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Original Article

Predictors of contrast induced nephropathy and the applicability of the Mehran risk score in high risk patients undergoing coronary angioplasty—A study from a tertiary care center in South India

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ABSTRACT

Objective: To study the incidence and predictors of Contrast induced nephropathy (CIN) in high risk patients undergoing coronary angioplasty. To study the applicability of the Mehran Risk Score (MRS) in the prediction of CIN in our population.

Methods: This was a prospective observational study where patients with an estimated glomerular filtration rate (eGFR) between 30 and 60 ml/mt undergoing elective percutaneous coronary intervention (PCI) over a period of 15 months were evaluated prospectively for the development of CIN. The patients who developed CIN were then analysed for the presence of specific risk factors. The patients were categorized into the 4 risk groups based on the MRS.

Results: 100 high risk patients underwent PCI during the study period. The incidence of CIN was 29%. On multivariate analysis, the presence of anemia ($p = 0.007$), increased contrast volume usage (as defined by >5* B.Wt/S.cr) ($p = 0.012$) and usage of loop diuretics ($p = 0.033$) were independently found to confer a significant risk of CIN. In patients belonging to the high Mehran risk group (MRS10- 15) and very high risk group (MRS >15) the risk of CIN was 3 fold (OR: 3.055, 95% CI: 1.18–7.94, $p = 0.022$) and 24 fold (OR: 24, 95% CI: 2.53–228.28, $p = 0.006$) higher respectively when compared to intermediate and low risk patients (MRS <10).

Conclusion: The incidence of CIN in high risk patients undergoing PCI is substantially higher in our population compared to similar studies in the west. The MRS risk prediction is pertinent even in an Indian population.

1. Introduction

Contrast induced nephropathy (CIN) is the Achilles heel of interventional cardiology. It carries significant morbidity and mortality. Despite burgeoning advances in the field of cardiac catheterization, and overall improvements in the hardware, scientists have been unable to tackle this serious complication. CIN is the acute worsening of renal function after parenteral administration of contrast media once other causes of deteriorating renal function have been excluded. CIN is currently the third most common cause of hospital acquired acute renal failure accounting for 10% of all cases.[1] The European Society of Urogenital Radiology {ESUR} defined CIN as an increase in the serum creatinine concentration of 0.5 mg/dL (44 mol/L) or 25% above the baseline within 48 h after contrast administration.[2] Preventive strategies for contrast induced nephropathy traditionally include pre- procedural hydration with isotonic saline, the usage of isoosmolar non-ionic contrast media, pre-medicating with *N*-acetyl cysteine, and the withdrawal of nephrotoxic drugs.[3,4,5,8,9] Despite the best of precautions, around 20–30% of patients with underlying risk factors for CIN undergoing percutaneous coronary intervention (PCI) go on to develop CIN.[6–8]

Abbreviations: CIN, contrast induced nephropathy; PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate; MRS, Mehran risk score; ESUR, European Society of Urogenital Radiology; CKD, chronic kidney disease; CAD, coronary artery disease; CTO, chronic total occlusion; CVP, central venous pressure; MDRD, modification of diet in renal disease.

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The current study was conducted with the intention to identify the incidence of CIN in patients with chronic kidney disease (CKD) stage III as defined by an eGFR of between 30 and 60 ml/mt and to analyse the risk factors for CIN. We also aimed to identify if the MRS could be used to accurately predict the incidence of CIN in patients belonging to the respective risk groups in an Indian population. It should be noted that the well validated MRS was formulated in a western population where the incidence of CIN was found to be 13.1%.[9] The population in the Indian subcontinent has higher atherogenic burden with a higher incidence of risk factors for CIN.

2. Materials and methods

2.1. Study design

This was a prospective observational study conducted at the Department of Cardiology, Government Medical College Trivandrum for a period of 15 months from January 2015.

2.2. Study protocol

2.2.1. Inclusion criteria

The study population included adult patients above the age of 18 years with coronary artery disease (CAD) who were admitted for elective PCI in the Dept of Cardiology, Medical College Trivandrum. All patients had impaired renal function as suggested by a reduced eGFR of: 30–60 ml/ min/1.73 m^2 calculated by the Cockcroft- Gault formula. None of the patients included had end-stage renal failure with the need for hemodialysis. These patients were prospectively evaluated for the development of CIN. To reinforce the baseline risk of the study population it was decided to include only those patients in whom the contrast usage was more than 100 ml.

2.2.2. Exclusion criteria

Patients undergoing routine hemodialysis or peritoneal dialysis, patients admitted with ST elevation myocardial infarction (STEMI) and patients with cardiogenic shock were excluded from the study.

All patients received standard prophylactic measures for prevention of CIN namely, continuous intravenous saline infusion (0.9%) 12 h before to 24 h after PCI (1 ml per kilogram of body weight per hour), oral *N*-acetylcysteine 600 mg twice orally on the day before and on the day of PCI and withdrawal of nephrotoxic drugs. In all patients Iodixanol, a non ionic isoosmolar contrast was used.[10] In heart failure patients the rate of saline infusion was lowered to 0.5 ml per kilogram of body weight per hour to prevent over hydration. The loop diuretics were not withheld in these patients.

2.3. Definitions

CIN: CIN was defined as an increase in serum creatinine concentration of 0.5 mg/dL (44 mol/L) or 25% above baseline within 48 h after contrast administration.[2]

Anaemia: The WHO definition of anaemia was used namely: haemoglobin of less than 13 g/dl in adult males or less than 12 g/dl in adult females.

2.4. Maximum permissible contrast volume

The upper limit of contrast usage for the prevention of CIN in PCI has been validated by Cigarroa et al and is given by the formula: 5 times the body weight in kilogram divided by the serum creatinine in mg/dl.[11]

Table 1
Baseline characteristics of the patients.

Variable	Percentage/Mean
Mean Age,y	61.76 ± 9.1
Male Sex n, (%)	83(83)
Mean LVEF,%	54.5
Anemia n,(%)	52(52)
Diabetes Mellitus n, (%)	57(57)
Systemic Hypertension n, (%)	64(64)
Heart failure n, (%)	18(18)
Peripheral artery disease n, (%)	26(26)
Dyslipidemia n, (%)	27(27)
Smoker n, (%)	64(64)
eGFR, ml/min	46.47 ± 8.9
Volume of Contrast used, ml	206.4 ± 58.3
Mehran Risk score	10.43 ± 3.5

The maximum permissible contrast volume for a given patient in relation to the creatinine clearance has also been validated in numerous studies.[12–16] The largest among them is the study conducted by Gurm et al., who enunciated that when the ratio of contrast volume to the creatinine clearance exceeded 3, the risk of CIN is dramatically increased.[17]

2.5. Periprocedural hypotension

Periprocedral hypotension was defined as a systolic blood pressure of less than 80 mmHg persisting for more than one hour, requiring inotropic support or an Intra-aortic balloon pump (IABP).

2.6. Statistical analysis

Continuous variables were expressed as minimum, maximum, mean, standard deviation (SD), and qualitative data were presented as percentages and frequencies. Continuous variables were analysed by a Student's *t*-test and categorical variables by the Chi square test when appropriate. The statistical analyses were performed with SPSS software (version 17.0). Multivariable logistic regression analysis was used to identify the independent risk factors associated with CIN. The results of this model were presented as an Odds Ratio (OR) and a 95% confidence intervals (95% CI) for OR. A 2-sided probability value of 0.05 was considered to indicate statistical significance throughout the analysis.

3. Results

3.1. Baseline characteristics

During the study period of 15 months, 100 high risk patients with CKD stage III underwent elective PCI and were prospectively evaluated for the development of CIN. The baseline characteristics of the patients are shown below in Table 1. The mean age of the patients was 61.76 ± 9.1 years and the majority were males. The prevalence of diabetes mellitus and systemic hypertension was

Table 2
Table showing the split up of patients based on the Mehran Risk Score.

MRS score	Risk Category	Patients		Predicted risk of cin from Mehran et al.
		N	%	
≤5	Low	3	3	7.5%
6–10	Intermediate	55	55	14%
11–15	High	36	36	26%
>15	Very High	6	6	57.3%
Total		100	100	

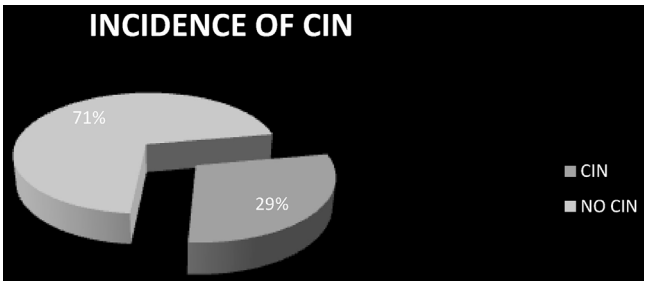


Fig. 1. The pie diagram showing the incidence of CIN in patients after PCI.

57% and 64%, respectively. The mean contrast usage per patient was 206.4 ± 58.3 ml. The higher contrast usage in our study was attributed to the higher number of multivessel PCI and CTO {Chronic total occlusion} interventions in our study.

The patients were analysed for the risk of CIN based on the MRS. The mean MRS of the study population was 10.43 ± 3.5. The split up of the patients based on the MRS is shown in Table 2. It was observed that a majority of the patients {55%, n = 55} belonged to the intermediate MRS (6–10). Further 42 patients (42%) had a high MRS of more than 10.

3.2. Analysis of the CIN patients

Out of the 100 high risk patients who were prospectively evaluated for the development of CIN, 29 patients developed CIN (29%). This is shown in Fig. 1 below.

3.2.1. Predictors of CIN

The traditional risk factors for CIN including anemia (hemoglobin <12 gm/dl), increased contrast volume usage as defined by Cigarroa et al (more than 5 times the body weight divided by the serum creatinine), ratio of contrast volume to the creatinine clearance >3, age more than 60 years, ejection fraction less than 50%, the presence of type 2 diabetes mellitus, usage of loop diuretics, periprocedural hypotension and systemic hypertension were analysed among the two groups of patients namely those who either developed CIN or did not develop CIN. Univariate analysis was performed for the above variables. The variables with a p value of less than 0.2 in the univariate analysis were then considered for multivariate analysis. The results are shown in Tables 3 and 4 below.

In both univariate and multivariate analysis presence of anaemia, increased contrast volume usage as defined by Cigarroa et al. {more than 5 times the body weight divided by the serum creatinine} and usage of loop diuretics were found to be statistically significant for prediction of CIN. In univariate analysis age >60 years predicted a trend towards risk of CIN among patients undergoing PCI.

3.2.2. Risk of CIN among the MRS subgroups

When the patients were subclassified based on the Mehran risk score {MRS} it was seen that no patient with an MRS <5 developed CIN but with higher MRS scores the incidence of CIN in this cohort increased exponentially. The incidence of CIN in the high risk group with MRS of 11–15 was 3 fold higher {OR: 3.055, 95% CI: 1.18–7.94, p = 0.022} compared to the reference group with MRS of <10. In the

Table 3
Univariate Analysis of binary logistic regression for the dependent variable CIN with predictors as anemia, increased contrast volume >5* B.Wt/S.cr, usage of loop diuretics, age >60 years, ejection fraction <50%, diabetes mellitus, ratio of contrast volume to creatinine clearance>3, systemic hypertension and periprocedural hypotension.

Risk factors for development of CIN	Patient%	Incidence of CIN%	p	OR	95% CI for OR	
					Lower	Upper
Anemia						
Yes	52	44	0.001	4.827	1.821	12.791
No	48	14.6				
Contrast Volume >5* B.Wt/S.cr						
Yes	37	45.9	0.004	3.613	1.466	8.903
No	63	19				
Loop Diuretics						
Yes	18	50	0.009	2.144	1.635	8.750
No	82	24.3				
Age >60 years						
Yes	51	37.2	0.063			
No	49	20.4				
Ejection Fraction <50%						
Yes	39	38.5	0.095			
No	61	22.9				
Diabetes Mellitus						
Yes	57	35.1	0.122			
No	43	20.9				
Contrast Volume/creatinine clearance >3						
Yes	91	30.8	0.215			
No	9	11.1				
Systemic Hypertension						
Yes	64	31.3	0.509			
No	36	27.8				
Periprocedural Hypotension						
Yes	5	40	0.578			
No	95	22.1				

Table 4
Multivariate analysis of binary logistic regression for the dependent variable CIN with predictors as anaemia, increased contrast volume >5* B.Wt/S.cr, usage of loop diuretics, age >60 years, ejection fraction <50% and diabetes mellitus.

Risk factors for development of CIN	p	OR	95% CI for OR	
			Lower	Upper
Anemia	0.007	3.661	1.483	10.667
Contrast Volume >5* B.Wt/S.cr	0.012	3.577	1.556	9.781
Loop Diuretics	0.033	2.211	1.887	8.645
Age >60 yr	0.156	2.885	0.865	6.552
Ejection Fraction <50%	0.408	1.724	0.475	6.264
Diabetes Mellitus	0.550	1.988	0.556	5.992

very high risk patients with MRS >15 the incidence of CIN was a staggering 24 fold higher (OR: 24, 95% CI: 2.53–228.28, p = 0.006) in comparison to the patients with MRS <10.

In addition it was noted that within each subcategory of MRS, the observed incidence of CIN in our cohort was significantly higher than the expected risk based on the MRS This is elaborated in Fig. 2 below.

3.2.3. Short term outcomes of the patients with CIN

The patients with CIN were followed up at 2 weeks and 6 weeks for requirement of hemodialysis, rehospitalization for heart failure and cardiac death. Out of the 29 patients who developed CIN two patients required hemodialysis (6.89%). Three patients were readmitted with symptoms of heart failure upto a follow-up period of 6 weeks (10.34%). There were 3 deaths in total (10.34%), two of which were out of hospital sudden cardiac deaths (probably arryhthmic deaths). One patient died of subacute probable stent thrombosis (Fig. 2).

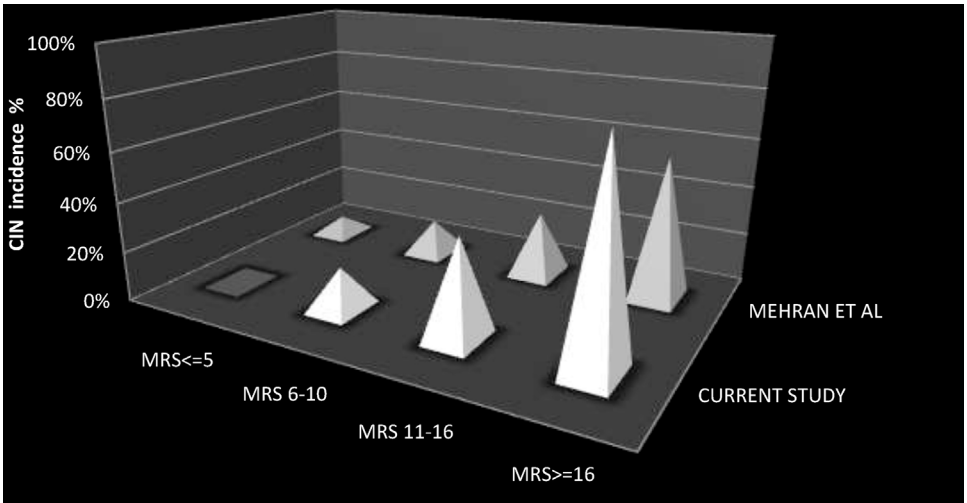
4. Discussion

Although studies show that the incidence of CIN in the general population to be around 2%, in high-risk patients with chronic renal impairment, diabetes mellitus, congestive heart failure, and older age, the incidence of CIN is significantly higher.[18,19] CIN is a danger lurking behind every high risk patient undergoing PCI and the current study highlights this often neglected fact. The incidence of CIN in our study population was 29% which indicates the high risk nature of the patients. Our cohort had a high incidence of the risk factors for CIN including type 2 diabetes, anemia, systemic hypertension and heart failure. Most importantly all our patients had CKD stage III (eGFR 30–60 ml/mt) and the mean contrast volume used was 206.4 ± 58.3 ml. The aggregate of all these risk factors probably contributed to the high incidence of CIN in our study.

4.1. Preexisting obscure renal dysfunction

A seemingly normal serum creatinine is practically a euphemism for a patient with low eGFR. Unless the practice of calculating the eGFR of patients undergoing PCI is made mandatory, we will miss out on many patients with a high risk of CIN. Consider a patient X, a 60 year old female with a body weight of 60 kg and a serum creatinine of 1.2 mg/dl undergoing a PCI. Despite her unassuming serum creatinine, it should be noted that her eGFR as estimated by the Cockcroft gault formula is 47.2 ml/mt and by the Modification of Diet in Renal Disease (MDRD) formula is 49 ml/mt. It is pertinent to recognize that the population in the Indian subcontinent has a lower body weight and body surface area compared to their western comrades. If we could generalize, once the serum creatinine of an average Indian male aged 60 years with a body weight of 65 kg rises to a mere 1.2 mg/dl, he gets relegated to the CKD stage III category, with eGFR of 60 ml/mt. With regards to the fairer sex, the Cockcroft Gault and the MDRD formula are more austere, as suggested by the formulae where we have to multiply the eGFR by 0.85 and 0.72, respectively.

The mean serum creatinine of this study population was 1.53 ± 0.4 mg/dl and the eGFR was 46.47 ± 8.9 ml/mt. Previous studies show that patient demographics like older patients, anemia,the presence of diabetes mellitus, a low ejection fraction, usage of loop diuretics and procedural characteristics like intra procedure hypotension, increased contrast volume confer a significant risk of CIN.[9–21]



	MRS<=5	MRS 6-10	MRS 11-16	MRS>=16
CURRENT STUDY	0%	16.90%	39.40%	83.30%
MEHRAN ET AL	7.50%	14%	26%	57.30%

Fig. 2. Figure showing Observed risk of CIN versus expected risk of CIN based on MRS.

4.2. Risk of iodinated radiocontrast media

Iodinated radiocontrast causes renal vasospasm by tilting the balance in favor of the vasoconstrictors in the renal medulla. The vasospasm is fuelled by the increased production of endothelin and adenosine. There is a direct renal tubular damage causing decreased nitric oxide and prostaglandin synthesis. The vasospasm triggers an ischemic reperfusion injury in the metabolically active renal medulla.[22,23] An interesting study dating two decades back identified the upper limit for contrast usage as five times the body weight of the patient divided by the serum creatinine.[11] In our population when the contrast usage exceeded this limit, the risk of CIN was significantly more by both univariate and multivariate analysis. This simple formula gives us a pre procedural cut off beyond which contrast usage portends a significantly higher risk of CIN. The lower body weight of the Indian population has practical implications, going by the current study where the mean body weight of the patients was 64.12 kg and the mean serum creatinine was 1.53, the maximum permissible contrast load would have been 209.54 ml.

Interestingly, the upper limit of contrast volume with reference to the creatinine clearance as given by the formula suggested by Gurm et al. {contrast volume/creatinine clearance more than 3} was not found to predict CIN in our study.[17] This could probably be due to the wide variation in the upper limit for this ratio ranging from 2.44 to 6.15 from numerous studies.[12–16]

4.3. Anemia as a risk factor for CIN

The second important risk factor which significantly predicted the risk of CIN was anemia. Ionic media increases the affinity of hemoglobin to oxygen molecules, this impairs the delivery of oxygen to the metabolically active renal medulla. The hypoxic renal injury is aggravated in the presence of anemia. With increasing severity of CKD the prevalence and severity of anemia increases.[24] With every 3% decrease in the haematocrit the odds of CIN in patients with CKD is significantly increased.[25]

4.4. Diabetes and CIN

Other risk factors like the presence of diabetes mellitus and an ejection fraction less than 50% were not significantly found to predict CIN. In a previous Indian study diabetes mellitus was found to predict CIN only if there was associated diabetic micro-angiopathy.[20] Though the incidence of diabetes mellitus in our study was as high as 57%, the incidence of diabetic neuropathy and retinopathy was only 5%. This could probably account for the discrepant findings.

4.5. CIN in heart failure patients on loop diuretics

It was observed that 39% of patients had an ejection fraction of less than 50%, however the incidence of symptomatic heart failure requiring loop diuretics was only 18%. It is interesting to note that presence of a low ejection fraction sans symptoms of heart failure requiring diuretic therapy per se did not predict an incremental risk of CIN. However, with the use of loop diuretics in these patients there was a significant risk of CIN by both univariate and multivariate analysis. When patients undergoing PCI are on diuretic therapy they always run the risk of over diuresis and dehydration. The highly viscous nature of the contrast media gets potentiated in the prescence of dehydration and this contributes to reduced renal tubular flow and aggravates medullary hypoxia.[26] In fact a Chinese study advocates the use of central venous pressure (CVP) guided fluid and diuretic administration in heart failure patients undergoing PCI to prevent CIN.[27] Notably the total mean volume of isotonic saline administered in the CVP-guided hydration group was significantly higher than the control group (1827 ± 497 ml vs. 1202 ± 247 ml; $p < 0.001$). This reiterates the fact that heart failure patients undergoing PCI are frequently underhydrated and the treating physician needs to tread a fine line of balance between dehydration and fluid overload. The incidence of periprocedural hypotension was relatively low and no patients required the use of IABP in our study.

4.6. Risk prediction scores for CIN

There are numerous risk scores for the prediction of CIN in patients undergoing interventions with radiocontrast media.[22,28] Of these the score promulgated by Mehran et al has been well validated in external populations other than in India and is provided with an online calculator. The MRS categorizes patients into 4 risk categories. The MRS offers not just the risk of CIN but also outlines the risk of hemodialysis specific to each category.[9] Strikingly in our study it was seen that with increasing MRS the observed risk of CIN was exponentially higher. The patients belonging to the high Mehran risk group (MRS: 10–15) had a threefold higher risk of CIN compared to patients with MRS <10 (OR: 3.055, 95% CI: 1.18–7.94, p = 0.022). In patients belonging to the very high risk group (MRS >15) the risk of CIN was 24 fold higher (OR: 24, 95% CI: 2.53–228.28, p = 0.006) in comparison to the intermediate and low risk groups (MRS <10). The MRS though formulated and tested in the western population, has not been previously validated in an Indian population. This prodigious increase in CIN risk was in stark contrast to the study by Sato et al conducted in a Japanese population undergoing PCI.[29] They demonstrated that the risk of CIN was increased only in the very high risk group (MRS >15) (OR:4.09, 95% CI: 1.72–9.17, p = 0.002) in comparison to the group with MRS <5. The current study also reinforces the fact that in the Indian population, a patient with a MRS of more than >10 has a substantially higher risk of CIN when compared to the expected risk. The only flaw with the MRS is that it can only be calculated once the interventional procedure is complete.

5. Study limitations

This was a single center study which was conducted to analyze the incidence and predictors of CIN in high risk patients undergoing PCI. Other parameters for evaluation of post PCI renal dysfunction like Neutrophil galectin associated lipocalyn {NGAL}, Cystatin C and Kidney injury molecule-1 (KIM-1) were not included in this study.

6. Conclusion

The current study highlights the three pressing facts. Most importantly, the incidence of CIN in high risk patients undergoing PCI in the Indian population is as high as 29% and this is higher than that predicted by the MRS score. These high risk patients can easily be identified by the eGFR between 30 and 60 ml/mt. Secondly when these high risk patients are admitted for elective PCI, the maximum permissible contrast load as suggested by Cigarroa et al should be calculated and all precautions should be taken to strictly adhere to this limit.[11] All patients should be categorized based on the Mehran risk score whenever a patient's MRS is found to be >10, extreme vigilance should to be practiced and measures for the prevention of CIN should be reinforced.

What is known

Patients with borderline renal disease i.e CKD stage 3 are commonly encountered during PCI and are at a high risk of CIN. Do

the traditional risk factors for CIN apply even in these high risk patients? Can we apply the Mehran risk score in the Indian population?

What this study adds

The risk of CIN in CKD stage 3 patients undergoing PCI is often underrated. Increased contrast volume, anemia and diuretic usage portend a significant risk of CIN in this high risk subgroup. The Mehran risk score has practical relevance even in the Indian population with increasing scores conveying a significant risk.

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