The Relationship Between Serum Urotensin II Level and Contrast-Induced Nephropathy and One-Year Clinical Follow-Up Findings in Patients with Coronary Slow Phenomenon Undergoing Percutaneous Coronary Intervention

Perkütan Koroner Girişim Yapılan Koroner Yavaş Akım Olgularında, Serum Ürotensin II Düzeyi ve Kontrast Kaynaklı Nefropati Gelişimi ile Bir Yıllık Klinik Takip Bulguları Arasındaki İlişki

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Abdtract

Objective	Coronary slow-reflow phenomenon (CSFP) and Contrast-Induced Nephropathy (CIN) are associated with an increased risk of major cardiovascular adverse events. This study aimed to evaluate the relationship between serum Urotensin II molecule (U-II) levels and CIN in patients with CSFP undergoing percutaneous coronary intervention (PCI).(Sakarya Med J 2019, 9(3):442-454).
Materials and Methods	We enrolled 227 patients (161 male and 66 female; mean age: 61,44 ± 12,44 years) with angiographically diagnosed CSFP. The patients were divided into two groups according to CIN development (Non-CIN (n=206) and CIN group (n=21)).
Results	CIN was observed in 9,25%(n=21) of the CSFP patients. Serum U-II level was significantly higher in CIN group than in non-CIN group (6,79±2,20 vs. 3,00±1,29, p<0,001). One year clinical follow-up findings including all-cause mortality (7(33,30%) vs. 24(11,70%), p=0,013), cardiovascular death(7(33,30%) vs. 18(8,70%), p=0,003) and Major Adverse cardiovascular events (MACE) (10(47,60%) vs. 46(22,40%), p=0,011) were significantly higher in CIN group. We also performed forward conditional logistic regression analysis and found that U-II (Odds ratio (OR)=3,983; 95% confidence interval (CI): 2,25 to 7,052; p <0,001) and Mehran score (OR=1,228, 95% CI: 1,083-1,393, p=0,001) were independently predicted CIN development, in patients with CSFP.
Conclusion	Baseline serum U-II concentrations and higher Mehran scores are independently associated with CIN in CSFP patients. One-year clinical follow-up findings including all-cause mortality, cardiovascular death and MACE were significantly higher in CIN group, but stroke and myocardial infarction rates were similar in both groups.

Keywords Urotensin II; kidney failure; contrast media; percutaneous coronary intervention

Öz

Amaç	*Koroner yavaş akım fenomeni (CSFP) ve kontrast kaynaklı nefropati (CIN), artmış major advers kardiyovasküler olay ile ilişkilidir. Bu çalışmada, CSFP'li perkütan koroner girişim (PCI) yapılan hastalarda, serum ürotensin II (U-II) düzeyi ile CIN arasındaki ilişkiyi değerlendirmeyi amaçladık. (Sakarya Tıp Dergisi 2019, 9(3):442-454)*
Gereç ve Yöntemler	*Anjiyografik olarak CSFP tanısı almış 227 hasta (161 erkek, 66 kadın; ortalama yaş 61,44±12,44) çalışmaya alındı. Hastalar CIN gelişmesine (CIN olmayan (n = 206) ve CIN grubu (n = 21)) göre iki gruba ayrıldı.*
Bulgular	*CSFP hastalarının %9,25'inde (n=21) CIN gözlendi. Serum U-II düzeyi, CIN grubunda CIN olmayan gruba göre anlamlı derecede yüksek saptandı (6,79±2,20 vs. 3,00±1,29, p<0,001). Tüm nedenlere bağlı mortalite (7(%33,30) vs. 24(%11,70), p=0,013), kardiyovasküler ölüm (7(%33,30) vs. 18(%8,70), p=0,003) ve major advers kardiyovasküler olay (MACE) (10(%47,60) vs. 46(%22,40), p=0,011) CIN grubunda anlamlı derecede yüksek saptandı. Ayrıca çalışmamızda ileri koşullu lojistik regresyon analizi yapıldı ve CSFP'li hastalarda CIN gelişimininin bağımsız öngördürücülerinin, yüksek serum U-II konsantrasyonları (Odss oranı(OR)=3,983; %95 güven aralığı(CI):2,25-7,052; p<0,001) ve yüksek Mehran skoru (OR=1,228, %95 CI: 1,083-1,393, p=0,001) olduğu saptandı.*
Sonuç	*Yaptığımız çalışmada, yüksek serum U-II konsantrasyonları ve yüksek Mehran skorları CSFP'li hastalarda CIN gelişimininin bağımsız öngördürücüleri olarak bulunmuştur. Bir yıllık klinik takipte, tüm nedenlere bağlı ölüm, kardiyovasküler ölüm ve MACE bulguları CIN grubunda anlamlı derecede yüksek saptanmış olup, inme ve miyokard infarktüsü oranları her iki grupta da benzer bulunmuştur.*

Anahtar Kelimeler *Ürotensin II; böbrek yetmezliği; kontrast madde; perkütan koroner girişim.*

INTRODUCTION

The TIMI II coronary flow and delayed coronary opacification in the absence of obstructive coronary artery disease is defined as a coronary slow-flow phenomenon (CSFP).[1] Also, TIMI 0-I flows without the presence of dissection, mechanical obstruction, significant residual stenosis, spasm or thrombus of the coronary vessel are defined as angiographic no-reflow.[2] CSFP is not a frequent finding with an incidence of approximately 1% in patients undergoing coronary angiography.[1,3] The pathophysiologies of slow-flow and no-reflow phenomenons are complex and multifactorial, such as, inflammation, atherothrombotic microembolization, activation of neutrophils and platelets, which cause releasing of oxygen-free radicals, proteolytic enzymes, and proinflammatory mediators that can cause tissue and endothelial damage.[4] Also, coronary spasm and reperfusion injury, myocardial dysfunction, valvular heart disease and certain connective tissue disorders involving coronary microvasculature, as well as genetic predisposition may play a part in the pathophysiology of slow-flow and no-reflow phenomenons.[5,6] CSFP also results from inadvertent air-embolism during angioplasty or may be due to an overlooked ostial lesion. CSFP is associated with poor short-and long-term clinical outcomes.[7,8] Contrast-induced nephropathy (CIN) is reversible acute renal failure following contrast media (CM) exposure. Contrast-induced nephropathy was defined as 0.50 mg/dL absolute increase in serum creatinine level above baseline or ≥25% relative increase in basal serum creatinine levels within 72 hours of contrast exposure.[9,10] The pathogenesis of CIN is complex and multifactorial and the underlying biological mechanisms have not yet been fully understood. Some studies have shown the pathogenesis of CIN to be related to the toxic effect of CM on the tubular epithelial cells due to apoptosis, disturbances in intrarenal hemodynamics, and medullary hypoxia.[11]

CIN incidence varies from 3.30% to 14.60%.[12,13] CIN is associated with risk of end-stage renal failure, worse clinical outcomes including prolonged hospitalization, increased cost, revascularization, and mortality.[14,15] Recent studies have extended these associations between CIN and cardiovascular diseases.[16,17] Patients who were experienced chronic kidney disease and diabetes mellitus and age over 75 are found to be the most important risk factors for CIN. Additionally, dehydration, congestive heart failure, anemia, volume and type of CM administered, and concurrent administration of nephrotoxic drugs were found to be potential risk factors in recent studies.[18] Urotensin II (U-II) is known as the most powerful vasoconstrictor peptide which is releasing from the endothelium.[19] U-II has 10 to 50-fold greater vasoconstrictor effects on arteries and veins compared to endothelin-1.[20] Serum U-II levels have been found to be high in patients with congestive heart failure, diabetes, hypertension, renal failure, atherosclerosis and portal hypertension.[21] The association between Urotensin-II protein levels and CIN in CSFP patients has not been addressed in the literature. Understanding which biologic pathways and markers are associated with cardiovascular disease (CVD) may allow to explore the mechanistic link between these pathways and to evaluate the efficacy of interventions designed to reduce the burden of CVD in these patients. The aim of this study was to evaluate the major clinical outcomes and the relationship between baseline serum U-II protein levels and CIN in patients with CSFP undergoing PCI.

MATERIALS and METHODS

For this single-center, cross-sectional study, we enrolled 247 patients between 18 and 90 years. But at the end of the study, we could not reach 20 patients follow-up data. So, we concluded this study with 227 stable angina patients (161 male and 66 female; mean age: 61,44 ± 12.44 years) who were diagnosed with coronary slow-flow and underwent PCI were included in this study between April 2016 and June 2018 in Bezmialem Vakif University Hospital. All patient's baseline serum Urotensin II levels and blood tests were measured. All patients referred to the cath lab. The slow-flow phenomenon was defined as a flow of TIMI II flow without the presence of dissection, mechanical ob-

struction or other possible causes. The patients were divided into two groups (non-CIN (n=206) and CIN group (n=21)). Contrast-induced nephropathy was defined as 0.5 mg/dL absolute increase in serum creatinine level above baseline or ≥25% relative increase in basal serum creatinine level within 72 hours of CM exposure.9 Patients excluded if they had coronary artery bypass grafting before, acute cardiac syndrome, cardiogenic shock, severe chronic kidney disease (glomerular filtration rate <30 mL/min/1.73 m2), stent thrombosis, acute or chronic infective disease, chronic liver disease, patients with exposure to a CM within the previous 10 days, autoimmune, or inflammatory diseases; or malignancy. All patients were given therapy of 100 mg acetylsalicylic acid and UF heparin (80mg/kg) prior to PCI. During in-hospital stay, one month, three months, six months and one year after discharge were set as time points for the evaluation of clinical endpoints.

The study was approved by the Medical Ethical Committee (Number:7/70-04/17) of the Bezmialem Vakif University medical center, and all participants gave written informed consents prior to participation. Furthermore, the study was conducted under the provisions of the Declaration of Helsinki. This study was funded by Bezmialem Vakif University, with 5.2016/17 funding number.

Biochemical Examination

Venous blood samples were taken at baseline to measure complete blood count, lipid profile, blood chemistry, high-sensitivity C-reactive Protein (hs-CRP) and U-II level were obtained from all of the patients on admission. 12-lead electrocardiograms (ECGs) were obtained at baseline and body mass index (BMI) was calculated using the formula weight (kg)/ height² (m^2). Estimated glomerular filtration rate (eGFR) of each patient was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Samples were centrifuged at 3000 rpm for 10 min, and the supernatant and plasma separated from the samples were frozen at 80 C until further analysis. Serum creatinine levels measurement was repeated at 72 hours after contrast medium administration. Human U-II ELISA Kit (ng/mL) (Elabscience Biotechnology Inc, Catalog no: E-EL-H2047, Wuhan, China) was measured in serum samples. This ELISA kit uses the Sandwich-ELISA principle in accordance with the manufacturer's guidelines. Routine blood chemistry and lipid parameters were measured with standard auto-analyzer. Blood counts were measured with a Sysmex K-1000 (Block Scientific, Bohemia, NY, USA) auto-analyzer.

Cardiovascular Risk Factors

After detailed examinations, medical history of each patient's was collected by the same investigator. Risk factors for coronary artery disease (CAD), cardiovascular risk factors, including age, gender, hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HPL), and smoking status, were noted. Patients who were previously using an antihypertensive therapy or whose blood pressures, measured at least twice, ≥140/90 mmHg were considered hypertensive.[22] Patients who were previously taking an oral antidiabetic and/or using insulin therapy or whose fasting blood glucose, measured at least twice, ≥125 mg/dL were considered diabetic.[23] The presence of HPL was considered when a measure of total cholesterol >200 mg/dL or low-density lipoprotein cholesterol (LDL-C) > 100 mg/dL was obtained or when the patient was previously using a lipid-lowering medication in accordance with the "Adult Treatment Panel III" guideline.[24] Patients who were still using tobacco products on admission to emergency service and those who had ex-smoker within the past month were considered smokers.

Transthoracic Echocardiography

Each patient underwent a transthoracic echocardiographic examination before discharge, by the same operator with a 3.5-MHz transducer (Vivid 7 GE Medical System, Horten, Norway). Examinations and measurements were performed with the patient lying in the supine position or in the left decubitus position in accordance with the rec-

ommendations of the American Echocardiography Unit. Simpson's method was used to calculate left ventricular ejection fraction (LVEF).[25]

Coronary Angiography

Coronary angiography and PCI were performed according to standard clinical practice with nonionic, iso-osmolar contrast medium (iodixanol, Visipaque 320 mg/100 mL; GE Healthcare, Cork, Ireland). Coronary angiography procedures were performed using Siemens (Axiom Sensis XP, Berlin, Germany) device via the femoral approach. Informed consents were obtained from all patients before the procedure. Total contrast medium volume was recorded in all patients.

The slow-flow was defined as TIMI (Thrombolysis In Myocardial Infarction) flow grades II, without the presence of dissection, mechanical obstruction, significant stenosis, or other plausible causes.[1] After the procedure, all the patients were taken intravenous hydration with isotonic saline (0.9% sodium chloride at a rate of 1 or 0.5 mL/kg/h in cases of overt heart failure) for at least 12 hours.

Statistical Analysis: Data analyses were performed using SPSS version 22.0 statistical software package (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as number (percentage). Normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. The Chi-square test was used to compare categorical variables. The independent samples t-test or the Mann-Whitney U test was used to compare continuous variables depending on whether statistical assumptions were fulfilled or not. The correlation between variables was performed using Spearman's rank-order correlation analysis. Univariate logistic regression analysis was performed, and the variables that were found to be statistically significant (p<0,100) were analyzed with multivariate logistic regression analysis. to determine the independent predictors of the CIN. Odds ratio and 95% confidence interval of each independent variable were calculated. A two-tailed p-value of <0,05 was considered significant.

RESULTS

This study included a total of 227 patients who were diagnosed with CSFP and underwent PCI. CIN was observed in 9,25% of the patients. Demographic findings described in Table 1. Regarding cardiovascular risk factors, diabetes mellitus type2 (DM) was significantly higher in the CIN group than in non-CIN group (14(66,70%) vs 59(28,60%), p<0,001) and hyperlipidemia (HL) was significantly higher in the CIN group than in non-CIN group (14(66,70%) vs 84(40,80%), p=0,023). Medications between groups were compared in Table 1. Oral antihyperglycemic drugs (OAD) usage was significantly higher in the CIN group than in non-CIN group (13(61,90%) vs 58(28,20%), p=.001) and diuretic usage was significantly higher in the CIN group than in non-CIN group (11(52,40%) vs 63(30,60%), p=0,042) but other medications of study groups were similar. Echocardiographic findings between groups were compared in Table 1. Left ventricular ejection fraction (LVEF) (%) was significantly lower in the CIN group than in non-CIN group (44,38±6,91 vs 52,93±6,84, p<0,001), Mitral regurgitation (MR) was significantly higher in the CIN group than in non-CIN group (15(71,40%) vs 62(30,10%), p<0,001) and Pulmonary Arterial Pressure (PAP) was significantly higher in the CIN group than in non-CIN group (34,47±10,33 vs 25,89±10,38, p<0,001). Age, gender, body mass index (BMI), hypertension (HT), smoker, family history, pulmonary arterial pressure (PAP) and chronic obstructive pulmonary disease (COPD) of study groups were similar (Table 1).

Baseline laboratory characteristics of the patients were described in Table 2. Urotensin-II was significantly higher in the CIN group than in non-CIN group (6,79±2,2 vs 3,00±1,29, p<0,001), glucose was significantly higher in the CIN group than in non-CIN group (176,04±85,40 vs 125,82±53,18, p<0,001), uric acid was significantly higher in the CIN group than in non-CIN group (7,43±1,84 vs

Table 1: Baseline characteristics, medications and echocardiographic findings of the patients.

Variable, n (%)	CIN Group n=21 (9,25)	Non-CIN group n=206 (90,75)	p-value
	Demographic findings		
Age, y.	65,24±12,51	61,06±12,40	0,134
Male gender, n (%)	17 (80,95)	144 (69,90)	0,288
BMI (kg/m²)	29,44±4,39	29,31±4,55	0,239
HT, n (%)	16(76,20)	118(57,30)	0,093
DM, n (%)	14(66,70)	59(28,60)	**<0,001**
HL, n (%)	14(66,70)	84(40,80)	**0,023**
Smoker, n (%)	14(66,70)	122(59,20)	0,507
Family History, n (%)	5(23,80)	71(34,50)	0,324
PAD, n (%)	1(4,80)	14(6,80)	1,000
COPD, n (%)	2(9,50)	31(15,00)	0,747
	Medications		
Ace inh, n (%)	9(42,90)	104(50,50)	0,662
ARB, n (%)	9(42,90)	69(33,50)	0,536
B blocker, n (%)	21(100,00)	196(95,10)	0,605
CCB, n (%)	8(38,10)	48(23,30)	0,218
Statin, n (%)	20(95,20)	179(86,90)	0,484
Nitrat, n (%)	3(14,30)	72(35,00)	0,055
OAD, n (%)	13(61,90)	58(28,20)	**0,001**
Plavix, n (%)	16 (76,20)	159 (77,20)	1,000
Aspirin, n (%)	21(100,00)	196(95,10)	0,605
Diuretic, n (%)	11(52,40)	63(30,60)	**0,042**
	Echocardiographic Findings		
LVEF, (%)	44,38±6,91	52,93±6,84	**<0,001**
MS, n (%)	1(4,80)	5(2,40)	0,445
AS, n (%)	4(19,00)	20(9,70)	0,252
AR, n (%)	7(33,30)	33(16,00)	0,067
MR, n (%)	15(71,40)	62(30,10)	**<0,001**
TR, n (%)	17(81,00)	131(63,60)	0,112
PAP (mmHg)	34,47±10,33	25,89±10,38	**<0,001**

Values are mean±SD or numbers and percentages. Y: year, BMI: Body Mass Index, HT: hypertension, DM: diabetes mellitus type 2, HL: hyperlipidemia, PAD: peripheral arterial disease, COPD: chronic obstructive pulmonary disease, ACE inh: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, B blocker: beta-blocker, CCB: calcium channel blockers, OAD: oral antihyperglycemic drugs, LVEF: left ventricular ejection fraction, MS: Mitral Stenosis, AS: Aortic Stenosis, AR: Aortic Regurgitation, MR: Mitral Regurgitation, TR: Tricuspid Regurgitation, PAP: Pulmonary Arterial Pressure, mmHg: millimeter of mercury.

5,56±1,56, p<0,001), urea mg/dl was significantly higher in the CIN group than in non-CIN group (49,28±31,49 vs 36,15±14, p=0,043), creatinine was significantly higher in the CIN group than in non-CIN group (1,28±0,57 vs 0,93±0,37, p=0,002), estimated glomerular filtration rate (eGFR) was significantly lower in the CIN group than in non-CIN group (65,27±30,10 vs 83,70±20,11, p=0,005), Mehran score was significantly higher in the CIN group than in non-CIN group (13,38±9,26 vs 4,62±3,79, p<0,001), Lymphocyte was significantly lower in the CIN group than in non-CIN group (1,81±0,89 vs 2,32±1,30, p=0,039), Platelet /Lymphocyte ratio (PLR) was signifi-

cantly higher in the CIN group than in non-CIN group (172,57±117,72 vs 133,32±112,02, p=0,028), hemoglobine (HB) was significantly lower in the CIN group than in non-CIN group (12,57±2,11 vs 13,53±1,73, p=0,034), hematocrit (HTC) was significantly lower in the CIN group than in non-CIN group (37,69±5,79 vs 40,26±5,34, p=0,022), length of in-hospital stay was significantly higher in the CIN group than in non-CIN group (4,29±1,97 vs 2,76±0,80, p<0,001), high-sensitivity C-reactive protein (hs-CRP) was significantly higher in the CIN group than in non-CIN group (1,52±2,13 vs 0,56±1,34, p<0,001), the New York Heart Association Functional Classification (NYHA) was significantly higher in the CIN group than in non-CIN group (2,42±0,50 vs 2,01±0,48, p<0,001), European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was significantly higher in the CIN group than in non-CIN group (4,42±4,27 vs 2,03±2,26, p<0,001). Monocyte, eosinophil, neutrophil, Neutrophil /Lymphocyte ratio (NLR), Monocyte /HDL ratio (MHR), White blood cell (WBC), platelet, Mean Platelet Volume (MPV), triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, aspartate aminotransferase (AST), alanine transaminase (ALT), sodium, potassium, heart rate and thyroid-stimulating hormone (TSH) levels of study groups were similar (Table 2).

Clinical follow-up findings including all-cause mortality, cardiovascular death, stroke, myocardial infarction, MACE was described in Table 3. For all-cause mortality was significantly higher in the CIN group than in non-CIN group (7(33,30%) vs. 24(11,70%), p=0,013), cardiovascular death was significantly higher in the CIN group than in non-CIN group (7(33,30%) vs. 18(8,70%), p=0,003), MACE was significantly higher in the CIN group than in non-CIN group (10(47,60%) vs. 46(22,40%), p=0,011) but stroke and myocardial infarction were similar between groups. Kaplan-Meier curve for MACE is described in Figure 1.

Uric acid, urea, creatinine, eGFR, eosinophil, hs-CRP, LVEF, NYHA and EuroSCORE II were significantly associated with U-II level (p<0,05) (Table 4). Also, age, glucose, uric acid, urea, creatinine, eGFR, lymphocyte, PLR, NLR, Hb, Htc, in-hospital stay, hs-CRP, heart rate, LVEF, PAP, NYHA, EuroSCORE II were significantly associated with Mehran score (p<0,05) (Table 5).

Forward conditional logistic regression analysis demonstrated that U-II (OR=3,983, 95% CI: 2,25-7,052, p<0,001) and Mehran score (OR=1,228, 95% CI: 1,083-1,393, p=0,001) were the independent predictors of CIN in CSFP (Table 6).

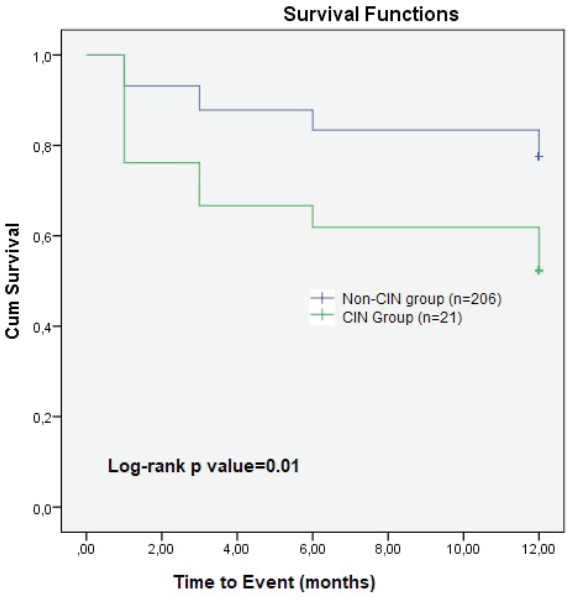

Figure 1: Kaplan-Meier curve for MACE

Table 2: Baseline laboratory characteristics of the patients.

Variable, n (%)	CIN Group n=21 (9,25)	Non-CIN group n=206 (90,75)	p-value
U-II ng/mL	6,79±2,20	3,00±1,29	<0,001
Glucose mg/dl	176,04±85,40	125,82±53,18	<0,001
Uric acid mg/dl	7,43±1,84	5,56±1,56	<0,001
Urea mg/dl	49,28±31,49	36,15±14,00	0,043
Creatinine mg/dl	1,28±0,57	0,93±0,37	**0,002**
eGFR (mL/min per 1.73 m2)	65,27±30,10	83,70±20,11	**0,005**
Mehran Score	13,38±9,26	4,62±3,79	<0,001
Monocyte 10^3/uL	0,85±0,46	0,73±0,27	0,329
Eosinophil 10^3/uL	0,22±0,15	0,19±0,17	0,292
Neutrophil10^3/uL	6,56±4,85	6,09±2,97	0,379
Lymphocyte 10^3/uL	1,81±0,89	2,32±1,30	0,039
PLR	172,57±117,72	133,32±112,02	0,028
NLR	5,58±7,57	3,82±7,86	0,471
MHR	25,49±28,94	18,16±6,92	0,355
WBC 10^3/uL	9,14±5,34	9,27±3,18	0,200
HB g/dl	12,57±2,11	13,53±1,73	0,034
HTC %	37,69±5,79	40,26±5,34	0,022
Platelet 10^3/uL	248,71±81,69	239,63±76,48	0,570
MPV fL	8,12±1,37	8,37±1,55	0,530
In-hospital stay, day	4,29±1,97	2,76±0,80	<0,001
Trigliseride (mg/dL)	143,38±53,94	154,64±59,24	0,478
HDL (mg/dL)	40,04±10,63	41,07±6,84	0,450
LDL (mg/dL)	114,42±50,48	124,05±35,98	0,264
T.Cholesterol (mg/dL)	186,95±57,72	201,36±40,79	0,403
hs-CRP (mg/dL)	1,52±2,13	0,56±1,34	<0,001
AST U/L	100,66±209,87	39,03±58,24	0,985
ALT U/L	59,90±91,98	27,20±21,85	0,370
Sodium mmol/L	138,23±3,57	138,38±7,25	0,355
Potassium mmol/L	4,20±0,48	4,20±0,40	0,450
Heart Rate (bpm)	83,47±16,03	78,80±13,79	0,200
TSH uIU/mL	1,45±0,78	1,51±3,26	0,284
NYHA class	2,42±0,50	2,01±0,48	<0,001
EuroSCORE II, (%)	4,42±4,27	2,03±2,26	<0,001

Values are mean±SD or numbers and percentages. The p-value for categorical data from Chi-square. The p-value for independent samples t-test or the Mann-Whitney U test was used to compare continuous variables. A two-tailed p-value of <.05 was considered significant and written in bold characters. U-II: Urotensin-II, eGFR: estimated glomerular filtration rate, PLR: Platelet /Lymphocyte ratio, NLR: Neutrophil /Lymphocyte ratio, MHR: Monocyte /HDL ratio, WBC: White blood cell, HB:hemoglobin, HTC: hematocrit, MPV:Mean Platelet Volume, HDL: high-density lipoprotein, LDL: low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, bpm: beat per minute, TSH: thyroid-stimulating hormone, ALT: Alanine transaminase, AST: Aspartate Aminotransferase, NYHA: the New York Heart Association Functional Classification, EuroSCORE II: European System for Cardiac Operative Risk Evaluation II.

Table 3: Clinical follow up findings including all-cause mortality, cardiovascular death, stroke, myocardial infarction, MACE.

Variable, n (%)	CIN Group n=21 (9,25)	Non-CIN group n=206 (90,75)	p-value
All-Cause Mortality, n (%)	7(33,30)	24(11,70)	**0,013**
Cardiovascular Death, n (%)	7(33,30)	18(8,70)	**0,003**
Stroke, n (%)	1(4,80)	8(3,90)	0,589
Myocardial infarction, n (%)	4(19,00)	22(10,70)	0,275
MACE, n (%)	10(47,60)	46(22,40)	**0,011**

Values are numbers and percentages. MACE: Major Adverse cardiovascular events. A two-tailed p-value of <.05 was considered significant and written in bold characters.

Table 4: Baseline characteristics significantly associated with U-II.

Variable	p[a]	p-value
Uric acid	0,146	0,028
Urea	0,208	0,002
Creatinine	0,279	<0,001
eGFR	-0,215	0.001
Eosinophil	0,174	0,009
hs-CRP	0,180	0,007
LVEF	-0,185	0,005
NYHA	0,162	0,014
EuroSCORE II	0,169	0,011

[a]Spearman's rank correlation coefficient. eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, hs-CRP: high-sensitivity C-reactive protein, NYHA: the New York Heart Association Functional Classification, EuroSCORE II: European System for Cardiac Operative Risk Evaluation II.

Table 5: Baseline characteristics significantly associated with Mehran score

Variable	p[a]	p-value
Age	0,582	<0,001
Glucose	0,357	<0,001
Uric acid	0,494	<0,001
Urea	0,529	<0,001
Creatinine	0,349	<0,001
eGFR	-0,596	<0,001
Lymphocyte	-0,217	0,001
PLR	0,186	0,005
NLR	0,117	0,010
HB	-0,602	<0,001
HTC	-0,586	<0,001
InHospital Stay	0,420	<0,001
hs-CRP	0,288	<0,001
Heart Rate	0,220	0,001
LVEF	-0,586	<0,001
PAP	0,431	<0,001
NYHA	0,454	<0,001
EuroSCORE II	0,771	<0,001

[a]Spearman's rank correlation coefficient. eGFR: estimated glomerular filtration rate, PLR: Platelet /Lymphocyte ratio, NLR: Neutrophil /Lymphocyte ratio, HB:hemoglobin, HTC: hematocrit, hs-CRP: high-sensitivity C-reactive protein, LVEF: left ventricular ejection fraction, PAP: Pulmonary Arterial Pressure, NYHA: the New York Heart Association Functional Classification, EuroSCORE II: European System for Cardiac Operative Risk Evaluation II.

Table 6: Independent predictors of CIN phenomenon in CSFP.			
Variable	OR	95% CI	p-value
U-II	3,983	2,25-7,052	<0,001
Mehran score	1,228	1,083-1,393	0,001
U-II: Urotensin II, OR: Odds ratio, CI: Confidence interval			

DISCUSSION

The main finding of this study was that in patients with CSFP, CIN was significantly associated with poor outcomes. Clinical follow-up findings including all-cause mortality, cardiovascular death and MACE were significantly higher in CIN group, but stroke and myocardial infarction rates were similar in both groups in one-year follow-up. Also, in this study, we revealed significantly higher U-II levels and higher Mehran scores in CIN patients compared to non-CIN patients with CSFP. In our study, we made forward conditional logistic regression analysis and we found that CIN was independently associated with baseline serum U-II concentrations and higher Mehran scores in CSFP patients. To the best of our knowledge, this is the first report in the literature demonstrating one-year clinical follow-up findings and the association between U-II concentration and CIN in patients with CSFP.

Although, the exact mechanism of CSFP is not consistently determined in the literature, there are several suggested mechanisms of CSFP. Tambe et al. suggested that small vessel dysfunction contributes to CSFP.[26] Intravascular ultrasound examinations identified epicardial CAD as a pathophysiological factor for CSFP, in addition to microvascular disease.[27] Yıldız et al. reported that reduced serum paraoxonase activity may be a biochemical marker of CSFP.[28] Enli et al. reported that increased serum malondialdehyde and erythrocyte superoxide dismutase, and decreased erythrocyte-reduced glutathione levels were found in patients with CSFP.[29] Kopetz et al. could not demonstrate any differences in endothelial function, asymmetric dimethylarginine levels, inflammatory proteins (myeloperoxidase and high-sensitivity CRP) and oxidative stress biomarkers (malondialdehyde and homocysteine) in patients with CSFP compared to healthy controls.[30] Therefore, the pathogenesis and mechanisms of CSFP remain controversial.

Zengin H. et al. found that serum U-II levels were significantly higher in the CSFP group, suggesting that U-II may be one of the underlying factors in the pathogenesis of CSFP.[31] U-II has been shown to be a very potent vasoactive peptide in mammalian vessels. U-II induces vasoconstriction and vascular smooth muscle cell proliferation.[32] The U-II receptor and U-II interaction stimulate the release of calcium (Ca2+) concentrations in vascular smooth muscle cells and this lead to cellular proliferation and activation of Ca2+-dependent kinases via calmodulin binding.[33] Recent studies have shown that U-II affects vascular endothelial growth factor (VEGF) expression in adventitial fibroblasts. By this way, VEGF plays an act in adventitial fibroblast proliferation and increased collagen synthesis. Besides, U-II may have an additional negative influence on vascular remodeling.[34] Regarding this knowledge, U-II continues to be released as a result of damage and also itself causing damage and the kidneys are vulnerable to direct damage. In our study, we found that CIN was independently associated with baseline serum U-II concentrations and higher Mehran scores in CSFP patients consistent with the literature.

Several studies have investigated the predictors of CIN. CIN generally develops within 72 h after CM exposure and the incidence of CIN varies from 3,30% to 14,60.[12,13] CIN is a multifactorial disease and baseline renal insufficiency, heart failure, DM, and myocardial infarction have been proposed to explain the development of CIN.[35] In our study, CIN was observed in 9,25%(n=21) of the CSFP patients. Our study results showed that DM, HL, OAD medications and diuretic usage were predicting CIN development. Physicians should avoid using diuretics especially in DM patients and high-risk patients except for pulmonary edema.

Marenzi et al. found that lower LVEF is associated with CIN.[36] Cowburn et al. found that patients developing contrast nephropathy also had higher systolic pulmonary artery pressures (PAP) as assessed non-invasively when compared with patients with maintained renal function.[37] Also, they found that patients developing CIN, had a markedly extended hospitalization stay when compared with patients whose renal function did not deteriorate. In this study, we have seen that lower LVEF and higher PAP were found in CIN development group. In addition, we found higher MR rates in CIN development group and we thought that it appears due to left ventricular enlargement due to ischemia. The in-hospital stay was also extended in CIN group like Cowburn et al. study. The extended hospital stays associated with contrast nephropathy has important clinical and health care implications due to the increased total cost. Physicians need to be aware of this potential risk.

Many studies have demonstrated that HB, HTC, hyperglycemia, and hs-CRP were independent risk factors for CIN.[38-40] Moreover, in the Mehran score, diabetes mellitus, congestive heart failure, CM volume, age >75 years, and IABP usage are recognized as risk factors for mortality.[41] The kidneys are vulnerable to ischemic injury and direct damage. CM could increase the oxygen affinity of hemoglobin and impaired oxygen delivery to the peripheral tissues. Hyperglycemia may lead to increased production of oxygen free radicals. Reactive oxygen species and activation of the sympathetic nervous system play an important role in the development of CIN.[38] In this study, we have seen that higher Mehran score, serum U-II, glucose, uric acid, urea, creatinine levels and lower eGFR levels were found in CIN development group. In addition, U-II and Mehran scores were shown to be the independent predictors of CIN development.

Sun et al. discovered that a higher PLR was an independent risk factor for the development of CIN in patients.[42] And Kocas et al. found that patients in the CIN group had significantly higher PLR and the PLR was an independent predictor of CIN in study patients.[43] In this study, we found significant-high lymphocyte levels and PLR in CIN group consistent with the literature.

Ulus et al. suggested that age, diabetes mellitus, contrast volume, eGFR, and MHR were independent predictors for CIN and MHR may be used as a simple marker of CIN.[44] Besides, Kaya et al. suggested that age, DM, low baseline glomerular filtration rate, reduced postprocedural ST resolution, high amount of contrast media, high NLR, and low left ventricular ejection fraction were independent predictors of CIN. The NLR may be used as a simple indicator of CIN.[45] In addition, Balta et al. suggested that NLR may predict all-cause mortality.[46] However, in our study, we did not find any difference between groups comparing NLR and MHR.

Iakovou et al. found that the female gender is an independent predictor of CIN development but we did not found gender as a significant difference between groups.[47] Additionally, Iakovou et al. found higher NYHA classifications in CIN development groups. Also, Zaytseva et al. found, higher NYHA classifications were associated with CIN development.[48] Konigstein et al. found high EUROScore levels in CIN development group.[49] In our study, we found similar findings. In CIN group we found significantly higher NYHA functional classifications and higher EUROScore II levels and also, we thought that these findings are associated with poor outcomes in CIN group.

Furthermore, previously published studies have shown that CIN is significantly associated with mortality and cardiovascular adverse events.[12,41,50-54] Pyxaras et al. demonstrated that among patients with acute myocardial infarction, CIN was associated with worse long-term outcomes.[55] Shacham et al. demonstrated that patients who were older and had worse renal function and history of heart failure were more likely to develop CIN and have higher all-cause mortality.[51]

In our study, patients who developed CIN had a higher all-cause mortality rate (33,30%) than those without CIN (11,70%), higher cardiovascular death (33,30%) than those without CIN (8,70%), and higher MACE (47,60%) than those without CIN (22,40%). Taken together with the published data, the results of our study indicating that there was a strong association between CIN and MACE. Thus, high-risk patients undergoing PCI should have monitored about renal functions during hospitalization and at discharge. The accepted strategies for preventing CIN were to monitor the contrast volume and reduce the usage of CM as possible as we could and hydrate the patient by saline solution 12 hours before and after catheterization at a speed of 1 mL/kg/h according to the European Society of Cardiology guidelines. Saline hydration and volume expansion could accelerate the excretion of the CM, reduce direct renal toxicity, and decrease the release of vasoconstrictors and reactive oxygen species.

We demonstrated, baseline serum U-II concentrations and higher Mehran scores are independently associated with CIN in CSFP patients. One year clinical follow-up findings including all-cause mortality, cardiovascular death and MACE were significantly higher in CIN group, but stroke and myocardial infarction rates were similar in both groups.

Limitations of the study: First; Although we performed a multivariate Cox model to adjust for confounding factors, a bias was unavoidable, because this was a single-center study. Second; The sample size was not big enough. A multicenter study involving more patients could have more significant results and data. Third; Only angiographic parameters were used in determining CSFP. These factors are limiting our study.

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