mg/dl	7.1±1.87	6.5±1.73	<0.001

Figures in parentheses are ranges. CK-MB = Creatine kinase myocardial band; eGFR = estimated glomerular filtration rate; HbA$_{1c}$ = hemoglobin A$_{1c}$.

lence of MVD, presence of CTO in non-culprit vessels, and a higher SYNTAX score as well as a lower stent diameter compared with those without CIN. However, the location of the culprit lesion, the contrast volume, procedure duration, and procedure success rate did not significantly differ between patients who developed CIN and those who did not. Angiographic and procedural characteristics of the study patients are listed in table 3. The ROC curve analysis of PLR for predicting CIN is shown in figure 2. PLR ≥148.3 measured on admission had a 75.6% sensitivity and 72.7% specificity in predicting CIN.

The effects of multiple variables were analyzed with univariate and multivariate logistic regression analyses. According to the results of univariate analysis, age, smoking, LVEF, hemoglobin, creatinine, PLR ≥148.3, total cholesterol, LDL cholesterol, hs-CRP, uric acid, troponin T, SYNTAX score, the presence of MVD, and the presence of CTO were analyzed with the multivariate logistic regression model. At multivariate analyses, PLR (OR 3.453, 95% CI 1.453–8.543; p = 0.004) and admission creatinine (OR 6.511, 95% CI 1.759–11.095; p = 0.002) were still significant independent predictors of the development of CIN after PCI in patients with ACS (table 4).

Discussion

To our knowledge, our study is the first to demonstrate that PLR is an important predictor of CIN in patients with ACS. Previous studies indicated that a higher PLR value emerged as a significant independent predictor of long-term survival in patients who presented with non-STEMI [12].

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Table 3. Angiographic and procedural characteristics and medications administered to patients

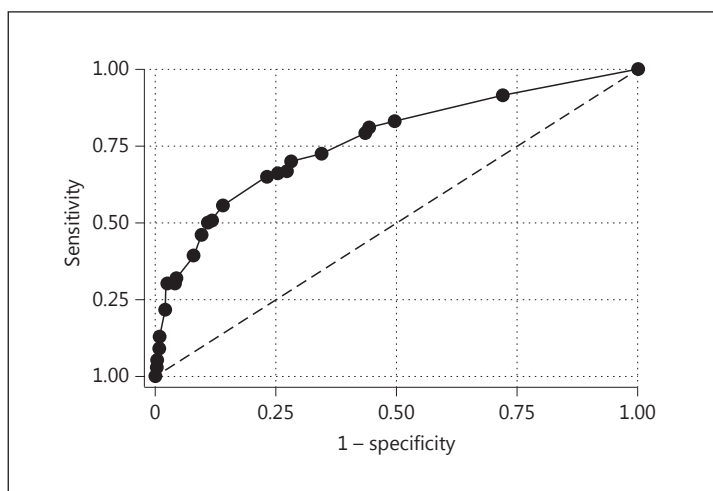| Variable	No-CIN group (n = 280)	CIN group (n = 53)	p value
Total time of procedure, min	36.56±17.01	39.08±13.13	0.153
Total amount of contrast, ml	160±15	168±19	0.234
High-contrast volume	168 (60)	33 (62.2)	0.546
MVD	143 (51.1)	39 (73.5)	0.003
CTO	45 (16.1)	19 (35.8)	0.007
SYNTAX score	14.34±8.23	19±12.46	<0.001
Culprit vessel			
Left main coronary artery	1 (0.4)	0 (0)	0.342
Left anterior descending artery	135 (48.2)	25 (47.1)	
Left circumflex artery	55 (19.6)	12 (22.6)	
Right coronary artery	76 (27.1)	15 (28.3)	
Saphenous vein graft stent implantation	13 (4.6)	1 (1.9)	
Door-balloon time, min	108±28	106±33	0.688
Stent implantation	260 (92.8)	45 (84.9)	0.01
Total length of stent, mm	23.11±10.87	24.18±11.43	0.565
Stent diameter, mm	3.21±0.41	3.13±0.54	0.124
Procedural success	220 (78.5)	36 (67.9)	0.07
In-hospital medications, %			
Statin	73.3	70.8	0.243
ACEI or ARB	72.6	65.9	0.645
Tirofiban	36.3	28.1	0.128
β-Blocker	89.1	78.2	0.06
Diuretic	22.8	26.1	0.778
Clopidogrel	97.6	95.1	0.189

Figures in parentheses are percentages. ACEI = Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Table 4. Univariate and multivariate logistic regression analysis of the association between CIN and multiple parameters

Variables	Univariate analysis	p value	Multivariate analysis	p value
Age	1.170 (1.053–1.195)	<0.001	1.023 (0.980–1.156)	0.325
Smoking	0.220 (0.114–0.425)	<0.001	0.372 (0.150–1.231)	0.117
PLR	19.432 (11.042–27.421)	<0.001	3.453 (1.435–8.543)	0.004
LVEF	0.897 (0.804–0.927)	<0.001	0.72 (0.934–1.013)	0.244
Hemoglobin	0.711 (0.604–0.776)	<0.001	0.968 (0.924–1.011)	0.165
Creatinine	13.563 (6.104–21.421)	<0.001	6.511 (1.759–11.095)	0.002
Uric acid	1.554 (1.1224–1.627)	<0.001	1.152 (1.260–1.486)	0.345
hs-CRP	1.111 (1.098–1.327)	<0.001	1.125 (0.895–1.414)	0.176
Troponin T	1.226 (1.180–1.358)	0.002	1.033 (0.932–1.146)	0.132
Total cholesterol (mg/dl)	0.991 (0.904–0.998)	0.030	1.122 (0.092–1.236)	0.145
LDL (mg/dl)	0.888 (0.814–0.929)	0.012	1.093 (0.995–1.140)	0.178
SYNTAX score	1.127 (1.104–1.328)	<0.001	1.111 (0.981–1.281)	0.213
MVD	2.281 (2.004–4.110)	0.003	0.563 (0.359–1.547)	0.111
CTO	2.108 (1.994–2.429)	0.008	1.151 (0.562–3.613)	0.129

Data are given as ORs with 95% CIs in parentheses. CK-MB = Creatine kinase myocardial band; eGFR = estimated glomerular filtration rate; HbA$_{1c}$ = hemoglobin A$_{1c}$.

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Fig. 2. PLR ROC curve for the development of CIN. The CIN ROC curve was plotted to verify the optimum cutoff point for PLR, which was 148.3. The AUC for PLR was 71.4% (95% CI 0.665–0.764), with a sensitivity of 75.6% and a specificity of 72.2%.

CIN after PCI is strongly associated with prolonged hospitalization, increased costs, increased rates of end-stage renal failure, myocardial infarction, repeat revascularization, and early and late mortality [3–5]. Patients who develop CIN and require dialysis after PCI have 40% in-hospital mortality and 80% 2-year mortality rates [13].

The development of CIN is a sign of poor short- and long-term prognosis after STE-ACS and NSTE-ACS despite successful early coronary revascularization [9, 14]. Preexisting renal impairment, diabetes, congestive heart failure, advanced age, anemia, use of high-contrast medium volume, and a reduced intravascular volume are risk factors for the development of CIN [7, 15, 16].

The pathophysiologic mechanisms of CIN are complex, multifactorial, and incompletely understood. Possible mechanisms include intrarenal vasoconstriction, reduced renal blood flow, medullary hypoxia, oxidative stress, inflammation, endothelial dysfunction, and direct tubular epithelial cell injury by contrast medium [17]. CIN is a specific type of cardiorenal syndrome [18]. Renal injury starts with hemodynamic effects of myocardial infarction. Abnormal hemodynamic states lead to a decrease in renal blood flow, and the activation of immune and neurohormonal systems, such as the sympathetic nervous system and the renin-angiotensin-aldosterone system, contributes to medullary hypoxia [19, 20]. Direct cytotoxicity to renal tubular cells caused by the contrast agent then occurs. The results of the injury include renal vasoconstriction, impaired vasodilation, medullary hypoxia leading to oxidative stress, and tubular injury [21].

A recent study showed that a higher PLR value is related to the presence of coronary artery disease and is correlated with CRP and fibrinogen levels [22]. Both thrombocytosis and lymphocytopenia correlate with the degree of systemic inflammation, and PLR represents a novel marker incorporating both hematologic indices. We have hypothesized that PLR is not directly but possibly a result of the inflammatory process in CIN. In the present study, we demonstrate that a higher PLR value may be related to CIN.

In a previous study, the neutrophil-to-lymphocyte ratio has been shown to be associated with CIN [23]. With similar results obtained by PLR, we show that hematologic markers can be used in the diagnosis of CIN availability.

In our study, MVD, the presence of CTO in non-culprit vessels, high SYNTAX scores, and low stent diameters were associated with a higher incidence of CIN. In our opinion, high SYNTAX scores, MVD, and the presence of CTO in non-culprit vessels are related to more serious presentations (e.g., shock, arrhythmia), longer procedural duration, more contrast

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medium use, a higher incidence of no-reflow, and a lower LVEF. Thus, the renal vasoconstrictive response and the resulting corticomedullar hypoxia [20] may be aggravated in patients with high scores. It appears (although not statistically significant) that procedural success was considerably lower in the CIN group as compared to the no-CIN group. We think it may be due to the amount of contrast agent used and the total time of the procedure in the CIN group compared to the no-CIN group (although not statistically significant). The use of a greater contrast volume is associated with greater rates of CIN [24]. However, it was shown that the contrast medium volume does not have an effect on CIN if low-osmolar contrast agents and adequate hydration are used [25]. In our study, we did not find any effect of contrast agent volume on CIN. Two factors might be responsible for this result. First, we used low-osmolar agents and adequate hydration for our patients. Second, the amount of contrast volume used during the procedure was similar in our study population.

Study Limitations

This study has several limitations. First, we measured PLR only once at admission and without correction for potential variability in PLR levels. Second, the follow-up assessment of renal function in our study was performed 1–3 days after PCI; therefore, we might have missed a later increase in serum creatinine in some patients who did not have renal function deterioration within 72 h of their procedure. This might have resulted in a slight underestimation of CIN. Finally, we did not measure inflammatory indices except for hs-CRP.

Conclusion

Admission PLR levels may predict the development of CIN after PCI in patients with ACS. The results may be of clinical significance because PLR is easily available, widely used, and relatively cheap compared to most other laboratory markers.

Disclosure Statement

There are no conflicts of interest.

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