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Volume of contrast to creatinine clearance ratio: a novel pharmacokinetic index for prediction of contrast induced nephropathy in stage three chronic kidney disease patients undergoing coronary angioplasty

Authors
Dr Sanjai Pattu Valappil MD.DM.DNB, Dr Praveen Velappan MD.DM, Dr Sunitha Viswanathan MD.DM.FESC.FSCAI, Dr Alummoottil George Koshy MD.DM.FESC.FSCAI.FACC.FRCP, Dr Prabha Nini Gupta MD.DM.FSCAI, Dr Radhakrishnan Vallikkattu Velayudhan MD.DM.FESC. FACC, Dr Mathew Iype MD.DNB.DM.DNB, Dr Dilip Mazhavancheri Narayanan MD.DM
Department of Cardiology, Government Medical College, Thiruvananthapuram

Abstract
Objective: *The aim of the study was to identify the optimal 'Volume of contrast to Creatinine Clearance ratio' {V/CrCl} for prediction of contrast induced nephropathy {CIN} in stage III chronic kidney disease {CKD} patients undergoing coronary angioplasty.*
Methods: *This was a prospective observational study where stage III CKD patients, with an estimated glomerular filtration rate (eGFR) between 30-60 ml/mt undergoing elective percutaneous coronary intervention {PCI} over a period of 15 months were evaluated prospectively for the development of CIN. Receiver-operator characteristic {ROC} curves were used to identify the optimal sensitivity and specificity for the observed range of V/CrCl. The predictive value of V/CrCl for the risk of CIN was assessed using multivariable logistic regression.*
Results: *100 stage III CKD patients underwent PCI during the study period. The incidence of CIN was 29 %. Based on the 'Volume of contrast /Creatinine clearance ratio {V/CrCl} the quartiles of the V/CrCl ratio for all the patients were as follows: quartile (Q1) (<3.45, n=25); Q2 (3.45-4.28, n=25); Q3 (4.28-5.31, n=25); and Q4 (>5.31, n=25). The receiver-operator characteristic curve analysis indicated that a V/CrCl ratio of 4 was a fair discriminator for the development of CIN {C-statistic 0.69}. After adjusting for other known predictors of CIN, a V/CrCl ratio of 4 was found to be significantly associated with the development of CIN {OR: 2.849, 95 % CI: 0.972-8.363, p=0.05}*
Conclusion: *A V/CrCl ratio of > 4 was a significant and independent predictor of CIN in stage III CKD patients undergoing PCI.*
Keywords: *Contrast; nephropathy; angioplasty.*

Introduction

Iodinated radiocontrast is an intergral tool of interventional cardiology. It was the serendipitous observation of Osborne that the urine of syphilitic patients who were treated with iodine based compounds turned radioopaque which blossomed into the birth of iodine based contrast media. Osborne then performed the first successful clinical pyelogram at the Mayo clinic in 1923[(1)]. Subsequently it was Brooks in 1924 who pioneered the use of sodium iodide to perform the first ever angiogram of the femoral artery[(2)].

Multitudes of experiments with the modifications in the structure of iodine containing contrast agents to reduce their toxicity and improve efficacy have been underway since then. In 1968 Almén proposed new, low-toxicity, nonionic, mono-meric and dimeric contrast media, and since then the toxicity of different contrast media has mainly been attributed to their osmolality, viscosity, and chemotoxicity[(3)(4)(5)]. The principal deterrent to the use of intravascular iodinated contrast media is the development of contrast induced nephropathy {CIN}. CIN is defined as the contrast mediated damage to the renal function as manifested by the increase in serum creatinine by 0.5 mg/dl or a 25 % increase from the baseline[(6)]. A number of preventive measures have been in practice to tackle this serious complication such as pre- procedural hydration with isotonic saline, the use of iso-osmolar non-ionic contrast media , loading with N- acetyl cysteine, and the withdrawal of nephrotoxic drugs[(7)(8)(9)(10)(11)]. However the sine qua non in the prevention of CIN is and will always be the judicious use of contrast media. Multiple studies have been undertaken to identify the upper limit of contrast media that would predict the risk of CIN. The ratio of the volume of contrast media to the creatinine clearance is an effective pharmaco-kinetic index that has been studied in various populations for the prediction of CIN. [(12)(13)(14)(15)] Across numerous studies there is a wide variation in this index from as high as 6.15 to as low as 2.62. The current study was undertaken to identify the optimal 'Volume of contrast to Creatinine Clearance ratio' {V/CrCl} for prediction of contrast induced nephropathy {CIN} in stage III chronic kidney disease {CKD} patients undergoing coronary angioplasty.

Materials and Methods

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.

Study protocol

Inclusion criteria

1. Adults aged >18 years with CKD stage III as defined as eGFR of: 30-60 mL/ min /1.73 m2 calculated by the Cockcroft-Gault formula.
2. Patients admitted for elective PCI.

Exclusion criteria

1. Patients undergoing routine hemodialysis or peritoneal dialysis.
2. Patients admitted with ST elevation myocardial infarction {STEMI}.
3. Patients with cardiogenic shock.

Prophylactic measures for prevention of CIN were instituted in all the patients namely , continuous intravenous saline infusion (0.9%) 12 hours before to 24 hours 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 .

Definitions

CKD stage III: eGFR of: 30-60 mL/ min /1.73 m2 calculated by the Cockcroft- Gault formula.

CIN: CIN was defined as an increase in serum creatinine concentration of 0.5 mg/dL (44mol/L) or 25% above baseline within 48 hours after contrast administration.[(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. Receiver-operator characteristic {ROC} curves were used to identify the optimal sensitivity and specificity for the observed range of V/CrCl. The risk predictors for CIN were initially screened for univariate associations at p=0.20 and the identified variables were then assessed in a forward stepwise manner using a p value criterion of <0.05. 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 .The statistical analyses were performed with SPSS software {version 17.0}. Based on the 'Volume of contrast /Creatinine clearance ratio {V/CrCl} the study patients were stratified and analysed into quartiles.

Results

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. Based on the 'Volume of contrast /Creatinine clearance ratio {V/CrCl} the quartiles of the V/CrCl ratio for all the patients were as follows: quartile (Q1) (<3.45, n=25); Q2 (3.45-4.28, n=25); Q3 (4.28-5.31, n=25); and Q4 (>5.31, n=25).

Baseline demographics

The baseline demographic characteristics of the patients among the various V/CrCl ratio quartiles are shown in table 1 and 2

Table1: Baseline demographic characteristics of the patients among the V/CrCl ratio quartiles.

	Dye Volume /eGFR								P
	Q1 (<3.45, N= 25)		Q2 (3.45–4.28, N= 25)		Q3 (4.28– 5.31, N= 25)		Q4 (>5.31, N= 25)		
	N	%	N	%	N	%	N	%	
Demographics									
Age >75	1	4	2	8	5	20	8	32	**0.048**
Male	20	80	19	76	21	84	23	92	0.479
HT	14	56	16	64	19	76	15	60	0.488
DLP	7	28	6	24	7	28	7	28	0.985
Smoker	14	56	9	36	8	32	13	52	0.239
Anemia	8	32	14	56	13	52	15	60	0.200
DM	14	56	16	64	14	56	13	52	0.855
EF <50%	15	60	17	68	18	72	17	68	0.835
Mehran Risk score									
MRS<10	16	64	15	60	16	64	11	44	**0.048**
11-15	9	36	10	40	8	32	9	36	0.656
>15	0	0	0	0	1	4	5	20	**0.032**

Table 2: Baseline demographic characteristics of the patients among the V/CrCl ratio quartiles

	Dye Volume /eGFR								p
	Q1 (<3.45, N= 25)		Q2 (3.45–4.28, N= 25)		Q3 (4.28– 5.31, N= 25)		Q4 (>5.31, N= 25)		
	mean	sd	mean	sd	mean	sd	mean	sd	
Demographics									
Age	58.7	8.9	62.0	8.0	65.9	8.8	68.5	8.7	**.023**
BMI{body mass index}	26.0	3.3	24.8	2.1	22.0	3.1	20.1	2.5	**.040**
Mehran Risk score	9.2	2.7	9.7	3.1	10.1	3.0	11.5	3.7	**.049**
Lab parameters									
Men LVEF	55.0	10.7	53.2	11.0	56.9	11.8	52.9	13.0	.603
Hb baseline	12.1	1.4	12.0	1.9	12.0	1.0	11.9	1.4	.971
S.Cr Baseline	1.48	0.20	1.48	0.23	1.5	0.17	1.60	0.22	.139
eGFR	51.2	8.8	47.2	5.6	46.6	8.9	41.4	6.4	**.001**
MDRD	51.6	7.2	51.6	6.8	50.4	6.0	46.2	7.9	**.021**

There was a definite trend among all the quartile of patients with the patients in the higher quartiles being older p=0.023}, with a lower BMI {body mass index} {p=0.040}, with a lower eGFR {p=0.001} and higher Mehran risk scores {MRS}{p=0.049}.

Procedural characteristics

The procedural characteristics of the patients are shown in table 3 and table 4.

Table 3: The procedural characteristics of the patients among the V/CrCl ratio quartiles

	Dye Volume /eGFR								P
	Q1 (<3.45, N= 25)		Q2 (3.45–4.28, N= 25)		Q3 (4.28– 5.31, N= 25)		Q4 (>5.31, N= 25)		
	N	%	N	%	N	%	N	%	
Procedural Characteristics									
Mutivessel PCI	12	48	13	52	16	64	17	68	**0.050**
CTO PCI	10	40	11	44	15	60	18	72	**0.037**
Events									
HD	0	0	0	0	1	4	1	4	0.564
Death	1	4	0	0	0	0	2	8	0.286
CIN	2	8	4	16	9	36	14	64	**0.034**

Table 4: The procedural characteristics of the patients among the V/CrCl ratio quartiles

	Dye Volume /eGFR								p
	Q1 (<3.45, N= 25)		Q2 (3.45–4.28, N= 25)		Q3 (4.28– 5.31, N= 25)		Q4 (>5.31, N= 25)		
	mean	sd	mean	sd	mean	sd	mean	sd	
Procedural Characteristics									
Number of stents used	1.5	1.2	1.9	1.2	2.2	1.2	2.4	1.2	**.033**
Volume of Dye used	154.8	30.3	176.8	23.6	219.2	46.5	274.8	59.4	**.001**

It was seen that the patients in the highest quartiles had more of multivessel PCI {p=0.050} and CTO {Chronic total occlusion} PCI {p=0.037}. Importantly higher numbers of stents were used with increasing V/CrCl quartiles {p=0.33}.

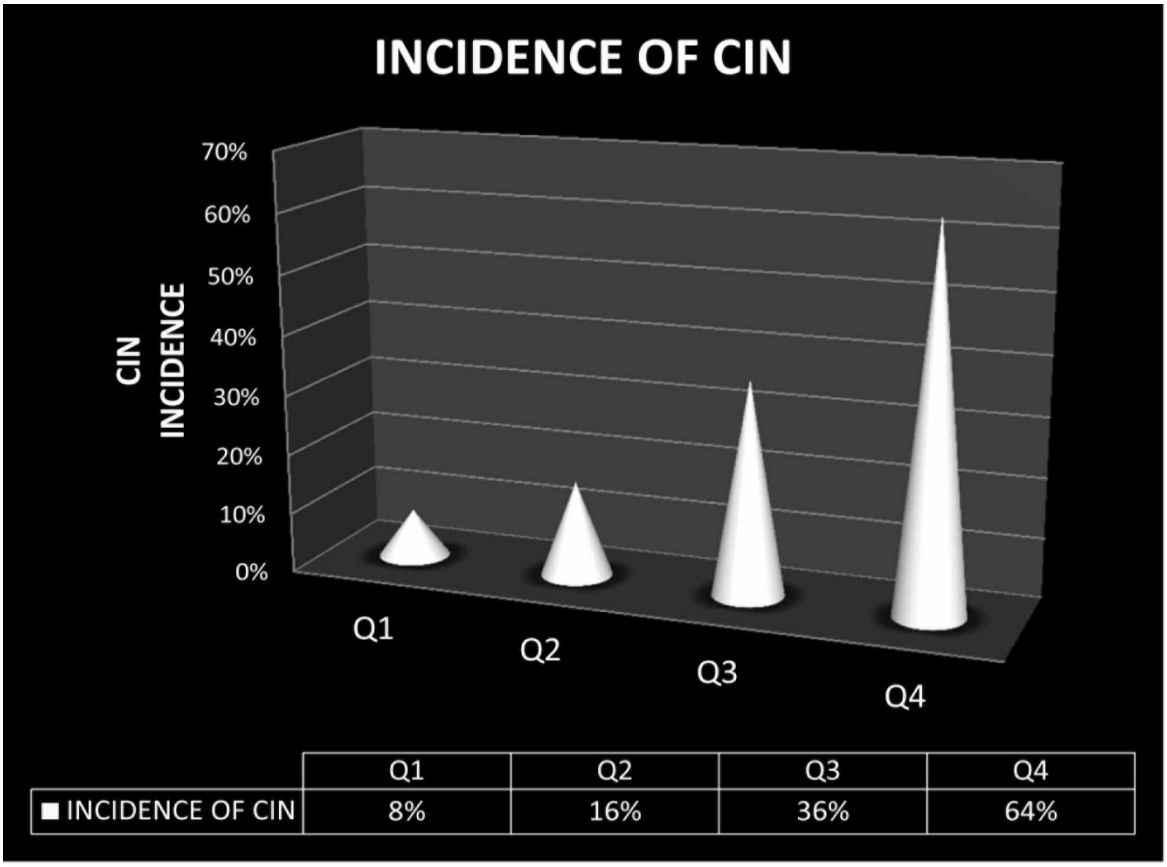
Events

There were a total of 29 patients who developed CIN. It was seen that with increasing quartiles of V/CrCl there was a significantly higher incidence of CIN among the patients {p=0.035}. The patients with CIN were followed up at 2 weeks and 6 weeks for requirement of hemodialysis and cardiac death. Among the 29 patients who developed CIN two patients required hemodialysis one each in the third and the fourth quartile. There were 3 deaths in total, two of which were in the highest quartile {V/CrCl>5.31} and one in the lowest quartile .This is shown in table 5 and Figure 1

Table 5: Table showing incidence of requirement of hemodialysis , death and CIN among the V/CrCl quartiles.

	Dye Volume /eGFR								P
	Q1 (<3.45, N= 25)		Q2 (3.45–4.28, N= 25)		Q3 (4.28– 5.31, N= 25)		Q4 (>5.31, N= 25)		
	N	%	N	%	N	%	N	%	
Events									
HD	0	0	0	0	1	4	1	4	0.564
Death	1	4	0	0	0	0	2	8	0.286
CIN	2	8	4	16	9	36	14	64	**0.034**

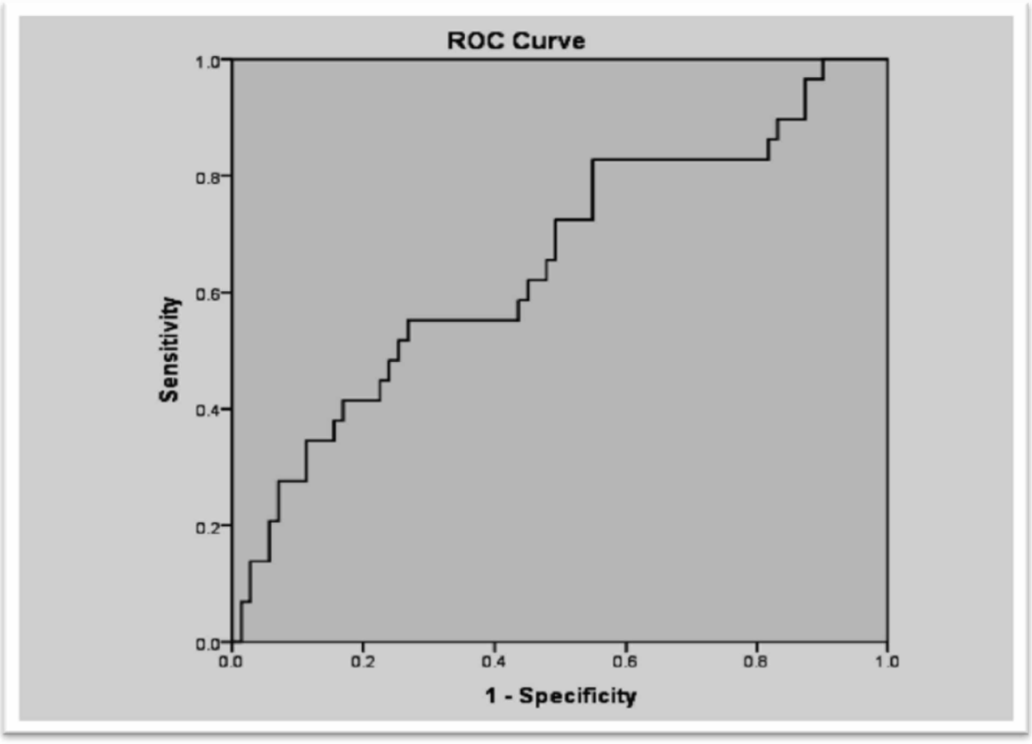
Figure 1: Figure showing the incidence of CIN among the V/CrCl quartiles.



Predictive accuracy of V/CrCl for CIN

The ROC curve analysis showed that the optimal cut-off level for the V/CrCl ratio was 4, which exhibited a 72.4% sensitivity, 50.7% specificity, 37.5% positive predictive value and 81.8% negative predictive value for predicting CIN {C statistic :0.64}.

Figure 2: ROC curve for finding the optimum cut off value of Dye volume EGFR ratio for predicting CIN



The conventional risk factors for CIN including anaemia, ratio of Volume of contrast to the creatinine clearance {V/CrCl} > 4, age more than 75 years, ejection fraction less than 50%, usage of loop diuretics, periprocedural hypotension, the presence of type 2 diabetes mellitus, 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 .On multivariate analysis it was seen that V/CrCl ratio of >4 {OR: 2.849, 95 % CI: 0.972-8.363, p=0.05}, anemia {OR: 3.136, 95 % CI: 0.822-7.773p=0.04} and usage of loop diuretics {OR: 2.112, 95 % CI: 0.776-6.563p=0.05} were found to be statistically significant.

Discussion

CIN has been a bane of interventional cardiology. The unforeseen rise in the serum creatinine after a successful intervention is nightmare for the treating physician. Numerous risk factors have traditionally been associated with an incremental risk of CIN; the foremost among these are the baseline renal dysfunction and the volume of contrast used. Several studies have sought to establish a relationship between the total volume of contrast media administered, baseline renal function, and risk of CIN after PCI. Cigarroa et al in 1989 established the upper limit of contrast exposure for prediction of CIN as five times the body weight divided by the serum creatinine [(16)]. Though this formula has been validated in other studies, it falls short as it does not include the patient's age, which by itself is a portentous risk factor for CIN [(17)]. The volume of contrast divided by the creatinine clearance {V/CrCl} ratio is an exceptional pharmacokintetic index as it takes into account the four major risk factors for CIN namely: volume of contrast, serum creatinine, body weight, age and sex of the patient. The first study which established the V/CrCl as an index for CIN was by Altmann in 1997 who studied 152 patients with chronic kidney disease (defined as a baseline creatinine > 2.0 mg/dl) who underwent angiography, it was seen that a ratio of > 6 predicted CIN[(18)]. Subsequently Laskey studied 3,179 consecutive unselected patients undergoing PCI and found that a V/CrCl ratio of > 3.7 predicted the patient at risk for an abnormal early postprocedural increase in creatinine {an increase of >0.5 mg/dl within 24 hours}[(13)]. The largest study to date which studied the V/CrCl ratio was by Gurm et al who analysed 58957 patients undergoing angiography [(12)]. The study established that restricting the contrast volume to less than thrice and preferably twice the creatinine clearance was valuable in reducing the risk of CIN.

Despite the multitude of data regarding the optimal ratio of V/CrCl in the prediction of CIN, there is a paucity of data analysing the ideal V/CrCl ratio in stage III CKD patients undergoing PCI. Our study cohort of CKD stage III patients had a high incidence of the baseline risk factors for CIN 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 (29%). In the current study it was unequivocally established the V/CrCl ratio > 4 was an independent risk factor for the development of CIN in stage III CKD patients undergoing PCI.

Interstingly there is a wide variation in the V/CrCl ratio for prediction of CIN among the available studies. Different studies have quoted different cut off values for predicting CIN ranging from V/CrCl >2.76 (Yong Liu et. al) to >6.15 (Barbieri et. al)[(14)(15)]. These data are not strictly comparable with those reported in the current study because of the differences in the total number of the patients studied, the number of patients with chronic kidney disease, the definition of CIN and the overall incidence of CIN. It is pertinent to recognize that the predictive value of V/CrCl depend upon the baseline incidence of CIN in the population which in turn depends on baseline risk parameters as well as the definition used for the diagnosis of CIN. For instance, in the study by

Altmann et. al CIN was defined as a rise in serum creatinine of more than 1mg/dl within 48hrs ,the austere criteria resulted in a low incidence of CIN in the study of only 7%[18]. Importantly this could have lead to the higher cutoff values for V/CrCl. Similarly the study by Laskey et al analysed patients only for the early {within 24 hours} rise in serum creatinine, in all probabability this could have underestimated the incidence of CIN and altered the V/CrCl ratio.

In contrast to the previous studies, we included patients with CKD Stage III and tried to establish a simple index, easily obtainable at the bedside by dividing the volume of contrast media received by the patient's creatinine clearance to predict the occurrence of CIN. Our study demonstrates that in even in patients with baseline renal dysfunction, the V/CrCl ratio can independently predict the occurrence of CIN when a threshold of 4 is exceeded.

Although numerous clinical, demographic, and procedural factors are significantly associated with CIN after PCI, the fact that V/CrCl remained independently associated with the risk of an early post procedural creatinine increase after adjustment for these important confounders is supportive of our original hypothesis. Thus, multiplying a patient's estimated creatinine clearance by 4 would give an estimate of the maximum amount of contrast to be used for a given procedure, above which the likelihood of developing renal injury would be monumental.

Limitations

Our study had a few limitations. Impotranaly our analysis is limited by its post hoc, observational nature. Further CIN has a multifactorial causation in which contrast media is only one of the many factors. Although statistical adjustment was attempted by means of a multivariable model, the impact of unidentified confounders on our findings cannot be entirely ruled out.

Abbreviations

Contrast induced nephropathy: CIN
Chronic kidney disease: CKD
Coronary artery disease: CAD
Chronic total occlusion: CTO
Estimated glomerular filtration rate: eGFR
Percutaneous coronary intervention: PCI
Mehran risk score: MRS
European Society of Urogenital Radiology: ESUR
Central venous pressure: CVP
Modification of Diet in Renal Disease: MDRD

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