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Original Article

Risk scoring system to predict contrast induced nephropathy following percutaneous coronary intervention

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ABSTRACT

Background: Contrast induced nephropathy (CIN) is associated with significant morbidity and mortality after percutaneous coronary intervention (PCI). The aim of this study is to evaluate the collective probability of CIN in Indian population by developing a scoring system of several identified risk factors in patients undergoing PCI.

Methods: This is a prospective single center study of 1200 consecutive patients who underwent PCI from 2008 to 2011. Patients were randomized in 3:1 ratio into development ($n = 900$) and validation ($n = 300$) groups. CIN was defined as an increase of $\geq$25% and/or $\geq$0.5 mg/dl in serum creatinine at 48 hours after PCI when compared to baseline value. Seven independent predictors of CIN were identified using logistic regression analysis - amount of contrast, diabetes with microangiopathy, hypotension, peripheral vascular disease, albuminuria, glomerular filtration rate (GFR) and anemia. A formula was then developed to identify the probability of CIN using the logistic regression equation.

Results: The mean (±SD) age was 57.3 (±10.2) years. 83.6% were males. The total incidence of CIN was 9.7% in the development group. The total risk of renal replacement therapy in the study group is 1.1%. Mortality is 0.5%. The risk scoring model correlated well in the validation group (incidence of CIN was 8.7%, sensitivity 92.3%, specificity 82.1%, *c* statistic 0.95).

Conclusion: A simple risk scoring equation can be employed to predict the probability of CIN following PCI, applying it to each individual. More vigilant preventive measures can be applied to the high risk candidates.

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1. Introduction

Contrast induced nephropathy (CIN) occurs due to acute kidney injury caused by the contrast media and is a common cause of hospital-acquired acute renal failure.[1] It is associated with increased morbidity and mortality as well as prolonged duration of hospital stay, need for renal replacement therapy and major cardiac events.[2] CIN is defined as a 25% increase in serum creatinine from the baseline value, or an absolute increase of at least 0.5 mg/dL (44.2 μmol/L), 48–72 hours after the administration of radiographic contrast media that is not attributable to other causes.[3,4] At least two significant processes are known to be involved in the pathophysiology of CIN- vasoconstriction resulting in medullary hypoxia and direct toxicity caused by the contrast media to renal tubular cells.[5] The mechanisms that have been implicated in these processes are dehydration, decreased prostaglandin and nitric oxide induced vasodilatation, impaired endothelial function, increase in renal adenosine concentration, increase in oxygen free radicals in response to hyperosmotic load, increased intratubular pressure owing to contrast induced diuresis, increased urinary viscosity and obstruction of the tubules.

Percutaneous coronary intervention (PCI) is a life saving procedure in the management of acute coronary syndrome and improves the quality of life in patients with stable coronary artery disease. However, PCI poses a risk of CIN due to the exposure to contrast media during the procedure. Various risk factors were identified based on studies conducted previously. Advanced age, female gender, anemia, pre-existing renal impairment, diabetes mellitus, reduced intravascular volume, congestive cardiac failure, presence of hypotension, presence of cardiogenic shock, use of intra aortic balloon pulsations (IABP), type of contrast media, large volumes of contrast media, co-administration of nephrotoxic drugs such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), proteinuria (including nephrotic syndrome), multiple myeloma, hypercholesterolemia, hyperuricaemia, hypercalcemia, sepsis, atopic allergy are some of the recognized risk factors.[6–8] Application of risk scoring systems can prognosticate the high risk patients for CIN after the exposure to contrast.[9]

Though there are various risk scoring systems available for prediction of CIN, the risk factor profile and their cumulative effect in Indian patients has never been considered in large studies, to our knowledge. This has prompted us to conduct this prospective study with an aim to detect the incidence of CIN, to identify the predictors and to determine their collective effect in the development of CIN in an unselected population of consecutive patients undergoing PCI in our institution. This risk scoring system is unique to the Indian subcontinent and may also form a model for other countries across the world with similar disease patterns.

2. Materials and methods

2.1. Aims

To evaluate the collective risk of CIN in Indian population by developing a scoring system of several identified risk factors, in patients undergoing PCI.

2.2. Objectives

1. To determine the incidence of CIN in the study group following PCI.
2. To identify the risk factor profile for CIN in Indians and to compare it with the results of studies conducted elsewhere.
3. To estimate the cumulative risk rendered by individual risk factors and to develop a simple risk score model to predict CIN.
4. To validate this model in a sample patient population.

2.2.1. Study population

This is a prospective single center observational study, conducted in Madras Medical Mission, Chennai, which is a tertiary cardiac referral center, from March 2008 to December 2011. 3152 patients underwent PCI during this period. Patients who were other than Indians, patients in whom the required data is missing were excluded from the study, apart from the defined exclusion criterion. Majority of the patients were excluded (approximately 80%) because PCI was performed within 14days of coronary angiogram (CAG). The remaining 1200 patients were analyzed for the study. Written informed consent was obtained from patients and the study is cleared by the institutional ethics committee.

2.2.2. Study protocol

Patients' age, history including diabetes, hypertension, hypothyroidism, liver disease, multiple myeloma, cerebro vascular accident (CVA), congestive heart failure (CHF), chronic kidney disease (CKD), nephrotoxic drugs and presence of acute coronary syndrome (ACS) were noted. Detailed clinical examination was done for all patients including testing for the presence of peripheral vascular disease (PVD), neuropathy or retinopathy. Diabetic microangiopathy was considered to be present when either retinopathy (fundus examination) or neuropathy (monofilament examination) was present. Patients with diabetic nephropathy were included in the CKD group. Presence of PVD was confirmed using Doppler ultrasound if the physical examination including ankle-brachial index was suggestive of the diagnosis. Hemoglobin, total and differential white cell count, erythrocyte sedimentation rate (ESR), serum bilirubin levels, plasma glucose levels, albuminuria, electrolytes, lipids and thyroid profile (if there is a clinical suspicion) were assessed before the procedure by standardized tests in our laboratory.

Electrocardiograms (ECG), chest X-ray, echocardiogram were done for all the patients. Serum creatinine, blood urea, cardiac enzymes were checked at baseline and 48 hours after the procedure. During the procedure – the number of vessels diseased, number of vessels stented, the type and amount of dye used, the presence of periprocedural hypotension and the duration of hypotension were noted meticulously. All patients underwent PCI using non ionic contrast media. Post procedure, patients' urine output, need for renal replacement therapy (RRT) and outcome were documented. All patients with raised creatinine levels were given hydration with half normal saline (1 ml/kg/h starting from 4 hours before and continued till 24 hours after the exposure to contrast media) and N-acetylcysteine (600 mg twice daily 1 day before and for 2 days post procedure) as per the hospital guidelines. All patients received dual anti platelets and a statin in recommended doses. Data was collected by persons who were blinded to the study objectives.

2.2.3. *Inclusion criteria*

All consecutive Indian patients who underwent PCI in our hospital from March 2008 to December 2011 were enrolled into the study.

2.2.4. *Exclusion criteria*

Patients with renal failure on regular dialysis, acute renal failure before PCI, cardiogenic shock, patients who were exposed to contrast media within 14 days, patients requiring intra-aortic balloon pump (IABP) support and patients who developed PCI related complications were excluded.

2.3. *Definitions*

CIN was defined as an increase of ≥25% and/or ≥0.5 mg/dl in serum creatinine at 48 hours after PCI when compared to baseline value.[10]

Anemia was defined as hemoglobin <13 g/dl in men and, <12 g/dl for women.[11]

CKD was defined as the estimated GFR <60 ml/mt/1.73 m^2 or baseline serum creatinine >1.5 mg/dl.[12]

Hypotension was defined as systolic blood pressure <80 mm Hg for at least 1 hour requiring inotropic support within 24 hours periprocedurally.[13]

Cardiogenic shock was defined as prolonged hypotension (systolic blood pressure <85 mm Hg) with evidence of decreased organ perfusion caused by severe left ventricular dysfunction, right ventricular infarction, or mechanical complications of infarction and not due to hypovolemia, bradyarrhythmias, or tachyarrhythmias.[14]

GFR was calculated using the Cockcroft–Gault formula[15]: (ml/mt)

$$(140 - \text{age in years}) \times \text{weight (kg)} \times 0.85 \text{ (if female)}/72 \times \text{serum creatinine (mg/dl)}$$

2.4. *Statistical analysis*

Data were collected and managed on the Excel worksheet. Quantitative variables were expressed as the minimum, maximum, mean, standard deviation (SD) and qualitative variables were expressed as frequencies and percentage. Unpaired student's 't' test was used to compare the mean of continuous variables. Chi-square test was used to compare proportions. Univariate and multivariate analysis was performed to identify individual risk factors. '*p*' value <0.05 was considered statistically significant. Analyses were conducted using SAS version 9.2 by Norwich clinical services, Bangalore.

2.5. *Risk score system development*

1200 consecutive patients undergoing PCI were randomized in a 3:1 manner to development and validation groups using simple random method. 900 patients were in the development set and 300 patients were in the validation set. The baseline clinical, laboratory and procedural characteristics of the patients in the development set were studied using univariate analysis to identify the individual risk factors. Significant individual risk factors were used as independent variables and CIN as the dependent variable in the final multivariate logistic regression model without intercept. No variables were transformed during model building. Forward step wise logistic regression analysis was used to elucidate the final risk factors with the strongest prediction of CIN using analysis of deviance. Probability value of 5% threshold was used in the forward selection model building process. The obtained logistic regression equation ($A = \sum \beta_i x_i$, where 'A' is estimated CIN occurrence, 'β' = logistic regression coefficient, 'x' = independent variable and 'i' = 1 to *n*), the probability of CIN was estimated with "$e^A/(1 + e^A)$", where 'e' is exponential. Chi square goodness of fit test was used to assess the final model accuracy for prediction of CIN and area under curve (AUC) of receiver operating characteristic (ROC) was used to evaluate the model discrimination between patients with and without CIN. The final estimate for CIN probability was evaluated using sensitivity and specificity analysis at various cut off levels (2.5%–60%). The final risk score system was then substantiated in the validation data set and its predictive accuracy was assessed using the 'c'-statistic.

3. Results

The baseline clinical, laboratory and procedural characteristics of the patients are in Table 1. The mean (±SD) age was 57.3 (±10.2) years. 83.6% were males. Diabetes and hypertension were prevalent at 53% & 52.2%. The total incidence of CIN in the development set was 9.7% (*n* = 87). 11.5%

Table 1 – The baseline clinical, laboratory and procedural characteristics of development data set.

Variable	Mean/%	SD
Age (in years)	57.3	10.2
Males	83.6%	($n = 752$)
Females	16.4%	($n = 148$)
Multivessel stenting	24.1%	($n = 217$)
Hypotension	4.9%	($n = 44$)
Mild LV dysfunction	24.2%	($n = 218$)
Moderate LV dysfunction	20.3%	($n = 183$)
Severe LV dysfunction	5.3%	($n = 48$)
Good LV function	50.1%	($n = 451$)
Hypertension	52.2%	($n = 470$)
Congestive heart failure	2.2%	($n = 20$)
Previous CABG	4.7%	($n = 42$)
Previous CAD	19.7%	($n = 177$)
ACS	10.2%	($n = 92$)
CVA	2.2%	($n = 20$)
Chronic kidney disease	5.8%	($n = 52$)
Peripheral vascular disease	3.1%	($n = 28$)
Hypothyroidism	5.6%	($n = 50$)
Chronic liver disease	1.6%	($n = 14$)
Smokers	28.4%	($n = 256$)
Diabetes	53%	($n = 477$)
DM with microangiopathy	5.9%	($n = 53$)
Albuminuria	12.1%	($n = 109$)
Heart Rate	76.9	12.9
Systolic BP	128	19.3
Diastolic BP	77.8	12
Hemoglobin (g/dl)	12.9	1.7
White cell count (/μl)	9111.1	2986.9
Serum creatinine (mg/dl)	0.9	0.3
Urea (mg/dl)	25.3	11.6
Total Bilirubin (mg/dl)	0.5	0.3
Na+ (mEQ/L)	136.3	4.3
K+ (mEQ/L)	4.0	0.4
Total Cholesterol (mg/dl)	148.6	41.5
Triglycerides (mg/dl)	148.1	91.4
LDL – Cholesterol (mg/dl)	88.9	35.4
HDL – Cholesterol (mg/dl)	33	8.7
GFR (ml/mt/1.73 m^2)	85.8	21.4
Duration of hospital stay (days)	4.1	1.4
Contrast volume (ml)	114.9	37.9

($n = 10$) in the CIN group had some form of renal replacement therapy and mortality was 5.7% ($n = 5$), there was no mortality in the group without CIN ($p < 0.05$). The average hospital stay in the non CIN group was 3.9 (±1.35) days where as it was 5.03 (±1.97) days in the CIN group ($p < 0.001$).

Table 2 – Univariate Analysis for predictors of CIN.

Variable	OR	95% CI	'p'
Age	2.96	1.72–5.09	<0.0001
Albuminuria	8.10	4.97–13.21	<0.0001
Anemia	1.58	1.01–2.46	0.04
CKD	14.18	7.75–25.95	<0.0001
Diabetes	2.88	1.74–4.75	<0.0001
Presence of ACS	2.83	1.61–4.97	0.0002
GFR	7.46	4.46–12.47	<0.0001
Severe LV dysfunction	3.30	1.99–5.46	<0.0001
Peripheral vascular disease	10.94	5.02–23.84	<0.0001
Contrast volume	51.65	12.62–211.32	<0.0001
Hypotension	13.55	7.12–25.81	<0.0001
Hypothyroidism	7.05	3.78–13.13	<0.0001
DM with microangiopathy	21.94	11.87–40.57	<0.0001

Table 3 – Independent Predictor variables of CIN using Forward Stepwise Logistic Regression without intercept.

Variable	β	'p'	OR	95% CI
Hypotension	1.6382	0.0004	5.15	2.06–12.83
Albuminuria	1.3392	0.0002	3.82	1.87–7.77
DM with microangiopathy	1.5274	0.0012	4.60	1.83–11.60
Anemia	−0.2889	<0.0001	0.75	0.67–0.83
Peripheral vascular disease	1.8777	0.0050	6.54	1.76–24.24
GFR	−0.0401	<0.0001	0.96	0.95–0.97
Contrast volume	0.0280	<0.0001	1.03	1.02–1.03

β = logistic correlation coefficient.

Univariate analysis has shown a total of 13 variables to be associated with CIN. These are – age >70 years, presence of hypotension during the procedure, CKD, PVD, hypothyroidism, presence of ACS, severe left ventricular dysfunction, diabetes as well as diabetes associated with microangiopathy, anemia, albuminuria, low GFR (<80 ml/mt/1.73 m^2) and contrast volume (Table 2). The factors that were significant in univariate analysis were then studied in multivariate analysis using forward logistic regression to discover independent predictors. Seven final variables (Table 3) were entered into the logistic regression equation and the final risk score system was developed (Table 4). This risk score system is expected to have a sensitivity of 83.9% and specificity of 89.5% at cut off probability of predicted CIN at 10% and above.

3.1. *Validation of risk scoring system*

The scoring system was then assessed in the validation data set to ensure accuracy. The incidence of CIN was 8.7% ($n = 26$) in the validation set. Rate of renal replacement therapy was 15.4% ($n = 4$) and mortality was 7.7% ($n = 2$) in the CIN group. The risk score system had a higher sensitivity than expected at 92.3%, specificity was 82.1% and demonstrated excellent discriminative power (c – statistic = 0.95) in the validation group. The model correlation between development and validation data sets has been shown in Fig. 1 and the relation between the increasing risk score and incidence of CIN is shown in Fig. 2. Figs. 3–5 depict the influence of decreasing

Table 4 – The final Risk Scoring System for prediction of CIN.

Clinical predictors	To be entered into the equation
GFR	Value (ml/mt/1.73m2)
Amount of Contrast	Value (ml)
Hemoglobin (mg/dl)	Value (mg/dl)
Diabetic microangiopathy	Yes
	No
Hypotension	Yes
	No
Albuminuria	Yes
	No
Peripheral vascular disease	Yes
	No

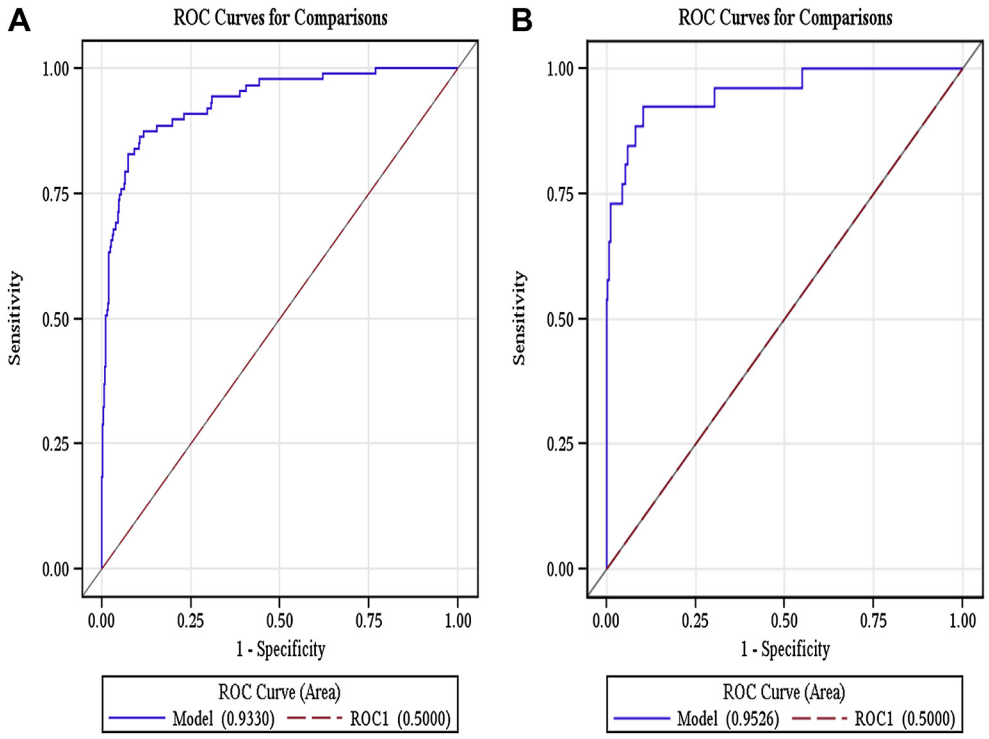

Fig. 1 – The observed high values of under curve (AUC) of ROC shown on the development data set and validation data set indicate that predicted CIN model correlated well on its calibration and discriminative characteristics. 'A' – development data set. 'B' – validation data set.

GFR, increasing contrast volume and hypotension on the outcome of CIN.

4. Discussion

Coronary artery disease has reached epidemic proportions in India. Percutaneous coronary intervention is a life saving procedure for many patients and occupies a significant place in the practice of interventional cardiology. As the number of coronary interventions increase, so do the consequent complications such as CIN. CIN contributes to significant morbidity and mortality after PCI. Hence, identification of high risk patients for CIN by risk stratification is indispensable.

Prior studies have reported varying levels of incidence of CIN; it is 9.7% in our study, 13.1% in the study conducted by

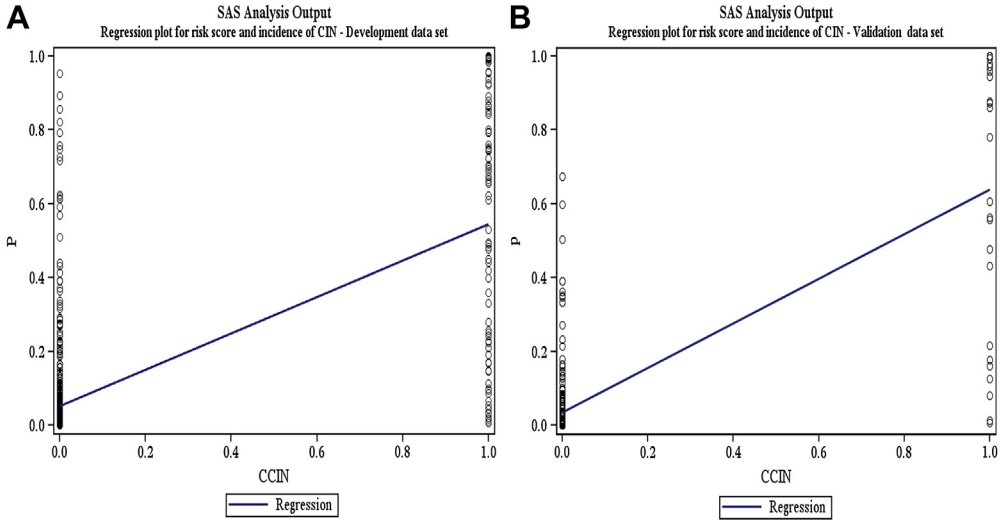

Fig. 2 – The relation between the increasing risk score and incidence of CIN. 'A' – development data set. 'B' – validation data set. The correlation coefficient of incidence of CIN with predicted score in development set, 'r' = 0.69 ($p < 0.0001$), and in the validation set, 'r' = 0.78 ($p < 0.0001$).

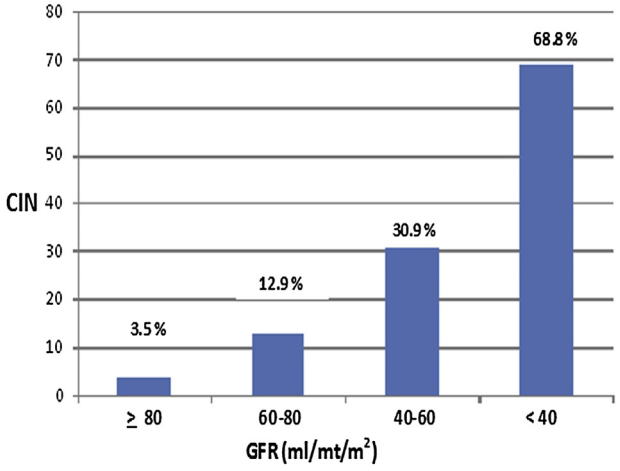

Fig. 3 – The increasing rates of CIN with decreasing GFR values are depicted below.

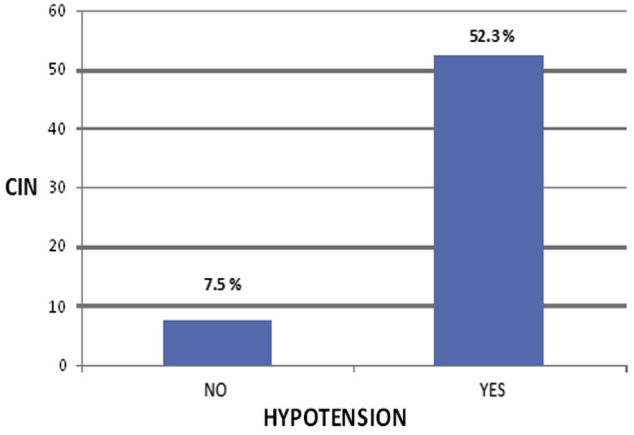

Fig. 5 – Occurrence of CIN with and without presence of hypotension.

Mehran et al[13] and 5.5% in the study conducted by Amal Abdel Ghani et al.[16] In an analysis by McCullough et al the incidence of CIN in patients undergoing PCI is 14.5% (in the derivation set of 1826 patients).[17] Overall, 0.8% required dialysis and the rate of dialysis was 35.7% in the CIN group. In-hospital mortality rates were 1.1% for patients without CIN and 7.1% for patients with CIN, all values were statistically significant. In our study, the rate of dialysis was 11.4% and mortality was 5.7% in the CIN group, there was no account of dialysis or mortality in the non CIN group. This may be due to the stringent exclusion criteria we have followed in our study to eliminate patients who are at high risk for events other than CIN.

Various factors have been identified as risk markers for CIN in different studies. Diabetes mellitus is proven to be a strong predictor for CIN.[13,17,18] However, in our study diabetes alone did not influence the outcome of CIN, but if it is associated with any microvascular consequences like retinopathy or neuropathy, then it is a strong predictor. This may be because of the higher ratio of diabetics (53%) in this study and it also indicates that diabetes not *per se* but when associated with

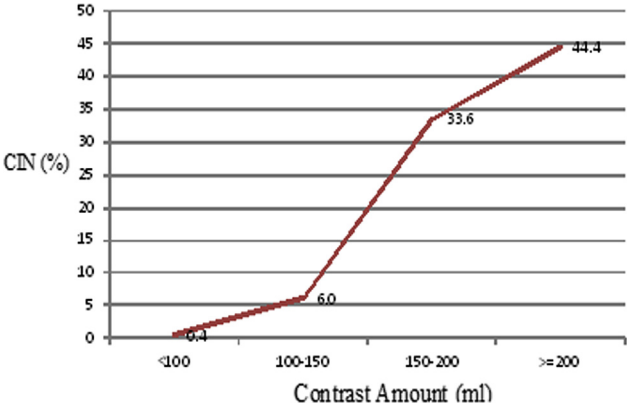

Fig. 4 – Line diagram showing the exponential rise of CIN with increasing contrast volume.

microangiopathy is a bad prognostic factor for CIN. Unlike other studies, we found that older age[13,18] or female gender[16,19] are not independent predictors for CIN, this may be due to the under representation of these subgroups in this study (age >70 years –13% and female gender – 16.4%). This is not uncommon in the Indian context where elderly or females receive fewer coronary interventions[20] and those who do receive usually belong to the higher economic strata and hence may represent lower risk peer group. Other established risk factors like peripheral vascular disease,[21,22] albuminuria,[23,24] anemia,[13,25] hypotension,[13,18] renal impairment[17,22] and high contrast volume[13,26] form the rest of the components of this risk scoring system.

Similar risk prediction models have been published previously.[13,16,21] Mehran et al developed and validated a scoring system in 8357 patients with eight variables consisting of hypotension (5 points), IABP (5 points), congestive heart failure (5points), chronic kidney disease (4 points), diabetes (3 points), age ≥75 years (4 points), anemia (3 points), and volume of contrast (1 point for each 100 cc). Based on the attained score, patients were further divided into low, moderate, high, very high risk groups, and the incidence of CIN, risk of RRT and mortality were calculated for each group. Our risk scoring system differs from this in few aspects. We have excluded IABP patients in our study as IABP use itself may precipitate renal dysfunction either by releasing atheroembolic milieu to renal circulation or by impeding the renal blood flow if placed low in the aorta and thus making it difficult to differentiate it from CIN. Albuminuria, which is a significant factor in our study, was not included in the analysis by Mehran et al. Our risk scoring system allows risk calculation pertaining to each individual rather than to a cluster. It also allows the actual values of the variables to be entered in to the formula rather than group them further, hence it is convenient to use, even when there is lack of standardized definitions pertaining to Indian population for diagnosis, as in the case of anemia. However, no formula to calculate individual risk of RRT or mortality was developed in this study. Thus, the scoring system proposed in this study is formed by easily available clinical, laboratory and procedural variables and allows

identification of high risk groups for developing CIN, allowing prophylactic measures to be employed early.

5. Study limitations

This is a study involving a single center in south India, hence multicentric validation across the country is required to authenticate this scoring system. This study does not involve the identification of long term implications of developing CIN. A further follow up of patients would have delineated the same.

6. Conclusions

CIN is a frequent complication following PCI, and is associated with complicated hospital stay and high mortality rate. The risk factor profile in Indian population as determined by this study is unique to the subcontinent and may also be applicable to other countries across the world. A simple risk scoring system can be developed using easily available clinical and procedural information to predict the probability of CIN following PCI. High risk groups can be identified using this risk scoring system and more vigilant preventive measures can then be applied for the prophylaxis of CIN.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ihj.2014.05.025.

Conflicts of interest

All authors have none to declare.

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