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A Study on Contrast-Induced Nephropathy Following Emergent And Elective Percutaneous Coronary And Peripheral Intervention: Diagnosis Through Biomarkers As Serum Creatinine And Cystatin C

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Abstract
Objective: *It was aiming to know the diagnostic efficacy of biomarkers as serum creatinine (SCr) and serum cystatine C (SCysC) to evaluate prognosis of CIN in the hospital-admitted patients among eastern Indians.*
Methods: *100 patients were selected for primary coronary angioplasty between February2015 – January2016. Out of 100 patients, 95 patients were evaluated for development of CIN and categorized into CIN and non-CIN groups, which was further divided into male, female and combination of them. SCr value was checked on day-1 (baseline), after 24hr (day-2) and 48hr (day-3). SCysC value was also estimated on day-1 (baseline) and after 24hr (day-2). Statistical analyses were done in all groups at P<0.05 level.*
Results: *The prospective study revealed that day-1 SCr values were significantly (P<0.01) higher in combined and male patients but in females no significant difference was observed for the CIN groups compared with non-CIN groups. The significantly increased values were also observed in both combined (P<0.001) and males (P<0.01) for day-2 and 3, when compared between CIN and non-CIN groups. But for female patients only significant difference (P<0.05) was found on day-3 SCr. Another marker, SCysC was also increased without statistical significant values in CIN groups after 24h duration, when compared to day-1. But in non-CIN groups, SCysC was found in decreasing trend with statistically significant (P<0.001, P<0.001 and P<0.05) for all groups in comparison with day-1. For diagnostic accuracy in relation to SCr and SCysC, it was observed that 78.95%, 81.71% and 61.54% for combined, males and females respectively.*
Conclusion: *The novel biomarker SCysC can be suitable diagnostic tool to predict the occurrence at early stage (24hr duration) of CIN. The present results revealed that SCysC was decreased indicating renal function improvement after intravenous fluid therapy.*

Keywords: *Biochemical biomarkers, Contrast-induced nephropathy, Percutaneous coronary and peripheral intervention, Risk of CIN, Serum creatinine and cystatin C*

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I. Introduction

Contrast-induced nephropathy (CIN) is now termed as contrast-induced acute kidney injury (CI-AKI) to align with the Kidney Disease International Global Outcomes (KDIGO) [1]. Contrast induced acute kidney injury (CI-AKI) is defined by KDIGO guidelines as an increase in serum creatinine of 0.3 mg/dl or greater within 48hr of contrast use or a 50% or greater increase from baseline serum creatinine. CI-AKI has been consistently associated with the risk for development of end stage renal disease, re-hospitalization for cardiac renal and other causes, and all-cause mortality.

CIN is the third most common cause of hospital acquired acute renal injury representing about 12% of the cases. The incidence of CIN varies between 0 and 24% depending on patient's risk factors [2]. It is generally a transient and reversible form of acute renal failure [3]. Generally, the patients who develop CIN need to have longer duration of hospitalization causing an increasing morbidity and mortality with financial overburden [4]. The treatment of CIN is mainly supportive, consisting of careful fluid and electrolyte management, although dialysis may be required in some cases [5]. The patients with pre-existing chronic kidney disease (CKD) are at increased risk of developing AKI post-PCI (percutaneous coronary intervention) [6]. The magnitude of this increased risk is directly associated with the severity of AKD (acute kidney disease) and may be as high as 50% in patients [7-8]. In addition, albuminuria, proteinuria, diabetes, heart failure, age older than 75 years, female

gender, anaemia, hyperglycaemia, contrast volume, cardiogenic shock, use of IABP (intra-aortic balloon pump), additional use of nephrotoxic drugs has all been identified as baseline risk factor for CI-AKI.

Several researchers have documented that CIN majorly occurred due to percutaneous coronary and peripheral intervention when iodinated contrast is used [9-11]. Moreover, in CIN, the detection of kidney function, biomarkers assessment with special reference to SCr and SCysC are the suitable parameters as per Briguori et al. [12]. In this context, Shukla et al. [11], Briguori et al. [12] and Herget-Rosenthal et al. [13] have reported SCysC is more reliable markers than SCr for the detection of AKI.

In the present study, it was aiming to evaluate diagnostic efficacy on biomarkers with special reference to SCr and SCysC, and prognosis along with risk of contrast-induced acute kidney injury (CI-AKI) in the hospital-admitted patients of eastern India, who were undergoing emergent and elective coronary and peripheral intervention.

II. Materials and Methods

2.1 Recruitment of patients

A total of 100 patients of average age (20-80 years) were selected, but 5 patients were lost in follow-up and finally 95 patients of which males (82 nos.) and females (13 nos.) were recruited in the present study. All the patients were admitted in cardiology unit, Nilratan Sircar Medical College and Hospital, Kolkata, India during the study period of February2015 – January2016. In present work, the patients were enrolled fulfilling the inclusion criteria such as chronic stable angina undergoing coronary angiography followed by angioplasty, haemodyanamically stable acute coronary syndrome patients undergoing percutaneous intervention and patients undergoing peripheral angiography and angioplasty. The present study was evaluated and approved by ethical committee of Nilratan Sircar Medical College and Hospital and all the patients were evaluated, prior written consent duly signed by them.

1.2 Exclusion criteria

The exclusion criteria were made for patients having pre-existing chronic kidney disease with e GFR<30ml/min/1.73m², systolic blood pressure ≥160mmHg and/or diastolic blood pressure ≥90mmHg, systolic blood pressure <90mmHg, with NYHA (New York Heart Association) class III and IV, with pulmonary edema, evidence of acute infection, advance liver failure, total leucocyte count >14,000/cmm and urine output in last 24 hrs<400 ml.

1.3 Study design

A total 100 patients were recruited in our study. Initially 50 patients were subjected to angiography (coronary and peripheral) only. And rest 50 patients were subjected to coronary angiography followed by PTCA (percutaneous coronary angioplasty). But consideration of coronary angioplasty after coronary angiography was guided by established guidelines and interventionist's opinion. Finally, after angiography 38 patients were subjected to single vessel or multi-vessel coronary angioplasty. 5 patients, among 38 patients died within 2days of index hospitalization (before collection of blood samples) and were excluded from study. The data of 95 patients were only analysed in our present study. 62 patients among underwent angiography (both coronary and peripheral) only and rest 33 patients underwent coronary angioplasty following coronary angiography. Baseline SCr estimation was done before intervention and 24hr and 48hr after intervention, respectively. SCr level was followed up at 3 month and 6 month. SCysC was measured before cardiac catheterization and 24hr after intervention. SCysC level was correlated with SCr level for predicting CIN. On the basis of SCysC, CIN was defined by >10% increase from baseline values in 24hr of contrast exposure and SCr based CIN was defined by increase of 0.3mg/dl in absolute value or 50% increase from baseline within 48hr. The patients received treatment according to the present guidelines. In patients without heart failure pre-catheterization hydration was done 0.9% normal saline at a rate of 1mi/kg/hr for 12hr pre and post operatively with the aim of post-procedural urine output 150ml/hr. The contrast media was used as low as possible. All patients were received omnipaque300 (Iohexol) during angiography or angioplasty. The SCr was estimated in standardized manner of the nephrology department. The SCysC was estimated by ELISA (Enzyme-Linked Immune Sorbent Assay) method in the biochemistry department. The patients were followed-up for one year.

1.4 Study of biochemical biomarkers in blood

A 4-ml blood sample was collected from each patient and kept in a plain vial. The blood samples were then centrifuged at 2500 rpm for 10 min at 4^{o}C to obtain serum for different biochemical test. Human SCysC was analysed by using ELISA kit (RayBio®), is an assay for quantitative measurement of human SCysC at a wavelength of 450nm. The SCr was analysed by modified Jaffe's method as mentioned by Delanghe and Speeckaert [14] at a wavelength of 520nm. The routine analyses for lipid profile, blood sugar, renal function test, liver function test were done in the biochemistry department by standardized method.

1.5 Study of cardiac parameters

The echocardiography was done by GE Vivid S6 Echocardiography machine and parameters measured are left ventricular ejection fraction, regional wall motion abnormality, valvular regurgitation, pericardial effusion and documentation of other possible complications of ischaemic heart disease. Left ventricular ejection fraction was measured by modified Simpson method as mentioned in literature [15]. Patients were subjected to coronary angiography (CAG), peripheral angiography (PAG) and percutaneous coronary angioplasty (PTCA) as per guidelines of American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC).

1.6 Study of CIN

The contrast-induced nephropathy (now known as contrast-induced acute kidney injury) was defined by KDIGO 2012 guideline [1] as increase in serum creatinine of 0.3mg/dl or greater or 50% or greater increase from baseline serum creatinine within 48hr of contrast use. It was also studied CIN as increase in SCysC of value ≥10% from baseline serum value at 24hr after contrast administration.

1.7 Study of CIN risk factor

SCysC level was correlated with creatinine level for predicting risk for CIN as per method developed by researchers [16-17]. Finally, the prognostic significance of risk score on rates of in-hospital dialysis and one-year mortality was estimated.

1.8 Follow-up

The assessment of serum urea/creatinine level, Na/K+ balance, etc. were followed up at 1 month, 3 month and 6 month for all the patients with CIN.

1.9 Statistical analysis

The statistical analyses were done by using software (SPSS, version 20). Categorical variables are expressed as number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes. Continuous variables are expressed as Mean ± Standard Deviation and compared across the 2 groups Mann Whitney test. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

III. Results

In our present work an incidence of CIN and probable risk factors were identified in the patients of acute renal failure following emergent and elective percutaneous coronary and peripheral intervention. Among the study populations 63.2% of patients underwent coronary angiography (CAG). 34.7% of patients underwent percutaneous coronary angioplasty (PTCA), 2.1% patients had peripheral angiography (PAG). The study was evaluated through prognosis of disease, biomarkers assessment and risk factor of CIN.

Table 1 describes details of baseline study characteristics among 95 patients and divided into two groups as without-CIN and with-CIN after 48h intervention. For each group, combined (n = 72 and n = 23), male (n =62 and n = 20) and female (n = 10 and n = 3) patients were evaluated separately. The mean ± SD age were 59.09 ± 8.57, 58.60 ± 8.79 and 62.11 ± 6.72 years for without-CIN group and 61.13 ± 9.04, 61.41 ± 9.32 and 59.25 ± 7.63 years in CIN group of combined, male and female sub-group respectively. In case of body weight (Kg), the mean ± SD values were 60.61 ± 10.37, 61.09 ± 10.92 and 57.67 ± 5.59 for without-CIN and 64.94 ± 14.57, 62.52 ± 15.48 and 61.00 ± 4.69 for with-CIN of combined, male and female sub-group respectively. The categorization of smoking habit revealed 32 (65.3%) only in males not in female of without-CIN group while combined 17 (34.7%), males 15 (31.9%) and females 2 (100.0%) of CIN group. 10 (73.0%) patients in combined, 8 (47.1%) patients in male and 2 (50.0%) patients in female of non-CIN groups while 11 (27.0%) patients in combined, 9 (52.9%) patients in male and 2 (50.0%) patients in female of CIN groups had CKD. The mean ± SD dye volumes (ml) used were 80.25 ± 40.38, 71.75 ± 31.06 and 132.22 ± 52.86 for without-CIN while 132.22 ± 52.86, 96.06 ± 57.14 and 99.93 ± 59.17 for with-CIN groups of combined, male and female sub-group respectively.

Fig 1. showed that on day-1 (baseline), the SCr data were significantly ($P<0.01$) increased of combined (1.37 ± 0.42) and males (1.40 ± 0.44) groups but was also increased without statistically significant ($P = 0.29$) in females (1.18 ± 0.26) with-CIN group compared to those without-CIN group of combined (1.16 ± 0.27), males (1.17 ± 0.27) and females (1.04 ± 0.22). On the day-2, SCr values were also significantly ($P<0.001$; $P<0.01$) increased for combined (1.50 ± 0.48) and males (1.59 ± 0.50) group but also increased in females (1.40 ± 0.24) without statistically significant ($P = 0.16$) of with-CIN group compared with those without-CIN group of combined (1.20 ± 0.28), male (1.21 ± 0.27) and female (1.14 ± 0.27) sub-group. After 48hr (day-3), SCr values were also observed significantly ($P<0.001$; $P<0.001$ and $P<0.05$) higher for combined (1.93 ± 0.67), males (2.04 ± 0.69) and females (1.63 ± 0.34) of with-CIN group compared with those without-CIN group of combined (1.22 ± 0.26), males (1.22 ± 0.27) and females (1.22 ± 0.24).

It was observed post 3 month and 6 month, SCr levels were decreased without statistically significant differences (P = 0.35, P = 0.49) and (P = 0.19, P = 0.40) in the non-CIN group of patients of combined (1.12 ± 0.24 and 1.13 ± 0.25) and males (1.11 ± 0.24 and 1.13 ± 0.26) but in females increased without any statistically significant differences (P = 0.36, P = 0.41) in females (1.14 ± 0.26 and 1.12 ± 0.20) compared to day-1 of combined (1.16 ± 0.27), males (1.17 ± 0.27) and females (1.04 ± 0.22) sub-groups. It was also observed an increasing trend without statistically significant level (P = 0.58, P = 0.87), (P = 0.62, P = 1.00) and (P = 0.68, P = 0.48) in the with-CIN groups of combined (1.43 ± 0.30 and 1.39 ± 0.39), male (1.46 ± 0.31 and 1.40 ± 0.42) and female (1.25 ± 0.10 and 1.30 ± 0.10) patients in comparison with day-1 of with-CIN group of for combined (1.37 ± 0.42), male (1.40 ± 0.44) and female (1.18 ± 0.26) patients respectively (Fig. 1).

The present data were evaluated on the basis of increasing baseline SCr concentrations (mg/dl) in the total studied population of CIN and non-CIN groups (Table 2). Most of the study population about 40 patients (42.11%) had found baseline SCr level between 1-1.3mg/dl. Among them about 10 patients (32.26%) developed CIN and about 30 patients (46.88%) did not develop CIN. About 16 patients (16.84%) had observed SCr between 1.3-1.6 mg/dl. Out of them, 9 patients (29.03%) developed CIN and 7 patients (10.94%) did not develop CIN. Only 17 (17.89%) patients had observed baseline SCr >1.6mg/dl. The patients with higher baseline SCr had the more increase risk for CIN with statistically significant level (P<0.05).

Table 1: Baseline characteristics of study population without and with-CIN

Parameters	Without-CIN			With-CIN		
	Combined (n = 72)	**Male (n = 62)**	**Female (n = 10)**	**Combined (n = 23)**	**Male (n = 20)**	**Female (n = 3)**
Age (Years), M±SD	59.09±8.57	58.60±8.79	62.11±6.72	61.13±9.04	61.41±9.32	59.25±7.63
Body weight (Kg), M±SD	60.61±10.37	61.09±10.92	57.67 ± 5.59	64.94±14.57	62.52±15.48	61.00±4.69
Smokers, n(%)	32(65.3)	32(65.3)	0(0.0)	17(34.7)	15(31.9)	2 (100.0)
History of CKD, n(%)	10(73.0)	8(47.1)	2(50.0)	11(27.0)	9(52.9)	2(50.0)
AWMI, n(%)	18(85.7)	14(87.5)	4(80.0)	3(14.3)	2(12.5)	1(20.0)
CSA, n(%)	25(59.5)	20(58.8)	5(62.5)	17(40.5)	14(41.2)	3(37.5)
IWMI, n(%)	4(36.4)	4(36.4)		7(63.6)	7(63.6)	
NSTEMI, n(%)	9(69.2)	9(69.2)		4(30.8)	4(30.8)	
PAD, n(%)	2(100.0)	2(100.0)		0(0.0)	0(0.0)	
UA, n(%)	6(100.0)	6(100.0)		0(0.0)	0(0.0)	
LSE, M±SD	81.81±12.33	80.44±11.05	90.22±16.75	79.99±14.27	77.96±11.09	89.00±28.76
SBP, M±SD	125.63 ± 17.98	125.45 ± 18.34	126.67 ± 16.58	131.87 ± 14.99	133.04 ± 13.82	124.00 ± 22.32
DBP, M±SD	75.50±8.73	75.13±9.02	77.78±6.67	74.32±9.40	74.52±9.63	73.00±8.87
LVEF, M±SD	53.28±10.79	56.11±10.54	52.82±10.85	55.94±11.80	57.00±11.80	48.75±10.31
Fluid/precath, M±SD	1159.86 ± 323.74	1187.84 ± 332.44	988.89 ± 202.76	1183.87 ± 287.88	1192.59 ± 274.46	1125.00 ± 478.71
Fluid/postcath, M±SD	1248.44 ± 290.04	1281.82 ± 295.70	1044.44 ± 133.33	1200.00 ± 333.67	1192.59 ± 333.89	1250.00 ± 378.59
UO precath, M±SD	1136.72 ± 257.93	1135.45 ± 196.66	1144.44 ± 512.62	1393.55 ± 344.18	1403.70 ± 314.07	1325.00 ± 567.89
UO postcath, M ± SD	1215.63 ± 280.00	1180.00 ± 244.31	244.31 ± 390.51	1380.65 ± 324.72	1396.30 ± 328.44	328.44 ± 320.16
D1-SCr (mg/dl), M±SD	1.16±0.27	1.17±0.27	0.27±0.22	1.37±0.42	1.40±0.44	0.44±0.26
D1-SCysC (mg/l), M±SD	13.41±3.03	13.59±3.08	12.32±2.52	13.12±1.90	13.48±1.26	10.71±3.08
Dye (ml), M±SD	80.25±40.38	71.75±31.06	132.22±52.86	96.06±57.14	99.93±59.17	70.00±35.59
NYHA 1, n(%)	37(66.1)	34(68.0)	3(50.0)	19(33.9)	16(32.0)	3(50.0)
NYHA 2, n(%)	23(65.7)	17(60.7)	6(85.7)	12(34.3)	11(39.3)	1(14.3)
NYHA 3, n(%)	4(100.0)	4(100.0)		0(0.0)	0(0.0)	
Diabetes, n(%)	27(60.0)	20(58.8)	7(63.6)	18(40.0)	14(41.2)	4(36.4)
Hypertension, n(%)	36(59.0)	29(58.0)	7(63.6)	25(41.0)	21(42.0)	4(36.4)
Risk score, M±SD	3.27±2.58	2.84±2.36	5.89±2.42	4.35±1.84	4.11±1.72	6.00±2.00
RISK, M ± SD	8.82±2.64	8.21 ± 2.05	12.56 ± 2.87	9.18 ± 2.89	9,19 ± 2.90	9.13±3.25

AWMI = Anterior wall myocardial infarction; CSA = Chronic stable angina; IWMI = Inferior wall myocardial infarction; NSTEMI = Non ST segment elevation myocardial infarction; PAD = Peripheral artery disease; UA = Unstable angina; UO = Urine output; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; LVEF = Left ventricular ejection fraction; Cr = Creatinine; CysC = Cystatin C; CIN-Contrast induced nephropathy; NYHA = New York Heart Association

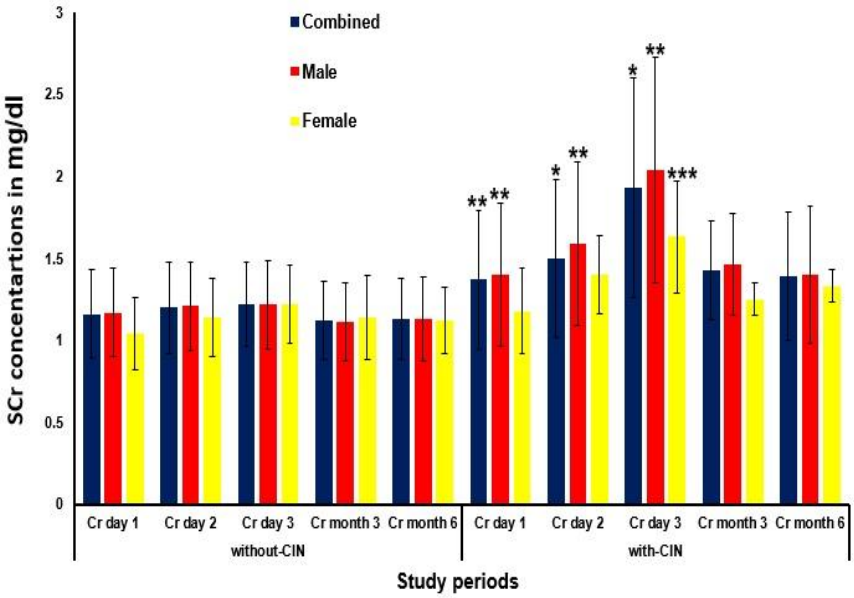

Fig 1: Comparison between without and with-CIN of combined, male and female subjects for the estimation of creatinine (mg/dl) [non-CIN combined n=72; males n=62 and females n=10 and CIN combined n=23; males n=20 and females n=3; *P<0.001; **P<0.01 and ***P<0.05]

Table 2: Statistical correlation of baseline SCr and incidence of CIN

		CIN by SCr		Total	P- value
		No	Yes		
D1-SCr	<1 mg/dl	18(28.13)	4(12.9)	22(23.16)	P<0.05
	1-1.3 mg/dl	30(46.88)	10(32.26)	40 (42.11)	
	1.3-1.6 mg/dl	7(10.94)	9(29.03)	16 (16.84)	
	>=1.6 mg/dl	9(14.06)	8(25.81)	17 (17.89)	
Total		64(100)	31(100)	95(100)	

In case of serum cystatin C (Fig. 2), it was observed for patients of without-CIN group, the baseline (day 1) value of SCysC (mg/l) for combined (13.41 ± 3.03), male (13.59 ± 3.08) and female (12.32 ± 2.52) group had lower value without any significant changes (P = 0.67, P = 0.88 and P = 0.37) when compared to with-CIN group of patients of combined (13.12 ± 1.90), males (13.48 ± 1.26) and females (10.71 ± 3.08).

It was also observed after 24h (day-2) duration, SCysC level was decreased with highly significant changes (P<0.001, P<0.001 and P<0.05) in the non-CIN group of patients of combined (7.53 ± 4.99), male (7.39 ± 4.23) and female (8.38 ± 4.59) sub-group compared to baseline data (day-1). The patients of with-CIN groups also showed a decreasing trend without significant differences (P = 0.53, P = 0.52 and P = 0.92) of combined (12.36 ± 5.44), male (12.65 ± 5.65) and female (10.45 ± 3.64) sub-groups in comparison to day-1 (Fig. 2).

Table 3 indicates SCysC measured in baseline just before coronary intervention (D1) and repeat SCysC was also measured 24 hours after (D2) coronary interventions. Among the total study population 23 patients (24.2%) had increased in SCysC more than 10% from baseline fulfilling criteria for CIN. About 12 patients (12.6%) patients had increased in SCysC from baseline but that was found less than 10%. About 60 (63%) patients had decreased in SCysC from baseline.

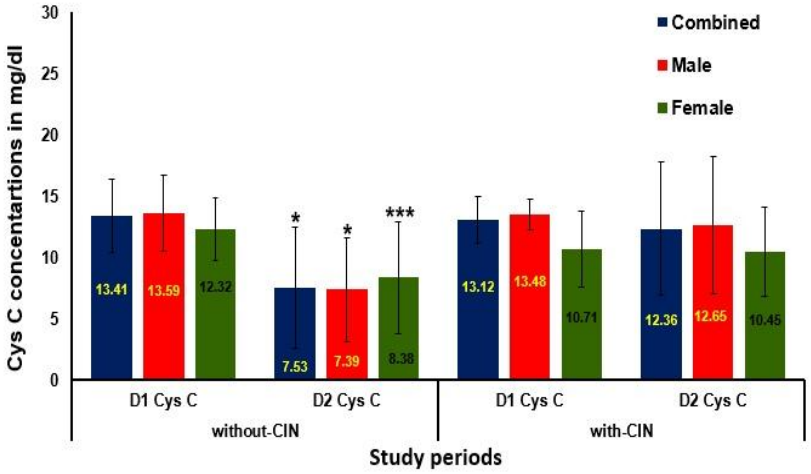

Fig 2: Comparison between with and without-CIN in relation to combined, male and female subjects for the serum cystatin C (mg/l) in pre intervention (D1) and after 24 hours [non-CIN combined: n=72; males n=62 and females n=10 and CIN combined: n=23; males n=20 and females n=3; *P<0.001 and ***P<0.05]

Table 3: Changes in SCysC in first 24 hr

Changes in SCysC	Frequency	Percentage
Decrease >=10%	60	63.2
Increase <10%	12	12.6
Increase >=10%	23	24.2
Total	95	100.0

In our present study, among the study population (Total 95 patients), in case of combined subjects, there were 17 patients (TP) who were diagnosed as contrast induced nephropathy according to the both SCr and SCysC value and 58 patients (TN) who did not develop CIN both in reference to SCr and SCysC value. It was found that diagnosis of CIN in combined groups by using increasing SCysC value has 54.84% sensitivity and 90.63% specificity with diagnostic accuracy 78.95% and positive predicted value was 73.91% and negative predictive value was 80.56%. In case of male patients, there were 16 patients (TP) who were diagnosed as CIN according to the both SCr and SCysC value, whereas there were 51 patients (TN) who did not develop CIN both in reference to SCr and serum cystatin C value. In the diagnosis of CIN by using increasing SCysC value had 59.26% sensitivity and 92.73% specificity with diagnostic accuracy 81.71%, positive predicted value was 80.00% and negative predictive value was 82.26% for males. In the female subjects, there were 1 patient (TP) who was diagnosed as CIN according to the both SCr and SCysC value, while there were 7 patients (TN) who did not develop CIN both in reference to SCr and SCysC value. It was also found in the diagnosis of CIN by using increasing SCysC value had 25.00% sensitivity and 77.78% specificity with diagnostic accuracy 61.54%, positive predicted value was 33.33% and negative predictive value was 70.00% (Table 4).

Table 4: Diagnosis of CIN by SCr and SCysC (Sensitivity and Specificity)

Scoring subjects	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
Combined	17	58	6	14	54.84	90.63	73.91	80.56	78.95
Males	16	51	4	11	59.26	92.73	80.00	82.26	81.71
Females	1	7	2	3	25.00	77.78	33.33	70.00	61.54

TP = True positive, TN = True negative, FP = False positive, FN = False negative, PPV = Positive predicted value, NPV = Negative predictive value

In this study, it was observed with total study population that pre and post catheterization fluid intake was directly associated with statistically significant (P<0.05 and P<0.001) lower incidence of CIN when compared with non-CIN groups. Mean pre-catheterization fluid intake was 1199.04 ± 325.36 ml and mean post-catheterization fluid intake was 1301.39 ± 305.58 ml was in patient population who did not develop CIN. In patient population who developed CIN had mean pre and post-catheterization fluid intake was 1069.57 ± 258.38ml and 1017.4 ± 172.3 ml respectively (Table 5).

Table 5: Statistical analysis of CIN by SCysC according to the fluid intake

CIN by SCysC		Fluid/precath	Fluid/postcath
No	Mean ± SD	1199.04±325.36	1301.39±305.58
Yes	Mean ± SD	1069.57±258.38	1017.39±172.29
	P-value	<0.05	<0.001

The total patients who were diagnosed as with-CIN by SCysC got statistically significant (P<0.001) larger dye volume (118 ± 52.5ml) than who did not (74.92 ± 39.81ml). The predicted risk score was higher (3.91 ± 2.17) in group who developed CIN as diagnosed by post intervention of increasing in SCysC than who did not (3.39 ± 2.42) found without any statistically significant difference. In case of the risk value (9.2 ± 2.92) for the groups of with-CIN was higher compared to the value (8.67 ± 2.52) for the groups of without-CIN but did not show statistically significant changes (Table 6).

Table 6: Statistical analysis of CIN by SCysC according to the risk score and contrast volume

	CIN by SCysC		
	No	Yes	
	Mean ± Std. Deviation	Mean ± Std. Deviation	P-value
Risk score	3.39±2.42	3.91±2.17	0.386
RISK	8.67±2.52	9. ±2.92	0.404
Dye (ml)	74.92±39.81	118.26±52.5	<0.001

IV. Discussion

The prospective study indicates that day-1 SCr values were significantly (P<0.01) higher in combined and male patients but in females no statistically significant difference was found for the with-CIN groups compared to without-CIN groups. The significantly increased values were also observed in both combined (P<0.001) and male (P<0.01) sub-groups for day-2 and 3 when compared between CIN and non-CIN groups. But for female patients only significant difference (P<0.05) was found for day-3 SCr value. Other parameter, SCysC was also increased without statistical significant values in CIN groups after 24h duration (day-2), when compared to day-1. But in non-CIN groups, SCysC was found in decreasing trend with statistically significant (P<0.001, P<0.001 and P<0.05) for all groups in comparison with day-1 (Fig. 1). For diagnostic accuracy in relation to SCr and Cys C, it was observed that 78.95%, 81.71% and 61.54% for combined, male and female sub-groups respectively (Fig. 2). The increasing trend of SCr in the CIN groups post 48hrs has an evidence of other research works [12]. Narang et al. [18] observed that the incidence is estimated to be 1% with intravenous contrast medium, 2-7% with intra-arterial contrast medium [19]. In diabetics with normal renal function it rises to 16% [18]. Patients with a pre-existing renal insufficiency prior to receiving contrast media have 33% incidence of developing CIN. According to the KIDGO [1] classification contrast induced nephropathy was defined as 0.3 mg/dl or 50% increase in serum creatinine from baseline at 48hr.

In Fig. 2, novel biomarker evaluation, SCysC was also increased without statistical significant values in CIN groups after 24hr duration, when compared to day-1. But in non-CIN groups, SCysC was found in decreasing trend with statistically significant (P<0.001, P<0.001 and P<0.05) for all sub-groups in comparison with day-1. In our present study, SCysC was correlating with established diagnosis test by increasing SCr. It was observed for incidence of CIN was 32.63% when it was diagnosed by increasing SCr and incidence was 21.24% when CIN was diagnosed by increasing SCysC value, which is supported by other results [12,18].

In our present study, 32.6% of patients were >65 years of age, which showed that higher age group (>65 years) are associated with statistically significant higher incidence of CIN. The present study dealt with 82% male patient population and the study failed to show any statistically significant difference in incidence of CIN between male and female. Ikovou et al. [19] reported that female gender is an independent predictor of CIN development after PCI and a marker of worse 1-year mortality after CIN in patients without baseline CRF (chronic renal failure). CIN was present in 23.6% of female versus 17.4% of male patients. According to several researchers, patients with higher SCr values, are associated with higher incidence of CIN [6,10,20-21]. It has been reported that SCysC increased faster than SCr, enabling earlier identification of acute kidney injury [13].

Diagnostic specificity of SCysC test was 90.63%, 92.73% and 77.78% whereas sensitivity was 54.84%, 59.26% and 25.00% with negative predictive value was 80.56%, 82.26% and 70.00% for combined, male and female sub-groups respectively. Wang et al. [22] showed that in their study diagnosis of CIN by SCysC had got sensitivity 89.7% and specificity 95.6%. In other studies, sensitivity and specificity of serum creatinine in diagnosis of CIN was 89.7% and 53.5% respectively. Ribichini et al. [23] reported that serum creatinine had got 43% diagnostic sensitivity and 93% diagnostic specificity. The data evaluation for biomarkers assessment in which researchers validated the diagnostic parameters through the measurement diagnostic accuracy [24]. In our present study (Table 2), the biomarkers SCr and SCysC were evaluated to detect patients without diseases (non-CIN) as FP (false positive) and with diseases (CIN) as TP (true positive) sensitivity and specificity, positive and

negative predictive values (PPV, NPV) and overall diagnostic accuracy for combined, male and female subjects, in which highest diagnostic accuracy (81.71%) in males followed by combined (78.95%) and lowest in females (61.54%). Generally, diagnostic accuracy is affected by disease prevalence, in which mainly the number of patients with disease (CIN) is known. In reference to same sensitivity and specificity, the diagnostic accuracy of a particular test when increased then the disease prevalence decreased [25]. These two biomarkers are suitable to diagnose CIN patients of eastern India, who were undergoing emergent and elective coronary and peripheral intervention. According to Zhang et al. [25], the combing effect of these two markers in the development of CIN still unclear [25-26].

V. Study limitations

In the present study, total population was ninety-five only. More number of patients with long duration of follow-up will definitely bring out more accurate result. It was used iohexol in all patients irrespective of the diabetic and hypertension status, which might be the cause of relatively higher incidence of CIN in the study population. These patients were referred to the tertiary care centre with a considerable time lag after acute myocardial infarction. The patients might have had unrecognized episode of hypotension causing renal hypoperfusion that might be the reason of relatively high rate of CIN in the hospital based study.

VI. Conclusion

Diagnosis of contrast-induced nephropathy (CIN) by SCysC was correlating with traditional diagnosis of contrast induced nephropathy by SCr. CIN can be diagnosed earlier by SCysC, which will affect long term prognosis. Diagnosis of CIN by SCysC had got high specificity 90.63% but sensitivity 54.84% with negative predictive value 80.56% and diagnostic accuracy 78.95% for all (combined) patients. In this study, increased age, higher baseline serum creatinine, lower pre-catheterization fluid intake, higher volume of contrast medium was associated with statistically significantly higher incidence of CIN. One-year survival rate (all causes mortality) was lesser in patients who were diagnosed as CIN by SCysC. Moreover, biomarkers assessment is suitable to predict CIN risk and can be taken measure of prior therapeutic strategies [25]. In future, it is suggesting that CIN should be prevented through newer therapeutic strategies for proper kidney function during emergent and elective percutaneous coronary and peripheral interventions mainly for high-risk patients [6,27]. Moreover, present study is indicating the novel biomarker SCysC can be suitable diagnostic tool to predict the occurrence at early stage (24hr duration) of CIN and SCysC was decreased indicating in renal function improvement after intravenous fluid therapy in the studied patients of CIN.

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Conflict of interest

Authors declare no conflict of interest in the present study and the article.

Ethical approval

The ethical approval has been given by Institutional Ethical Committee, NRS Medical College, Kolkata, which is registered with Central Drug Research Control Organization (CDSCO), Government of India in consonance with Rule 122D of the revised drugs and cosmetics Rules, 1945-Registration No. ECR/609/Inst/WB/2014. This committee functions in accordance with revised Schedule Y and Indian Council of Medical research (ICMR).

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