Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2025.349376.3770 Volume 31, Issue 3, March. 2025
Manuscript ID: ZUMJ-2412-3770
DOI: 10.21608/zumj.2025.349376.3770

ORIGINAL ARTICLE

Serum Kidney Injury Molecule-1 and Cytochrome C as Biomarkers for Early Detection of Contrast-Induced Nephropathy in Elderly Patients with ST-Elevation Myocardial

Ahmed Salah Amin Al Allam[1], Mohammed Mohammed Mohammed Hassaan[1], Zeinab Maher Mohammed[1*], Malak Emad Samy[2], Hala M. Allam[1], Haytham Kamal Ahmed Mahrous[3], Ahmed Said Ibrahim Eldamanhory [4], Mahmoud M. Magdy[1]

[1]Internal Medicine, Faculty of Medicine, Zagazig University
[2]Medical student, Faculty of Medicine, Zagazig University,
[3]Clinical pathology, Faculty of Medicine, Zagazig University,
[4]Cardiology, Faculty of Medicine, Zagazig University,

[*]**Corresponding author:**
Zeinab Maher Mohammed

Email:
zmahr8366@gmail.com

Submit Date: 31-12-2024
Accept Date: 02-02-2025

ABSTRACT

Background: Research indicates a high correlation between contrast-induced nephropathy (CIN) as well as an elevated risk of major adverse cardiovascular events (MACE). Kidney Injury Molecule 1 (KIM-1) as well as cytochrome c (Cyt c) are two examples of new renal biomarkers that are demonstrating promising capabilities for the early revealing of CIN. This study aimed to evaluate the potential of KIM-1 and Cyt c as early biomarkers for detection of CIN before creatinine in elderly patients who underwent primary percutaneous coronary intervention (PCI) following ST-elevation myocardial infarction (STEMI).

Methods: Sixty elderly patients were included in this case control study patients 40 of them with clinical, biochemical evidence of STEMI who received primary PCI treatment at the cardiology Department who then classified into 3 groups: Group 1 consists of 20 healthy controls; Group 2 consists of 20 STMI patients who acquired CIN after primary PCI; and Group 3 consists of 20 STMI patients who did not exhibit this complication following primary PCI. We measured the serum levels of KIM-1 and Cyt c using an enzyme-linked immunosorbent assay (ELISA).

Results: When comparing the groups' levels of KIM-1 and Cyt c at baseline and before 1st 24 hours after contrast delivery, statistically substantial changes were found. In the group with CIN, these biomarkers were substantially higher ($p<0.001$). Blood urea nitrogen (BUN), KIM-1, Cyt c and left ventricular ejection fraction (LVEF) were substantial predictors for CIN ($p=0.003$, <0.001, <0.001, <0.001 respectively). In the diagnosis of CIN, a Cyt c cutoff value of >0.635 resulted in a sensitivity of 79.3%, specificity of 80%, and a negative predictive value (NPV) of 89.1%. On the other hand, for KIM-1, a cutoff value of >9.5 produced a sensitivity of 80%, specificity of 83%, PPV of 75%, and NPV of 90%.

Conclusion: Serum cytochrome c and kidney damage molecule-1 could be used to predict contrast induced nephropathy before creatinine among elder patients having PCI intervention following an ST-elevation myocardial infarction.

Keywords: Serum Kidney Injury Molecule-1, Cytochrome C, ST-Elevation Myocardial Infarction, Contrast-Induced Nephropathy, Elderly.

INTRODUCTION

Contrast-Induced Nephropathy (CIN) is an acute kidney injury (AKI) that occurs after the utilization of iodinated contrast media (CM) during imaging procedures or interventions, such as primary percutaneous coronary intervention (PCI) [1]. Hospitalizations, deaths, and morbidity are all worsened by contrast-induced nephropathy, which occurs when diagnostic or therapeutic vascular operations use intravenous or intra-arterial contrast material (CM) [2].

With an incidence rate of 1% to 2% in the general hospitalized population and up to 50% among high-risk patients, contrast-induced acute kidney injuries account for approximately 33% of all hospital-acquired AKI [3]. Previous studies have shown that the general population's age is a significant risk factor for CIN [4].

Diabetic problems, chronic renal failure, and contrast use are additional risk factors for CIN development; strategies to prevent this include hydration therapy, medication as directed, and issue monitoring [5]. In general, coronary artery disease is more complex in people aged 75 and up, which raises the risk of complications and dangers related to STEMI [6].

Some new renal biomarkers, such as cytochrome c and kidney damage marker 1, have been suggested as potential early biomarkers of CIN. [7]. When the proximal tubule of the apical membrane sustains damage, the expression of the type-1 transmembrane protein KIM-1 changes [8]. A large body of research indicates that KIM-1, particularly in cases of AKI , is both a sensitive and specific diagnostic of kidney damage and a predictive marker [9].

Cytochrome c is an essential hemoprotein involved in oxidative phosphorylation; it normally forms an association with the inner mitochondrial membrane's outer surface, where it binds to cardiolipin [10]. Apoptosis is triggered when the mitochondrial membrane releases cyt c into the cytoplasm, which in turn activates caspase 3. Research has linked systemic inflammatory response syndrome, myocardial infarction, AKI as well as high levels of circulating cyt c [11].

The KIM-1 and Cyt c together, could offer a comprehensive understanding of CIN pathogenesis and serve as early, reliable biomarkers for predicting and managing CIN in elderly STEMI patients undergoing PCI. Therefore, this study aimed to evaluate the potential of KIM-1 and Cyt c as early biomarkers for detection of CIN before creatinine in elderly patients who underwent primary percutaneous coronary intervention following ST-elevation myocardial infarction.

METHODS

Between October 2022 to October 2024, we performed this case-control study that included 60 elderly patients 40 of them with clinical, biochemical evidence of STEMI who received primary PCI treatment in the cardiology Department. The study was carried out in Cardiology care unit (CCU), and Internal Medicine Departments Zagazig University Hospitals., Faculty of Medicine, and the technical part was done at clinical pathology Department in Zagazig University.

Written informed consent was obtained from all participants after explaining the procedure and medical research. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. This study was carried out after the approval of the Institutional Review Board (IRB) (IRB#9896-3-10-2022).

Cases with the following criteria were included: those aged ≥ 65 years, from both sexes 40 of them with clinical, biochemical evidence of STEMI, 20 were healthy control individuals with matched age and sex. Group1: Healthy control their numbers were 20. Group 2: patients with STEMI after primary PCI developed CIN and their numbers were 20. Group 3: patients with STEMI after primary PCI not developed CIN and their numbers were 20.

Cases with the following characteristics were excluded: patients who had acute metabolic disturbance like (acute sever infection, hyperosmolar status, or ketoacidosis), chronic renal disease or on dialysis, autoimmune disease, malignant cancer, decompensated liver cell failure, or acute cerebral infarction. Normal kidney function is assessed primarily by the estimated glomerular filtration rate (eGFR) and serum creatinine levels. According to the kidney disease:

A complete medical history involving age, sex, diabetes mellitus, hyperlipidemia, hypertension, as well as smoking status. A complete physical examination, including anthropometric measurements (height and weight) and resting brachial blood pressure (obtained using a mercury sphygmomanometer), will be performed on each participant.

Improving Global Outcomes (KDIGO) guidelines, normal kidney function is indicated by an eGFR of ≥90 mL/min/1.73 m². The normal range of

serum creatinine varies depending on age, sex, and muscle mass, with typical values ranging from 0.7–1.3 mg/dL for men and 0.6–1.1 mg/dL for women. In older adults, the normal range may be slightly lower due to reduced muscle mass associated with aging [11].

Contrast-induced nephropathy, also known as contrast-associated acute kidney injury is defined as an absolute increase in serum creatinine by ≥0.5 mg/dL or a relative increase of ≥25% from baseline within 24–72 hours after the administration of iodinated contrast media, as outlined by KDIGO guidelines. Alternatively, a ≥25% decrease in eGFR from baseline within the same timeframe can also indicate CIN. Typically, CIN peaks within 3–5 days and resolves within 7–10 days if no underlying kidney injury persists. Postprocedural kidney function was closely monitored using eGFR, as a drop of >25% in eGFR after contrast administration may indicate contrast-induced nephropathy or acute kidney injury. Monitoring is particularly crucial within the first 24–48 hours, as creatinine levels typically begin to rise during this period following contrast exposure, allowing for the early detection of renal impairment [12].

Blood tests included hemoglobin A1c, triglycerides, total cholesterol, HDL-c, and LDL-c; creatinine, blood urea nitrogen, cardiac troponin I, CK-MB, and estimated glomerular filtration rate (eGFR) using the MDRD equation; and liver function tests, coagulation profile, and complete blood count were also part of the laboratory evaluations.

***Measurement of serum Kidney Injury Molecule-1 (Kim-1) ELISA*:** using Human Kidney injury molecule 1(Kim-1) ELISA Kit, (Catalogue No. 201-12-1100 Shanghai; China). To find the assay sensitivity, which is the minimum detectable protein concentration above background, we looked at twenty zero-standard duplicates and calculated the concentration that was two standard deviations below the mean optical density. With a reference interval of 0.20-0.35 ng/mL, the assay ranged from 0.1-10 ng/mL. In the context of contrast-induced nephropathy, serum creatinine levels are known to rise approximately 24 to 48 hours post-procedure. However, KIM-1 levels could increase earlier, so it was assessed at baseline and before 24 hours post-procedure.

***Measurement of serum Cytochrome C (Cyt c) ELISA*:** using Cytochrome C (Cyt c) Kit Catalogue No. 201-12-3590 Shanghai; China: Using a two-standard-deviation-below-mean-optical-density (OD50) calculation, the assay was able to determine that the minimum detectable protein concentration (LOD) was 0.225 ng/mL. With a reference interval of 0.25-0.4 ng/mL, the analytical measurement range of the assay extended from 0.3 to 70 ng/mL

***Echocardiography*:** We used an echocardiographic Machine: Siemens – Acuson X300 (made in India) with measurements of Dimensions, ejection fraction (EF) and fractional shortening (FS).

***ECG measurement*:** We obtained usual 12-lead ECGs with a paper speed of 25 mm/s and a voltage calibration of 10 mm/mV before and one day after the surgery.

The CHA_2DS_2-VASc score was used to determine the risk of thromboembolic complications in patients with NVAF; this score has shown to be useful in predicting the prognosis of many cardiovascular diseases [13].

Statistical analysis

All statistical tests were executed using IBM's 2021 SPSS (Statistical Package for the Social Sciences) version 28. We compared the absolute frequencies of categorical variables using chi-square and, when needed, Monte Carlo testing. To ensure that the assumptions employed in parametric testing were correct, the Kolmogorov-Smirnov test was administered. For quantitative variables, the available statistics allowed us to choose between medians, interquartile ranges, standard deviations, and means. Using one-way ANOVA for normal data and the Kruskal Wallis test for non-normal data, we compared quantitative data across many groups. We employed pairwise comparison and Tukey HSD to isolate variations between each group when a substantial variation was detected. Finding the best cutoff value for a quantitative parameter to diagnose a specific health risk was done using the ROC curve. In order to determine the nature and direction of the link between the two variables, the Spearman rank correlation coefficient was used. The independent factors that were found to be connected with the dependent component were measured using linear regression analysis. A significance level of $P<0.05$ was selected for statistical analysis. There was determined to be a highly substantial variation, presuming $p\leq 0.001$.

RESULTS

Table 1 shows that the CIN group had higher CHA_kDS_k-VASc ratings, which is statistically substantial (p<0.001). With a median (IQR) of 54.27 (45-69) and a p-value of 0.007, the ejection fraction (EF) decreased statistically in the CIN group (Table 2). The values of cardiac enzymes were considerably higher in Groups 2 and 3 (p<0.05) compared to Group 1, as shown in Table 3.

The CIN group had substantially greater creatinine and BUN levels compared to the non-CIN group, even though eGFR was lower in the CIN group (P value <0.001). The two groups that were tested showed notable disparities in BUN, Creatinine, and eGFR (p<0.001). (Table 4).

There were substantial variations between the groups at both the beginning and before 1st 24 hours after contrast injection, with the CIN group showing higher levels of KIM-1 and Cyt c (p<0.001). (Table 5).

Substantial predictors of CIN were found in the univariate regression analysis to be Cyt c, BUN, KIM-1, CHA_2DS_2-VASc score, and LVEF, with p-values of 0.005, <0.001, <0.001, and 0.002, respectively. A substantial predictor for CIN in multivariate regression analysis was LVEF, followed by blood urea nitrogen (BUN), kidney injury marker 1 (KIM-1), and Cyt c (p=0.003, <0.001, <0.001, <0.001 respectively). (Table 6).

Using a CHA_2DS_2-VASc score cutoff of >4 yielded 85.71% sensitivity, 84.78% specificity, and with 95.1% NPV and 63.2% PPV for CIN diagnosis. A cytochrome c (Cyt c) cutoff of >0.635 resulted in 79.3% sensitivity, 80% specificity, 73.7% PPV, and 89% NPV. Finally, a KIM-1 cutoff of >9.5 demonstrated 80% sensitivity, 83% specificity, 75% PPV, and 90% NPV for CIN diagnosis (Table 7, Supplementary Figure 1).

Table 1: Demographic basal data of studied patients:

		Group(1) Healthy control (n=20)	Group(2) CIN (n=20)	Group(3) No CIN (n=20)	t-test	LSD	P
Sex	**Male (N&%)**	50%)(10	50%)(10	10(50%)	0.175	0.89 [1] 0.74 [2] 0.62 [3]	0. 617
	Female	50%)(10	50%)(10	50%)(10			
Age (Years) (Mean±SD)		70.6 ± 5.5	69 ± 4.1	71.6 ± 6.5	0. 185	0.09 [1] 0.64 [2] 0.22 [3]	0.634
BMI (Kg/m2) (18.5 – 24.9) (Mean±SD)		26.2 ± 2	25.5±2.2	26.2 ± 1.9	0.165	0.06 [1] 0.35 [2] 0.33 [3]	0.426
CHA2DS2 VASC score		2 [1- 2]	4 [4- 5]	1 [1-2]	432.3	0.01* [1] 0.٠5* [2] 0.٠3* [3]	< 0.001
Previous MI (N&%)		0(0%)	11(55%)	10 (50%)	0. 115	0.02* [1] 0.٠3* [2] 0.73 [3]	0.834
Smoking (N& %)		3(15%)	12(60%)	10(50%)	0. 275	0.81 [1] 0.65[2] 0.73 [3]	0.764
DM	**Yes**	0(0%)	13 (65%)	8(40%)	0.151	0.04*[1] 0.01*[2] 0.63 [3]	**<0.05**
	No	100(20%)	7 (35%)	12(60%)			
HTN	**Yes**	0(0%)	12(60%)	7(35%)	0.160	0.01* [1] 0.05*[2] 0.93[3]	**<0.05**
	No	100(20%)	8(40%)	13(65%)			

LSD: least significant difference P1: Group 1 versus Group 2 P2: Group 1 versus Group 3 P3: Group 2 versus Group 3 *: Significant

Table 2: Echocardiographic data among the study groups

ECHO parameter	*Group(1) Healthy control (n=20)*	*Group(2) CIN group (n=20)*	*Group(3) No CIN (n=20)*	*Test of Sig. U*	*LSD*	*P*
LVEDD (mm) Min. – Max. Median (IQR)	4.6-5.1 5.15 (4.9-5.9)	5.1-6.1 5.6 (5.17-6.02)	4.3-7.1 5.15 (4.7-5.8)	58	0.001* 1 0.03 * 2 0.69*3	**<0.05**
LVESD (mm) Min. – Max. Median (IQR)	2.9-5.8 3.4 (3-4.52)	2.9-3.8 3.4 (2.97-3.75)	2.7-5.5 3.2 (3-4.12)	86	0.03* 1 0.05*2 0.80 3	**<0.05**
EF (%) Min. – Max. Median (IQR)	60 – 79 67.06 (50-70)	34 -45 35.2 (32-48)	39 – 73 60.06 (39- 74)	-2.748	0.04* 1 0.05*2 0.01* 3	**<0.05**

LSD: least significant difference P1: Group 1 versus Group 2 P2: Group 1 versus Group 3 P3: Group 2 versus Group 3 *: Significant.
U: Mann Whitney test: p-value >0.05: Non-significant (NS); p-value <0.05: Significant(S); p-value< 0.01: highly significant (HS).

Table 3: CPK – MB and Troponin, and baseline kidney function tests of studied groups using independent t-test:

		Group(1) Healthy control (n=20)	**Group(2) CIN group (n=20)**	**Group(3) No CIN (n=20)**	**t-test**	**LSD**	**P**
CPK – MB Up to 6.22 ng/ml		5.6 ± 1.4	62.3 ± 0.5	57.8 ± 1.6	1.8	0.05* 1 0. 3* 2 0.73 3	<0.05
Troponin Up to 100 pg/ml		80.8 ± 19.7	922.1 ± 16.1	890.8 ± 20.7	1.0	0.04* 1 0.05* 2 0.63 3	<0.05 S
S.creat (mg/dl) baseline	**Mean ± SD**	0.89 ± 0.15	0.72 ± 0.22	0.79 ± 0.25	-0.688	0.71 1 0.24 2 0.67 3	0.493
	Range	0.6 - 1.3	0.5 - 1.5	0.5 - 1.5			
eGFR (ml/min)	**Mean ± SD**	93.52 ± 11.3	91.55 ± 12.6	89.72 ± 12.3	-0.232	0. 88 1 0. 28 2 0. 59 3	0.817
	Range	72.49 - 116.50	64.91 - 114.55	70.69 - 114.55			
BUN (mg/dL)	**Mean ± SD**	6. 1 ± 7.28	20.15 ± 6.08	18.91 ± 9.28	0.247	0.02* 1 0. 43 2 0.94 3	0.657
	Range	6.4 – 40	11.5 - 40	9.1 - 39.5			

LSD: least significant difference P1: Group 1 versus Group 2 P2: Group 1 versus Group 3 P3: Group 2 versus Group 3 *: Significant

Table 4: kidney function tests of the studied groups after 48 hours of contrast injection

		Group(2) CIN group (n=20)	**Group(3) No CIN (n=20)**	**P value**
Creatinine (mg/dL)	**Mean ± SD**	2.11 ± 0.98	0.91 ± 0.19	**<0.001***
	Range	1.32 - 3.75	0.52 - 1.29	
BUN (mg/dL)	**Mean ± SD**	51.78 ± 27.65	19.25 ± 7.11	**<0.001***
	Range	21.2 – 136	3.6 - 46.4	
eGFR ($mL/min/1.73m^2$)	**Mean ± SD**	36.87 ± 13.02	80.04 ± 26.84	**<0.001***
	Range	23.71 - 50.55	63.19 - 114.55	

BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, *: significant as P value ≤ 0.05

Table 5: Specific biomarkers basal data and before 24 hours of contrast injection of studied groups using independent t- test

	Group(1) Healthy control (n=20)	Group(2) CIN group (n=20)	Group(3) No CIN (n=20)	t-test	LSD	P
KIM-1(ng/mL)	0.25 (0.20-0.35)	10.02 (9.53-15.90)	4.41 (3.41-9.03)	2.34	0.03* 1 0.57 2 0.04* 3	<0.001 HS
Cyt c (ng/mL)	0.2 (0.25-0.4)	0.55±0.08	0.50±0.1	2.5	0.01* 1 0.73 2 0.02* 3	<0.001 HS
Before 1st 24 hours of contrast injection						
		Group(2) CIN group (n=20)	**Group(3) No CIN (n=20)**	**t-test**	**LSD**	**P**
KIM-1(ng/mL)		18.02 (12.53-24.90)	9.41 (7.41-13.03)	2.34	0.01* 1 0.53 2 0.01* 3	<0.001 HS
Cyt c (ng/mL)		0. 95±0.04	0. 78±0. 3	2.5	0.01* 1 0.33 2 0.01* 3	<0.001 HS

LSD: least significant difference P1: Group 1 versus Group 2 P2: Group 1 versus Group 3 P3: Group 2 versus Group 3 *: Significant

Table 6: Logistic regression analysis of different parameters in relationship with the development of CIN in studied groups (n=60):

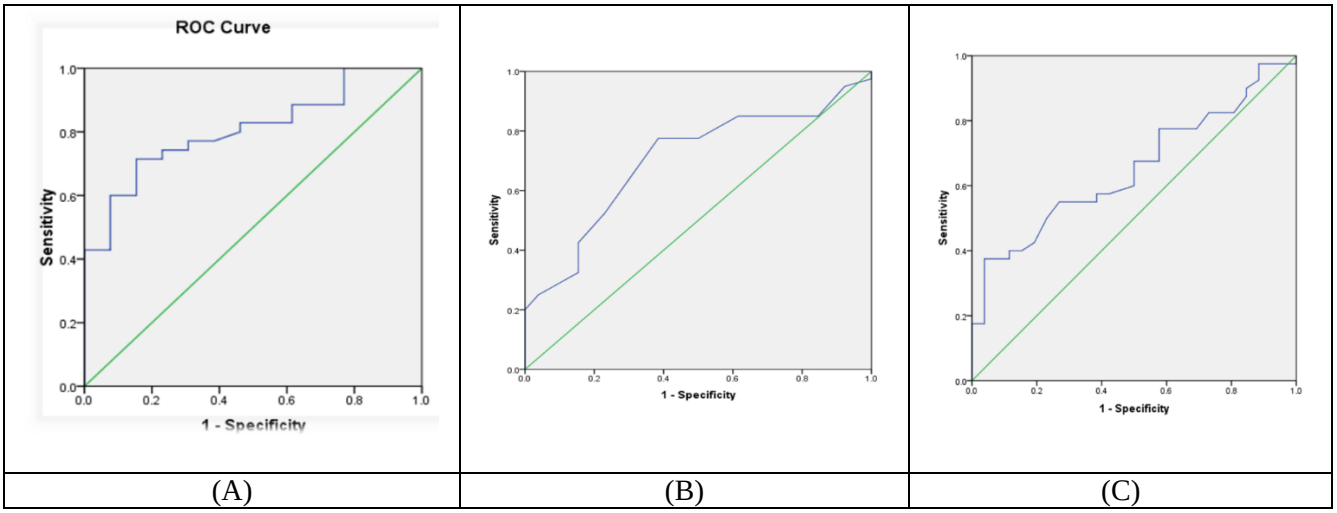
	Univariate		Multivariate	
	OR	**P value**	**OR**	**P value**
Troponin I	1	0.708	1	0.678
Creatinine	1.18	**0.016***	1.34	0.147
KIM-1(ng/mL)	2.11	**<0.001***	1.76	**<0.001***
Cyt c (ng/mL)	1.78	**<0.001***	1.65	**<0.001***
LVEF	1.54	**0.002***	1.96	**<0.001***
CHA_2DS_2VASC score	1	**0.005***	1	0.604
CPK_MB	3.46	0.195	1.42	0.809
BUN (mg/dL)	1.11	**<0.001***	1.13	**0.003***
eGFR (mL/min/1.73m^2)	0.97	0.061	0.97	0.222

BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, OR: odds ratio, CI: confidence interval, *: significant as P value ≤ 0.05

Table 7: shows the validity of the studied marker as predictors of CIN:

Predicted outcome	*Cut-off*	*AUC*	*Sensitivity %*	*Specificity %*	*PPV %*	*NPV %*	*accuracy*
CHA_2DS_2VASc score	>4	0.857	85.71%	84.78%	63.2%	95.1%.	80.5%
***KIM-1* (*ng/mL*)**	>9.5 ng/mL	0.843	80	83	75	90	92.0 %
Cyt c (ng/mL)	>0.635	0.761	80	60.1	73.7	98	91%

AUC: Area Under curve, PPV: positive predictive value, NPV: Negative predictive value,



(A) (B) (C)

Supplementary Figure 1: ROC curve for accuracy of (A) KIM-1 (B) CHA2DS2VASc score, (C) Cyt c in diagnosis of CIN. KIM -1: Kidney Injury Molecule-1, Cyt c: Cytochrome c, CIN: contrast-induced nephropathy

DISCUSSION

While primary percutaneous coronary intervention has substantially improved outcomes for STEMI patients, it has also significantly increased the prevalence of contrast-induced nephropathy. Reason being, it's not always easy to spot individuals who are particularly vulnerable before treatments begin, allowing for necessary safety measures to be done. The emergency room has special difficulties, such as dealing with patients who are haemodynamically unstable and who need larger quantities of contrast owing to a STEMI. Recently, two new renal biomarkers—kidney injury molecule 1 and cyst c—have surfaced as potential early indicators of CIN [7].

The incidence and severity of CIN was strongly linked with KIM-1 and Cyt c in older STEMI patients receiving Primary PCI. When used together, these early biomarkers have the potential to improve diagnostic precision, open the door to earlier intervention, and boost patient outcomes [7].

In the current study, there were no statistically substantial variations in terms of age, sex, or BMI between the groups in this investigation. The CIN group, however, had a substantially higher $CHA_kDS_■$ -VASc score than the other groups. Furthermore, compared to the control group, the CIN and No CIN groups had substantially greater prevalence of hypertension and diabetes mellitus.

The association between higher CHA2DS2-VASC scores and increased prevalence of diabetes mellitus (DM) and hypertension (HTN) in the CIN group likely arises from shared mechanisms that heighten renal vulnerability. Both DM and HTN contribute to chronic kidney disease, microvascular damage, and impaired renal function, making the kidneys more susceptible to contrast agents used during PPCI. These conditions also promote endothelial dysfunction, oxidative stress, and chronic inflammation, which further exacerbate CIN. As a result, patients with higher CHA2DS2-VASC scores face increased risk of CIN due to compromised renal resilience and susceptibility to injury [15,16].

Patient risk factors for CIN were studied by Abdel-Ghany et al. [17] during primary percutaneous coronary intervention in patients with STEMI. In this investigation, they discovered a substantial variance in CHA_kDS_k-VASc scores between the groups that had and did not have CIN ($p < 0.001$).

According to a meta-analysis by Song et al. [18], the risk of contrast-induced acute kidney injury is at least twice as high in older individuals. Similarly, a study by Ye et al. [19] identified age and comorbidities, including hypertension, diabetes mellitus, and a history of heart failure, as substantial risk factors associated with contrast induced AKI.

As for echocardiographic data among the study groups, there was a statistically significance decrease in EF in CIN group, the median (IQR) was 54.27(45-69), p-value= 0.007.

The fact that the CIN group's ejection fraction (EF) was substantially lower suggests that patients with compromised cardiac function are at a higher risk of developing contrast-induced nephropathy. A reduced EF reflects impaired myocardial function, leading to decreased cardiac output and reduced renal perfusion. This diminished blood flow exacerbates renal hypoxia and heightens the susceptibility of renal tubules to injury from contrast agents used during PPCI. Consequently, the combination of

compromised heart function and decreased renal blood flow creates a precarious environment, increasing the risk of CIN in patients with lower EF [20,21].

Consistent with our findings, Yildiz et al. [22] also discovered that patients experiencing CIN following STEMI exhibited lower LVEF values.

Groups 2 and 3 had much greater cardiac enzyme levels than Group 1, as shown in our study. Those in Groups 2 and 3 exhibited far more severe myocardial damage than those in Group 1, as indicated by the much higher levels of cardiac enzymes in those groups compared to Group 1. In STEMI situations, the heart muscle is injured, which releases these enzymes into the bloodstream, similar to troponins. Patients having primary percutaneous coronary intervention (PPCI) had a constant degree of myocardial injury, as indicated by the identical elevated enzyme levels in both groups, irrespective of the development of CIN. Consequently, there is no direct relationship between CIN and elevated cardiac enzyme levels; rather, they indicate the severity of the cardiac event. By decreasing cardiac output and renal perfusion, which puts additional strain on the kidneys when exposed to contrast chemicals, increasing myocardial damage may indirectly increase the risk of CIN [23].

In line with our findings, Khalfallah et al. [14] reported no statistically substantial variation in CK-MB levels between the No CIN (Group I) and CIN (Group II) groups ($p>0.05$).

In terms of specific biomarker baseline data, Statistical analysis revealed striking disparities among the studied groups. More specifically, Cyt c and KIM-1 were higher in the CIN group. There were notable disparities in KIM-1 and Cyt c when comparing the two groups before 1st 24 hours following contrast injection; the CIN group exhibited elevated levels as well.

The highly substantial variations in KIM-1 and cytochrome c (Cyt c) levels between the CIN group and other groups, both at baseline and before 1st 24 hours post-contrast injection, emphasize their importance in indicating renal injury mechanisms. Elevated baseline levels of KIM-1, a marker of tubular injury and inflammation, along with Cyt c, which reflects mitochondrial dysfunction and apoptosis, suggest pre-existing renal stress in CIN patients. Following contrast exposure, the substantial rise in these biomarkers further indicates acute renal damage, as contrast agents exacerbate oxidative stress and induce apoptosis in renal cells. The sustained elevation of KIM-1 and Cyt c underscores their utility in detecting and monitoring renal injury, reflecting mechanisms of contrast-induced nephropathy, including enhanced tubular injury and apoptotic cell death [20,24] **.**

Based on their quick elevation in the early post-exposure period, biomarkers including NGAL, cystatin C, and KIM-1 allow for earlier diagnosis and treatment of contrast-induced acute kidney injury, which is supported by our findings and those of Fähling et al. [20].

Linking cellular stress to autophagy, The release of cytochrome c into the cytosol and subsequent depolarisation of the mitochondrial membrane are both caused by iohexol-induced oxidative stress, as demonstrated by Ko et al. [25].

The potential of kidney injury molecule-1 (KIM-1) for the early detection of CIN was studied by Akdeniz et al. [26]. The results of their investigation demonstrated that six hours after contrast, KIM-1 levels substantially rose in CIN patients ($p<0.01$; median rise from 0.27 to 0.70 mg/dL), in contrast to the control group ($p=0.107$). Both the pre-contrast and before 1st 24 hours KIM-1 levels in the CIN group were substantially different ($p=0.001$; median increase from 0.27 to 0.60 mg/dL).

It was also the goal of Li et al. [27] to determine whether urine kidney damage molecular 1 has any predictive value for the diagnosis of acute kidney injury caused by contrast during cardiac catheterization. When it came to diagnosing contrast induced AKI in patients who had cardiac catheterization, their study found that urine KIM-1 was quite predictive.

In their study, Anadón et al. [28] showed that KIM-1 mRNA and protein levels, which are normally low in healthy kidneys, are substantially increased in injured kidneys, especially in differentiated proximal tubular cells. This upregulation is seen in a wide range of kidney injury models, including ischaemia, drug-induced nephrotoxicity, renal cell carcinoma, inflammation, tubulointerstitial fibrosis, and chronic and acute kidney diseases.

After contrast treatment, the CIN group had substantially higher serum creatinine, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) values compared to the non-CIN group ($p<0.001$). Although there were some discernible variations in eGFR between the groups, these variations were not statistically different.

We found that CIN was significantly associated with contrast agent volume and EF, in contrast to baseline renal function (serum creatinine and

estimated glomerular filtration rate; eGFR). Bigger contrast volumes and lower EF both raise the risk of kidney injury, and there is a clear link between the two and the occurrence of CIN. Increasing the contrast volume can increase the exposure to nephrotoxins, which can worsen renal medullary hypoxia and oxidative stress. Lower renal perfusion owing to reduced EF, an indication of impaired cardiac function, further increases vulnerability [29].

While baseline kidney function did not predict CIN risk, the interplay between haemodynamic stress from reduced EF and the nephrotoxic burden from higher contrast volumes is more important in predicting CIN, as shown by the substantially higher creatinine, eGFR, and BUN levels in the CIN group after contrast. [29].

Statistically substantial variations ($p<0.001$) in blood creatinine and eGFR values were found by Andò et al. [29] between patients with and without CIN, which aligns with our findings.

Univariate regression analysis identified CHA_2DS_2-VASc score, BUN, KIM-1, cytochrome c (Cyt c), and LVEF as substantial predictors of CIN. Multivariate analysis confirmed BUN, KIM-1, Cyt c, and LVEF as independent predictors of CIN.

Baseline cytochrome c (Cyt c) levels in 240 patients with STEMI who underwent percutaneous coronary intervention (PCI) were studied by Tang et al. [12], who supported our results. Patients who later developed CIN had noticeably higher Cyt c levels at baseline (0.65±0.08 vs. 0.58±0.1, p=0.001). Cyt c was found to be an independent risk factor for CIN (OR 7.421, 95% CI 6.471-20.741, p=0.034) in multivariate logistic regression analysis, even after controlling for age, hypertension, diabetes mellitus, creatinine, uric acid, and glucose levels.

The incidence of CIN and its connection with many risk variables were examined by He et al. [30] in STEMI patients following PCI. Their meta-analysis demonstrated positive associations between CIN and hypertension (OR 1.85, 95% CI 1.57–2.18, $p<0.00001$), diabetes mellitus (OR 1.83, 95% CI 1.47–2.29, $p<0.00001$), prior myocardial infarction (OR 2.14, 95% CI 1.46–3.14, $p<0.0001$), age (OR 7.79, 95% CI 5.24–10.34, $p<0.00001$), left anterior descending artery damage (OR 1.92, 95% CI 1.15–3.22, p=0.01), Killip class ≥2 (OR 3.12, 95% CI 2.21–4.40, $p<0.00001$), lower eGFR (OR -6.15, 95% CI -9.52 to -2.79, p=0.0003), LVEF <40% (OR -15.06, 95% CI -24.75 to -5.36, p=0.002), and a specific interaction with LVEF (OR 5.53, 95% CI 1.10–27.95, p=0.04).

Lastly, with a PPV of 63.2% and NPV of 95.1%, sensitivity was 85.71% and specificity was 84.78% when the cutoff value for the CHA2DS2VASc score was adjusted at >4. A sensitivity of 79.3%, specificity of 80%, and PPV of 73.7% and NPV of 89% were achieved when the cutoff value for Cyt c was set to >0.635. When the KIM-1 cutoff was set at >9.5, the sensitivity was 80%, the specificity 83%, the PPV 75%, and the NPV 90%.

Consistent with our findings, Abdel-Ghany et al. [17] also found that a CHA_2DS_2-VASc score >2 was a 73.5% overall predictor of CIN, with a sensitivity of 50% and specificity of 82%. Additionally, Tang et al. [12] found that cytochrome c (cyt c) had a ROC AUC of 0.697 (95% CI, 0.611-0.783; p=0.001) when it came to projecting CIN. When the cyt c threshold was set at >0.605 ng/mL, a sensitivity of 79.3% and a specificity of 56.9% were achieved.

Lin et al. [31] investigated promising biomarkers for early CIN prediction. Their meta-analysis revealed a pooled AUC of 0.79 (95% CI: 0.76–0.83, I^2=89%, p=0.000, n=7760) for urinary KIM-1 in predicting CIN, suggesting its potential clinical utility.

Our study demonstrated that both KIM-1 and Cyt c showed strong predictive value for early detection of CIN, with sensitivities of 80% and 79.3% respectively, at defined cutoff values. These biomarkers significantly outperformed traditional markers like serum creatinine, which rises later in the course of kidney injury.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is another early biomarker of acute kidney injury AKI, with reported elevation within hours of renal injury. However, studies indicate that NGAL is influenced by systemic inflammatory responses, which may limit its specificity compared to KIM-1 and Cyt c in isolated renal injury scenarios [32]

Cystatin C, a marker of glomerular filtration, has been proposed as a sensitive alternative to serum creatinine. However, unlike KIM-1 and Cyt c, it lacks specificity for tubular injury, which is the primary mechanism in CIN. Combining biomarkers like KIM-1 and Cyt c with Cystatin C could offer complementary diagnostic insights [20].

The early rise of KIM-1 and Cyt c suggests a paradigm shift in monitoring renal function, particularly for high-risk groups undergoing contrast administration. Routine adoption of these biomarkers could improve patient stratification, guide preemptive hydration strategies, and facilitate real-time monitoring during interventions. Incorporating these biomarkers into clinical workflows may reduce

reliance on delayed diagnostic markers like serum creatinine, potentially lowering the burden of CIN-related morbidity and healthcare costs.

One potential drawback of our study is the limited sample size (20 patients per group), which could affect how applicable the results are to a broader population. Another drawback is that the study could have benefited from a more diverse patient group if it hadn't relied on volunteers from only one center. It is not possible to evaluate the long-term effects and development of CIN due to the absence of evidence from long-term follow-up studies. In addition, other possible biomarkers and confounding factors were not investigated, even though KIM-1 and Cyt c were recognized as important biomarkers. Finally, it should be noted that the study did not take into account the effects of various contrast agents or dosages, which may have impacted the outcomes. Future research should focus on multicenter studies to confirm the utility of KIM-1 and Cyt c in diverse patient populations and healthcare settings.

CONCLUSION

Serum cytochrome c and kidney damage molecule-1 could be used to predict contrast induced nephropathy before creatinine among elder patients having PCI intervention following an ST-elevation myocardial infarction.

No potential conflict and financial disclosure of interest was reported by the authors.

REFERENCES

1. Sonali G., Pradeep G., Nishant G., Harpreet S, Vivek K.Contrast-Induced Nephropathy: Current practice. J Urol Neph St, 2018; 1(1)- JUNS. MS.ID.000103.
2. Lazaros G, Tsiachris D, Tousoulis D, Patialiakas A, Dimitriadis K, Roussos D, et al. In-hospital worsening renal function is an independent predictor of one-year mortality in patients with acute myocardial infarction. *Int J Cardiol*. 2012; 155(1): 97-101.
3. Ronco F, Tarantini G, McCullough PA. Contrast induced acute kidney injury in interventional cardiology: an update and key guidance for clinicians. *Rev Cardiovasc Med*. 2020; 21(1): 9-23.
4. Golshahi J, Nasri H, Gharipour M. Contrast-induced nephropathy; A literature review. *J Nephropathol*. 2014;3(2):51-6.
5. Kumar BV, Mohan T. Retrospective Comparison of Estimated GFR using 2006 MDRD, 2009 CKD-EPI and Cockcroft-Gault with 24 Hour Urine Creatinine Clearance. *J Clin Diagn Res*. 2017; 11(5): 9-12.
6. Thomas MP, Moscucci M, Smith DE, Aronow H, Share D, Kraft P,et al. Outcome of contemporary percutaneous coronary intervention in the elderly and the very elderly: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *Clin Cardiol*. 2011; 34(9): 549-54.
7. Wu R, Kong Y, Yin J, Liang R, Lu Z, Wang N, et al. Antithrombin III is a Novel Predictor for Contrast Induced Nephropathy After Coronary Angiography. *Kidney Blood Press Res*. 2018; 43(1): 170-80.
8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization [published correction appears in N Engl J Med. 2008;18(4):4]. *N Engl J Med*. 2004; 351(13): 1296-305.
9. Yin C, Wang N. Kidney injury molecule-1 in kidney disease. *Ren Fail*. 2016; 38(10): 1567-73.
10. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med*. 2007; 357(11): 1121-35.
11. Tang C, Hou J, Yan G, Qiao Y, Wang D, Zhu B,et al. Effects of Serum Cytochrome c on Contrast-Induced Nephropathy in Patients with ST-Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention. *Biomed Res Int*. 2019;2019:9357203.
12. Rudnick MR, Leonberg-Yoo AK, Litt HI, Cohen RM, Hilton S, Reese PP. The Controversy of Contrast-Induced Nephropathy With Intravenous Contrast: What Is the Risk?. Am J Kidney Dis. 2020; 75(1): 105-13.
13. Goudis C, Daios S, Korantzopoulos P, Liu T. Does CHA2DS2-VASc score predict mortality in chronic kidney disease?. *Intern Emerg Med*. 2021; 16(7): 1737-42.
14. Khalfallah M, Allaithy A, Maria DA. Incidence, Predictors and Outcomes of Contrast Induced Nephropathy in Patients with ST Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *Glob Heart*. 2021; 16(1): 57.
15. Abd-AlKhaleq A, Hamoda M A, Khalil M M. Comparison of Novel Risk Score CHA2DS2-VASc-HSF to CHADS2and CHA2DS2-VASc

Scores to Predict the Risk of Severe Coronary Artery Disease. BMFJ, 2024.
16. Querfeld U, Mak RH, Pries AR. Microvascular disease in chronic kidney disease: the base of the iceberg in cardiovascular comorbidity. *Clin Sci (Lond)*. 2020; 134(12): 1333-56.
17. Abdel-Ghany M, Morsy G, Kishk Y T Predictors of contrast-induced nephropathy in ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention. EJIM,2021; 33, 1-5.
18. Song W, Zhang T, Pu J, Shen L, He B. Incidence and risk of developing contrast-induced acute kidney injury following intravascular contrast administration in elderly patients. *Clin Interv Aging*. 2014; 9: 85-93.
19. Ye J, Liu C, Deng Z, Zhu Y, Zhang S. Risk factors associated with contrast-associated acute kidney injury in ST-segment elevation myocardial infarction patients: a systematic review and meta-analysis. *BMJ Open*. 2023; 13(6):e070561.
20. Fähling M, Seeliger E, Patzak A, Persson PB. Understanding and preventing contrast-induced acute kidney injury. *Nat Rev Nephrol*. 2017; 13(3): 169-80.
21. Koo HM, Doh FM, Ko KI, Kim CH, Lee MJ, Oh HJ,et al. Diastolic dysfunction is associated with an increased risk of contrast-induced nephropathy: a retrospective cohort study. *BMC Nephrol*. 2013; 14:146.
22. Yildiz C, Yuksel Y, Efe SC, Altintas MS, Katkat F, Ayca B, et al. Value of systemic inflammation-response index in predicting contrast-induced nephropathy in patients with ST-elevation myocardial infarction. *Acta Cardiol*. 2023; 78(8): 930-6.
23. Kurniawan P. R, Setiawan A. A, Limantoro C, Ariosta A. The variations in troponin I and CK-MB values in acute myocardial infarction patients with ST elevation and without ST elevation. *Jurnal Kedokteran Diponegoro DIMJ* 2021; 10(2): 138-44.
24. Tanase DM, Gosav EM, Radu S, Costea CF, Ciocoiu M, Carauleanu A,et al. The Predictive Role of the Biomarker Kidney Molecule-1 (KIM-1) in Acute Kidney Injury (AKI) Cisplatin-Induced Nephrotoxicity. *Int J Mol Sci*. 2019; 20(20): 5238.
25. Ko GJ, Bae SY, Hong YA, Pyo HJ, Kwon YJ. Radiocontrast-induced nephropathy is attenuated by autophagy through regulation of apoptosis and inflammation. *Hum Exp Toxicol*. 2016; 35(7): 724-36.
26. Akdeniz D, Celik HT, Kazanci F, Yilmaz H, Yalcin S, Bilgic MA, et al. Is Kidney Injury Molecule 1 a Valuable Tool for the Early Diagnosis of Contrast-Induced Nephropathy?. *J Investig Med*. 2015; 63(8): 930-4.
27. Li Q, Huang Y, Shang W, Zhang Y, Liu Y, Xu G. The Predictive Value of Urinary Kidney Injury Molecular 1 for the Diagnosis of Contrast-Induced Acute Kidney Injury after Cardiac Catheterization: A Meta-Analysis. *J Interv Cardiol*. 2020; 2020: 4982987.
28. Anadón A, Martínez-Larrañaga M, Ares I, Martínez M.A. Biomarkers of Drug Toxicity and Safety Evaluation.2019; 655-91.
29. Andò G, Morabito G, de Gregorio C, Trio O, Saporito F, Oreto G. Age, glomerular filtration rate, ejection fraction, and the AGEF score predict contrast-induced nephropathy in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2013; 82(6): 878-85.
30. He H, Chen XR, Chen YQ, Niu TS, Liao YM. Prevalence and Predictors of Contrast-Induced Nephropathy (CIN) in Patients with ST-Segment Elevation Myocardial Infarction (STEMI) Undergoing Percutaneous Coronary Intervention (PCI): A Meta-Analysis. *J Interv Cardiol*. 2019; 2019: 2750173.
31. Lin J, Chen J, Wu D, Li X, Guo X, Shi S, et al. Biomarkers for the early prediction of contrast-induced nephropathy after percutaneous coronary intervention in adults: A systematic review and meta-analysis. Angiology. 2022; 73(3): 207-17.
32. Albert C, Zapf A, Haase M, Röver C, Pickering JW, Albert A, et al. Neutrophil Gelatinase-Associated Lipocalin Measured on Clinical Laboratory Platforms for the Prediction of Acute Kidney Injury and the Associated Need for Dialysis Therapy: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2020; 76(6): 826-841.e1.

Figure Legend

Supplementary Figure (1): ROC curve for accuracy of (A) KIM-1 (B) CHA2DS2VASc score, (C) Cyt c in diagnosis of CIN

Citation

Al Allam, A., Hassaan, M., Mohammed, Z., Samy, M., Allam, H., Mahrous, H., Eldamanhory, A., Magdy, M. Serum Kidney Injury Molecule-1 and Cytochrome C as Biomarkers for Early Detection of Contrast-Induced Nephropathy in Elderly Patients with ST-Elevation Myocardial. *Zagazig University Medical Journal*, 2025; (1234-1245): -. doi: 10.21608/zumj.2025.349376.3770