Relationship Between Serum Procalcitonin Level and Contrast-Induced Nephropathy in Patients Undergoing Primary Percutaneous Coronary Intervention

Primer Perkütan Koroner Girişim Uygulanan Hastalarda Serum Prokalsitonin Düzeyi ile Kontrast Nefropatisi Arasındaki İlişki

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ABSTRACT Objective: We aimed to investigate the relationship between serum procalcitonin level and contrast-induced nephropathy (CIN) in patients with ST-elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (PPCI). **Material and Methods:** Three hundred forty-one consecutive STEMI patients (mean age: 57±11 years; 67.1% male) who underwent PPCI in our clinic between April 2013 and December 2013 were studied. CIN was defined as an increase in serum creatinine concentration ≥ 25% over baseline. Biochemical tests, including determination of serum procalcitonin level, were performed before (baseline) and 48 h after PPCI. **Results:** Of 341 study patients, 96 (28.2%) developed CIN. The median (interquartile range) baseline procalcitonin level was significantly higher in the CIN (+) group [0.075 μg/L (0.70-1.20 μg/L) versus 0.05 μg/L (0.75-1.00 μg/L), p<0.001)]; however, high procalcitonin was not an independent predictor of CIN in multivariate logistic regression analysis (p=0.274). On the other hand, high serum C-reactive protein level (odds ratio: 1.02 [1.01-1.04], p=0.002), high amount of contrast media used (odds ratio 1.12 [1.08-1.17], p<0.001), and low rate of post-procedural thrombolysis in myocardial infarction (TIMI) grade 3 flow (odds ratio 0.05 [0.01-0.49], p=0.01) were identified as independent predictors of CIN. **Conclusion:** Serum procalcitonin level does not have a clear association with CIN; however, underlying reasons for the higher serum procalcitonin levels in patients who developed CIN need to be explored with further studies.

Key Words: Contrast media; glomerulonephritis, membranous; procalcitonin; infarction; myocardial revascularization

ÖZET Amaç: Bu çalışmada primer perkütan koroner girişim (PPCI) uygulanan ST-yükselmeli miyokardiyal infarktüs (STEMI) hastalarında serum prokalsitonin düzeyi ile kontrast nefropatisi (CIN) arasındaki ilişkinin değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Kliniğimizde Nisan 2013 ve Aralık 2013 tarihleri arasında PPCI geçiren 341 ardışık STEMI hastası (yaş ortalaması: 57±11 yıl; %67,1 erkek) çalışmaya dahil edilmiştir. CIN, serum kreatinin konsantrasyonunda ≥%25 artış olarak tanımlanmıştır. Serum prokalsitonin düzeyi dahil olmak üzere biyokimyasal testler PPCI öncesi (bazal) ve 48 saat sonrasında yapılmıştır. **Bulgular:** Çalışmaya dahil olan 341 hastadan, 96'sında (%28,2) CIN gelişmiştir. Medyan (interkuartil aralık) bazal prokalsitonin düzeyi CIN gelişen hastalarda daha yüksek bulunmuştur [0,075 μg/L (0,70-1,20 μg/L) vs. 0,05 μg/L (0,75-1,00 μg/L), p<0,001)]. Ancak çok değişkenli lojistik regresyon analizinde yüksek prokalsitonin düzeyi anlamlı bir bağımsız değişken değildir (p=0,274). Diğer taraftan, bu analizde yüksek serum C-reaktif protein düzeyi (odds oranı: 1,02 [1,01-1,04], p=0,002), kullanılan kontrast madde hacmi (odds oranı 1,12 [1,08-1,17], p<0,001) ve miyokardiyal infarktüs prosedürü sonrası düşük tromboliz oranı (TIMI grad 3 akış) (odds oranı 0,05 [0,01-0,49], p=0,01) CIN için bağımsız belirleyicilerdir. **Sonuç:** Serum prokalsitonin düzeyinin CIN ile aşikar bir ilişkisi yoktur, ancak CIN gelişen hastalardaki yüksek prokalsitonin düzeyinin altında yatan nedenler ileri çalışmalarla aydınlatılmalıdır.

Anahtar Kelimeler: Kontrast madde; glomerulonefrit, membranöz; prokalsitonin; infarktüs; miyokardiyal revaskülarizasyon

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Contrast-induced nephropathy (CIN) is a condition characterized by acute deterioration of renal function after exposure to contrast agents, and is associated with increased mortality and morbidity.[1] The risk of CIN reportedly ranges between 5% and 25%, being more frequent after coronary imaging, particularly in primary percutaneous coronary intervention (PPCI) due to hemodynamic instability or in more complex and prolonged procedures.[2-4] CIN does not have any specific treatment; thus, early prediction based on risk factors carries utmost importance to prevent its development. Many etiological factors, including age, diabetes mellitus, the amount of contrast material used, and baseline renal function, are well-established.[5] Predictive value of blood parameters, such as blood neutrophil gelatinase–associated lipocalin cystatin-C and neutrophil to lymphocyte ratio, however, may show conflicting results.[3,6] Thus, there is still a need to identify biomarkers that are easily accessible and applicable in clinical practice to predict CIN development with high sensitivity and specificity.

Procalcitonin, a 13-kDa protein, is a new type of inflammatory marker that is physiologically synthetized by the C-cells of the thyroid gland and pulmonary neuroendocrine cells.[6,7] Procalcitonin level aids in making clinical decisions such as initiating antibiotic treatment for bacterial infections and predicting lethal multiple organ failure. Recent studies have suggested that procalcitonin is not only a marker of infection, but is presumably a cytokine-like proinflammatory mediator.[8] Indeed, the release of procalcitonin as a response to nonspecific and non-infectious stimulations (*i.e.*, polytrauma, surgery with tissue injury, cardiac surgery, heat shock, and burn injuries) has been demonstrated.[9] However, its relationship to CIN has not been reported thus far.

In this study, we aimed to investigate the predictive role of procalcitonin in CIN development among patients with ST-elevation myocardial infarction (STEMI) who underwent primary PPCI.

MATERIAL AND METHODS

STUDY POPULATION

A total of 360 consecutive patients who presented to our emergency department between April 2013 and December 2013 and who underwent PPCI after diagnosis of STEMI were enrolled in this prospective follow-up study. STEMI was defined as an ST elevation of at least 1 mm at ≥2 successive leads (or 2 mm in V1-V3) or a newly developed left bundle branch block. Patients who were hypersensitive to contrast agents and statins, those suffering from cardiogenic shock (n=5), chronic renal failure patients undergoing dialysis (n=4), and cases with lower creatinine clearance values (<60 mL/min) (n=10) were excluded from the study. In total, 341 patients (mean age: 57±11 years; 67.1% male) were included in the analysis. The study was approved by the local ethics committee (Institutional Ethics Committee of Mehmet Akif Training and Research Hospital, date 06.10.2011, no. 41) and was conducted in accordance with the latest version of the Declaration of Helsinki. All patients gave written informed consent before any study-related procedure.

STUDY PROCEDURES

Demographics, vital signs, medical history including comorbidites and concomitant medications, and clinical findings were recorded. All patients underwent PPCI within at most 12 h after the onset of chest pain and received 300 mg of chewable aspirin, 600 mg of clopidogrel, and intravenous heparin at a dose of 12 μ/kg before beginning the procedure. For PPCI, iopromide (Ultravist®, Bayer Healthcare, Leverkusen, Germany) was used as the non-ionic iso-osmolar contrast agent.

After the procedure, all patients received twice-daily doses of 1 mg/kg enoxaparin SC, 100 mg acetylsalicylic acid, and 75 mg clopidogrel; they were also hydrated with sodium chloride 0.9% (1 mL/kg/h) for 12 h after the procedure. After stenting, patients were evaluated based on TIMI flow grades. TIMI flow grades below 3 were defined as "no reflow."

Electrocardiography (ECG) was performed on admission and immediately after and 90 min after the procedure. On ECG, no reflow was defined as <75% resolution of the ST segment at the end of the procedure compared with baseline. Left ventricular ejection fraction (LVEF) was measured by transthoracic echocardiographic examination within the first 24 h using the biplane Simpson method. All the echocardiographic examinations were performed in the coronary intensive care unit by the same cardiologist, who was blind to study groups. CIN was defined as an increase in serum creatinine ≥0.5 mg/dL above baseline.[9]

LABORATORY EVALUATION

Blood samples were collected from patients at two times: before PPCI and 48 h after PPCI. The parameters that may be related with CIN, which are procalcitonin, glomerular filtration rate, and red blood cell distribution width were measured in blood samples collected before and after PPCI. However, other parameters, which are C-reactive protein, creatinine, hemoglobin, glucose, glycated hemoglobin, platelet count, peak troponin, peak creatine kinase MB isoenzyme (CK-MB), uric acid, and lipids were measured in blood samples collected before PPCI.

Serum procalcitonin level was measured using the enzyme-linked fluorescent assay (ELFA) method from a specific procalcitonin kit on mini-VIDAS equipment (VIDAS® B.R.A.H.M.S PCT™, BioMérieux's Diagnostics, Marcy l'Etoile, France). Serum creatinine level was determined using the Jaffe method on kinetic colorimetric equipment with commercial kits (Cobas 6000 c501, Roche Diagnostics, Mannheim, Germany). To calculate the GFR via creatinine clearance, the Cockgroft–Gault formula was used.[10]

STATISTICAL ANALYSIS

The data were summarized using descriptive statistics (*i.e.*, mean, standard deviation, median, interquartile range, frequency, and percentage). For the univariate intergroup comparisons of continuous variables with normal distribution, Student's t-test was used; the Mann-Whitney U-test was utilized for those without a normal distribution. The chi-square test was used for univariate comparison of categorical data. The variables included in the univariate analysis were listed in Table 1. In order to determine the independent predictive factors for the development of CIN after PPCI, multivariate logistic regression analysis was performed by including the variables that were significant in the univariate analysis. Odds ratios are given with a 95% CI.

All statistical analyses were performed using NCSS package program (Number Cruncher Statistical System Statistical Software, 2007, Kaysville, Utah, USA). Results were evaluated at a statistical significance level of $p < 0.05$.

RESULTS

Of the 341 study patients, 96 (28.2%) developed CIN (Table 2). The mean age of patients in the CIN

TABLE 1: The variables included in univariate analyses.

Age (years)
Gender
Heart rate (bpm)
Blood pressure (mmHg)
Comorbidity
Cardiologic findings (Killip class for AMI ≥2, ST resolution on ECG, left ventricular ejection fraction)
Laboratory findings
Procalcitonin (μg/L)
Glomerular filtration rate (mL/min/1.73 m²)
Red blood cell distribution width (fL)
Creatinine (mg/dL)
C-reactive protein (mg/L)
Hemoglobin (g/dL)
Glucose (mg/dL)
Glycated hemoglobin (%)
Platelet count (x 10³/mm³)
Peak troponin (ng/mL)
Peak CK-MB (mg/dL)
Uric acid (mg/dL)
Lipids (mg/dL)
Amount of contrast media (mL)
Medications
Angiographic findings

CK-MB; Creatine kinase MB; Isoenzyme; ECG: Electrocardiography; AMI: Acute myocardial infarctus.

TABLE 2: Comparison of demographic and clinical characteristics of patients who did or did not develop CIN after primary percutaneous coronary interventions.

	CIN (-) n=245	CIN (+) n=96	p
Age (years)	52.58±11.32	58.77±12.88	<0.001
Gender			
Women	30 (12.24)	15 (15.63)	0.407
Men	215 (87.76)	81 (84.38)	
Heart rate (bpm)	77.29±11.97	76.61±13.14	0.649
Blood pressure (mmHg)			
Systolic	130.42±20.44	129.38±22.53	0.681
Diastolic	78.13±14.1	77.32±15.91	0.649
Comorbidity			
Diabetes mellitus	89 (36.33)	45 (46.88)	0.073
Hypertension	91 (37.30)	48 (50.00)	0.032
Smoking	135 (55.10)	55 (57.29)	0.714
Hyperlipidemia	117 (47.76)	49 (51.04)	0.585
Previous coronary artery disease	3 (1.22)	6 (6.25)	0.009
Family history of coronary artery disease	52 (21.22)	19 (19.79)	0.769
Cardiologic findings			
Killip class for AMI ≥2	36 (14.69)	37 (41.57)	<0.001
ST resolution on ECG (%)	168 (68.57)	41 (42.71)	<0.001
Left ventricular ejection fraction (%)	49.11±8.12	47.23±10.18	0.074

CIN; contrast induced nephropathy, AMI; acute myocardial infarction ECG; electrocardiography, Data are presented as mean±standard deviation or n (%).

(+) group was significantly higher than that of the CIN (–) group ($p < 0.001$). The prevalence of hypertension and history of coronary artery disease was also significantly higher in CIN (+) patients than in CIN (–) patients ($p = 0.032$ and $p = 0.009$, respectively). On cardiologic evaluation, compared to CIN (–) patients, the CIN (+) group had significantly more patients with Killip class ≥ 2, a measure of severity of acute myocardial infarction, and less patients with ST resolution on ECG, a measure indicating the efficacy of reperfusion therapy ($p < 0.001$) (Table 2).

LABORATORY EVALUATION

The most remarkable laboratory finding was that serum procalcitonin levels before and after PPCI, as well as % change, were significantly higher in CIN (+) patients than in CIN (–) patients ($p < 0.05$ for all). Additionally, compared with CIN (–) patients, CIN (+) patients had significantly lower GFR after PPCI ($p < 0.001$); the % changes in both creatinine and GFR were also significant ($p < 0.001$ for both). CRP was significantly higher and hemoglobin level was significantly lower in the CIN (+) group ($p < 0.001$ for both). However, there was no difference between groups with respect to HbA1c levels ($p = 0.598$). Although red blood cell distribution width was significantly higher in CIN (+) patients at both admission and at 48 h, there was no significant difference between CIN (+) and CIN (–) patients in terms of % change. The remaining biochemical parameters did not show significant differences between CIN (+) and CIN (–) patients (Table 3).

ANGIOGRAPHIC AND TREATMENT-RELATED VARIABLES

Among the angiographic and treatment-related variables, only the amount of contrast media and post-procedural TIMI grade 3 flow showed a significant difference between CIN (+) and CIN (–) patients (Table 4). The mean amount of contrast agent used in the CIN (+) group was significantly

TABLE 3: Comparison of laboratory findings of patients who did or did not develop CIN after PPCI.

	CIN (-) n=245	CIN (+) n=96	p
Procalcitonin (µg/L)			
Before PPCI	0.05 (0.75-1.00)	0.075 (0.70-1.20)	<0.001
After PPCI	0.06 (0.80-1.00)	0.09 (1.00-1.59)	<0.001
% change	0 (0-0)	0.01 (0-52.02)	0.001
Glomerular filtration rate (mL/min/1.73 m²)			
Before PPCI	101 (87-123.8)	98 (65-118.2)	0.022
After PPCI	101.6 (84.9-126.7)	77.8 (50.5-97.9)	<0.001
% change	0 (-12.48-10.05)	-24.44 (-42.19--11.07)	<0.001
Red blood cell distribution width (fL)			
Before PPCI	12.87±1.15	13.16±0.97	0.033
After PPCI	13.2±7.21	15.94±16.64	0.035
% change	0 (-1.61-2.43)	0.74 (-2.32-2.77)	0.663
Creatinine (mg/dL)	0.88 (0.75-1)	0.8 (0.7-1)	0.348
% change	7.15 (0-11.28)	29.72 (22.22-37.5)	<0.001
C-reactive protein (mg/L)*	14.34 (4.5-33.12)	22.14 (10-60.29)	0.001
Hemoglobin (g/dL)*	14.48±1.65	13.83±1.77	0.001
Glucose (mg/dL)*	158.96±76.4	153.09±88.98	0.544
Glycated hemoglobin (%)*	6.54±1.67	6.65±1.83	0.598
Platelet count (×10³/mm³)*	274.03±84.69	258.73±62.55	0.109
Peak troponin (ng/mL)*	13.37±15.6	13.51±15.84	0.941
Peak CK-MB (mg/dL)*	61.11±84.75	56.36±77.41	0.708
Uric acid (mg/dL)*	5.38±1.47	5.70±1.75	0.114
Lipids (mg/dL)*			
Total cholesterol	192.36±45.91	196.71±42.63	0.426
Low-density lipoprotein cholesterol	127.16±37.15	130.26±37.82	0.492
High-density lipoprotein cholesterol	39.55±10.05	42.18±21.46	0.126
Triglyceride	146.87±86.56	148.84±114.48	0.864

CIN; contrast induced nephropathy, PPCI; primary percutaneous coronary interventions, CK-MB; creatine kinase MB isoenzyme.

*Measured in blood samples collected before PPCI.

Data are presented as mean±standard deviation or median (interquartile range).

higher relative to the CIN (–) group ($p < 0.001$). The percentage of patients with post-procedural TIMI grade 3 flow, which indicates a favorable outcome after the interventional procedure, was significantly lower among the CIN (+) group than the CIN (–) group ($p < 0.001$) (Table 4).

PREDICTIVE FACTORS FOR THE DEVELOPMENT OF CIN

To determine the predictive values of variables for the development of CIN after PPCI, we performed multivariate logistic regression analysis that included variables showing a significant difference between the CIN (+) and CIN (–) groups in univariate analysis (Table 5). According to multivariate logistic regression analysis, the independent predictors of CIN were as follows: high serum CRP level (odds ratio: 1.02, 95% CI 1.01–1.04, $p = 0.002$), high amount of contrast media used (odds ratio: 1.12, 95% CI 1.08–1.17, $p < 0.001$), and a low rate of post-procedural TIMI grade 3 flow (odds ratio: 0.05, 95% CI 0.01–0.49, $p = 0.01$). However, serum procalcitonin level before or after PPCI was not an independent predictor of CIN ($p = 0.274$ and $p = 0.488$, respectively) (Table 5).

DISCUSSION

In this prospective follow-up study, we primarily found that STEMI patients who developed CIN

TABLE 4: Comparison of angiographic and treatment variables of patients who did or did not develop CIN after primary percutaneous coronary interventions.

	CIN (-) n=245	CIN (+) n=96	p
Amount of contrast media (mL)	243.55±24.41	335.57±37.8	<0.001
Medications			
ARB/ACE inhibitors	53 (21.63)	15 (15.63)	0.212
Beta-blocker	24 (9.80)	11 (11.46)	0.649
Calcium channel blocker	16 (6.53)	9 (9.38)	0.365
Statin	40 (16.33)	14 (14.58)	0.692
Insulin	13 (5.31)	8 (8.33)	0.296
Oral antidiabetic drugs	38 (15.51)	17 (17.71)	0.620
Angiographic findings			
Post-procedural TIMI flow 3	227 (92.65)	75 (78.13)	<0.001
Left anterior descending artery	34 (13.88)	15 (15.63)	0.912
Left circumflex artery	93 (37.96)	29 (30.21)	0.198
Right coronary artery	8 (3.27)	2 (2.08)	0.683
Other (intermediary. obtus marginalis. etc.)	1 (0.41)	0 (0.00)	0.498

CIN: Contrast induced nephropathy; ARB/ACE: Angiotensin reseptör blocker/angiotensin converting enzyme; TIMI: Thrombolysis in myocardial infarction.
Data are presented as mean±standard deviation or n (%).

after PPCI had higher serum procalcitonin levels. However, increased procalcitonin levels on admission and 48 h later were not identified as independent predictors for CIN.

As a precursor of calcitonin, procalcitonin is produced in the thyroid gland and contains 32 amino acids. Procalcitonin was first described by Ghillani et al. in 1989.[11] Previously, procalcitonin levels were preferably used in the determination of severity and progression of bacterial infections; subsequent studies have also demonstrated its potential utility in the evaluation of systemic inflammatory response, monitorization of treatment, and prognosis. Recent studies revealed that increased procalcitonin concentrations indicate the extent of atherosclerosis in patients with coronary artery disease and predict cardiovascular mortality.[12] Procalcitonin concentrations have been also associated with deterioration of renal function and high mortality in patients with chronic renal disease.[8] In other studies, however, increased procalcitonin levels in acute coronary syndrome showed no correlation with the extent of coronary artery disease or early-stage mortality.[13]

Although an increase in procalcitonin level in inflammation has not been fully understood, its modulatory role in the inflammatory response has been suggested.[14] After the onset of local or systemic inflammatory processes, subsequent monocytic activation is a prerequisite for procalcitonin production. Experimental data have shown that procalcitonin acts as a chemoattractant for peripheral blood mononuclear cells (PBMCs).[9,15] However, as demonstrated in various studies, pro calcitonin functions temporarily like PBMC-derived secretion factors.[14] Mediators released from PBMCs play important roles in inflammatory processes.[9,14] In another study, parallel increases in procalcitonin and nitric oxide levels were demonstrated, which were presumably associated with vasodilatation in sepsis.[16]

Although the developmental mechanism of CIN has not been fully elucidated, medullary hypoxia caused by renal vasoconstriction and direct toxic destructive effects of contrast agents has been demonstrated.[3] The release of various mediators (*e.g.*, endothelin and vasopressin, etc.) and a decrease in the release of nitric oxide result in renal vasoconstriction, decreased renal medullary blood

TABLE 5: Independent predictors of CIN in multivariate logistic regression analysis.

Variables included in the analysis	B	Standard error	p	Odds ratio	95% CI Lower r	95% CI Upper r
Age (year)	-0.02	0.03	0.639	0.99	0.93	1.05
Hypertension	0.69	0.76	0.368	1.99	0.45	8.85
Previous coronary artery disease	-3.03	1.85	0.101	0.05	0.00	1.80
Killip class for AMI ≥2	0.07	0.71	0.919	1.08	0.27	4.36
ST resolution on ECG	0.83	0.72	0.249	2.30	0.56	9.51
Glomerular filtration rate after PPCI (mL/min/1.73 m^2)	0.00	0.03	0.995	1.00	0.94	1.06
Red blood cell distribution width after PPCI (fL)	-0.01	0.06	0.912	0.99	0.88	1.12
Procalcitonin before PPCI	0.38	0.17	0.274	0.22	0.09	1.16
Procalcitonin after PPCI	-0.11	0.16	0.488	0.90	0.65	1.23
Hemoglobin (g/dL)	-0.39	0.24	0.099	0.67	0.42	1.08
C-reactive protein (mg/L)	0.02	0.01	0.002	1.02	1.01	1.04
Amount of contrast media (mL)	0.12	0.02	<0.001	1.12	1.08	1.17
Post-procedural TIMI flow 3	-2.93	1.14	0.01	0.05	0.01	0.49

CIN: Contrast induced nephropathy; B: Coefficient for the constant; CI: Confidence interval; AMI: Acute myocardial infarction; ECG: Electrocardiography; TIMI: Thrombolysis in myocardial infarction; PPCI: Primary percutaneous coronary intervention.

flow, and the development of renal damage.[15,17] Another important mechanism involves the impact of tubular obstruction induced by protein precipitates that are produced as an outcome of increased activity of proinflammatory cytokines, free oxygen radicals, and complements.[18] Renal vascular and tubular endothelium undergo structural and functional changes following exposure to a nephrotoxic contrast agent. Subsequently, an increase in inflammatory cells (such as macrophages, natural killer cells, lymphocytes, and particularly neutrophils), and the destructive enzymes they secrete, further aggravate renal damage.[3,18]

Inflammation plays an important role in the onset of CIN and progression of acute renal injury.[19] Previous studies have also identified inflammation as a key contributor to the onset of atherosclerotic vascular disease and pathophysiology of acute coronary syndromes,[2,20,21] especially in cases involving plaque rupture and erosion.[22] Increased procalcitonin levels have also been reported in patients with acute coronary syndrome.[9] In our study, serum procalcitonin levels were higher in patients who developed CIN after PPCI than those without CIN; however, we found that serum procalcitonin level did not independently predict the development of CIN. On the other hand, we found that CIN was significantly and independently associated with a high serum CRP level, a high amount of contrast media used, and a low rate of TIMI flow 3. High serum CRP level and high amount of contrast media used are well-known risk factors for development of CIN.[23,24] However, there are conflicting reports on the role of low rate of TIMI flow 3 as a risk factor for CIN.[25,26] In this respect, there is a novelty in our finding, which is low rate of TIMI flow 3 is a significant predictor of CIN. We think that this finding is due to endothelial dysfunction in coronary arterial and renal vascular structures.

When compared with elective coronary interventions, CIN is seen more frequently in acute syndromes due to the increased amount of contrast agent used for complex lesions and adverse hemodynamic effects.[22] Many biochemical methods have been utilized to predict CIN. Liu et al. found a significant and independent relationship between elevated hs-CRP levels and contrast nephropathy, and Kaya et al.[3] detected a significant correlation between CIN and the pre- and post-procedural neutrophil to lymphocyte ratios.[23] If we consider that procalcitonin can exert acute and transient ef-

fects on the progression of inflammation, as well as vasodilatory effects via nitric oxide, procalcitonin may have complex effects in the pathophysiology of CIN. The increased procalcitonin levels at the onset of CIN may result in a destructive process through the development of CIN; however, at a later stage, one can speculate that this increase may exert protective effects.

CIN is one of the major problems of interventional cardiology and develops under the effects of many factors and complex underlying mechanisms. It can be difficult to determine the dominant pathophysiologic mechanism in a specific patient, which complicates the prediction and management of CIN. We believe that further studies should be conducted to determine the exact role of procalcitonin in the development of CIN.

The main limitations of this study to be noted are its observational, single-center, and relatively small sample size design, which was subject to various unaccounted confounders inherent for such an analysis. Furthermore, in addition to procalcitonin, other inflammatory markers, such as fibrinogen or myeloperoxidase, could not be evaluated in our study, which precludes us from making further conclusions on the inflammatory process in the development of CIN. Additionally, our results were limited to 48 h after PPCI without long-term follow-up data, which limits the evaluation of the change in serum procalcitonin level in longer term.

CONCLUSION

In conclusion, serum procalcitonin is increased in patients with STEMI who develop CIN after PPCI, but procalcitonin has no independent predictive value for the development of CIN. We suggest that because many mechanisms are involved in the onset and progression of CIN, although the level of procalcitonin is increased, it is not an independent predictor of CIN *per se*. Further studies should be conducted to elucidate the relationship between procalcitonin level and CIN.

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Authorship Contributions

MHS, AB, OA, NI, SG, SOO, KMS, and AE designed and performed the study and did the analysis and interpretation. All the authors participated in writing and critical revision of the manuscript and have approved of the final version.

Conflict of Interest

Authors declared no conflict of interest or financial support.

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