Rev Nefrol Dial Traspl. 2022;42(2):109-16

Evaluation of Dickkopf-3 in acute kidney injury in patients undergoing coronary angiography: A pilot atudy

Evaluación de Dickkopf-3 en insuficiencia renal aguda en pacientes sometidos a angiografía coronaria: un estudio piloto

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ABSTRACT

Introduction: Urinary dickkopf-3 (DKK3), which is a kidney tubular stress marker has been suggested recently for preoperative identification of patients at risk of acute kidney injury. We aimed to assess the predictive role of urinary DKK3/creatinine (Cr) ratio in contrast-induced nephropathy (CIN) in patients undergoing percutaneous coronary intervention (PCI). **Methods:** This prospective observational study included patients undergoing elective PCI. The association between the ratio of precontrast urinary concentrations of DKK3/Cr and post contrast CIN was evaluated. The serum Cr, urinary DKK3 and Cr levels of the patients were measured before and after contrast media administration, and the sensitivity of urinary DKK3/Cr ratio in diagnosing CIN in the early stage was assessed by the area under receiver operating characteristic curve. **Results:** A total of 44 patients (33 males) undergoing PCI were enrolled and mean age of the patients was 61.5 ± 10.0 years. 22.7% of the patients developed CIN, none of them received hemodialysis during hospitalization. The mean urinary DKK3/Cr ratio was 950 ± 491 pg/mg in the CIN patients versus 386 ± 272 pg/mg in the non-CIN patients before contrast media administration (p=0.001). The mean urinary DKK3/Cr ratio was 1266 ± 738 pg/mg in the CIN patients versus 305 ± 192 pg/mg in the non- CIN patients at 12th hour after contrast media infusion (p<0.001). The roc-curve for the urinary DKK3/Cr ratio before contrast administration (AUC=0.835, p=0.001). **Conclusions:** Pre-contrast urinary DKK3/Cr ratio is a predictor for CIN. Urinary DKK3/Cr ratio may help in the identification of patients who are at risk of CIN.

KEYWORDS: dickkopf-3, acute kidney injury, contrast-induced nephropathy, biomarker

RESUMEN

Introducción: Recientemente se ha sugerido el dickkopf-3 (DKK3) urinario, que es un marcador de estrés tubular renal, para la identificación preoperatoria de pacientes con riesgo de lesión renal aguda. Nuestro objetivo fue evaluar el papel predictivo de la relación DKK3/Cr (creatinina) urinaria en la nefropatía inducida por contraste (NIC) en pacientes sometidos a intervención coronaria percutánea (ICP). **Material y métodos:** Este estudio observacional prospectivo

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Financiamiento:
Ninguno

Conflicto de intereses:
Ninguno

Recibido: 27-01-2021
Corregido: 12-03-2021
Aceptado: 28-04-2021

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incluyó pacientes sometidos a ICP electiva. Se evaluó la asociación entre las concentraciones urinarias precontraste de DKK3/Cr y la CIN poscontraste. Se midieron los niveles séricos de Cr, DKK3 urinario y Cr de los pacientes antes y después de la administración de medios de contraste y se evaluó la sensibilidad de la relación DKK3/Cr urinaria para diagnosticar NIC en la etapa temprana mediante el área bajo la curva característica operativa del receptor. **Resultados:** Se inscribieron un total de 44 pacientes (33 hombres) sometidos a ICP y la edad media de los pacientes fue de 61,5 ± 10,0 años. El 22,7% de los pacientes desarrollaron NIC, ninguno recibió hemodiálisis durante la hospitalización. La relación urinaria media DKK3/Cr fue de 950 ± 491 pg/mg en los pacientes con NIC versus 386 ± 272 pg/mg en los pacientes sin NIC antes de la administración del medio de contraste (p=0,001). La relación urinaria media DKK3/Cr fue 1266 ± 738 pg/mg en los pacientes con NIC versus 305 ± 192 pg/mg en los pacientes sin NIC a las 12 horas después de la infusión del medio de contraste (p=<0,001). La curva de roc para la relación urinaria DKK3/Cr antes de la administración de contraste (AUC=0,835, p=0,001). **Conclusiones:** El cociente DKK3/Cr urinario previo al contraste es un predictor de NIC. La proporción urinaria DKK3/Cr puede ayudar en la identificación de pacientes con riesgo de NIC.

PALABRAS CLAVE: dickkopf-3, lesión renal aguda, nefropatía inducida por contraste, biomarcador

INTRODUCTION

Contrast-induced nephropathy (CIN) is characterized by a decrease in kidney function that occurs within days after the intravascular administration of iodinated contrast media. With the wildly using of iodinated contrast media at interventional and imaging techniques which applied to diagnose and treat diseases, the frequency of CIN has increased in the last decades. CIN is the third most common cause of hospital-acquired acute kidney injury (AKI) after impaired renal perfusion and the use of nephrotoxic medications. [1] The pathophysiology of CIN is complex and partially understood. Direct tubular toxicity of the contrast media and medullary hypoxia are accepted as the main pathophysiological mechanisms of CIN.[2-4] CIN is defined as the impairment of renal function, measured as either a 25% increase in serum creatinine (sCr) from baseline or a 0.5 mg/dL (44 μmol/L) increase in absolute sCr value within 48-72 hours after intravenous contrast administration. [5] Serum creatinine is the most used biomarker to detect AKI but exhibits delayed accumulation following renal injury, a characteristic intrinsically limiting its utility as an early marker of AKI.

Dickkopf-3 (DKK3) is a stress-induced, profibrotic molecule that is derived from renal tubular epithelial cells.[6] Studies have shown that urinary DKK3/Cr is a predictor of postoperative AKI and subsequent acute kidney injury-chronic kidney disease (AKI-CKD) transition in individuals undergoing elective cardiac surgery.[7] Also, urinary DKK3 levels identify patients at high risk for eGFR decline over the next 12 months regardless of the cause of kidney injury.[8] Therefore, in the present study, we assessed the predictive role of the urinary DKK3/Cr ratio in patients undergoing percutaneous coronary intervention (PCI) to explore its usage in the early diagnosis of CIN.

METHODS

Subjects

The inclusion criteria were: being older than 18 years of age and having an estimated glomerular filtration rate (eGFR) higher than 60/ml/min/1.73 m^2. All the patients met the diagnostic criteria of coronary heart disease and had indications for coronary stent implantation. From September 2019 to February 2020, all consecutive patients (n=70) who underwent coronary stent implantation undergoing PCI admitted to our hospital were considered for enrollment in the study. Six patients refused to participate, four were exposed to contrast media within 7 days; There were eight patients without data on serum creatinine during the 72th hours following the procedure, two patients had end-stage renal disease on hemodialysis and finally six patients with an estimated glomerular filtration rate (eGFR) lower than 60/ml/min/1.73 m^2 were excluded. The remaining 44 eligible patients were enrolled. Patients with AKI caused by another reason before PCI, patients using nephrotoxic drugs or received contrast media within 7 days before PCI, patients with severe heart failure or other organ failures, patients with acute myocardial infarction, and patients with acute infection were excluded from the study. No patient received intravenous

 ISSN 0326-3428

(iv) normal saline at the day before contrast media infusion was administred and all patients received iv saline infusion at the day of intervention. No patient received iv saline infusion after the day of intervention since patients were discharged after 24 hours coronary stent implantation. CIN is defined as an increase in the sCr level by 0.5 mg/dL (44 μmol/L), or by 25% compared with the baseline value, within 72th after intravascular injection of iodine contrast agent [5], on the premise of excluding other causes. eGFR was calculated using the CKD-Epidemiology Collaboration equation. The sex, age, underlying diseases, dose of iodine contrast agent, and relevant laboratory examination results of the patients were collected. Signed written informed consent was obtained from all participants before the study. This study was approved by local Ethics Committee (approval number: 2019-337).

Specimen collection

We collected 5 mL venous blood and 10 mL urine specimens from all subjects before angiography and at 12th and 72nd hours after coronary angiography. Specimen were centrifuged at 4000 rpm for 10 min, then the supernatant was placed into sterile Eppendorf Tubes (EP), which were labeled and stored at -80°C for centralized detection and avoidance of repeated freezing and thawing.

Specimen detection

We used a BECKMAN COULTER AU5800 full-automatic biochemistry analyzer for biochemical assessment and BECKMAN COULTER AU480 for spot urine creatinine. The picric acid rate method (Jaffe reaction) was used for the measurements of serum and urine creatinine. The DKK3 levels were measured by ELISA (Bioassay Technology Laboratory, Human Dickkopf-3 ELISA Kit) according to the experimental procedures in the reagent instructions, and the corresponding level in each sample was calculated based on the absorbance detected.

Statistical analysis

All statistical analyses were performed using SPSS 22.0 software (IBM, Armonk, NY, USA). Normally-distributed quantitative data are expressed as mean ± standard deviation, and the *t*-test was used to compare differences between groups. Rates were compared using the chi-square test. Non-normally distributed data were compared by the Mann-Whitney rank-sum test. Statistical significance was set at p=<0.05.

To determine the sensitivity and specificity of urinary DKK3/Cr ratio in predicting CIN before PCI, the area under receiver operating characteristic curve (ROC-AUC) for urine DKK3/Cr before PCI was calculated.

Results

The mean age of the patients (33 men) was 61.5 ± 10.0 years. Twenty-one patients (47.7%) had diabetes mellitus (DM), thirty-nine patients (86.6%) had hypertension (HT) and all patients (100%) had hyperlipidemia. 19 (43.2%) patients were current smokers. All patients received iohexol. The mean volume of contrast media (CMV) was 277 ± 145 ml. Baseline clinical and procedural related characteristics were shown in **Table 1**.

A total of 10 patients (22.7%) developed CIN, none of them received hemodialysis during hospitalization. The median dose of contrast media was higher in patients with CIN than non-CIN groups (250 ml vs 200 ml, respectively). The median time of PCI was longer in patients with CIN than non-CIN groups (27.5 min vs 20 min, respectively).

Demographic data and p values of patients with and without AKI are given in **Table 2**. In addition, gender (p=0.516), smoking (p=0.687), HT (p=0.689) and DM (p=0.072) did not reach significant differences between patients with and without CIN.

The mean serum creatinine level was 0.79 ± 0.17 mg/dL in the CIN patients versus 0.88 ± 0.15 mg/dL in the without CIN patients before contrast media administration (p=0.183) and 1.07 ± 0.24 mg/dl versus 0.93 ± 0.17 mg/dL 72th hour after contrast media infusion (p=0.104). The mean eGFR was 71.7±19.6 ml/min/1.73 m^2 in patients with CIN versus 82.9 ± 14.2 ml/min/1.73 m^2 in patients without CIN at 72nd hour after contrast media infusion (p=0.043). The mean serum urea level was 47.8 ± 18.9 mg/dL in the CIN patients versus 35.0 ± 7.8 mg/dL in the without CIN patients at 72nd hour after contrast media infusion (p=0.013). The percentage change of creatinine at 72nd hour was statistically different between CIN and non-CIN patient groups (p=<0.001).

Table 1. Baseline clinical and procedural related characteristics of patients undergoing elective percutaneous coronary implantation

Parameters	**All Patients (*n*=44) (Baseline)**	**CIN group (*n*=10)**	**Non-CIN group (*n*=34)**	***P***
Age (years)	61.5 ± 10.0	63.50 ± 13.0	60.9 ± 9.1	
Body Mass Index (kg/m^2)	28.2 ± 4.6	27.61 ± 6.3	28.38 ± 4.1	
Systolic Blood Pressure (mmHg)	128 ± 20	120.6 ± 14.4	131.21 ± 21.2	0.081
Diastolic Blood Pressure (mmHg)	73 ± 12	70.5 ± 7.7	74.8 ± 13.9	0.216
Hemoglobin (g/dL)	12.7 ± 1.1	12.8 ± 1.28	12.6 ± 1.0	0.801
Albumin (g/L)	3.92 ± 0.40	3.77 ± 0.34	3.97 ± 0.43	0.223
AST	27.2 ± 13.6	34.3 ± 23.8	25.1 ± 8.2	0.157
ALT	24.9 ± 14.0	29.4 ± 22.9	23.6 ± 10.3	0.790
Cholesterol (mg/dl)	199 ± 51	195.9 ± 36.6	200.5 ± 56.1	0.654
High Density Lipoprotein (mg/dl)	42 ± 11	43.3 ± 9.28	41.6 ± 12.5	0.433
Low Density Lipoprotein (mg/dl)	150 ± 160			
Triglycerides (mg/dl)	177 ± 116			
Uric acid (mg/dL)	5.6 ± 1.4	5.12 ± 1.53	5.84 ± 1.38	0.138
Fasting glucose (mg/dL)	139 ± 89	93.5(IQR 79.7-123.5)	110(IQR 96.7-157.5)	*0.023*
Ejection fraction (%)	54.8 ± 8.0	57.5(IQR 55-60)	60(IQR 48-60)	0.712
LVIDd (cm)	5.35 ± 0.87	4.7 ± 0.1	4.8 ± 0.3	
Duration of PCI (minutes)	31.5 ± 18.4			
Contrast volume (ml)	277 ± 145	250(IQR: 200-362.5)	200(IQR: 200-285)	0.265
Hypertension	88.6%	90.0%	88.2%	
Diabetes	47.4%	20%	55.9%	
Current smoker	43.2%	50% (5)	47.1% (16)	(Total 21)
Past smoker	4.5%	10%	2.9%	
C-Reactive Protein	6.78 ± 5.78	6.87 ± 5.62	6.75 ± 5.92	0.813

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; **LVIDd:** Left Ventricular Internal End-Diastolic Dimension; **PCI:** Percutan Coronary Implantation

Table 2. Baseline, 12th, and 72nd-hour biochemical data of patients with and without Contrast-Induced Nephropathy (data are presented as mean ± SD)

Parameter	**Timing**	**CIN group (*n*=10)**	**Non-CIN group (*n* = 34)**	***p***
Serum creatinine (mg/dL)	Baseline	0.79 ± 0.17	0.88 ± 0.15	0.183
	12th hour	1.07 ± 0.24	0.93 ± 0.17	0.104
	72nd hour	1.07 ± 0.24	0.93 ± 0.17	0.104
Serum urea (mg/dL)	Baseline	35.5 ± 7.8	34.4 ± 7.7	0.183
	12th hour	47.8 ± 18.9	35.0 ± 7.8	*0.013*
	72nd hour	47.8 ± 18.9	35.0 ± 7.8	*0.013*
eGFR	Baseline	93.2 ± 14.9	86.1 ± 11.8	0,227
	12th hour	71.7 ± 19.6	82.9 ± 14.2	*0.043*
	72nd hour	71.7 ± 19.6	82.9 ± 14.2	*0,043*
Urinary DKK3/Cr ratio before CM (pg/mg)	Baseline	950 ± 491	386 ± 272	*0.001*
Ur DKK3/Cr ratio after CM (pg/mg)	12th hour	1266 ± 738	305 ± 192	*<0.001*

eGFR: Estimated Glomerular Filtration Rate; **Ur DKK3/Cr:** Urinary Dickkopf 3/Creatinine; **CM:** Contrast media

ISSN 0326-3428

Pre-intervention urinary DKK3/Cr ratio was significantly higher in patients with CIN. The mean urinary DKK3/Cr ratio was 950 ± 491 pg/mg in the CIN patients versus 386 ± 272 pg/mg in the without CIN patients before contrast media administration (p=0.001) and 1266 ± 738 pg/mg versus 305 ± 192 pg/mg at 12th hour after contrast media infusion (p=<0.001).

Serum urea, creatinine and urinary Dickkopf 3/Creatinine concentrations before and 12th hour after contrast media administration was shown in **Table 2**. The ROC curve analysis was performed to determine the cutoff value of urinary DKK3/Cr ratio to predict CIN. **Figure 1** shows the roc-curve for the urinary DKK3/Cr ratio before contrast administration (AUC=0.835, p=0.001).

There was no significant difference between precontrast urinary DKK3/Cr ratio and postcontrast urinary DKK3/Cr ratio (p=0.902).

Systolic and diastolic blood pressure were lower in patients with CIN (120.6 ± 14.4 versus 131.21 ± 21.2 mmHg; 70.5 ± 7.7 vs 74.8 ± 13.9, respectively). There was no statistically significant difference between patients with CIN and without CIN (p=0.081, p=0.216 respectively).

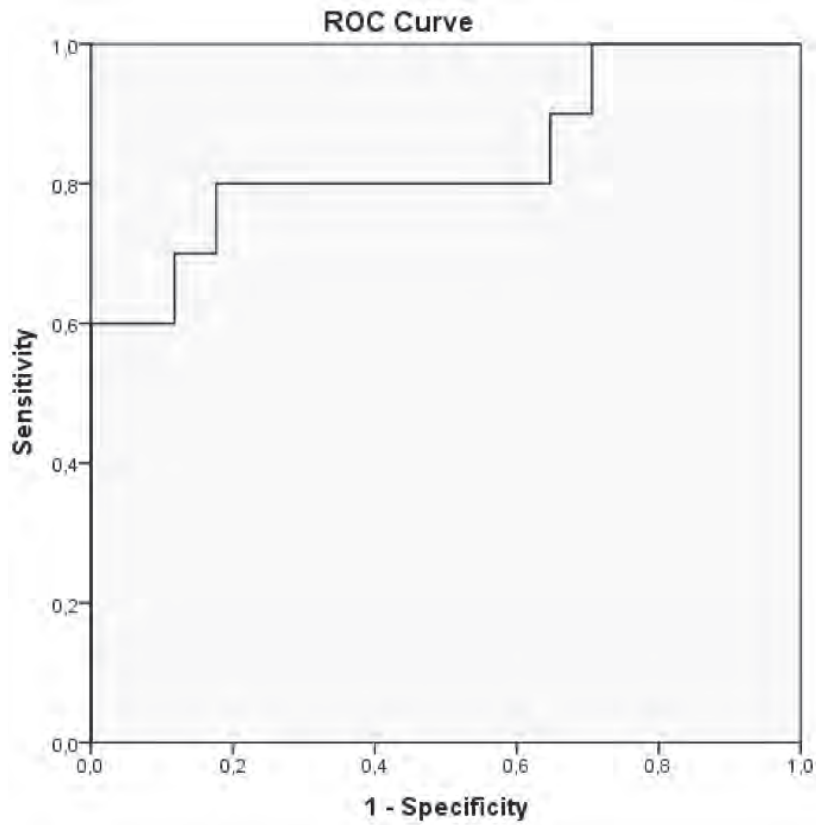

Figure 1. The roc-curve for the urinary Dickkopf 3/Creatinine ratio before contrast media administration (AUC:0.835 p: 0.001)

DISCUSSION

We investigated the association between urinary DKK3/Cr ratio and the risk of CIN in patients who were having PCI. We found that higher pre-intervention urinary DKK3/Cr concentrations were associated with an increased risk of CIN with independent of baseline kidney function which was evaluated with eGFR. Despite the prevention such as intravenous hydration, avoiding nephrotoxic agents, and low dose contrast administration to reduce nephrotoxicity, CIN may occur due to contrast agent in patients undergoing PCI. CIN is associated with high hospital mortality and morbidity, a longer hospitalization duration, and an increase of healthcare costs, identification of patients at risk for CIN before PCI is important, but challenging at the same time.[9] The diagnosis of CIN mainly depends on the changes in sCr level, but the difference in sCr sensitivity can not diagnose CIN in the early stage, and the identification of patients who are at high risk of CIN is especially important for early treatment strategies. The reported incidence of CIN varies depending on the definition of AKI. In the general

population, the incidence of CIN is estimated to be 1% to 6%.[10-12] Patients with diabetes and pre-existing renal impairment are at high risk, and CIN incidence increases in patients with multiple comorbidities.[11] Despite the prevention methods, the reported risk of CIN is 21.8% to 26% following coronary angiography with or without intervention in high-risk patients.[13-14] 22.7% of patients had CIN in our study, higher than most of the current literature. This may be since we accept the diagnosis of CIN with a 25% increase in serum creatinine. Likely *et al*. and Aspelin *et al*. have found CIN in 21.8% and 26% of their patients, respectively.[13-14]

It is mandatory to use of AKI markers rather than following urine output in determining AKI, because of the non-oliguric course of CIN.[15-16] But AKI markers such as creatinine, neutrophil gelatinase-associated lipocalin, urine kidney injury molecule-1, and urinary tissue inhibitor of metallopeptidase-2 and insulin-like growth factor binding protein 7 start to increase after the kidney injury has developed. These markers allow early detection of AKI, but not a pre-intervention prediction. DKK3/Cr ratio should be evaluated separately from these biomarkers that are currently used for the early detection of kidney damage.[7] he high urinary DKK3/Cr ratio allows the pre-intervention prediction of CIN.

Although it is still not fully understood, the main pathophysiological mechanisms of CIN is considered to be due to the direct toxic effect of the contrast agent on renal tubular cells and the medullary hypoxia that causes renal vasoconstriction which is mediated by changes in the release of nitric oxide, endothelin and adenosine.[2-4] DKK3 is a stress-induced glycoprotein that is secreted from renal tubular epithelial cells and leads to tubulointerstitial fibrosis through the Wnt/β-catenin pathway. The profibrotic effects of DKK3 in the kidney were independent from the cause of initial damage.[6] Since DKK3 is secreted into the urine under tubular stress circumstances, it may also serve as a noninvasive diagnostic biomarker for short-term eGFR loss. Urinary DKK3/Cr ratio was evaluated as a predictive biomarker of AKI in adult cardiac surgery cohorts and it was assessed for identifying patients at high risk for eGFR loss regardless of the cause of kidney injury, providing a tool to monitor CKD progression and assessing the effects of interventions.[7-8] However, there are limited data available on DKK3 levels in patients who are undergoing PCI.

In an observational cohort study carried on with 733 adult patients who are undergoing cardiac surgery in 2019, Schunk *et al.* reported that 26% of patients developed AKI and preoperative urinary DKK3/Cr ratio was an independent predictor for postoperative AKI and the subsequent loss of kidney function.[7]

In other prospective observational study carried on patients with different etiologies of CKD in 2018, Zewinger *et al.* reported that; urinary DKK3/Cr ratio identifies patients at high risk for eGFR loss over the next 12 months regardless of the cause of kidney injury, potentially providing a tool to monitor CKD progression and assess effects of interventions.[8]

Another study carried on patients with diabetic nephropathy, Sanchez Alamo *et al* reported that: High urinary DKK3/Cr ratio identifies patients with established diabetic nephropathy at risk for faster eGFR decline. The urinary DKK3/Cr ratio should be considered as a potential biomarker in CKD progression and could be useful in fitting treatment management.[17]

In a recently published prospective study carried on with 490 adult patients who are undergoing coroner angiography, *Seibert et al.* reported that; Urinary DKK3 is an independent predictor of CI-AKI even in the absence of overt CKD. They found that patients with CI-AKI had a 3.8-fold higher pre-procedural DKK3/creatinine ratio than without AKI after intravenous contrast media administration. They found the accuracy of urinary DKK3/creatinine in the detection of CI-AKI that assessed by ROC curve analysis, AUC 0.61, similar to our study.[18]

In our study, the pre-intervention urinary DKK3/Cr ratio was significantly higher in patients with CIN. We found a statistically significant difference in urinary DKK3/Cr ratio before and after contrast administration, between the patients with and without CIN ($p=0.001$ and $p=<0.001$). Also, while the AUC of urinary DKK3/Cr ratio before PCI was detected 0.835 in our study. Schunk *et al.* had found AUC 0.783; similar to our study.[7] These findings highlight the pre-intervention urinary DKK3/Cr ratio as a novel and useful predictor of CIN.

High dkk3 levels measured prior to PCI may be a predictor of increased renal stress that cannot

 ISSN 0326-3428

be determined by the serum creatinine level, and it may play a role in predicting CIN after exposure to contrast. Since the severity of coronary artery disease and post-pci cardiac follow-up of the patients were not included in the scope of this study and its relationship with the preoperative dkk3 level was not examined, one can speculate that the increased dkk3 level may also be a marker of cardiac events. However, in a recent study by Piek et al., In their cohort of 2090 patients, they showed that increased serum dkk3 levels were strongly associated with heart failure risk factors and comorbidities, including age, kidney function in multivariate analysis.[19] The relationship between increased dkk3 and renal function may be an indicator of increased renal tubular stress due to cardiorenal syndrome. The relationship between Dkk3 and cardiac dysfunction needs further investigation.

In our study, systolic and diastolic blood pressure were lower in patients with CIN (120.6 ± 14.4 versus 131.21 ± 21.2 mmHg; 70.5 ± 7.7 versus 74.8 ± 13.9 mmHg, respectively). Although hypotension is a risk factor for the development of CIN; in our study, patients who developed CIN were more hypotensive than those who did not, and it did not pose a statistically significant risk for the development of CIN. This may be caused by the mean arterial pressure of these groups not being low.

Although Acute Renal Injury is defined as an increase in sCr concentration ≥ 0.3 mg/dl within 48 hours regardless of causes, the rise in serum creatinine concentration begins within the first 24 to 48 hours (peaks at 2 to 3 days) after contrast exposure.[20-21] We used another commonly used definition of CIN in the literature which is defined as a rise in SCr of X0.5 mg/dl or a 25% increase from baseline value, assessed at 72 hours after a contrast administration at our study. To measure the sCr level, we took a blood sample at the 72nd hour, not at the 48th hour. If we had measured the sCr level at 48 hours, we might have missed some cases. If the criteria were used to define Acute Renal Injury (regardless of the cause): increase equal to or greater than 0.3 mg/dl, 6 patients would have had an acute renal injury.

Our results showed that the urinary DKK3/Cr ratio is a useful predictive and noninvasive biomarker for CIN. Using the urinary DKK3/Cr ratio might provide a basis for preventive diagnostic and therapeutic strategies in the preoperative, perioperative, and postoperative management of the patients.

The major limitations of our study are the limited number of patients included as it was designed as a single-center study and 75% of patients were male. And we did not evaluate whether patients have albuminuria which shows baseline kidney damage before PCI.

CONCLUSIONS

Our findings suggest that the urinary DKK3/Cr ratio might be a predictive and noninvasive biomarker of CIN, thereby contributing to early patient risk stratification. Urinary DKK3/Cr ratio might serve as a novel tool to identify patients who might benefit from specific preventive strategies. However, our data needs to be validated in large patient cohorts.

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 ISSN 0326-3428