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ORGINAL ARTICLE

Pre-Contrast Urinary DKK-3/Urinary Creatinine as a Predictor for Contrast-Induced Acute Kidney Injury

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ABSTRACT

Background: Contrast-induced acute kidney injury (CI-AKI), specifically after percutaneous coronary intervention (PCI) constitutes a highly challenging health concern. Thus, the prediction of patients at risk is paramount for early detection and prevention. A novel and promising biomarker, Dickkopf3 (DKK-3), has been investigated for its role in the prediction of CI-AKI. Yet, its role in the prediction of CI-AKI after PCI is not well recognized. Therefore, this study aimed to assess the predictive value of pre-contrast urinary DKK-3/urinary creatinine (Ur DDK-3/Ur Cr) for post-PCI-CI-AKI.

Methods: This prospective cohort study included 150 patients who underwent PCI, their serum creatinine, urinary creatinine, estimated glomerular filtration rate (eGFR), 24-hour urinary protein, urinary DKK-3 level, and Ur DDK-3/Ur Cr were measured pre-contrast, then repeated 48 hours post-contrast.

Results: CI-AKI was diagnosed in 14% of patients after PCI, and their pre-contrast Ur DKK-3 and Ur DKK-3/Ur Cr were significantly higher than patients without CI-AKI ($p<0.001$). Pre-contrast eGFR, serum, and urinary creatinine did not show significant differences in both groups. Significant predictors of CI-AKI included diabetes mellitus, age, BMI, pre-contrast HbA1C%, random blood sugar, eGFR, platelets count, proteinuria, and Ur DKK-3. Importantly; pre-contrast Ur DKK-3/Ur Cr had the highest odds ratio (OR 6) for predicting CI-AKI. At a cut-off value of 18.5 pg/mg, Ur DKK-3/Ur Cr has 87.5% sensitivity and 64% specificity for predicting post-PCI CI-AKI ($p<0.001$).

Conclusions: Increased pre-contrast Ur DDK-3/Ur Cr may independently predict patients at risk of developing post-PCI-CI-AKI.

Keywords: Urinary DKK-3/urinary creatinine; Contrast-induced acute kidney injury; Percutaneous coronary intervention.

INTRODUCTION

Acute kidney injury (AKI) is defined as a sudden but often reversible deterioration in kidney function, and reduction of glomerular filtration rate (GFR) [1]. The KDIGO guidelines define AKI by any of the following; a rise in serum creatinine (Cr) by ≥ 0.3 mg/dl in 48 hours, or by 1.5 folds or more its baseline level in the last 7 days, or urine output < 0.5 mL/ kg/ hour for at least 6 hours [2]. Causes of AKI include hypovolemia, trauma, acute tubular necrosis, acute interstitial nephritis, infection, medications, contrast, renal stones, or tumors [3].

Contrast-induced AKI (CI-AKI) is suspected if there is a deterioration in kidney function after

recent intravascular contrast media administration, after excluding other causes of AKI such as urinary obstruction, nephrotoxic drugs, shock, or rhabdomyolysis [4]. Risk factors for developing CI-AKI include the use of hyper-osmolar contrast media (CM), large doses of contrast, hypovolemia, diabetes mellitus, pre-existing renal dysfunction, or congestive heart failure [5].

Mechanisms involved in CI-AKI include oxidative stress, renal arteries vasoconstriction, ischemia, inflammation, and tubular obstruction [6]. Traditionally, serum Cr and GFR were used as biomarkers for CI-AKI, but new markers are being used such as Clusterin, Cystatin C, Osteopontin, β-2 Microglobulin, and Dickkopf-3 (DKK-3) [7].

The DKK-3, a 38 kDa secreted glycoprotein, is involved in cellular differentiation, and apoptosis, through the Wnt/β-catenin pathway [8], which is transiently activated to promote tubular regeneration after AKI [9]. DKK-3, a profibrotic glycoprotein, is secreted from tubular epithelium under stress and may be useful as a marker for tubular injury and fibrosis, and promotes both acute regeneration and progression to chronic kidney disease (CKD) [10].

Preoperative urinary DKK-3 (Ur DKK-3) levels strongly predict AKI after cardiac surgery [11]. The urinary DKK-3 (Ur DKK-3) and the urinary DKK-3/urinary creatinine (Ur DKK-3/Ur Cr) are independent predictors for CI-AKI [12]. As early prediction of patients at risk for post-PCI CI-AKI may allow its prevention, finding an easy, low-cost, and accurate marker could be of great help in reducing its risk. This study aimed to evaluate the pre-contrast Ur DKK-3/Ur Cr as a promising predictor for post-PCI CI-AKI.

METHODS

Study Design and Population:

A prospective cohort study was conducted in Cardiac Care Units, at Ahmed Maher Teaching Hospital, Cairo, and Zagazig University Hospitals, Zagazig, Egypt, during the period from October 2022 to March 2023. Using the Open Epi, assuming the mean DKK3 was 7.5±17.3 versus 1.38±7.4 in CI-AKI versus non-AKI. At 80% power and 95% CI, the estimated sample was 150 [12].

Inclusion and Exclusion Criteria:

Patients aged > 18 years, who had PCI either primary or elective were included in this study, while patients aged < 18 years, with associated cardiogenic shock, congestive heart failure, obstructive uropathy, cancer, pyuria, hemodialysis, or other nephrotoxic agents were excluded from the study.

Ethical Approvals:

Written consent was taken from participants in this study. The protocol was approved by the Institutional Research Board (IRB), and Ethical Committee, at the Faculty of Medicine, Zagazig University, Egypt, under the Number IRB#:9813-3-10-2022, according to the Helsinki's Declaration.

Assessment of studied patients:

Patients were subjected to full medical history, clinical examination, and laboratory investigations (serum creatinine in mg/dl, serum uric acid in mg/dl, HbA1C%, random blood sugar (RBS) in mg/dl, complete blood picture (CBC), total cholesterol and triglycerides in mg/dl, urinary protein in mg/24-hours, CK-MB in IU/L, Troponin I in ng/ml, urinary creatinine in mg/dl, estimated glomerular filtration rate (e-GFR) in ml/min/1.73m^2 using MDRD formula). Baseline blood and urine samples were collected 24 hours before PCI. A second sample of urine and blood was obtained 48 hours after the administration of contrast media. The used contrast media in all patients was Iopromide (Ultravist), a low-osmolar iodinated contrast media.

Biochemical Data:

Urinary Dickkopf-3 (DDK-3) (Ur DKK-3) Assay by Enzyme-linked immunosorbent assay (ELISA): Urine samples: 10 ml of urine was collected and stored at (-20 °C) until assayed. Assay Summary: Using Human (DDK-3) ELISA Kit: Shanghai SunRed Biological Technology Co., Ltd, Catalog No. 201-12-5966. Assay Summary: Well plates were pre-coated with

specific antibodies. Then standards or samples were added. Then after washing, and adding Biotinylated antibodies, another washing was done followed by adding HRP-streptavidin. Then, TMB substrate was added and color intensity was measured at 450 nm. Assay range (5ng/L-1000ng/L) (ng/L=pg/ml).

Outcome Measures:

Post-PCI CI-AKI was identified as a rise in serum Cr concentration at 48 hours ≥ 0.3 mg/dl, a 1.5-fold rise from the baseline, or a reduction in the urinary output <0.5 ml/ kg/ hour for more than 6 hours [13].

STATISTICAL ANALYSIS

Statistical Package for Social Science IBM SPSS Statistics 25 was used; (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). The mean, SD, or percentages were used as descriptive statistics for quantitative variables. The Chi-square test was used to test the significance between categorical variables, the Student t-test for continuous variables with normal distribution, and the Mann-Witney U/ Kruskal Wallis test for non-normally distributed variables. Kolmogorov–Smirnov test was used to test the normality of the distribution of data. Paired t-test to compare pre and post-contrast values. The correlation between different parameters and the Ur DKK-3/Ur Cr was assessed by Pearson's correlation. Multivariate logistic regression analysis (odds ratios) was performed to assess factors determining CI-AKI. The diagnostic accuracy of the Ur DKK-3/Ur Cr was assessed with the ROC analysis to determine the cut-off value that best detected post-contrast PCI-CI-AKI, using Youden's index. Then, diagnostic accuracy was determined by the AUC (range 0-1, 0.5 as good as random choice, 0.5-0.7 OK, 0.7-0.8 good, >0.8 very good). Results were considered statistically significant at a p-value ≤0.05 and highly significant at a p-value ≤0.001.

RESULTS

In our study, we included 150 patients, 14% of whom had post-PCI CI-AKI. We used that incidence to categorize the study participants into two groups (CI-AKI group and no CI-AKI group). Regarding patients' characteristics, the mean age was 59 years with a male predominance among all participants. We noticed that CI-AKI was significantly associated with higher age, and body mass index (BMI), in addition to a higher incidence of diabetes mellitus. , on the other hand, gender, hypertension, smoking, history of chronic kidney disease, and cerebrovascular stroke were not remarkably linked to CI-AKI (Table 1).

Concerning baseline laboratory tests, we found that the means of some parameters were higher in a significant way in the group that developed CI-AKI. This included platelet count, random blood sugar (RBS), HbA1C%, CK-MB, and proteinuria. However, no statistically significant difference between both groups regarding other baseline laboratory tests such as hemoglobin, total white cell count, serum total cholesterol and triglycerides, serum uric acid, or troponin I (Table 2).

Table 3 demonstrates a comparison of kidney function tests between both groups, before and after administration of contrast media. There was a significant decline in kidney functions in the CI-AKI group in terms of eGFR and urinary creatinine reduction, and increased serum creatinine, Ur DKK-3, and Ur DKK-3/Ur Cr. Although pre-contrast eGFR, serum, and urinary creatinine did not significantly differ in both groups, Ur DKK-3 and Ur DKK-3/Ur Cr were significantly elevated in patients who developed post-PCI CI-AKI.

Pearson correlation between Ur DKK-3/Ur Cr and demographic characteristics and laboratory data were tested. It revealed a significant positive correlation with each of the following: age, BMI, platelets count, HbA1C%, CK-MB, and pre-and post-contrast serum creatinine. While, in contrast, a significant negative correlation was detected with pre-contrast urinary creatinine and pre and post-contrast eGFR (Table 4).

The multivariate logistic regression analysis (odds ratios) for prediction of CI-AKI showed that significant predictors were pre-contrast Ur

DKK-3/Ur Cr, diabetes mellitus, BMI, age, and pre-contrast HbA1C%, RBS, eGFR, platelets count, proteinuria, and Ur DKK-3, but no significant predictive value for hypertension, smoking, pre-contrast serum, and urinary creatinine (Table 5).

The receiver operating characteristics (ROC) curve for the diagnostic accuracy for pre-contrast Ur DKK-3 showed that at a cutoff: 1176 pg/mg, AUC: 0.72, CI 95% (0.62-083), it has 50% sensitivity, and 59% specificity, with 18% positive predictive value (PPV), and 86% negative predictive value (NPV), for predicting CI-AKI. Regarding Ur DKK-3/Ur Cr, at a cutoff: 18.5 pg/mg, AUC: 0.75, CI 95% (0.67-0.83), it has 87.5% sensitivity, and 64% specificity, with 31% PPV, and 96% NPV, for predicting CI-AKI (Table 6 & Figure 1).

Table 1: Demographic data of studied patients & comparison of both groups.

Variables	**Total** N = 150	**CI-AKI** N = 21 (14**%**)	**No-CI-AKI** N = 129 (86%)	**P-value**
Gender: **Male** **Female**	 127 (84.6%) 23 (15.4%)	 19 (90.4%) 2 (9.6%)	 108 (83.7%) 21 (16.3%)	0.4
Age in years	59 ± 6	60 ± 5.9	55.7 ± 4.7	**0.001***
Body mass index in Kg/m2	28.4 ± 2.1	28.7 ± 2	26.8 ± 1.6	**<0.001****
Smoking: Yes **No**	112 (74.6%) 38 (25.4%)	17 (80.9%) 4 (19.1)	95 (73.6%) 34 (26.4%)	0.4
Diabetes mellitus: Yes **No**	64 (42.7%) 86 (57.3%)	16 (76.1%) 5 (23.8%)	48 (37.3%) 81 (62.7%)	**<0.001****
Hypertension: Yes **No**	138 (92%) 12 (8%)	19 (90.4%) 2 (9.6%)	119 (92.3%) 10 (7.7%)	0.07
Chronic kidney disease: Yes **No**	9 (6%) 141 (94%)	1 (4.7%) 20 (95.3%)	8 (6.2%) 121 (93.8%)	0.6
Cerebrovascular stroke: Yes **No**	6 (4%) 144 (96%)	0 (0) 21 (100%)	6 (4.6%) 123 (95.4%)	0.3

Chi-square test was used for categorical variables, and an independent t-test was used for continuous variables.

Table 2: Laboratory investigations in studied patients & comparison of both groups.

Variables	**Total** N = 150	**CI-AKI** N = 21 (14%)	**No-CI-AKI** N = 129 (86%)	**P-value**
Hemoglobin (g/dl)	11.4 ± 2	11.8 ± 1.7	11.3 ± 2	0.2
Leucocytic count (x10^6/µl)	7.6 ± 2.5	7.6 ± 2.7	7.8 ± 2.3	0.7
Platelets (x10^3/µl)	258.7 ± 105	302.3 ± 98.5	250.4 ± 105	**0.02***
Random blood sugar in mg/dl	166.3 ± 52.2	187.3 ± 51.7	162.3 ± 51.5	**0.03***
HbA1C (%)	7.2 ± 1.4	8.1 ± 1.3	7.0± 1.3	**<0.001****
S. Total cholesterol (mg/dl)	211.6 ± 38	222.8 ± 50.2	209.6 ± 36	0.12
S. Triglycerides (mg/dl)	296.7 ± 119	270.5 ± 95.1	301.7 ± 123	0.2
S. Uric acid (mg/dl)	5.8 ± 2	5.7 ± 2.2	5.9 ± 2	0.7
CK-MB (IU/L)	83.8 ± 54	134.8 ± 72.1	74.1 ± 43.8	**<0.001****
Troponin I (ng/ml)	69.3 ± 27.6	60 ± 31.1	71.1 ± 26.7	0.07
Proteinuria (mg/24 hours)	411.3 ± 520	579.1 ± 53	369 ± 51	**<0.001****

An independent t-test was used for continuous variables.

Table (3): Comparison of pre and post-contrast kidney function tests, Ur DKK-3 & Ur DKK-3/Ur Cr.

Variables	**Total** (N = 150)	**CI-AKI** (N = 21)	**No-CI-AKI** (N = 129)	**P-value**
eGFR (ml/min/1.73m2)				
Pre-contrast	83.2 ± 25.4	92 ± 24.5	81.6 ± 25	**0.06**
Post-contrast	46.1 ± 24.9	15.5 ± 2.2	51.9 ± 22.9	**<0.001****
	<0.001**	**<0.001****	**<0.001****	
Serum Cr (mg/dl)				
Pre-contrast	1.2 ± 0.5	1.1± 0.5	1.2 ± 0.6	0.18
Post-contrast	1.7 ± 1.2	4.2 ± 0.**4**	1.2 ± 0.4	**<0.001****
	<0.001**	**<0.001****	**>0.05**	
Urinary Cr (mg/dl)				
Pre-contrast	65.6 ± 23	73.3 ± 17.9	64.1 ± 23.6	**0.07**
Post-contrast	18.8 ± 13.6	22 ± 10.1	19.2 ± 13.2	0.3
	<0.001**	**<0.001****	**<0.001****	
Ur DKK-3 (pg/mg)				
Pre-contrast	1135.2 ± 388.1	1439.3 ± 364.5	1077.3 ± 366	**<0.001****
Post-contrast	3831.5 ± 335.4	4646.3 ± 252.5	3676.4 ± 364.4	**<0.001****
	<0.001**	**<0.001****	**<0.001****	
Ur DKK-3/Ur Cr (pg/mg)				
Pre-contrast	17.4 ± 3.2	19.6 ± 1	17 ± 3.3	**<0.001****
Post-contrast	223.3 ± 35	226 ± 38.1	209.5 ± 10.6	**0.03***
	<0.001**	**<0.001****	**<0.001****	

An independent t-test was used for continuous variables. Paired t-test for pre and post-contrast values.

Table 4: Correlation between pre-contrast Ur DKK-3/Ur Cr and other parameters.

Variables	**r**	**P-value**
Age in years	0.3	**0.007***
Body mass index in kg/m^2	0.2	**0.01***
Pre-contrast investigations	**r**	**P-value**
Platelets (x10^3/µl)	0.2	**0.02***
HbA1C %	0.2	**0.002***
CK-MB ng/ml	0.2	**0.03***
Proteinuria (mg/24 hours)	0.1	**0.06**
eGFR ml/min/1.73m^2	- 0.3	**<0.001****
Serum Cr mg/dl	0.3	**<0.001****
Urinary Cr mg/dl	- 0.2	**0.01***
Post-contrast investigations	**r**	**P-value**
eGFR ml/min/1.73m^2	- 0.2	**0.004***
Serum Cr mg/dl	0.2	**0.002***
Urinary Cr mg/dl	- 0.05	0.5

Pearson correlation efficient was used.

Table 5: Multivariate logistic regression analysis (odds ratios) for predictors of post-PCI CI-AKI.

Variables	OR	CI (95%)	P-value
Age in years	1.6	0.8 – 9.0	**0.01***
Body mass index in kg/m^2	2.9	2.0 – 16.0	**0.003***
Diabetes mellitus	5.4	1.7 - 11.9	**<0.001****
Hypertension	1.0	1.0- 10.0	0.09
Smoking	1.1	1.0 – 10.0	0.9
Pre-contrast investigations	**OR**	**CI (95%)**	**P-value**
Random blood sugar in mg/dl	1.2	0.7 – 20.0	**0.01***
HbA1C%	1.7	1.0- 3.0	**<0.001****
Platelets (x10^3/µl)	1.2	1.1-1.9	**0.01***
Proteinuria (mg/24 hours)	1.2	1.0-1.3	**0.04***
Serum Cr in mg/dl	1.1	0.9 – 22.0	**0.07**
Urinary Cr in mg/dl	1.0	0.5 – 16.0	0.4
eGFR in ml/min/1.73m^2	1.7	1.0 – 5.0	**0.001***
Ur DKK-3 in pg/mg	1.1	1.01-1.4	**0.001***
Ur DKK-3/Ur Cr in pg/ml	6.0	1.9 – 19.0	**<0.001****

OR: odds ratio. CI: confidence interval.

Table 6: Diagnostic accuracy of pre-contrast Ur DKK-3 & Ur DKK-3/Ur Cr for predicting post-PCI CI-AKI.

Variables	Cutoff point	PPV	NPV	Sensit.	Specif.	AUC 95% CI	P-value
Ur DKK-3 in pg/mg	1176	18%	86%	50%	59%	0.72 (0.62-0.83)	**0.01***
Ur DKK-3/Ur Cr in pg/mg	18.5	31%	96%	87.5%	64%	0.75 (0.67-0.83)	**<0.001****

PPV: positive predictive value; NPV: negative predictive value; Sensit. Sensitivity; Specif. Specificity; AUC: area under the curve; CI: confidence interval.

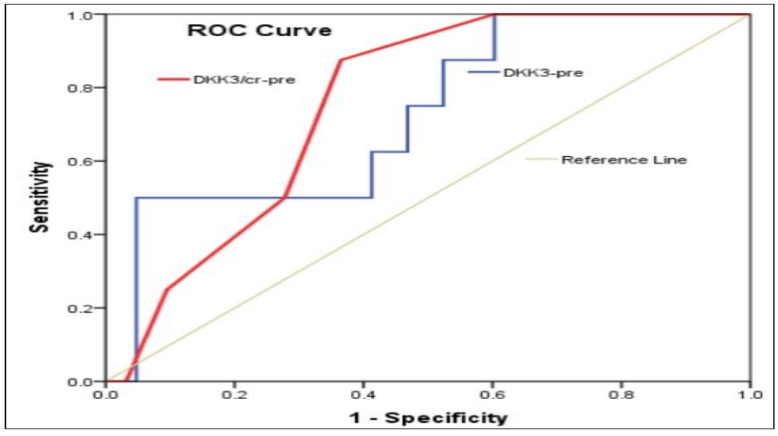

Figure 1: ROC curve of pre-contrast Ur DKK-3 & Ur DKK-3/Ur Cr accuracy for predicting post-PCI CI-AKI.

DISCUSSION

In the current study, we found that measuring the pre-contrast Ur DKK3/Ur Cr, in patients undergoing PCI, predicted their development of CI-AKI after PCI, with a good predictive value. This prospective cohort study included 150 patients who had PCI, and 14% of them developed CI-AKI. Davenport et al. mentioned that CI-AKI has a lower incidence than reported cases, mostly caused by co-incident nephrotoxic causes rather than the contrast media itself and that the term contrast-associated AKI (CA-AKI) is preferred [14].

Patients who developed post-PCI CI-AKI had older age, higher BMI, and a higher percentage of diabetes mellitus than those with no-CI-AKI. This agrees with Qin et al. who found that the incidence of CI-AKI was higher in diabetic patients, with older age and higher blood pressure [15].

The pre-contrast platelets count, RBS, HbA1C%, CK-MB, and proteinuria were significantly increased in patients with CI-AKI compared to those with no-CI-AKI. This agrees with Vlachopanos et al. who stated that the presence of diabetes mellitus and diabetic nephropathy are predictors for CI-AKI and mortality after contrast [16]. Also, Tao et al. found that CI-AKI after cerebrovascular angiography was present in 4.2%, and the risk was five times higher with proteinuria [17].

Post-contrast eGFR was significantly lower, and post-contrast serum creatinine was significantly increased in patients with CI-AKI compared to those with no-CI-AKI. This agrees with the definition of CI-AKI as an increase in serum creatinine ≥ 0.5mg/dl within 48-72 hours of contrast media, or ≥ 25% of the pre-contrast level, after exclusion of other causes of renal damage [18], and a rise ≥0.3 mg/dL in serum creatinine 48 hours post-PCI predicts overall mortality [19].

Contrast agents may cause fluctuations in renal blood flow, through vasoactive substances, an increase in blood viscosity, microvascular thrombosis, and an increase in osmotic force during its excretion, with a reduction in the GFR [20]. In the present study, low-osmolar iodinated contrast was used, however, Zhao et al. found that although the use of low-osmolar contrast was associated with fewer side effects, the incidence of CI-AKI did not differ from iso-osmolar contrast use in diabetic patients [21].

Before contrast administration, there was no significant difference between both groups as regards eGFR, serum creatinine, and urinary creatinine. Connolly et al. stated that although serum creatinine is widely used as a marker for CI-AKI, its delay in rising after kidney injury limits its value as an early marker. However, higher pre-contrast creatinine and lower GFR were associated with CI-AKI [22].

The Dickkopf-3 (DDK-3) glycoprotein, a tubular-derived molecule, with immune-suppressive, and profibrotic effects, has both therapeutic and diagnostic roles, and its urinary levels may be used as a marker for AKI [23]. We found that in patients with CI-AKI, the pre-contrast urinary DKK3 (Ur DKK-3) (1439.3 ± 364.5), and urinary DKK3/urinary creatinine) Ur DKK-3/Ur Cr (19.6 ± 1) were significantly increased compared to those without CI-AKI (1077.3 ± 366), and (17 ± 3.3), with no difference as regards pre-contrast urinary creatinine between the 2 groups.

This agrees with Seibert et al. who found that CI-AKI patients had a higher pre-contrast Ur DKK-3/Ur Cr (7.5 pg/mg) than those without CI-AKI (2.0 pg/mg) [12]. Piek et al. reported that plasma DKK-3 is not as accurate as urinary DKK-3 for predicting AKI, as it is secreted from various tissues. Ur DKK-3 levels predicted the progression of chronic kidney disease (CKD), tubular fibrosis, and the development of AKI after cardiac surgery [24]. Roscigno et al. found that adding baseline Ur DKK-3/Ur Cr to the scores by Mehran, and Gurm improved their predictive value for post-PCI CI-AKI [25].

Patients with CI-AKI had higher post-contrast serum creatinine, Ur DKK-3, and Ur DKK-3/Ur Cr, and lower urinary creatinine and eGFR than pre-contrast levels. DKK-3 is secreted in urine under tubular stress and may serve as a non-invasive diagnostic biomarker for tubulo-interstitial fibrosis, and acute GFR loss [26].

Moreover, Ur DKK-3/Ur Cr more than 1000 pg/mg was associated with a reduction of the GFR [27]. Also, Torigoe et al. concluded that measuring 24-hour levels of Ur DKK-3 can predict the loss of residual renal function [28].

Pre-contrast (baseline) Ur DKK-3/Ur Cr was positively related to age, BMI, pre-contrast platelets count, HbA1C%, CK-MB, and serum creatinine, and negatively related to pre-contrast urinary creatinine, but no relation with pre-contrast proteinuria. Schafer et al. found that high urinary levels of DKK-3 with resistant hypertension were associated with higher eGFR loss [29]. Also, Luft et al. stated that Ur DKK-3/Ur Cr levels are increased in patients with CKD with GFR reduction, and predicted AKI after cardiovascular surgery [30]. Schunk et al. found that DKK-3 is expressed in other organs, and urinary DKK-3 may also result from glomerular injury, from filtered plasma, and may correlate with albuminuria in CKD patients [31].

The independent predictors for CI-AKI were pre-contrast Ur DKK-3/Ur Cr (OR 6.0), diabetes mellitus (OR 5.4), and pre-contrast HbA1C% (OR 1.7), BMI (OR 2.9), pre-contrast eGFR (OR 1.7), age (OR 1.6), pre-contrast random blood sugar (OR 1.2), platelets count (OR 1.2), proteinuria (OR 1.2), and pre-contrast Ur DKK-3 (OR 1.1). This agrees with Schunk et al. who concluded that Ur DKK-3/Ur Cr levels >471 pg/mg before cardiac surgery were associated with higher AKI (OR 1·94), (p=0·026) [11]. Whereas, Mo et al. found 3 independent CI-AKI risk factors in patients with normal kidney function; baseline serum uric acid, CK-MB, and NT-proBNP (brain-natriuretic peptide) [32].

The ROC curve for the diagnostic accuracy for pre-contrast Ur DKK-3 showed that at a cutoff: 1176 pg/mg, AUC: 0.72, CI 95% (0.62-083), it has 50% sensitivity, and 59% specificity, with 18% PPV, and 86% NPV, for predicting post-PCI CI-AKI. Regarding Ur DKK-3/Ur Cr, at a cutoff: 18.5 pg/mg, AUC: 0.75 (good), CI 95% (0.67-0.83), it has 87.5% sensitivity, and 64% specificity, with 31% PPV, and 96% NPV, for predicting CI-AKI.

Preoperative urinary DKK3 predicted postoperative AKI after cardiac surgery with an AUC of
0.783 [33]. Similarly, Kullmar et al. concluded that the AUC for pre-operative urinary DKK-3 for predicting moderate and severe AKI was 0.629 [34].

Early prediction of patients at risk of developing post-PCI CI-AKI, may allow the use of preventive
measures [35], thus the availability of easy and low-cost early markers is mandatory [36]. Risk factors for post-PCI CI-AKI include older age, diabetes mellitus, anemia, congestive heart failure,
kidney impairment, hemodynamic instability, and the volume of contrast media [37].

Lanktree et al. stated that Ur DKK3 alone (OR 1.65–1.94), cannot predict AKI with high accuracy, and combining Ur DKK-3 levels with other biomarkers can improve its predictive value [38]. Sanchez-Alamo et al. concluded that Ur DKK-3/Ur Cr can be a more valuable marker for kidney disease, compared to serum creatinine and proteinuria [39]. Preventive measures against post-PCI CI-AKI include prediction of patients at risk, adequate hydration, avoidance of nephrotoxic agents, using low or iso-osmolar iodinated contrast, and reducing contrast dose [40].

To our knowledge, this is the first study to investigate the prognostic role of pre-contrast Ur DKK-3/Ur Cr in the prediction of post-PCI CI-AKI among Egyptian patients. The main limitation of this study was the limited number of patients. More extended studies on larger numbers of patients, and their follow-up for longer time could be more informative.

CONCLUSIONS

Increased pre-contrast Ur DKK-3/Ur Cr may independently predict patients at risk for post-PCI CI-AKI. The availability of an easy and low-cost pre-contrast urinary marker to identify patients at risk for CI-AKI may allow measures for its prevention.

Conflicts of Interest: None
Financial Disclosures: None.

Contributors: All authors participated in all steps of this research and agreed to publish it. NS, SA, NM, AM, and GS participated in the study design, collection of samples, statistical analysis, and writing and reviewing the paper. In addition, NM had made the laboratory assays.

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ABBREVIATIONS:

CI-AKI	Contrast-induced acute kidney injury
eGFR	Estimated glomerular filtration rate
S. Cr	Serum Creatinine
Ur DKK-3	Urinary Dickkopf3
Ur DKK-3/Ur Cr	Urinary Dickkopf3/urinary creatinine
PCI	Percutaneous coronary intervention (PCI)
MDRD	Modification of diet in renal disease
CKD	Chronic kidney disease
CVS	Cerebrovascular stroke

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