Research Paper

Incidence and Predictors of Contrast-induced Nephropathy in Patients Undergoing Percutaneous Coronary Interventions at an Indian Tertiary Care Center

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This investigation is aimed to assess the incidence and possible risk factors of contrast-induced nephropathy and also the utility of Mehran risk score for prediction of contrast-induced nephropathy in patients undergoing percutaneous coronary interventions. A cross-sectional observational study was conducted on 480 patients who underwent percutaneous coronary interventions. Patients with and without contrast-induced nephropathy were evaluated to recognize the predictive factors of contrast-induced nephropathy and explored the benefit of Mehran's risk score for prediction of contrast-induced nephropathy using receiver operating characteristics curve, Youden's index and a likelihood ratio test. The incidence of contrast-induced nephropathy was 5.2 % (95 % confidence interval- 4.75 to 5.65). The associated risk factors were diabetes mellitus, hypertension, age >75 years and contrast volume ≥100 ml (p>0.001). Multivariate analysis identified age >75 years and hypertension as independent risk factors. Low Mehran risk category (score <5) patients had a higher occurrence (56 %) of contrast-induced nephropathy compared to other Mehran risk groups. Mehran risk scoring had high sensitivity (63.1 %) and low specificity (44 %), which was affirmed by Youden's index (0.071) and an area under the receiver operating characteristics curve of 0.592. Contrast-induced nephropathy is a possible risk factor for all patients undergoing percutaneous coronary interventions. Contrast volume ≥100 ml, age >75 years, diabetes mellitus and hypertension were the predictors of contrast-induced nephropathy. Mehran risk score appeared irrelevant in stratifying the risk of contrast-induced nephropathy in patients undergoing percutaneous coronary interventions.

Key words: Contrast-induced nephropathy, Mehran risk score, percutaneous coronary intervention, sensitivity, specificity

Percutaneous coronary intervention (PCI), a procedure used to open clogged coronary arteries, involves temporary insertion and inflation of a balloon into the stenosed artery in order to widen it. A metallic scaffold, either bare metal or drug eluting, is often inserted during the procedure (coronary stenting) to maintain the patency of the artery and to decrease the chances of restenosis. This intervention needs visualization of the blood vessels by way of injecting a radio-contrast agent during fluoroscopy. The incidence of renal insufficiency is elevated in patients subjected to PCI due to the use of radiographic contrast media in angiographic procedures. Contrast-induced nephropathy (CIN), also known as contrast-induced acute kidney injury (AKI), is a self-generated renal injury that occurs after intra-arterial administration of radio-opaque contrast media[1]. The European Society of Urogenital Radiology (ESUR) defines CIN as an elevation of serum creatinine of >25 % or ≥0.5 mg/dl absolute value compared to the baseline within 48-72 h following the administration of radio-opaque contrast media in the absence of other alternative causes of AKI[2].

The pathophysiology of CIN identifies that the ascending loop of Henle has an increased exposure to ischemia where oxygen requirement is high due to active sodium re-absorption[3]. Following the intra-

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arterial administration of contrast media, the vascular endothelium releases various vasoactive mediators like nitrous oxide, adenosine, endothelin, prostaglandins, and reactive oxygen species (ROS) causing imbalance leading to vasoconstriction[4]. The ischemic tissue further releases more toxic vasoactive mediators thus extending the duration of vasoconstriction. The increased viscosity and hyperosmolality of the contrast media cause further reduction in medullary blood flow[3]. As the contrast media is filtered and concentrated within the tubules, there will be an increase in viscosity causing tubular block, which when combined with the release of ROS result in acute renal tubular injury. Thus a combination of cytotoxicity, prolonged vasoconstriction and increase in viscosity leads to initiation of medullary ischemia[5].

Reported incidence of CIN varies (<2 to 30 %) depending up on the study population, the prevalence of associated risk factors and the definition of CIN[3,6-8]. Patients undergoing coronary angiography or PCI have the highest CIN incidence compared to other procedures using contrast media for diagnostic or therapeutic purposes. Similarly, patients with underlying risk factors have a high incidence of CIN. Few risk scoring scales[9-11] were developed to predict CIN risk, but none have been adequately validated. Relevance of Mehran risk scoring[10] for prediction of CIN risk has been recently questioned[12] and the CIN consensus working panel[13] does not currently recommend it for CIN prediction. Hence our objectives were to assess the incidence and risk factors of CIN in patients undergoing PCI in a tertiary care centre and to determine the predictive value of Mehran risk score in assessing CIN.

MATERIALS AND METHODS

A cross-sectional observational study was carried out on adult patients admitted to the coronary care unit of a tertiary care hospital (AIMS, Kochi) for diagnostic or therapeutic PCI during September 2017 to February 2018. Patients who gave informed signed consent and who had a serum creatinine measurement prior to contrast administration and 24-48 h after the coronary intervention were eligible for the study. Patients receiving long term peritoneal and haemodialysis, patients with a previous episode of acute kidney injury, patients who died during PCI, who underwent renal intervention, who were allergic to radio contrast media, and patients with incomplete data were excluded. The study was approved by Institutional Ethics Committee (IEC) of AIMS (IEC-AIMS-2017-PHARM-361, September 17, 2017). The flow chart of the study process is shown in fig. 1. CIN was defined as an increase in serum creatinine concentration of

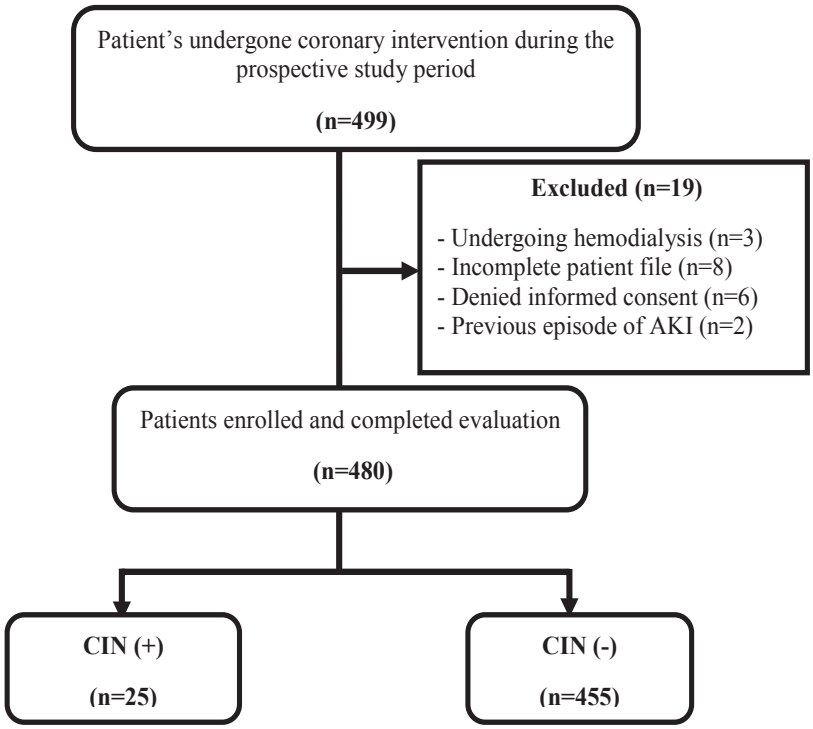

Fig. 1: Flow chart of the study process
CAG- coronary angiogram, PTCA- percutaneous transluminal coronary angioplasty, CIN- contrast-induced nephropathy, AKI- acute kidney injury

≥0.5 mg/dl or 25 % above baseline within 48-72 h after contrast administration as per ESUR[2]. Anemia was defined as a haematocrit value of <39 % in men and <36 % in females. Hypotension was defined as a systolic blood pressure of <80 mmHg for at least 1 h with requirement of inotropic support.

Serum creatinine concentration was measured 6-12 h prior to the procedure and was repeated post PCI during the hospital stay. The glomerular filtration rate (GFR) was calculated using modification of diet in renal disease equation[14]. Medications such as metformin, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, non-steroidal antiinflammatory agents, and aminoglycosides were withheld from patients prior to PCI and restarted 24-48 h post PCI. Most of the patients received hydration with normal saline or dextrose 6-12 h pre and post-procedure as well as N-acetylcysteine 600 mg twice daily for 6 doses at 12 h intervals. Charlson co-morbidity index (CCI) of the patients was calculated using an online calculator. The CIN risk was predicted using Mehran risk prediction scale[10]. The tri-iodinated nonionic low-osmolar radiocontrast media iohexol (Omnipaque® manufactured by GE Healthcare (Shanghai Co., Ltd, China) or non-ionic iso-osmolar radiocontrast media iodixanol (Visipaque® manufactured by GE Healthcare (Shanghai Co., Ltd, China) were the contrast media used.

Statistical analysis was carried out using IBM statistical package for social sciences (SPSS) version 20 for windows. Categorical data were reported as percentages and absolute values and continuous data were expressed as mean values±standard deviation. Comparison between groups of categorical variables such as sex, smoking, co-morbidities, nephrotoxic drugs, contrast type, catheter insertion site, CIN risk categories, CIN (+) and CIN (-) were made using Chi square test whereas student's t- test was employed for comparison between groups of continuous variables like height, weight, body mass index, age, laboratory values, fluoroscopy time, contrast volume, duration of hospital stay, and CCI score. A p value <0.05 was considered as significant. Reliability of Mehran's score in predicting CIN was tested by determining the sensitivity, specificity, positive predictive value and negative predictive value of Mehran risk scoring. Positive likelihood ratio, negative likelihood ratio, Youden's index, and ROC curve were also determined in order to evaluate the risk prediction scale.

RESULTS AND DISCUSSION

Out of the 499 patients who underwent coronary intervention, 480 were included in the study. Among these, 25 patients developed CIN (fig. 2) with an incidence of 5.2 % (95 % confidence interval (CI)-4.75-5.65). The incidence of CIN associated with PCI in our patients was higher than that reported by Kumar *et al*.[15] from Pune, India where an overall CIN incidence of 2.4 % was observed. They included PCI patients with normal renal parameters and excluded patients with risk of CIN such as known chronic kidney disease (stage 5), baseline creatinine >1.5 mg/dl, significant hypotension, anaemia and patients with myocardial infarction. Another study by Valappil *et al*.[6] from Trivandrum, Kerala found a CIN incidence of 29 % where they included only patients with impaired renal function (GFR of 30-60 ml/min/1.73 m^2) and excluded patients with ST elevated myocardial infarction and cardiogenic shock as well as patients undergoing haemodialysis or peritoneal dialysis. These inconsistencies of inclusion and exclusion criteria may be a reason for the variability in incidence of CIN as both the studies used the same definition of CIN as ours. A prospective study conducted at Chennai by Victor *et al*.[7] found a CIN incidence of 9.7 % where the inclusion and exclusion criteria were similar to our study.

Males were predominant among the global patients (332/480, 69.1 %) as well as among patients with CIN (17/25, 68%) and without CIN (316/455, 69.2%). Mean age of patients with CIN was 61.40±13.86 y (median- 63 y, range- 26-79 y) and for those without CIN, the mean age was 60.55±10.13 y (median-

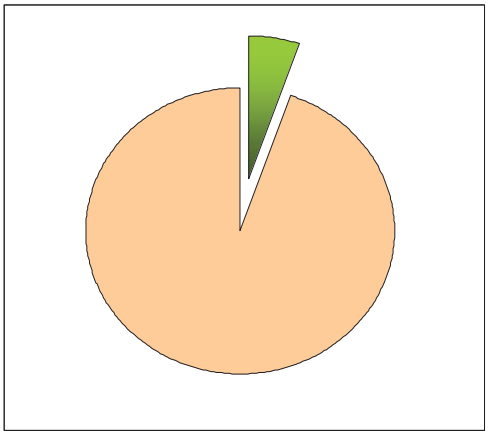

Fig. 2: Incidence of CIN in study patients after percutaneous coronary intervention
■ Patients with CIN (5.2 %); ■ patients without CIN (94.8 %); CIN- contrast-induced nephropathy

TABLE 1: BASELINE SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF STUDY PATIENTS WITH AND WITHOUT CIN

Patient characteristics	Global population (n=480)		CIN (+) (n=25)		CIN (-) (n=455)		p value
	No.	%	No.	%	No.	%	
Age>75 y	38	7.9	6	24	32	7	0.002**
Males	332	69.1	17	68	315	69.2	0.897
Smokers	232	48.3	12	48	220	48.4	0.973
Diabetes mellitus	229	47.7	17	68	212	46.5	0.037**
Hypertension	269	56.0	19	76	250	55	0.039**
Dyslipidemia	211	43.9	12	48	199	44	0.676
Anemia*	116	24.1	6	24	110	24.1	0.979
CHF†	30	6.2	3	12	27	6	0.222
Hypotension‡	8	1.6	0	0	8	1.7	0.457
Mean BMI (kg/m^2)±SD	24.37±3.51		24.21±2.92		24.54±4.11		0.523

*Male- haematocrit value <0.39, female- haematocrit value <0.36, †New York Heart Association Class IV heart failure, ‡systolic blood pressure <80 mmHg for hypotension. **Statistically significant. BMI- body mass index, SD- standard deviation, CHF- congestive heart failure, CIN (+)- patients with contrast-induced nephropathy, CIN (-)-patients without contrast-induced nephropathy

TABLE 2: CLINICAL CHARACTERISTICS AND PROCEDURE RELATED VARIABLES OF STUDY PATIENTS

Clinical parameters	Global population (n=480)	With CIN (n=25)	Without CIN (n=455)	p value
Mean serum creatinine (baseline, mg/dl) ±SD	1.02±0.46	0.98±0.26	1.07±0.67	0.682
Mean serum creatinine (After 48 h, mg/dl) ±SD	1.12±0.47	1.23±0.37	1.02±0.58	0.683
Mean eGFR (baseline, mg/dl) ±SD	78.28±22.21	83.30±27.75	78.00±21.87	0.191
Mean eGFR (after 48 h, mg/dl) ±SD	98.57±379.75	65.53±23.78	78.00±21.87	0.754
Mean fluroscopy time (min) ±SD	19.43±64.71	30.27±119.34	8.6±10.08	0.374
Mean contrast volume (ml) ±SD	114.05±52.13	152.80±28.97	75.3±28.97	0.541
Mean LVEF (%) ±SD	54.39±10.05	53.47±10.44	55.31±9.67	0.340
Contrast volume ≥100 ml, no. (%)	128 (26.6)	25 (100)	103 (22.6)	<0.001**
ACEI use, no. (%)	8 (1.6)	1 (4)	7 (1.5)	0.349
ARB use, no. (%)	59 (12.2)	3 (12)	56 (12.3)	0.964
Location of culprit artery (No. (%)				
- Left main artery	77 (16.5)	6 (24)	71 (15.6)	0.070
- LAD	218 (45.4)	9 (36)	209 (45.9)	
- Circumflex	39 (8.1)	5 (20)	34 (7.5)	
- Right coronary	146 (30.4)	5 (20)	141 (30.9)	

CIN- contrast-induced nephropathy, SD- standard deviation, CHF- congestive heart failure, LVEF- left ventricular ejection fraction, eGFR- estimated glomerular filtration rate, ACEI- angiotensin converting enzyme inhibitor, ARB- angiotensin receptor blocker. LAD- left anterior descending, **statistically significant

61 y, range- 23-86 y). The baseline demographical and social characteristics of the patients with and without CIN are shown in Table 1 and clinical characteristics and procedure related variables of study patients are shown in Table 2. CIN was observed to be more common in patients with risk factors like hypertension (19/25, 76 %), diabetes mellitus (17/25, 68 %), patients who received ≥100 ml of contrast media (25/25, 100 %, p<0.001) and those with age >75 y (6/25, 24 %). Other previously reported risk factors[15,16] such as hypotension, dyslipidaemia, anaemia, chronic heart failure and pre-existing renal impairment were not significant in our study patients. Higher the baseline serum creatinine, higher would be the risk of CIN, but not in patients with mild decrease in renal function. In our study, the mean pre-procedural baseline serum creatinine was 0.98±0.26 mg/dl in the CIN (+) group and 1.07±0.67 mg/dl in the CIN (-) group whereas, the post-procedural mean serum creatinine was 1.23± 0.37 mg/dl and 1.02±0.67 mg/dl in the CIN (+) and CIN (-) group, respectively and there was no significant association of CIN with baseline serum creatinine. The results of our study were comparable to a study by Pérez *et al*.[16] from Mexico in which similar creatinine levels pre and post-PCI were reported. None of our patients required haemodialysis after PCI.

Even though, 39.6 % (190/480) of patients had a history of statin use, 40 % (10/25) of them developed CIN and prior statin use had no significant association with CIN in our patients. But, studies[17,18] have suggested

that chronic use of statins have a preventive effect on CIN and a beneficial effect in reducing the incidence of dialysis and long-term mortality. Of 466/480 (97.1 %) patients who underwent PCI via trans-radial access, 25 developed CIN whereas none of those who underwent PCI via trans-femoral access had a CIN incidence (p=0.654). Since none of our patients who underwent PCI via trans-femoral access developed CIN, the trans-femoral access for PCI may reduce the incidence of CIN. This reduction in CIN incidence may also be due to the fact that majority (466/480, 97.1 %) of our patients underwent PCI through trans-radial approach and further studies with more number of patients via trans-femoral access are needed to confirm the possible association. But a study by Mann *et al.*[19] compared the radial approach with femoral approach for coronary stenting in patients with acute coronary syndromes in 142 patients and concluded that coronary stenting from radial approach is more efficacious than that via trans-femoral access. Out of 359/480 (74.8 %) patients who received preventive strategies with either N-acetylcysteine or hydration using normal saline or dextrose, 22/25 (88 %) developed CIN. But, these preventive strategies had no significant association (p=0.118) with CIN in our study. Saline hydration plays a role in intravascular volume expansion and inhibition of rennin-angiotensin-aldosterone pathway[20]. A study by Weisbord *et al.*[21] concluded that peri-procedural intravenous isotonic sodium bicarbonate showed no benefit over intravenous isotonic sodium chloride with respect to the risk of major adverse kidney events, death or AKI. In addition, they found no benefit of oral administration of N-acetylcysteine over placebo in decreasing CIN risk. Other studies[22,23] reported that reduction in effective intravascular volume associated with reduced cardiac output decrease the renal perfusion and increase the risk of CIN in patients with congestive heart failure (CHF) but it was not a significant risk factor in our study, which may be due to lesser number of patients (30/480, 6.25 %) with CHF.

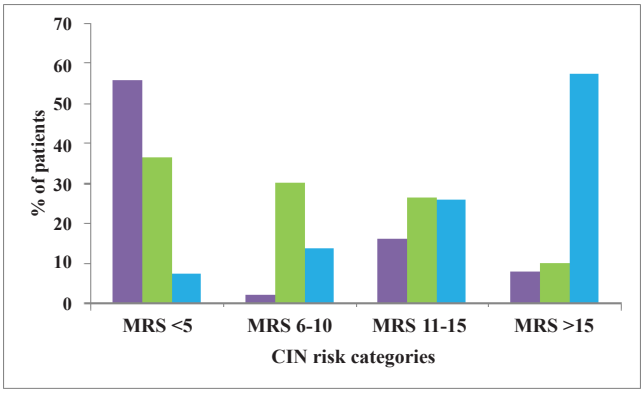

Fig. 3: CIN incidence in various Mehran risk categories
CIN incidence in various Mehran risk categories of the current study compared to a French study[12] and Mehran's data ■ current study; ■ Ivans *et al.*[12]; ■ Mehran *et al.*[10]; MRS-Mehran risk score

In the present study, a CIN risk stratification scoring by Mehran *et al.*[10] was utilized, a higher score indicating increased risk of CIN. The mean Mehran risk score of the study patients was 6.46±4.94. But our patients in the very high Mehran risk category (score >15) had a lower incidence (2/25, 8 %) of CIN as compared to patients of high (4/25, 16 %), moderate (5/25, 20 %) and low (14/25, 56 %) Mehran risk categories. This discrepancy was also found in another study[12] (fig. 3). Majority of our patients (301/480, 62.7 %) belonged to low risk category and 56 % (14/25) of them developed CIN while only 8 % (2/25) belonging to very high risk category developed CIN. In univariate and multivariate analysis, hypertension and age >75 y were found to be significant risk factors for the development of CIN. In univariate analysis, the risk factors like diabetes mellitus and use of ≥100 ml of contrast media were significantly associated with CIN while, in multivariate analysis, the location of culprit artery had a significant association with development of CIN (Table 3). Out of 8 risk factors of CIN identified by Mehran[10] only three factors, namely, age >75 y, volume of contrast media >100 ml and diabetes mellitus were predictive of CIN in

TABLE 3: UNIVARIATE AND MULTIVARIATE ANALYSIS OF CIN RISK FACTORS

	Univariate analysis		Multivariate analysis	
Risk factors	p value	OR (CI)	p value	OR (CI)
Age >75 y	<0.001**	5.21 (1.91-14.15)	0.019**	5.08 (1.3-19.81)
Diabetes mellitus	0.039**	2.41 (1.02-5.70)	0.037**	1
Hypertension	0.041**	2.57 (1.0-6.56)	0.027**	4.56 (1.18-17.58)
Contrast volume ≥100 ml	<0.001**	1.24 (1.14-1.35)	<0.001**	1
Location of culprit artery-				
- Left main	0.001**	1	0.001**	18.36 (3.15-10.86)
- LAD	0.727		0.727	0.80 (0.22-2.79)
- Circumflex	0.026**		0.026**	4.86 (1.20-19.60)

OR- odds ratio, CI- confidence interval, LAD- left anterior descending, **statistically significant

our study patients. Hypertension is not included in the Mehran risk prediction scale. But it was found to have a significant association (p=0.039) with the occurrence of CIN[24,25]. The role of hypertension in predisposing to CIN can be associated with advanced atherosclerosis of the aorta and may also be due to atheroembolization of the kidney during the coronary intervention[26,27]. The Mehran risk score[10] for CIN was proposed for quick identification of the variables and risk allocation but, is not recommended for daily use by the CIN consensus working panel[13], an international multidisciplinary group summoned to address the challenges of CIN. Though, few studies have considered the use of Mehran's score in predicting CIN incidence[9,10,28] its relevance has been challenged in a recent French study[12].

TABLE 4: RELEVANCE OF MEHRAN RISK SCORE FOR PREDICTION OF CIN

Parameters	Risk category based on Mehran's score			
	Low (0-5)	Moderate (6-10)	High (11-15)	Very high (>15)
[a]No.,(%) of patients with CIN	14 (56)	5 (20)	4 (16)	2 (8)
Sensitivity (%)	63.1	31.6	5.1	0.2
Specificity (%)	44	80	84	92
Positive predictive value (%)	95.3	96	85.2	33.3
Negative predictive value (%)	6.1	6	4.6	4.8
Youden's index	0.071	0.116	- 0.109	- 0.078
Positive likelihood ratio	1.12	1.58	0.31	0.02
Negative likelihood ratio	0.83	0.85	1.13	1.08

[a]Calculated based on total number of CIN (+) patients (n=25), CIN-contrast-induced nephropathy

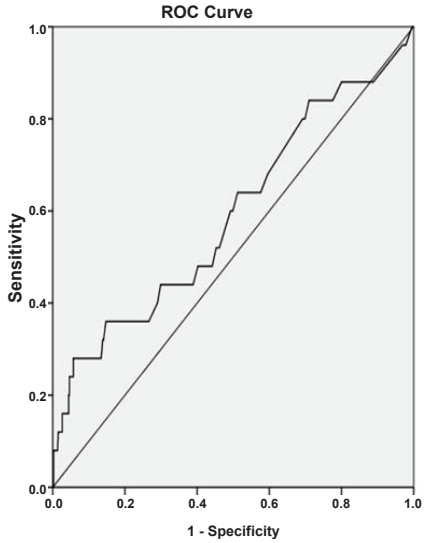

Fig. 4: ROC curve for Mehran's score applied to the study patients
ROC- receiver operating characteristic curve. Diagonal segments are produced by ties

Though, Mehran risk score had a high specificity for moderate, high and very high Mehran risk categories, its sensitivity was low for these risk categories (Table 4). The area under the receiver operating characteristic (ROC) curve (fig. 4) was found to be 0.592 showing poor validity of Mehran risk prediction score in our patients. An ROC curve that lies close to the upper left corner of a graph plotted between (1-specificity) and sensitivity is considered to have a higher overall accuracy. A test or scale with an area under the ROC curve of 0.6-0.7 has poor accuracy while that with an area >0.9 is considered to be of excellent accuracy. A study[7] from Chennai has reported the use of another CIN risk prediction scale in patients undergoing PCI, the validity of which has yet to be confirmed in future studies, but the reported ROC curve area was 0.933. A systematic review on risk prediction models for CIN reveals that most of the models have only modest predictive ability and there is a need to develop better models for clinical decision making[29].

Our study found that 84 % (21/25) of patients who received low osmolar (884 mOsm/kg**)** contrast media iohexol developed CIN compared to 16 % (4/25) of patients who received iso-osmolar (290 mOsm/kg**)** contrast media iodixanol but the difference was not significant. The decrease of CIN incidence in iodixanol group may be due to difference in either the osmolarity or the chemotoxicity of the contrast media or their ionic composition[30,31]. The osmolar diuresis induced by low osmolar contrast medium is generally greater than that induced by isoosmolar contrast medium. This diuresis may enhance distal sodium delivery, increasing medullary work and inducing hypoxia or volume depletion, with consequent activation of vasoregulatory hormones. If these vasoregulatory mechanisms are impaired, such impairment might be a major cause for renal damage[32]. The first study by Chalmers *et al*.[33] suggested that there was reduced incidence of nephropathy with iodixanol where the patients were randomly assigned to receive either iohexol or iodixanol. The incidence of nephropathy in the iodixanol group was less than half of that in the iohexol group[33].

All the patients (128/480, 26.6%) who received ≥100 ml of contrast media in our study developed CIN while none of the patients who received <100 ml of contrast agent suffered CIN and there was a significant association of CIN with the use of contrast media ≥100 ml in our study patients (Table 3). The risk of CIN was minimal if the patients received <100 ml of contrast agent during the procedure[34,35]. The initial volume of contrast administered in our study was 30-60 ml and additional volume of contrast was given in case of poor visualization. But, a study by Mekan *et al*.[36] found that the contrast media-induced reduction in renal function was not significantly higher with a volume of ≥100 ml. To demonstrate a relationship between the volume of contrast media and the risk of CIN following coronary intervention, further studies are required especially with a larger sample size.

Besides being single centric, our study has the following limitations. Some of our patients with PCI had co-existing cardiac procedures such as aortic valve replacement; atrial septal defect device insertion and the influence of these could not be evaluated. Renal function of some of the patients were monitored only up to 48 h after PCI due to patient discharge and we could not assess any decrease in renal function during the remaining period in the first week of PCI. This might have resulted in underestimation of CIN.

The incidence of CIN was 5.2 % in our patients undergoing PCI. CIN is a potential risk for all patients having diagnostic or therapeutic procedures with radio contrast media. The risk factors like contrast media volume ≥100 ml, age >75 y, diabetes mellitus and hypertension were the predictors of CIN in patients undergoing PCI in our study. Mehran risk scoring appeared not relevant in stratifying the CIN risk in PCI patients of our study population.

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Conflict of interest:

Authors have no conflicts of interest

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