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Original Article

A Novel Biomarker to Predict the Risk of Contrast-induced Nephropathy in Patients Undergoing Coronary Angiography: Total Bilirubin Phosphorus Ratio

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Abstract

Objective: Identifying patients at high risk for contrast-induced nephropathy (CIN) is essential for implementing effective preventive strategies. This study aimed to evaluate the predictive value of the total bilirubin-phosphorus ratio (TBPR) for CIN development.

Methods: This retrospective, observational study included 2217 patients who underwent coronary angiography between June 2020 and January 2022. Patients were categorized into two groups based on CIN occurrence: those who developed CIN (Group 1) and those who did not (Group 2). Baseline characteristics, CIN status, and TBPR were compared between the groups.

Results: CIN incidence was highest among patients with ST-elevation myocardial infarction (STEMI) (39.4%), followed by those with Non-STEMI (27.2%) and stable/unstable angina pectoris (12.1%) ($p<0.05$). Multivariate analysis identified advanced age, pre-procedural hydration, severe coronary artery disease, STEMI diagnosis, and a low TBPR as independent predictors of CIN. Patients who developed CIN had significantly lower TBPR values (0.133 vs. 0.214, $p<0.001$). Receiver operating characteristic curve analysis demonstrated that a TBPR threshold of <0.155 predicted CIN with 85% sensitivity and 63% specificity (area under the curve [AUC]: 0.759, $p<0.001$). In addition, TBPR was a stronger predictor of CIN than total bilirubin or phosphorus alone (AUC comparison, $p<0.001$).

Conclusion: This study highlights TBPR as a potential independent predictor of CIN development.

Keywords: Contrast-induced nephropathy; coronary angiography; phosphorus; total bilirubin.

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Koroner Anjiyografi Uygulanan Hastalarda Kontrast Maddeye Bağlı Nefropati Riskini Öngörmek İçin Yeni Bir Biyobelirteç: Toplam Bilirubin Fosfor Oranı

Özet

Amaç: Kontrast kaynaklı nefropati (CIN) açısından yüksek risk taşıyan hastaların belirlenmesi, etkili koruyucu stratejilerin uygulanabilmesi için büyük önem taşımaktadır. Bu çalışmanın amacı, toplam bilirubin-fosfor oranının (TBPR) CIN gelişimini öngörmedeki değerini değerlendirmektir.

Gereç ve **Yöntem:** Bu retrospektif, gözlemsel çalışmaya Haziran 2020 ile Ocak 2022 tarihleri arasında koroner anjiyografi uygulanan 2.217 hasta dahil edildi. Hastalar, CIN gelişimine göre iki gruba ayrıldı: CIN gelişenler (Grup 1) ve gelişmeyenler (Grup 2). Gruplar arasında demografik özellikler, CIN durumu ve TBPR değerleri karşılaştırıldı.

Bulgular: CIN insidansı en yüksek STEMI hastalarında görüldü (%39,4), bunu NSTEMI (%27,2) ve stabil/instabil angina pektoris (%12,1) hastaları izledi (p<0,05). Çok değişkenli analizde ileri yaş, işlem öncesi hidrasyon, ciddi koroner arter hastalığı, STEMI tanısı ve düşük TBPR değeri CIN için bağımsız belirleyiciler olarak saptandı. CIN gelişen hastalarda TBPR değerleri anlamlı şekilde daha düşüktü (0,133 vs. 0,214; p<0,001). ROC eğrisi analizine göre TBPR'nin <0,155 eşiği, %85 duyarlılık ve %63 özgüllük ile CIN'i öngördü (AUC: 0,759; p<0,001). Ayrıca, TBPR'nin tek başına total bilirubin veya fosfora kıyasla CIN'i öngörme gücü daha yüksekti (AUC karşılaştırması, p<0,001).

Sonuç: Bu çalışma, TBPR'nin CIN gelişimi için potansiyel bağımsız bir prediktör olabileceğini ortaya koymaktadır.

Anahtar sözcükler: Kontrast nefropatisi; koroner anjiyografi; fosfor; total bilirubin.

Introduction

Contrast-induced nephropathy (CIN) represents a prevalent subtype of acute kidney injury (AKI) that emerges after exposure to contrast agents during coronary angiography.[1] As contrast-based diagnostic and interventional procedures become more widely utilized, the occurrence of CIN has escalated, leading to elevated morbidity and mortality rates.[2–4] This trend emphasizes the urgent requirement for preventive measures to reduce contrast-related renal impairment.

While the exact pathophysiological processes behind CIN are not fully understood, various contributors have been proposed, such as hypoxia in the renal medulla, oxidative stress, direct cellular toxicity, apoptosis, inflammation, and microvascular dysfunction.[5] In light of the increasing burden of CIN, there remains a critical need for accessible and cost-effective biomarkers that offer strong sensitivity and specificity, enabling early detection of vulnerable patients and informed implementation of prophylactic strategies.[6,7]

Bilirubin, generated from heme catabolism through heme oxygenase activity, is known for its antioxidant and anti-inflammatory properties.[8] Evidence from prior research indicates a possible protective influence of bilirubin against CIN.[9,10] On the other hand, phosphorus is vital for renal physiology, and disturbances in its regulation have been linked to worsening kidney function and vascular calcification, both contributing to increased renal risk.[11–13]

The present study evaluates the prognostic significance of a new biomarker, the total bilirubin-to-phosphorus ratio (TBPR), for identifying individuals susceptible to CIN. By leveraging widely available and low-cost laboratory data, this investigation aims to offer a pragmatic approach for clinical risk assessment and support the adoption of tailored preventive interventions.

Materials and Methods

Study Population

This retrospective, observational analysis enrolled 2217 patients who consecutively underwent coronary angiography at our institution between June 2020 and January 2022. Clinical, demographic, and laboratory data, including complete blood counts and biochemical markers, were obtained from the hospital database. Exclusion criteria comprised active hepatitis, ongoing infections, advanced kidney dysfunction (glomerular filtration rate [GFR] <15 mL/min or dialysis), malignancy, recent contrast exposure (within 2 weeks), use of contrast agents exceeding 4 mL/kg, hemodynamic instability (Killip class ≥2 or cardiogenic shock), heart failure, and absence of bilirubin, phosphorus, or creatinine values within 48–72 h post-procedure. All patient data were anonymized. Ethical approval was granted by the Harran University Ethics Committee (Approval Date: April 04, 2022, Number: HRU.22/07/02), and exemption from informed consent was approved due to the retrospective design. The study complied with the STROBE reporting standards.

Study Protocols and Definitions

Of the 2852 patients initially assessed, 2217 satisfied the eligibility criteria and were included in the analysis (Fig. 1). Participants were stratified into two groups based on CIN occurrence: Group 1 (CIN−) and Group 2 (CIN+). They were further categorized into three diagnostic groups according to angiographic indications: ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and stable/unstable angina pectoris (SAP/UAP). All diagnostic and therapeutic procedures adhered to current clinical guidelines.[14]

Post-procedural hydration was administered to all patients using 0.9% saline at a rate of 1 mL/kg/hr for 24 h unless urgent care was required. In individuals with acute heart failure, this rate was halved. Congestive heart failure encompassed cases with preserved or reduced ejection fraction and a prior history of decompensation. Acute heart failure refers to newly diagnosed cases with reduced ejection fraction and no previous heart failure diagnosis. Hemodynamically unstable individuals before angiography were excluded. The contrast agent used was a non-ionic, low-osmolality iodine-based compound (Iohexol-Omnipaque®), with volume capped at 4 mL/kg to minimize bias from high-dose exposure.

CIN was defined by either a ≥0.5 mg/dL increase in serum creatinine or a ≥25% elevation from baseline within 48–72 h of contrast administration. Coronary artery disease (CAD) was identified by ≥50% luminal narrowing in at least one major coronary artery, and severity was assessed based on the number of vessels involved.[15]

Laboratory Parameters

Venous blood samples were obtained at admission, before any hydration therapy. Routine laboratory evaluations – including serum biochemistry and complete blood counts – were performed both before and 48–72 h after coronary angiography. Hemoglobin, leukocyte count, and platelet levels were assessed using the Coulter LH 750 Hematology Analyzer (Beckman Coulter, Miami, FL, USA). Serum concentrations of total biliru-

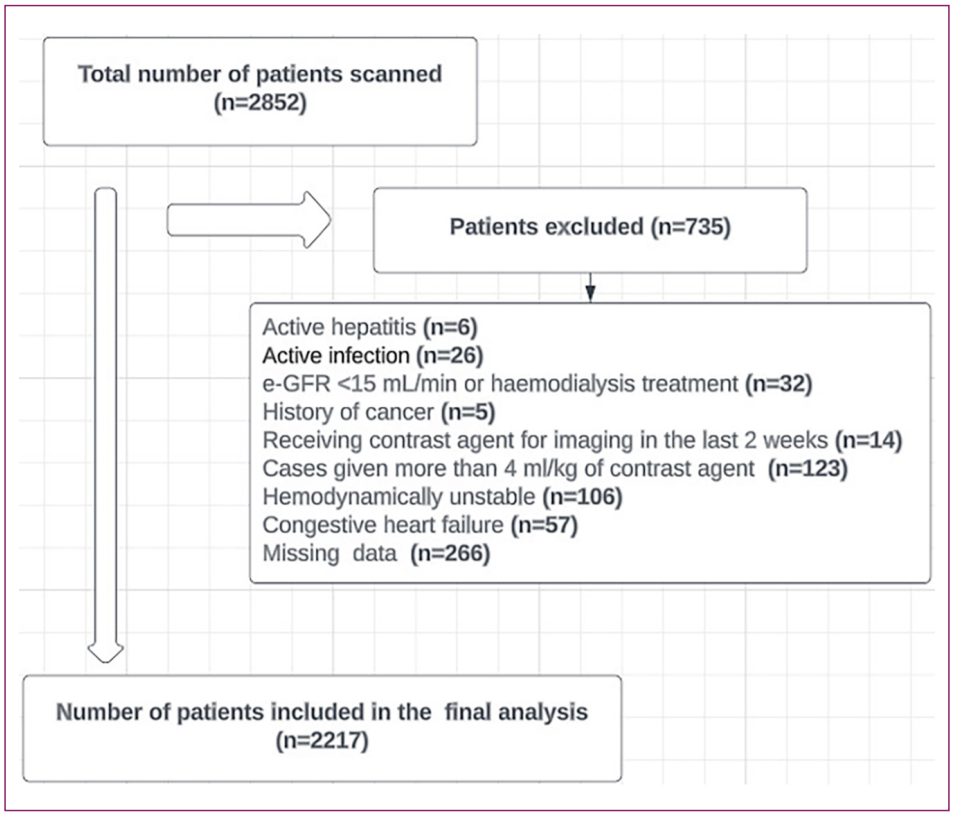


Figure 1. Flowchart of the study participants.

bin, phosphorus, calcium, glucose, total cholesterol, LDL-cholesterol, uric acid, and creatinine were analyzed with the AU 2700 AutoAnalyzer (Beckman Coulter, Japan). The estimated glomerular filtration rate (e-GFR) was computed using the CKD-EPI equation. TBPR was calculated by dividing the total bilirubin value by the serum phosphorus level. Comparisons were made between groups based on demographic data, clinical status, laboratory markers, Percutaneous coronary intervention (PCI) history, TBPR values, and CIN occurrence.

Statistical Analysis

Statistical computations were carried out using Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test assessed the distribution of continuous variables. Data with normal distribution were reported as mean ± standard deviation (SD) and analyzed using the Student's t-test, whereas non-normally distributed variables were described using medians with interquartile ranges and assessed with the Mann–Whitney U test. For comparisons across diagnostic categories (e.g., CIN status and TBPR levels), one-way analysis of variance followed by Bonferroni post hoc analysis was applied. Non-parametric data across groups were examined using the Kruskal–Wallis test, supplemented by Brown–Forsythe post hoc evaluation when appropriate.

Categorical variables were presented as numbers and percentages (n, %) and compared using the Chi-square (χ^2) test. Correlations between serum creatinine changes and continuous parameters were assessed using Pearson's correlation coefficient. Logistic regression models, both univariate and multivariate, were constructed to identify independent determinants of CIN. Variables showing statistical significance in univariate testing ($p<0.05$) were entered into the multivariate model using forward selection. Model adequacy was verified with the Hosmer–Lemeshow goodness-of-fit test. ROC curve analysis was used to determine the optimal TBPR threshold for predicting CIN, quantified by the area under the curve (AUC). AUC comparisons were conducted using MedCalc 16 software. Sample size requirements were determined using R statistical software (R Core Team, 2020), assuming an effect size of 0.75, alpha error of 0.05, and 80% power, indicating a minimum of 108 subjects per group. A $p<0.05$ was considered statistically significant for all comparisons.

Results

Following exclusion, 2217 individuals were included in the final analysis based on CIN status (Table 1). Of these, 1507 (67.9%) were male, and 710 (32.1%) were female. Coronary angiography indications included NSTEMI (48.7%, n=1,076), STEMI (25.7%, n=570), and SAP/UAP (25.6%, n=569). CIN occurred in 27.2% of NSTEMI cases, 39.4% of STEMI cases, and 12.1% of SAP/UAP cases (Fig. 2). The frequency of CIN was notably greater among patients with STEMI compared to those with NSTEMI or SAP/UAP, and in NSTEMI patients compared to SAP/UAP (all $p<0.05$). Pre-procedural hydration was more common in those without CIN (77.7%) compared to those who developed CIN (60.6%), showing a significant association ($p<0.001$).

Table 1. Distribution of clinical and demographic characteristics of the patients according to the development of contrast-induced nephropathy

	Group 1 (CIN−) (n=1630)	Group 2 (CIN+) (n=587)	p[a]
Age, years	60 (52–67)	64 (56–74)	**<0.001**
Gender, Female (%)	495 (78.5)	214 (36.4)	**0.022**
Body mass index, kg/m2	25.4±4.2	26.8±4.3	0.135
Diabetes mellitus (%)	550 (33.7)	247 (42.0)	**0.001**
Hypertension (%)	1088 (66.7)	433 (73.7)	**0.002**
Hyperlipidemia (%)	1308 (80.2)	513 (87.3)	**<0.001**
Smoking (%)	1018 (62.4)	337 (57.4)	**0.032**
CRF (e-GFR <15–60 mL/min) (%)	206 (12.6)	102 (17.4)	**0.004**
SBP (mmHg)	122.2±7.8	129.3±11.0	0.091
DBP (mmHg)	81.7±4.9	83.2±8.7	0.205
Heart rate, beats/min	79.1±14.3	80.5±15.3	0.306
Fasting plasma glucose (mg/dL)	118.0 (87.0–165.0)	130.0 (99.0–178.0)	0.186
Initial creatinine (mg/dL)	0.9 (0.75–1.07)	0.8 (0.60–1.00)	**<0.001**
Uric acid (mg/dL)	5.2 (4.3–6.2)	5.0 (4.2–6.1)	0.102
LDH (U/L)	256 (210–350)	254 (211–309)	0.291
Albumin (g/dL)	4.2 (3.9–4.5)	4.0 (3.7–4.3)	**<0.001**
Total cholesterol (mg/dL)	174 (144.0–207.0)	178.0 (146.0–211.0)	**0.044**
LDL-C (mg/dL)	105 (82.0–132.0)	106 (81.0–137.0)	0.290
CRP (mg/dL)	0.54 (0.18–1.58)	0.59 (0.22–1.65)	0.074
e-GFR (mL/min)	90 (72–100)	90 (73–102)	0.379
WBC (×1000/mm^3)	9.8 (7.8–12.7)	9.7 (7.7–12.7)	0.549
Hemoglobin (g/dL)	14 (13-15)	13 (12–15)	**<0.001**
Hematocrit (%)	44 (40.0–47.0)	41 (37–46)	**<0.001**
Platelet count (×1000/mm^3)	257 (216–305)	262 (208–310)	0.493
Amount of contrast agent (mL)	90 (80–180)	90 (80–180)	0.330
Severity of CAD	2 (1.0–2.0)	2 (2.0–≥3.0)	**<0.001**
PCI applied (%)	1246 (79.6)	341(88.3)	**<0.001**
Total bilirubin (mg/dL)	0.71 (0.46–0.80)	0.50 (0.40–0.60)	**<0.001**
Phosphorus (mg/dL)	3.2 (2.7–3.7)	3.4 (2.9–4.0)	**<0.001**
Calcium (mg/dL)	9.1 (8.8–9.5)	9.0 (8.3–9.3)	**<0.001**
TBPR	0.214 (0.166–0.288)	0.133 (0.096–0.190)	**<0.001**
Pre-hydration (%)	1266 (77.7)	356 (60.6)	**<0.001**
Pre-procedure medication			
Antiplatelet	378 (23.1)	116 (19.7)	0.341
β-blocker	457 (28.0)	153 (26.0)	0.419
Statins	711 (43.6)	291 (49.5)	0.116
CCB	325 (19.9)	136 (23.1)	0.124
ACEI/ARB	581 (35.6)	211 (35.9)	0.853

Values are mean±SD, n (%), or median (interquartile range) unless otherwise stated. [a]: Bold values define the statistical significance of p<0.05. ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; CCB: Calcium channel blocker; CAD: Coronary artery disease; CRF: Chronic renal failure; CRP: C-reactive protein; e-GFR: Estimated glomerular filtration rate; CIN: Contrast-induced nephropathy; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDH: Lactate dehydrogenase; LDL-C: Low -density lipoprotein cholesterol; PCI: Percutaneous coronary intervention; TBPR: Total bilirubin phosphorus ratio; WBC: White blood cell. Group 1 refers to the group that does not develop contrast nephropathy; and Group 2 refers to the group that develops contrast nephropathy.

When stratified by diagnostic category, CIN was observed in 13.5% of SAP/UAP, 27.2% of NSTEMI, and 39.4% of STEMI patients. Median TBPR values across these subgroups were 0.21 (0.16–0.27), 0.18 (0.13–0.26), and 0.18 (0.12–0.25), respectively, with no statistically significant difference (Table 2). Similarly, neither left ventricular ejection fraction nor contrast

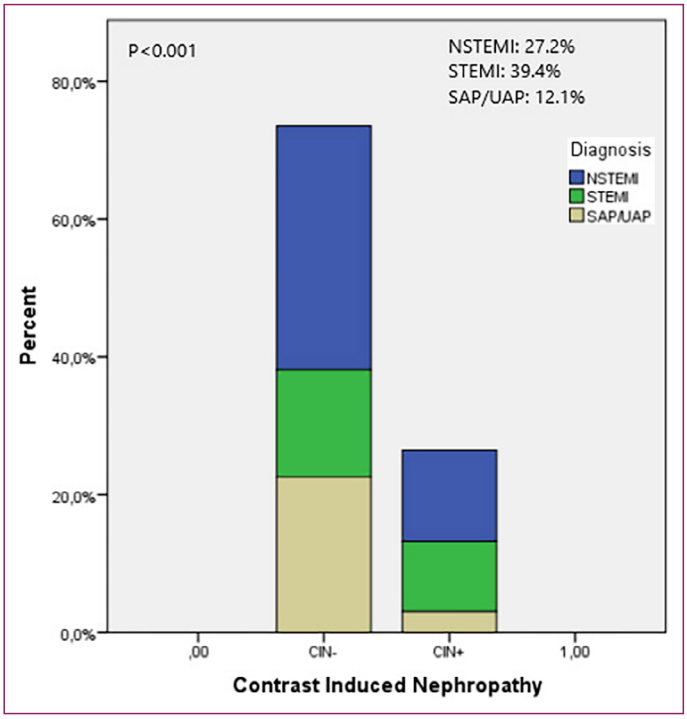


Figure 2. Incidence of CIN among the three groups of patients (SAP/UAP, 12.1%; UAP/NSTEMI, 27.2%; STEMI, 39.4%; all, p<0.001).

CIN: Contrast-induced nephropathy; SAP: Stable angina pectoris; UAP: Unstable angina pectoris; NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction. CIN - refers to the group that does not develop nephropathy, CIN + that do.

volume varied significantly among these diagnostic groups (p=0.127 and p>0.05, respectively).

Individuals who experienced CIN were generally older and more likely to be female, with a greater prevalence of comorbid conditions such as diabetes, hypertension, hyperlipidemia, and smoking history. They also had higher rates of PCI, more extensive CAD, and significantly lower levels of hemoglobin, hematocrit, albumin, initial creatinine, calcium, bilirubin, and TBPR, while showing elevated phosphorus levels (all p<0.05; Table 1). CIN occurrence was significantly more common in those with existing chronic kidney disease (p=0.004) and less frequent in patients who received prophylactic hydration before the procedure (p<0.001).

Correlation analysis indicated that increases in serum creatinine were inversely associated with both total bilirubin (r=–0.072, p=0.010) and TBPR (r=–0.050, p=0.029), as shown in Table 3.

In multivariate logistic regression, age, absence of pre-hydration, higher CAD burden, STEMI presentation, and low TBPR emerged as independent predictors of CIN (all p<0.001; Table 4). TBPR was significantly reduced in patients who developed CIN compared to those who did not (0.133 [0.096–0.190] vs. 0.214 [0.166–0.288], p<0.001; Fig. 3a).

When categorized by TBPR quartiles, CIN rates were found to be 48.1%, 15.4%, 8.9%, and 6.7% across the first to fourth quartiles, respectively (p<0.001; Fig. 3b). Receiver operating characteristic (ROC) analysis identified a TBPR threshold of <0.155 as optimal for predicting CIN, yielding an AUC of 0.759 with 85% sensitivity and 63% specificity (p<0.001; Fig. 3). Furthermore, TBPR showed superior diagnostic performance compared to total bilirubin or phosphorus alone (AUC comparison, p<0.001; Fig. 4).

Discussion

The primary finding of our study was that the patients with lower TBPR values exhibited a significantly higher risk for developing CIN. This association implies a potential mechanistic link involving diminished antioxidant defense and altered phosphorus regulation in CIN pathogenesis. By integrating bilirubin and phosphorus into a single ratio, TBPR appears to provide enhanced predictive accuracy over the use of either variable alone. As such, TBPR may represent a feasible and straightforward biomarker to assist in the identification and management of patients at elevated risk.

Even with the advent of newer contrast agents engineered for lower nephrotoxicity, CIN continues to be a major contributor to adverse outcomes, including extended hospitalization and increased mortality, due to the frequent application of contrast imaging techniques such as angiography.[16] Hence, early detection of high-risk individuals and deployment of tailored protective strategies remain critical. Mechanistic studies have pointed to a range of contributing factors, such as medullary hypoxia, endothelial injury, inflammatory responses, vasoconstriction, direct tubular damage, and oxidative imbalance as culprits in CIN onset.[2–4] In particular, heightened reactive oxygen species (ROS) production, both in susceptible individuals and in response to contrast-induced hypoxia, plays a pivotal role. In addition, the impairment of nitric oxide (NO) pathways due to ROS interference has been recognized as a central mechanism.[17–20] These insights have fueled interest in antioxidant thera-

Table 2. Laboratory and clinical analysis of diagnosis subgroups

Variables	*SAP/UAP group (n=569)	NSTEMI group (n=1078)	STEMI group (n=570)	p[a]
CIN developed (%)	69 (12.1)	294 (27.2)	225 (39.4)	**<0.001**
Amount of contrast agent (mL)	124.6±53.4	130.8±57.1	132.7±58.8	0.108
TBPR	0.21 (0.16–0.27)	0.18 (0.13–0.26)	0.18 (0.12–0.25)	0.225
LVEF (%)	53.3 (52.0–58.1)	52.4 (45.3–54.0)	51.2 (43.0–53.0)	0.127

Values are mean±SD, n (%), or median (interquartile range) unless otherwise stated. [a]: Bold values define the statistical significance of p<0.05. *: SAP/UAP group taken as reference. CIN: Contrast-induced nephropathy; LVEF: Left ventricular ejection fraction; SAP: Stable angina pectoris; UAP: Unstable angina pectoris; NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; TBPR: Total bilirubin phosphorus ratio.

Table 3. Correlation analysis between creatinine increase rate and laboratory parameters

Variables	r	p[a]
e-GFR (mL/min)	0.014	0.530
Uric acid (mg/dL)	-0.026	0.231
WBC (×1000/mm^3)	-0.026	0.329
Hemoglobin (g/dL)	-0.002	0.932
CRP (mg/dL)	0.011	0.603
Amount of contrast medium (ml)	0.029	0.181
Total bilirubin (mg/dL)	-0.072	**0.010**
Phosphorus (mg/dL)	0.018	0.432
TBPR	-0.050	**0.029**

[a]: Bold values define the statistical significance of p<0.05. CRP: C-reactive protein; e-GFR: Estimated glomerular filtration rate; TBPR: Total bilirubin phosphorus ratio; WBC: White blood cell.

pies, with agents such as N-acetylcysteine and ascorbic acid showing potential in lowering CIN incidence.[21]

Bilirubin, generated through heme oxygenase-mediated degradation of heme, functions as a natural antioxidant and anti-inflammatory agent. Its vasoprotective and antiatherogenic roles are believed to stem in part from its ability to attenuate oxidative stress.[22,23] Specifically, bilirubin may prevent low-density lipoprotein oxidation, inhibit vascular smooth muscle proliferation, and reduce monocyte infiltration into vascular tissues.[24–26] Several investigations have reported a protective association between higher bilirubin levels and reduced CIN risk. Huang et al.[27] notably demonstrated an inverse relationship between bilirubin concentration and both CIN development and cardiovascular complications. Similar findings have been observed in patients with STEMI undergoing PCI and in those with peripheral vascular disease receiving contrast imaging.[9,28]

Phosphorus is integral to renal physiology, and its serum concentration is tightly regulated by the kidneys. Elevated phosphorus levels, especially in individuals with end-stage renal disease, have been correlated with greater cardiovascular risk and mortality.[29,30] Importantly, even modest increases within the reference range have been linked to worsened outcomes and faster progression to renal failure in both CKD and non-CKD populations.[31,32] Sim et al.[33] reported a heightened risk for end-stage renal disease associated with elevated phosphorus levels in subjects with otherwise normal renal function. These effects are thought to stem from mechanisms such as vascular calcification and renal tissue injury.[34,35] Moreover, high phosphorus levels have been associated with early-stage atherosclerosis in patients with preserved renal function, potentially increasing their vulnerability to AKI.[36]

Bilirubin has been shown to neutralize reactive nitrogen species, which are implicated in CIN pathogenesis throughout NO-dependent pathways.[4] Conversely, excessive phosphorus intake may promote calcium deposition in renal tissues and lead to tubular damage – effects that are especially pronounced under conditions of endothelial NO synthase deficiency, where oxidative clearance is impaired.[37] While the direct relationship between high phosphorus and contrast-related kidney injury has not been extensively explored, our results suggest a meaningful

Table 4. Univariate and multivariate logistic regression analysis of CIN

Variable	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p[a]
Age	1.035 (1.027–1.044)	<0.001	1.029 (1.018–1.039)	**<0.001**
Diabetes mellitus	1.425 (1.175–1.729)	<0.001	1.213 (0.835–1.764)	0.311
Gender	0.761 (0.624–0.928)	0.026	1.107 (0.635–1.931)	0.719
Hypertension	0.810 (0.669–0.982)	0.032	1.207 (0.815–1.789)	0.348
Smoking	0.810 (0.669–0.982)	0.032	1.093 (0.654–1.829)	0.734
Hyperlipidemia	1.708 (1.301–2.243)	0.001	0.814 (0.449–1.476)	0.497
Chronic renal failure	1.494 (1.152–1.939)	0.003	0.986 (0.709–1.369)	0.631
Pre-hydration	0.443 (0.362–0.543)	<0.001	0.355 (0.224–0.562)	**<0.001**
Albumin	0.568 (0.464–0.695)	<0.001	0.805 (0.536–1.207)	0.293
Total bilirubin	0.573 (0.405–0.811)	0.002	1.615 (0.928–2.128)	0.064
Phosphorus	1.287 (1.178–0.701)	<0.001	1.099 (0.984–1.229)	0.095
Hemoglobin	0.886 (0.845–0.929)	<0.001	0.912 (0.825–1.026)	0.091
CRP	1.008 (0.997–1.019)	0.134	-	-
PCI	0.804 (0.655–0.988)	<0.001	0.875 (0.518–1.478)	0.617
Diagnosis (STEMI)	2.763 (2.074–3.680)	<0.001	3.124 (1.672–4.548)	**<0.001**
Severity of CAD	1.789 (1.611–1.988)	<0.001	1.423 (1.253–1.615)	**<0.001**
TBPR	0.014 (0.005–0.041)	<0.001	0.012 (0.002–0.063)	**<0.001**

[a]: Bold values define the statistical significance of p<0.05. CAD: Coronary artery disease; CRP: C-reactive protein; e-GFR: Estimated glomerular filtration rate. PCI: Percutaneous coronary intervention, TBPR: Total bilirubin phosphorus ratio, STEMI: ST-segment elevation myocardial infarction.

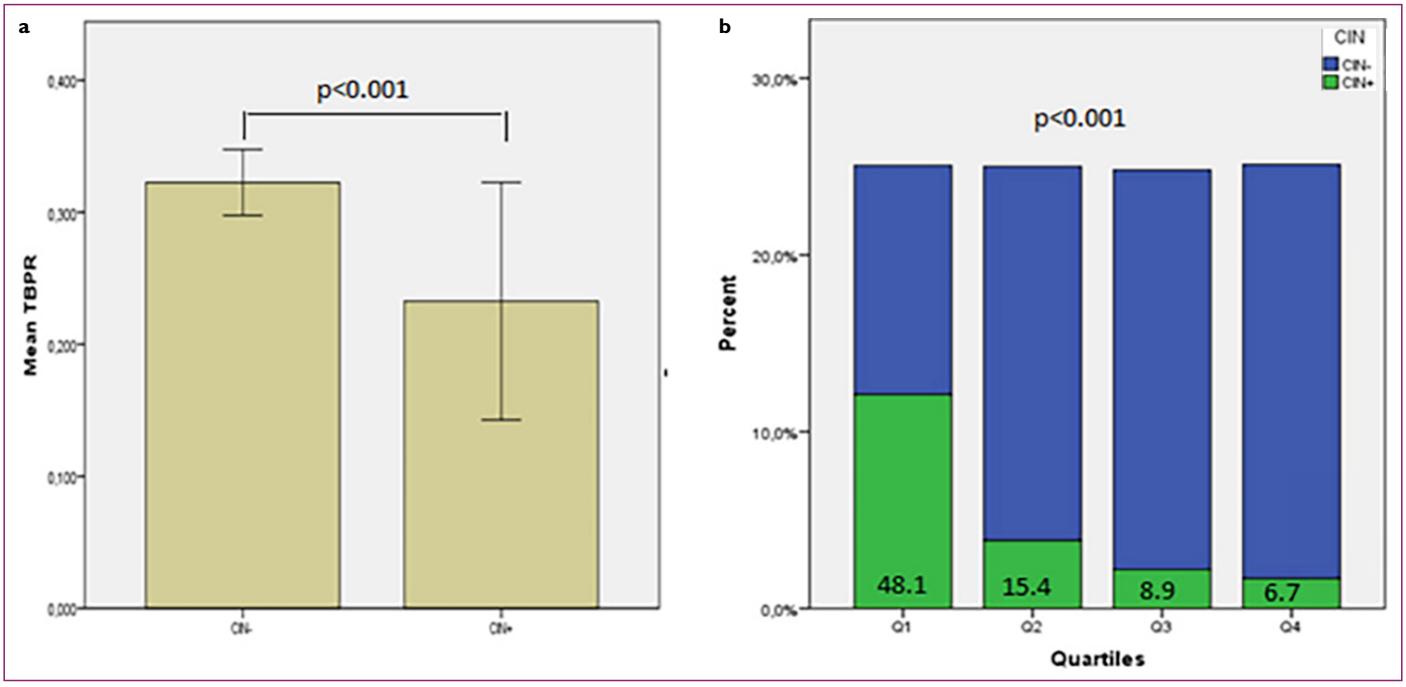


Figure 3. Comparison in the level of TBPR between CIN− and CIN+ group (a), and the incidence of CIN according to the quartiles (Q) of TBPR (b).

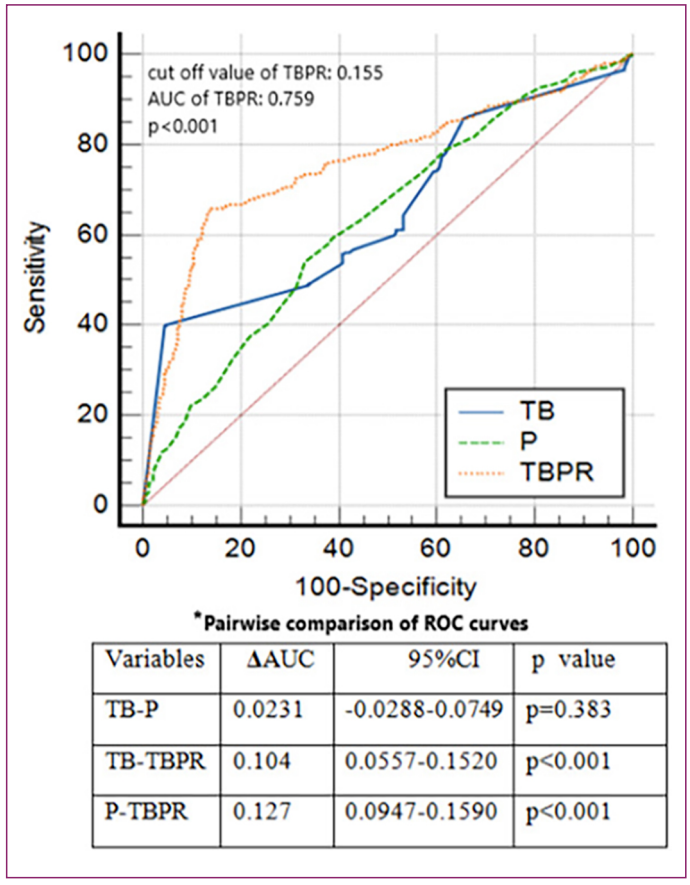
CIN: Contrast-induced nephropathy; TBPR: Total bilirubin phosphorus ratio.

association. Considering that AKI and chronic kidney disease are increasingly viewed as stages within a shared pathological spectrum, with CKD both predisposing to and accelerating CIN, it is conceivable that elevated phosphorus may intensify renal dysfunction and thereby contribute to the CIN onset.[38]

Notably, our analysis revealed that individuals with lower baseline serum creatinine were more likely to meet CIN criteria, which contrasts with traditional expectations. This paradox may stem from the definition of CIN, which relies on relative changes (e.g., a ≥25% increase) rather than absolute thresholds. For example, a modest rise in creatinine (e.g., 0.1 mg/dL) in a patient with an initially low baseline (e.g., 0.4 mg/dL) would represent a disproportionately large relative increase, triggering the CIN diagnosis. This nuance suggests that current definitions may overestimate CIN incidence in patients with very low baseline renal markers.

Our findings also indicated that the extent of CAD independently predicted CIN risk. CAD severity was determined by evaluating for ≥50% luminal narrowing in major epicardial vessels, and disease burden was quantified using the SYNTAX scoring system.[15] Prior studies have postulated that extensive coronary atherosclerosis may reflect systemic vascular pathology, including early-onset renal arterial disease, thereby predisposing such patients to CIN during contrast exposure.

Overall, our results support the concept that combining bilirubin's protective effects with the detrimental influence of elevated phosphorus into a unified biomarker, TBPR, yields enhanced predictive utility for CIN. We identified TBPR as an independent determinant of CIN, with lower ratios consistently linked to higher CIN incidence. While these findings are promising, validation through larger-scale prospective studies is warranted to confirm their clinical applicability.



*Pairwise comparison of ROC curves

Variables	ΔAUC	95%CI	p value
TB-P	0.0231	-0.0288-0.0749	p=0.383
TB-TBPR	0.104	0.0557-0.1520	p<0.001
P-TBPR	0.127	0.0947-0.1590	p<0.001

Figure 4. Pairwise comparison of Receiver operating characteristics (ROC) curves of TB, P, and TBPR for predicting CIN.

CIN: Contrast-induced nephropathy; TB: Total bilirubin; P: phosphorus; TBPR: Total bilirubin to phosphorus ratio; ΔAUC: The differences between the area under the curve.

This study has several limitations. Its retrospective, single-center design limits causal inference and generalizability despite the large sample size. CIN was defined using short-term changes in serum creatinine without urine output criteria, potentially underestimating subclinical or delayed renal injury. Although multivariable adjustment was performed, residual confounding from unmeasured procedural or biochemical factors cannot be excluded. In addition, bilirubin and phosphorus were assessed only at baseline, precluding evaluation of temporal changes. Finally, TBPR has not yet been externally validated or compared directly with established CIN risk scores, warranting confirmation in prospective multicenter studies.

Conclusion

TBPR has emerged as an independent and practical predictor of CIN. By integrating bilirubin's protective antioxidant and anti-inflammatory roles with the detrimental impact of elevated phosphorus into a single ratio, TBPR offers clinical utility in forecasting CIN risk. Considering the substantial burden CIN imposes on patient outcomes, incorporating TBPR into routine assessments may aid in the timely identification of at-risk individuals and support proactive preventive care.

Disclosures

Ethics Committee Approval: The study was approved by the Harran University Ethics Committee (no: HRU.22/07/02, date: 04/04/2022).

Informed Consent: Informed consent was obtained from all participants.

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