

Association Between Plasma Osmolality and Contrast-Induced Nephropathy in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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Abstract

Objective: Contrast-induced nephropathy (CIN) is a clinically relevant complication of percutaneous coronary intervention (PCI), particularly in acute coronary syndrome (ACS). Calculated plasma osmolality (PO), derived from routine laboratory measurements, may reflect fluid and solute disturbances associated with renal vulnerability. This study evaluated the relationship between admission PO and CIN in patients with ACS undergoing PCI. **Methods:** This retrospective, single-center study included 542 patients with ACS who underwent coronary angiography and PCI between January 2016 and December 2017. The cohort comprised 81 patients with unstable angina pectoris, 288 with non-ST-segment elevation myocardial infarction, and 173 with ST-segment elevation myocardial infarction. PO was calculated from admission sodium, glucose, and blood urea nitrogen levels. CIN was defined as an absolute increase of ≥ 0.5 mg/dL or a relative increase of $\geq 25\%$ in serum creatinine within 72 hours after contrast exposure. Associated factors were examined using multivariable logistic regression. **Results:** CIN developed in 62 patients (11.4%). Admission PO was higher among patients who developed CIN than among those who did not (295.4 [290.9–302.3] vs. 287.7 [283.4–292.6] mOsm/kg H₂O, $p < 0.001$). Patients with CIN were older and had higher potassium, baseline creatinine, and red cell distribution width, together with lower estimated glomerular filtration rate and left ventricular ejection fraction (LVEF). In the adjusted model, PO remained independently associated with CIN (OR: 1.070; 95% CI: 1.030–1.111; $p = 0.001$). Potassium, baseline creatinine, and red cell distribution width were also independently associated with CIN, whereas LVEF showed an inverse association. **Conclusions:** Higher calculated admission PO was independently associated with CIN in patients with ACS undergoing PCI. This readily available parameter may contribute to renal risk assessment, although prospective studies are needed to establish its clinical utility and relevant thresholds.

Keywords: Acute Coronary Syndrome; Percutaneous Coronary Intervention; Acute Kidney Injury; Contrast Media; Osmolar Concentration.

1. Introduction

Acute coronary syndrome (ACS) frequently requires coronary angiography and percutaneous coronary intervention (PCI), both of which involve exposure to iodinated contrast media. Despite improvements in procedural techniques and preventive measures, an acute decline in renal function following contrast administration remains a clinically relevant complication. Contemporary literature increasingly uses the term *contrast-associated acute kidney injury* when a causal relationship cannot be established with certainty; however, *contrast-induced nephropathy* (CIN) remains widely used in PCI studies and is retained in the present study in accordance with its predefined creatinine-based definition¹. The development of renal dysfunction after coronary angiography has been associated with increased short- and long-term mortality and a greater risk of adverse cardiovascular outcomes^{1,2}.

The likelihood of CIN is influenced by the interaction of patient-related and procedure-related factors. Pre-existing renal impairment, advanced age, diabetes mellitus, anemia, hemodynamic instability, impaired left ventricular function, and greater contrast exposure have been incorporated into established risk-assessment models³. Nevertheless, the performance of these models may vary across clinical settings, particularly in heterogeneous ACS populations. This has encouraged investigation of additional parameters that can be obtained rapidly from routine admission laboratory measurements.

Calculated plasma osmolality (PO), which is derived principally from serum sodium, glucose, and blood urea nitrogen concentrations, provides an integrated estimate of circulating solute concentration. An increased PO may accompany relative water deficit, hyperglycemia, azotemia, or acute neurohormonal and metabolic stress. It may therefore identify a physiological state associated with renal vulnerability without necessarily representing a direct cause of kidney injury. Previous studies have linked higher calculated PO with adverse outcomes in patients with ST-segment elevation myocardial infarction (STEMI)⁴ and with acute kidney injury and mortality following PCI⁵.

More specifically, Yildiz et al. reported an association between admission serum osmolality and CIN among patients with STEMI undergoing primary PCI⁶. A similar relationship was subsequently observed in patients undergoing elective coronary angiography⁷. More recent evidence from a high-risk elective PCI population also suggested that increased calculated osmolality may contribute to the identification of patients susceptible to postprocedural renal injury⁸. However, the available studies differ in their clinical populations, osmolality equations, renal outcome definitions, and proposed cutoff values. Moreover, evidence encompassing the broader ACS spectrum—including unstable angina, non-ST-segment elevation myocardial infarction, and STEMI—remains comparatively limited.

Accordingly, the present study aimed to examine the relationship between admission calculated PO and CIN in patients hospitalized with ACS and undergoing PCI. A further objective was to evaluate whether PO remained associated with CIN after accounting for relevant renal, hematologic, metabolic, and cardiac variables.

2. Methods

2.1. Study Design and Participants

This retrospective, single-center observational study included 542 adult patients who were hospitalized with acute coronary syndrome (ACS) and underwent coronary angiography followed by percutaneous coronary intervention (PCI) at the Department of Cardiology, Çukurova University Faculty of Medicine, between January 2016 and December 2017. The study population comprised 81 patients with unstable angina pectoris (USAP),

288 with non-ST-segment elevation myocardial infarction (NSTEMI), and 173 with ST-segment elevation myocardial infarction (STEMI).

ACS subtypes were determined from presenting symptoms, electrocardiographic findings, and cardiac biomarker measurements in accordance with the contemporaneous guidelines. STEMI was defined by symptoms consistent with acute myocardial ischemia accompanied by persistent ST-segment elevation in at least two contiguous leads or an accepted STEMI-equivalent electrocardiographic pattern. NSTEMI was diagnosed in patients with a rise and/or fall in cardiac troponin, with at least one value above the 99th-percentile upper reference limit, together with clinical or electrocardiographic evidence of myocardial ischemia but without persistent ST-segment elevation. USAP was defined by ischemic symptoms at rest or with minimal exertion in the absence of a diagnostic rise in cardiac biomarkers and persistent ST-segment elevation.

Patients were excluded if they had advanced chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², or were receiving renal replacement therapy; had been exposed to iodinated contrast medium during the preceding month; or had active infection, systemic inflammatory or autoimmune disease, active malignancy, severe chronic hepatic disease, severe chronic pulmonary disease or respiratory failure, a history of coronary artery bypass graft surgery, or pregnancy. Patients with incomplete clinical records, unavailable admission laboratory measurements, or insufficient serial serum creatinine measurements during the first 72 hours following PCI were also excluded.

2.2. Clinical and Laboratory Data

Baseline demographic characteristics, anthropometric measurements, cardiovascular risk factors, ACS presentation, smoking status, medical history, and medication use were obtained from hospital records. Recorded medications included aspirin, angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), anticoagulants, and diuretics. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters and was categorized as normal weight, overweight, or obesity according to conventional BMI thresholds.

Laboratory values obtained at hospital admission were recorded, including glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, sodium, potassium, blood urea nitrogen (BUN), and serum creatinine. Complete blood count parameters included white blood cell, neutrophil, lymphocyte and platelet counts, hemoglobin, hematocrit, and red cell distribution width (RDW). For the calculation of plasma osmolality, sodium, glucose, and BUN values obtained from the same admission blood sample were used.

Baseline serum creatinine was defined as the admission value obtained before contrast exposure. Serum creatinine was subsequently monitored during hospitalization. Peak creatinine was defined as the highest value recorded within 72 hours after PCI, and the final available value before discharge was recorded as discharge creatinine. Baseline eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation⁹.

2.3. Calculation of Plasma Osmolality

Calculated plasma osmolality (PO) was determined from admission sodium, glucose, and BUN values using the following equation:

$$\text{PO (mOsm/kg H}_2\text{O)} = (2 \times \text{serum sodium [mmol/L]}) + (\text{glucose [mg/dL]}/18) + (\text{BUN [mg/dL]}/2.8).$$

PO was evaluated primarily as a continuous variable. It was entered into the multivariable logistic regression model as the change in CIN odds associated with each 1-mOsm/kg H₂O increase.

2.4. Definition of Contrast-Induced Nephropathy

The primary outcome was the development of CIN which was defined as an absolute increase of ≥ 0.5 mg/dL or a relative increase of $\geq 25\%$ in serum creatinine from the preprocedural baseline value within 72 hours following contrast exposure, in the absence of another documented explanation for acute deterioration in kidney function¹. Accordingly, patients were categorized as those with or without CIN.

2.5. Coronary Angiography and Percutaneous Coronary Intervention

Coronary angiography and PCI were performed using standard interventional techniques through femoral or radial arterial access, as selected by the operator. A nonionic low-osmolar iodinated contrast medium was used during the procedures. Decisions regarding balloon angioplasty, stent implantation, stent type, and adjunctive pharmacological treatment were made by the treating interventional cardiologist according to the angiographic findings and contemporaneous clinical practice.

Total contrast volume and total procedure duration were obtained from catheterization laboratory records. The percentage stenosis of the left anterior descending, left circumflex, and right coronary arteries was determined from the index coronary angiogram. Periprocedural preventive strategies documented in the medical records were categorized as oral hydration alone, N-acetylcysteine plus oral hydration, intravenous isotonic saline plus oral hydration, or N-acetylcysteine plus intravenous isotonic saline and oral hydration. Selection of the preventive strategy was based on the treating physician's assessment of renal risk, clinical status, and volume tolerance.

2.6. Echocardiographic Assessment

Transthoracic echocardiographic examinations were performed during the index hospitalization by an experienced cardiologist, using a Vivid E95 ultrasound system (GE Healthcare, Vingmed Ultrasound AS, Horten, Norway). Standard two-dimensional, M-mode, pulsed-wave Doppler, continuous-wave Doppler, and tissue Doppler measurements were obtained in accordance with the echocardiographic recommendations in effect during the study period¹⁰⁻¹².

Left atrial (LA) diameter, interventricular septum (IVS), and left ventricular posterior wall (LVPW) thickness, left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) were measured using standard techniques. Left ventricular ejection fraction (LVEF) was calculated using the modified biplane Simpson method. Valvular stenosis and regurgitation were evaluated and graded according to contemporaneous echocardiographic recommendations^{11,12}.

Peak tricuspid regurgitation velocity was measured using continuous-wave Doppler. In the absence of right ventricular outflow tract obstruction or pulmonary stenosis, systolic pulmonary artery pressure (sPAP) was estimated using the modified Bernoulli equation:

$$\text{sPAP} = 4 \times (\text{peak tricuspid regurgitation velocity})^2 + \text{estimated right atrial pressure.}$$

Right atrial pressure was estimated from inferior vena cava diameter and its inspiratory collapse.

2.7. Statistical Analysis

Categorical variables were summarized as numbers and percentages. Continuous variables were reported as mean $\pm$ standard deviation when normally distributed and as median with interquartile range when non-normally distributed. Distributional assumptions were evaluated using the Kolmogorov–Smirnov test and visual examination of the data.

Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Normally distributed continuous variables were compared using the

independent-samples t-test, whereas non-normally distributed variables were compared using the Mann–Whitney U test.

Binary logistic regression analysis was performed to identify factors independently associated with CIN. Variables demonstrating significant univariable associations and variables considered clinically relevant were evaluated for inclusion. Correlated variables were not entered into the model simultaneously to reduce multicollinearity. Given the 62 CIN events, the final model was restricted to seven variables: age, potassium, hemoglobin, RDW, LVEF, baseline creatinine, and PO. PO was entered as a continuous variable. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). All tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA).

2.8. Ethical Considerations

The study protocol was approved by the Çukurova University Faculty of Medicine Ethics Committee with decision number 75 on March 2, 2018. The study was conducted in accordance with the principles of the Declaration of Helsinki.

3. Results

3.1. Baseline Characteristics

The study included 542 patients with a mean age of 61.6 ± 11.3 years (range, 29–89 years); 339 (62.5%) were men and 203 (37.5%) were women. According to BMI categories, 126 patients (23.2%) had normal weight, 287 (53.0%) were overweight, and 129 (23.8%) had obesity. Diabetes mellitus was present in 196 patients (36.2%), hypertension in 329 (60.7%), and 335 patients (61.8%) were nonsmokers. The clinical presentation was NSTEMI in 288 patients (53.1%), STEMI in 173 (31.9%), and USAP in 81 (14.9%).

CIN developed in 62 patients (11.4%), whereas 480 patients (88.6%) did not develop CIN. Accordingly, subsequent comparisons were performed between patients with and without CIN. Patients who developed CIN were older than those who did not (66.13 ± 9.98 vs. 60.99 ± 11.35 years, $p = 0.001$). BMI category distribution differed between the groups ($p = 0.045$), with a higher prevalence of obesity in the CIN group (33.9% vs. 22.5%) and a lower prevalence of overweight status (38.7% vs. 54.8%). Diuretic use was more frequent among patients who developed CIN (16.1% vs. 5.8%, $p = 0.007$). The proportion of patients classified as having high PO was also greater in the CIN group (29.0% vs. 16.0%, $p = 0.011$).

No significant between-group differences were observed in sex, ACS subtype, diabetes mellitus, hypertension, smoking status, aspirin dose, or the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or anticoagulants. Weight, height, waist circumference, and hip circumference were also comparable between the groups (Table 1).

Table 1. Baseline demographic and clinical characteristics of patients with and without Contrast Induced Nephropathy

		Contrast Induced Nephropathy		<i>P</i>
		No	Yes	
Age (years)		60.99±11.35	66.13±9.98	0.001
Weight (kg)		78.11±11.41	78.06±12.92	0.976
Height (cm)		168.34±6.93	167.23±6.68	0.234
Waist circumference (cm)		99(93-112)	96(92-106)	0.852
Hip circumference (cm)		100(93.5-110)	100(91-113)	0.557
Sex	Female	178(37.1)	25(40.3)	0.620
	Male	302(62.9)	37(59.7)	

		Contrast Induced Nephropathy		P
		No	Yes	
ACS	STEMI	147(30.6)	26(41.9)	0.150
	USAP	75(15.6)	6(9.7)	
	NSTEMI	258(53.8)	30(48.4)	
DM	No	309(64.4)	37(59.7)	0.469
	Yes	171(35.6)	25(40.3)	
HT	No	192(40)	21(33.9)	0.352
	Yes	288(60)	41(66.1)	
BMI	Normal	109(22.7)	17(27.4)	0.045
	Overweight	263(54.8)	24(38.7)	
	Obese	108(22.5)	21(33.9)	
ASA	100 (mg)	259(56.4)	28(45.2)	0.094
	300 (mg)	200(43.6)	34(54.8)	
Smoking status	Non-smoker	299(62.3)	36(58.1)	0.519
	Smoker	181(37.7)	26(41.9)	
ACE –I	No	195(40.6)	31(50)	0.159
	Yes	285(59.4)	31(50)	
ARB	No	423(88.1)	52(83.9)	0.338
	Yes	57(11.9)	10(16.1)	
Anticoagulant	No	265(55.2)	28(45.2)	0.135
	Yes	215(44.8)	34(54.8)	
Diuretic	No	452(94.2)	52(83.9)	0.007
	Yes	28(5.8)	10(16.1)	

ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; USAP, unstable angina pectoris; NSTEMI, non-ST-segment elevation myocardial infarction; DM, diabetes mellitus; HT, hypertension; BMI, body mass index; ASA, acetylsalicylic acid; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. Results were reported as mean $\pm$ SD or median (IQR) or n(%) as appropriate. *p* values represent comparisons between patients with and without CIN. Bold values indicate statistical significance ($p < 0.05$).

3.2. Preventive Treatment and Angiographic Findings

The distribution of periprocedural preventive strategies differed significantly between the CIN and non-CIN groups ($p < 0.001$). Oral hydration alone was less frequently documented in patients who developed CIN (14.5% vs. 42.3%), whereas combined N-acetylcysteine, intravenous isotonic saline, and oral hydration was more frequently used in this group (45.2% vs. 23.5%). The frequencies of N-acetylcysteine plus oral hydration were 14.5% and 4.0%, while those of intravenous isotonic saline plus oral hydration were 25.8% and 30.2%, respectively.

Severe mitral regurgitation was more prevalent among patients who developed CIN than among those who did not (19.4% vs. 8.6%, $p = 0.007$). Severe mitral stenosis was also more frequent among patients who developed CIN (6.5% vs. 1.5%, $p = 0.028$). No statistically significant differences were observed in aortic regurgitation or aortic stenosis.

Median contrast volume did not differ significantly between patients with and without CIN (100 [75–130] vs. 80 [70–120] mL, respectively; $p = 0.085$). Total procedure duration and the percentage stenosis of the LAD, LCx and RCA were also comparable between the groups (Table 2).

Table 2. Preventive treatment, valvular (echocardiographic), procedural, and angiographic characteristics according to the presence of contrast-induced nephropathy

		Contrast Induced Nephropathy		<i>p</i>
		No	Yes	
Preventive Treatment	Oral hydration	203(42.3)	9(14.5)	<0.001
	NAC+Oral hydration	19(4)	9(14.5)	
	NS+Oral hydration	145(30.2)	16(25.8)	
	NAC+NS+Oral hydration	113(23.5)	28(45.2)	
MR	non-severe	439(91.4)	50(80.6)	0.007
	Severe	41(8.6)	12(19.4)	
AR	non-severe	464(96.7)	60(96.8)	0.965
	Severe	16(3.3)	2(3.2)	
MS	non-severe	473(98.5)	58(93.5)	0.028
	Severe	7(1.5)	4(6.5)	
AS	non-severe	469(97.7)	59(95.2)	0.208
	Severe	11(2.3)	3(4.8)	
Contrast volume (ml)		80(70-120)	100(75-130)	0.085
Total time (min)		25(20-30)	25(20-35)	0.113
LAD stenosis (%)		40(30-60)	47.5(30-70)	0.654
RCA stenosis (%)		35(30-70)	90(30-95)	0.123
LCx stenosis (%)		30(30-70)	65(40-85)	0.073

NAC, N-acetyl-cysteine; NS, Normal saline; MR, Mitral regurgitation; AR, Aortic regurgitation; MS, Mitral stenosis; AS, Aortic stenosis; LAD, Left anterior descending coronary artery; LCx, Left circumflex coronary artery; RCA, Right coronary artery. Data are presented as median (IQR) or *n*(%), as appropriate. *p* values represent comparisons between patients with and without CIN. Bold values indicate statistical significance ($p < 0.05$).

3.3. Laboratory and Echocardiographic Findings

Admission glucose was higher in patients who developed CIN than in those who did not (124 [101–197] vs. 110 [97–147.5] mg/dL, $p = 0.046$). Total cholesterol and TG levels were significantly higher in the CIN group (195.59±47.77 vs. 181.18±48.87 mg/dL, $p = 0.026$; and 156.5 [111–216] vs. 130 [108–171] mg/dL, $p = 0.032$, respectively), whereas HDL-C was lower (32 [29–40] vs. 36.5 [31–42.5] mg/dL, $p = 0.023$). LDL-C did not differ significantly between the groups ($p = 0.478$).

Patients who developed CIN had higher potassium (4.5 [4.1–4.9] vs. 4.3 [4.0–4.6] mmol/L, $p < 0.001$), BUN (38.45 [31.7–48.6] vs. 35.7 [29.0–45.05] mg/dL, $p = 0.049$), and baseline creatinine levels (1.16 [1.03–1.61] vs. 0.79 [0.70–0.90] mg/dL, $p < 0.001$). Peak and discharge creatinine levels were also higher in the CIN group (both $p < 0.001$), whereas baseline eGFR was lower (78.95 [49.7–90.1] vs. 98.25 [82.45–105.5] mL/min/1.73 m², $p < 0.001$). Serum sodium did not differ significantly between the groups.

White blood cell and neutrophil counts and RDW were higher in patients who developed CIN, whereas lymphocyte count, hemoglobin, and hematocrit were lower (all $p < 0.05$). Platelet counts did not differ significantly between the groups.

Echocardiographic examination showed a lower median LVEF in the CIN group (45% [36–55] vs. 55% [45–60], $p = 0.001$). Patients with CIN also had a greater LVESD (30 [26–36] vs. 29 [24–32] mm, $p = 0.013$), greater LA diameter (38 [36–42] vs. 37 [32–40] mm,

$p=0.003$), and higher sPAP (31 [26–42] vs. 27 [22–34] mmHg, $p<0.001$). LVEDD, IVS and LVPW thickness were comparable between the groups.

Calculated PO was significantly higher in patients who developed CIN than in those who did not (295.4 [290.9–302.3] vs. 287.7 [283.4–292.6] mOsm/kg H₂O, $p<0.001$; Table 3 and Figure 1).

Table 3. Laboratory and echocardiographic findings according to the presence of contrast-induced nephropathy

	Contrast Induced Nephropathy		<i>p</i>
	No	Yes	
Blood glucose (mg/dL)	110(97-147.5)	124(101-197)	0.046
Total Cholesterol (mg/dL)	181.18±48.87	195.59±47.77	0.026
HDL-C (mg/dL)	36.5(31-42.5)	32(29-40)	0.023
LDL-C (mg/dL)	114(91-140)	119(91-143)	0.478
TG (mg/dL)	130(108-171)	156.5(111-216)	0.032
Na (mmol/L)	139(137-141)	139(137-142)	0.162
K (mmol/L)	4.3(4-4.6)	4.5(4.1-4.9)	<0.001
BUN (mg/dL)	35.7(29-45.05)	38.45(31.7-48.6)	0.049
Admission Creatinine (mg/dL)	0.79(0.7-0.9)	1.16(1.03-1.61)	<0.001
Peak Creatinine (mg/dL)	0.82(0.75-0.96)	1.71(1.22-2.69)	<0.001
Discharge Creatinine (mg/dL)	0.79(0.7-0.9)	1.38(1.13-2.5)	<0.001
eGFR (mL/min/1.73 m ²)	98.25(82.45-105.5)	78.95(49.7-90.1)	<0.001
WBC (×10 ³ /μL)	8.32(6.8-10.45)	9.8(7.5-12)	0.004
Neutrophils (×10 ³ /μL)	4.9(3.76-6.8)	6.2(4.92-9.3)	<0.001
Lymphocytes (×10 ³ /μL)	2.3(1.7-3)	1.8(1.2-2.5)	0.001
RDW (%)	11(10.4-12)	12(11-13.1)	<0.001
HCT(%)	41.25±4.8	39.08±6.52	0.014
HGB (g/dL)	13.76±1.85	12.87±2.54	0.010
PLT (×10 ³ /μL)	245.63±74.57	235.82±89.92	0.342
LVEF (%)	55(45-60)	45(36-55)	0.001
LVEDD (mm)	46(43-49)	46(44-49)	0.483
LVESD (mm)	29(24-32)	30(26-36)	0.013
IVS thickness (mm)	10(9-11)	10(9-11)	0.679
LVPW thickness (mm)	10(9-10)	9(8-10)	0.430
LA diameter (mm)	37(32-40)	38(36-42)	0.003
sPAP (mmHg)	27(22-34)	31(26-42)	<0.001
PO (mOsm/kg H ₂ O)	287.7(283.4-292.6)	295.4(290.9-302.3)	<0.001

HDL, High-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol; TG, Triglycerides; BUN, Blood urea nitrogen; eGFR, Estimated Glomerular filtration rate; WBC, white blood cell count; RDW, red cell distribution width; HCT, hematocrit; HGB, hemoglobin; PLT, platelet count; LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular end-diastolic diameter; LVESD, Left ventricular end-systolic diameter; IVS, interventricular septum; LVPW, Left ventricular posterior wall; LA, Left atrium; sPAP: Systolic pulmonary artery pressure; PO, Plasma osmolality. Data are presented as mean±standard deviation or median (IQR), as appropriate. *p* values represent comparisons between patients with and without Contrast Induced Nephropathy. Bold values indicate statistical significance ($p<0.05$).

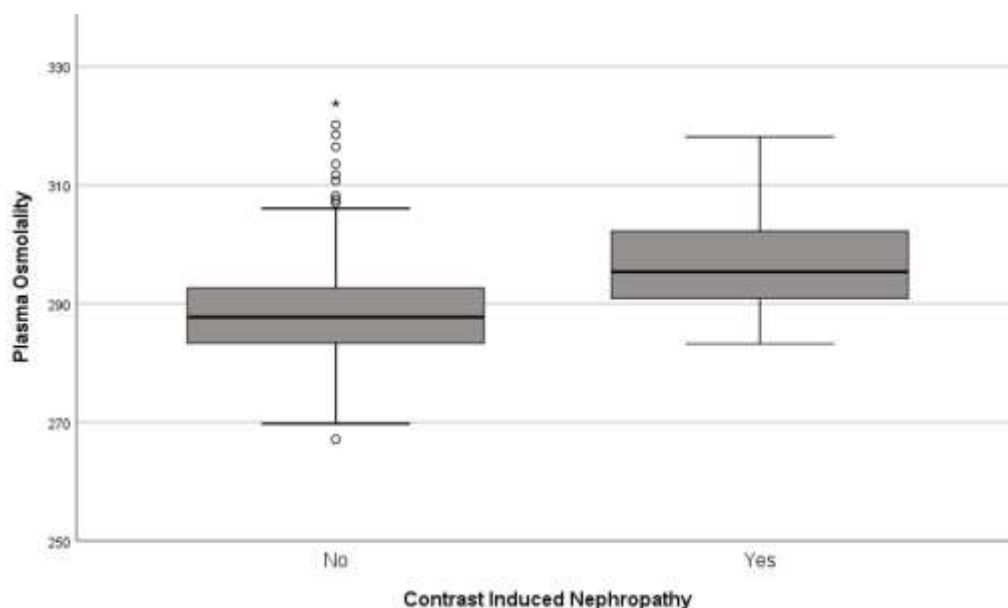


Figure 1: Relationship between plasma osmolality and Contrast Induced Nephropathy

3.4. Multivariable Analysis

Variables associated with CIN in univariable comparisons included age, BMI category, diuretic use, PO, admission glucose, total cholesterol, HDL-C, triglycerides, potassium, BUN, baseline creatinine, lymphocyte count, RDW, hemoglobin, LVEF, left atrial diameter, and sPAP. To reduce multicollinearity, correlated variables were not entered simultaneously into the multivariable model.

In the final multivariable logistic regression analysis, potassium (OR: 2.110; 95% CI: 1.266–3.517; $p=0.004$), baseline creatinine (OR: 2.313; 95% CI: 1.231–4.345; $p=0.009$), RDW (OR: 1.339; 95% CI: 1.092–1.642; $p=0.005$), and PO (OR: 1.070; 95% CI: 1.030–1.111; $p=0.001$) were independently associated with higher odds of CIN. In contrast, LVEF was independently associated with lower odds of CIN (OR: 0.964; 95% CI: 0.939–0.990; $p=0.007$). Age and hemoglobin were not independently associated with CIN in the adjusted model (Table 4 and Figure 2).

Table 4. Factors associated with Contrast Induced Nephropathy in multivariable logistic regression analysis

	OR	95% CI for OR		<i>p</i>
		Lower	Upper	
Age (years)	1.014	0.984	1.045	0.373
K (mmol/L)	2.110	1.266	3.517	0.004
HGB (g/dL)	1.015	0.875	1.179	0.840
RDW (%)	1.339	1.092	1.642	0.005
LVEF (%)	0.964	0.939	0.990	0.007
Creatinine (mg/dL)	2.313	1.231	4.345	0.009
PO (mOsm/kg H ₂ O)	1.070	1.030	1.111	0.001

HGB, hemoglobin; RDW, red cell distribution width; LVEF: Left ventricular ejection fraction; PO, Plasma osmolality. OR:Odds ratio, CI:confidence interval, For continuous variables, ORs represent the change in the odds of Contrast Induced Nephropathy associated with a one-unit increase. For RDW and LVEF, one unit corresponds to one percentage point.

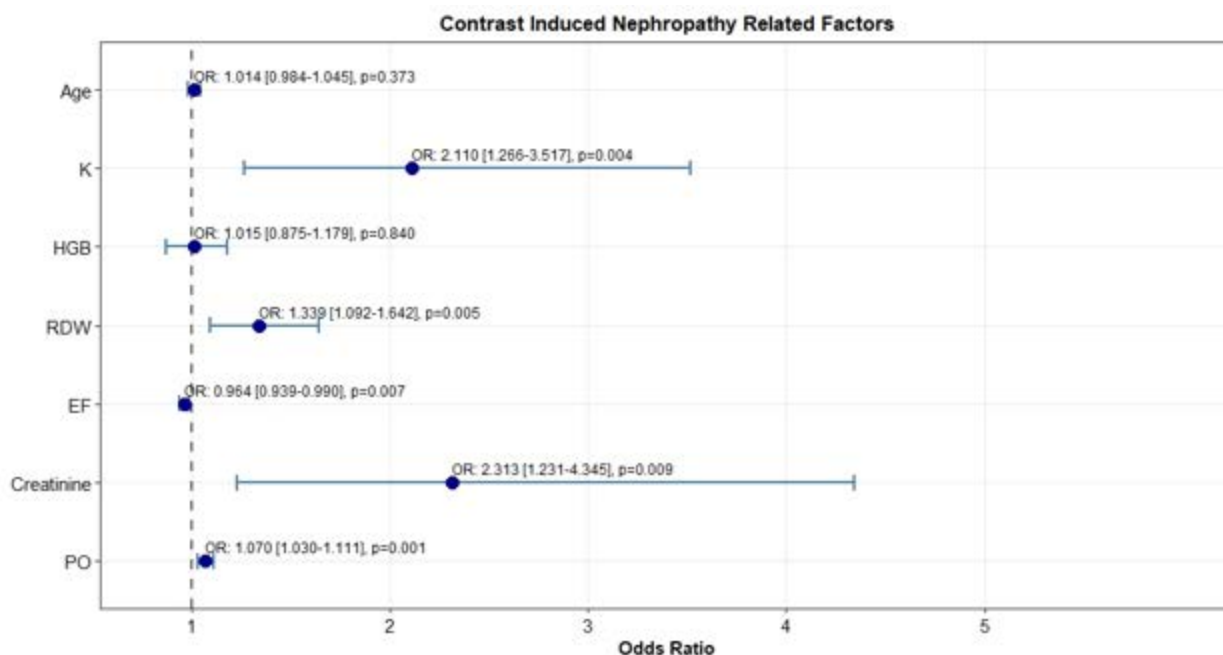


Figure 2: Factors associated with Contrast Induced Nephropathy in multivariable logistic regression analysis

4. Discussion

The principal finding of this study was that calculated plasma osmolality (PO) at admission was higher in patients who developed CIN after PCI and remained independently associated with CIN after adjustment for selected clinical, hematologic, renal, and echocardiographic variables. Baseline creatinine, RDW, and potassium were also independently associated with higher odds of CIN, whereas LVEF showed an inverse association. In addition, patients who developed CIN were older and had a less favorable metabolic, inflammatory, renal, and hemodynamic profile in unadjusted comparisons. Taken together, these findings suggest that calculated PO may reflect a composite state of osmotic, metabolic, and renal vulnerability rather than an isolated electrolyte abnormality.

CIN occurred in 11.4% of the present cohort. This rate is broadly consistent with the incidence reported in populations exposed to intra-arterial contrast media. A systematic review and meta-analysis including 120 studies reported an overall CIN incidence of approximately 9%, increasing to 9.9% in heart-related angiographic procedures¹³. Conversely, a large contemporary PCI registry using an Acute Kidney Injury Network–based definition reported contrast-associated acute kidney injury in 4.3% of patients¹⁴. Differences in clinical presentation, baseline renal risk, contrast administration, creatinine-monitoring intervals, and diagnostic criteria probably account for part of this variation. Our study included only patients hospitalized with ACS, used the traditional composite definition of an absolute creatinine increase of ≥ 0.5 mg/dL or a relative increase of $\geq 25\%$, and monitored creatinine for 72 hours. These features may have increased event detection compared with studies involving broader or predominantly elective PCI populations.

The association between calculated PO and CIN was the most clinically relevant finding of the present analysis. Median PO was approximately 8 mOsm/kg H₂O higher in patients who developed CIN, and the association persisted after baseline creatinine and other relevant covariates were included in the regression model. This finding is consistent with previous PCI studies, although their designs and populations differ. Farhan et al. found that patients in the highest calculated serum osmolality quartile had an increased incidence of acute kidney injury following PCI⁵. Yildiz et al. reported an association between admission serum osmolality and CIN in patients with STEMI undergoing primary PCI⁶, whereas Kanbay et al. observed a similar relationship in an elective coronary

angiography population⁷. More recently, Samir et al. reported that increased calculated osmolality was associated with CIN among high-risk patients undergoing elective coronary angiography or PCI⁸. The present study extends these observations to a broader ACS cohort comprising patients with USAP, NSTEMI, and STEMI. However, because subgroup-specific associations and interaction effects were not evaluated, the consistency of this relationship across individual ACS subtypes remains uncertain.

Calculated PO integrates sodium, glucose, and BUN and may therefore capture several physiological disturbances simultaneously. In the present cohort, sodium concentrations were comparable between patients with and without CIN, whereas glucose and BUN were higher among those who developed CIN. The observed association with PO therefore appears unlikely to be attributable to sodium alone. Increased PO may accompany relative water deficit, hyperglycemia, azotemia, or acute neurohormonal stress, each of which may reduce renal tolerance to hemodynamic and nephrotoxic insults. Proposed mechanisms of contrast-related renal injury include intrarenal vasoconstriction, medullary hypoxia, oxidative stress, endothelial dysfunction, increased tubular workload, and direct tubular toxicity¹⁵. A hyperosmolar physiological state could plausibly coexist with or intensify some of these processes. Nevertheless, the present study did not directly evaluate intravascular volume, vasopressin activity, oxidative stress, renal perfusion, or tubular injury. Accordingly, calculated PO should be interpreted primarily as a potential risk marker rather than as evidence of a causal osmotic mechanism.

Baseline renal function remained central to CIN susceptibility. Patients who developed CIN had higher admission creatinine and lower eGFR, and baseline creatinine remained independently associated with CIN in the adjusted analysis. Contemporary PCI risk models likewise include preprocedural renal function among their most influential variables¹⁴. A recent systematic review of risk-prediction models in ACS populations also identified creatinine or eGFR as recurrent components, although the review noted considerable methodological heterogeneity and limited external validation¹⁶. Our findings are consistent with the concept that even moderate reductions in renal reserve may become clinically relevant during ACS and PCI. This relationship was observed despite excluding patients with an eGFR below 30 mL/min/1.73 m², suggesting that susceptibility was not confined to patients with advanced chronic kidney disease.

Potassium was independently associated with CIN, but this finding requires cautious interpretation. The absolute difference between groups was modest, and median potassium values remained within or close to the conventional reference range. Potassium is not consistently incorporated into established CIN risk models. Higher values may reflect subtle impairment of renal excretory capacity, acid–base disturbances, tissue injury, medication effects, or other acute metabolic changes not fully captured by baseline creatinine. Although the use of ACE-I and ARB did not differ between groups, information regarding acid–base status, hemolysis, and temporal changes in potassium was unavailable. Therefore, potassium should not currently be regarded as a specific CIN marker, and its independent association in this cohort requires confirmation in other populations.

Another notable finding was the independent association between RDW and CIN. Kurtul et al. evaluated 662 patients with ACS undergoing PCI and reported a CIN incidence of 12.2%; RDW, baseline creatinine, age, and LVEF were independently associated with CIN¹⁷. The effect estimate reported for RDW in that study was also similar to that observed in our analysis. A subsequent systematic review and meta-analysis supported associations between CIN and several inflammatory or hematologic indices, including RDW, hematocrit, and neutrophil-to-lymphocyte ratio¹⁸. In the present study, patients who developed CIN also had higher white blood cell and neutrophil counts and lower lymphocyte counts, suggesting a greater inflammatory or physiological stress burden. RDW may reflect inflammation, oxidative stress, impaired erythrocyte maturation,

nutritional deficiencies, renal dysfunction, or altered erythrocyte deformability. It is therefore unlikely to represent a kidney-specific mechanism. Although hemoglobin and hematocrit were lower in patients with CIN, hemoglobin was not independently associated with CIN after adjustment. This distinction is relevant because meta-analytic evidence has linked anemia with contrast-associated kidney injury¹⁹, whereas our findings suggest that RDW may convey information beyond hemoglobin concentration alone. However, iron status, vitamin B12, folate, reticulocyte indices, and inflammatory biomarkers were not available, limiting mechanistic interpretation.

Cardiac functional status also appeared relevant. LVEF was lower in patients who developed CIN and remained inversely associated with CIN in the adjusted model. LVEF is included in contemporary preprocedural risk assessment because impaired systolic function may be accompanied by reduced forward flow, renal hypoperfusion, venous congestion, and limited tolerance of hydration¹⁴. Previous primary PCI data have similarly identified reduced LVEF as an independent factor associated with CIN²⁰. In our cohort, patients with CIN also had higher sPAP and LA diameter, while severe mitral regurgitation and mitral stenosis were more frequent. Diuretic use was also more common. Collectively, these findings may indicate a greater hemodynamic and volume-management burden among patients who developed CIN. However, sPAP, LA diameter, valvular abnormalities, and diuretic use were not retained simultaneously in the final model, and the numbers of patients with severe valve disease were small. These findings should therefore be regarded as supportive clinical context rather than evidence that individual valvular abnormalities directly contributed to CIN.

Several metabolic variables differed between groups. Patients who developed CIN had higher admission glucose, total cholesterol, and triglyceride levels and lower HDL-C, despite a similar prevalence of diagnosed diabetes. Previous studies have linked composite markers of insulin resistance, particularly the triglyceride–glucose index, with contrast-associated kidney injury in patients with ACS and diabetes²¹. In our cohort, the combination of higher glucose and triglycerides may similarly indicate an adverse metabolic state, although the triglyceride–glucose index was not calculated. Furthermore, admission glucose may be influenced by acute stress, and lipid concentrations obtained during ACS may not accurately represent stable outpatient values. Because these variables were not included in the final model, their independent contribution cannot be determined. The higher prevalence of obesity among patients with CIN may also be relevant, but the absence of significant differences in body weight, waist circumference, and hip circumference argues against drawing conclusions from BMI category alone.

The lack of a statistically significant difference in contrast volume warrants consideration. Median contrast volume was higher among patients who developed CIN, but the between-group difference did not reach statistical significance. Contrast exposure has been associated with CIN incidence in meta-regression analyses, and contrast volume is included in contemporary postprocedural risk models^{13,14}. The present result should therefore not be interpreted as evidence that contrast dose is unimportant. The relatively restricted range of contrast volumes, limited event count, operator-dependent procedural decisions, and absence of a renal function–adjusted measure such as the contrast volume-to-eGFR or contrast volume-to-creatinine clearance ratio may have reduced the ability to detect this relationship. Procedure duration and the angiographic severity of individual coronary lesions were also comparable between groups.

The distribution of preventive strategies differed considerably according to CIN status. Patients who subsequently developed CIN more frequently received combined N-acetylcysteine, intravenous isotonic saline, and oral hydration, whereas oral hydration alone was more common among those who did not develop CIN. This pattern should not be interpreted as indicating that intensive preventive treatment increased CIN risk.

Because treatment was selected by the treating physician rather than assigned randomly, patients perceived to be at greater renal or hemodynamic risk were more likely to receive intensive prophylaxis, creating substantial confounding by indication. Moreover, evidence regarding the additional benefit of N-acetylcysteine remains inconsistent across trials and meta-analyses²². The present observational data cannot compare the effectiveness of the recorded preventive strategies.

From a clinical perspective, calculated PO has several practical advantages: it is available before PCI, requires no additional blood sampling, and can be calculated from routinely measured variables. However, its clinical value should not be inferred solely from an independently significant regression coefficient. Because PO is mathematically derived from sodium, glucose, and BUN, it partly overlaps with established renal and metabolic risk indicators. Before clinical implementation, future studies should determine whether PO provides incremental discrimination and calibration beyond validated risk models and whether it improves clinical decision-making. External validation, evaluation of non-linear relationships, standardized cutoff determination, and assessment of whether PO-guided monitoring or hydration strategies improve renal outcomes are also needed. PO should therefore be considered a potential complementary marker rather than a replacement for established assessment of renal function, hemodynamic status, and contrast burden.

In conclusion, higher admission PO was independently associated with CIN in patients with ACS undergoing PCI. Baseline creatinine, RDW, and potassium were positively associated with CIN, whereas LVEF was inversely associated. Calculated PO may therefore be a simple, inexpensive adjunct to renal risk assessment. Prospective multicenter studies are needed to confirm these findings and establish clinically relevant thresholds.

4.1. Limitations

This study has several limitations. Its retrospective, single-center design and the use of data collected in 2016–2017 limit causal inference and generalizability to current practice. CIN was defined solely by serum creatinine changes within 72 hours; urine output, renal biomarkers, and postdischarge renal measurements were unavailable. PO was calculated from a single admission sample rather than measured directly, and the osmolar gap was not assessed. Moreover, because BUN and glucose are included in the PO formula, their individual contributions could not be fully separated. The limited number of CIN events restricted extensive adjustment and subgroup analyses, and model calibration, validation, and incremental predictive value were not evaluated. Preventive treatments were not randomized, leaving the results susceptible to confounding by indication. Exclusion of patients with an eGFR <30 mL/min/1.73 m² further limits generalizability. Finally, echocardiography was not performed at a uniform preprocedural time point, and cardiac findings may partly reflect ACS severity.

Statement of Ethics: This study is approved by the Ethical Committee of Çukurova University Faculty of Medicine (Approval No. 75, date: 02 March 2018). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Data Availability: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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