Original Article

Predictive value of serum Cystatin C in post-operative renal dysfunction following coronary artery bypass grafting

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Abstract

Context: Acute kidney injury (AKI) is a potential complication following coronary artery bypass grafting (CABG). Thecurrent pilot study evaluates the predictive value of serum Cystatin C (Cys C) for post-operative renal disease (PORD) after CABG. **Methods:** Patients admitted for coronary artery bypass grafting in Sir J J Hospital, Mumbai, were prospectively studied and their serum creatinine, Cys C, troponin I and potassium levels were measured pre and post operatively. Unpaired t test used to compare 2 groups. ROC curve analysis was done to measure the cut-off value of serum Cys C to predict PORD in patients after CABG. **Results:** Serum Cys C showed a significant rise in subjects who developed PORD post CABG compared to the non- PORD group ($p < 0.0001$). Mean GFR based upon serum creatinine and Cys C was significantly lower in PORD group as compared to the non-PORD group but the difference was more significant when Cys C based GFR was used ($p < 0.0001$) in comparison to the GFR based upon serum creatinine ($p < 0.05$). **Conclusion:** Measurement of serum Cys C along with cardiac Troponin I and other routine biochemical tests can be useful to improve the strategies for myocardial protection, to assess degree of damage to myocardium following CABG procedure and predicting surgical and adverse outcomes in the form of PORD.

Key Words: Acute renal failure, coronary artery bypass surgery, serum Cys C.

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INTRODUCTION

Acute kidney injury (AKI) is commonly seen in the perioperative period and in the intensive care unit (ICU). It is associated with a prolonged hospital stay and high morbidity and mortality[1]. Postoperative renal dysfunction is relatively common and one of the serious complications of cardiac surgery. Renal dysfunction or failure occurs nearly in 8% of all patients undergoing myocardial revascularization. It is multifactorial in origin. Acute renal failure occurs in up to 30% of patients who undergo cardiac surgery, with dialysis being required in approximately 1% of all patients. The development of ARF is associated with substantial morbidity and mortality independent of all other factors. The pathogenesis of ARF involves multiple pathways. Hemodynamic, inflammatory, and nephrotoxic factors are involved and overlap each other in leading to kidney injury[2]. Each year, 600,000 patients worldwide undergo coronary artery bypass surgery. With an increasing number of elderly populations coming for coronary artery bypass surgery, clinicians will continually be challenged to mitigate perioperative renal failure[3]. Despite substantial improvements in surgical techniques and perioperative management, ARF-associated morbidity and mortality remain high. The current AKI diagnostic criteria are based on changes in the serum creatinine level and clinical oliguria as a rough measure of overall renal function and to evaluate glomerular filtration rate (GFR)

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in clinical practice[4] However, the serum creatinine level is not an early indicator during acute changes in renal function. Its concentration fails to increase until 50% of kidney function has already been lost[5]. The mechanisms of renal injury are multifactorial and the incidence of significant renal failure requiring is Renal Replacement Therapyor dialysis iscomparatively low. Therefore, there is the need of established and clinically reliable marker to measure GFR for early diagnosis of AKI and is an area of recent interest to find a better diagnostic biochemical marker of post-operative renal dysfunction. Cys C is a cysteine protease inhibitor that is synthesized and released into the blood at a relatively constant rate by all nucleated cells. It is freely filtered by the glomerulus, completely reabsorbed and metabolized by the proximal tubules, and is not secreted. These inherent properties make serum Cys C an attractive and promising biomarker for assessing renal glomerular function, compared to serum creatinine. Measuring the serum Cys C level may provide new insight into the early diagnosis of AKI. Various studies have shown that Cys C is superior to conventional biomarkers in predicting AKI soon after adult cardiac surgery in adults and children (6,7and 8). Relatively little data is available so far from India about the predictive value of serum Cys C in post-operative renal dysfunction. So the aim of present study was to determine the predictive value of serum CysC over serum creatinine clinical outcomes in terms of post-operative renal dysfunction following CABG procedurein Indian population.

MATERIAL AND METHODS

Study Design: The present prospective cohort study was conducted in collaboration with Department of Biochemistry of Sir J. J. hospital, Mumbai and CVTS dept at KEMH, Mumbai. It is a prospective, observational Cohort study.

Patient recruitment and sampling: For sampling, consecutive strategy was used. All the patients fulfilling inclusion criteria and admitted during the study period in CVTS dept. and ICU for coronary artery bypass graft (CABG) procedure were enrolled in the study. The Inclusion criteria for the study were: All patients of either gender above 40 years of age with no major inflammatory condition and history of renal dysfunction in the past 6 months undergoing CABG procedure were included in the study. The exclusion criteria were: age < 40 years; k/c/o Hypothyroidism/ Hyperthyroidism; Preceding history of any major cardiovascular event in past 6 months; Pre-operative serum creatinine concentration more than 3.0 mg/dl; Albumin to creatinine ratio of more than 2 or ESRD; Subjects undergoing concomitant valve surgery; Subjects developing post-operative complications and Operative technique and graft surgery was conducted as per standard protocol for off pump CABG strategy. The study was approved by ethics committee of Sir J.J. Hospital, Mumbai. Written informed consent was obtained from the patient before their enrollment in the study. Patient's demographic (age, gender), anthropometric (height, weight, BMI) details, medical history and preoperativelaboratory investigations results were noted in case record forms. Renal profile including serum creatinine, Cys C, albumin creatinine ratio (ACR), calculated GFR using serum creatinine and Cys C were measured preoperatively. GFR was calculated using standard formula by National Kidney Foundation calculator, for both creatinine and Cys C and the grade of kidney disease and risk of progression was graded as 1 : Stage 1 : Mild, 2 : Stage 2 : moderate, 3: Stage 3 : high, 4: Stage 4 : very high Cardiac profile (serum potassium and troponin I) were measured preoperatively as well as post operatively at different time interval (post-operative 6 hours, 12 hours, 24 hours and 36 hours) were recorded to monitor cardiac functioning and extent of myocardial damage. Blood samples were collected by trained phlebotomist before and after surgery in plain evacuated tubes. Serum was separated and used for estimation of serum creatinine, serum Cys C and Troponin I. Heparinised syringes were used for electrolyte estimation pre and post-surgery. The samples were analysed immediately for the said parameters and transported as per standard protocol mentioned by manufacturers. Serum Cys C was measured using Immunoturbidimetry principle on AU-400 using standard kit by Agappe. Serum creatinine was measured using modified Jaffe's method of estimation. Serum electrolytes were measured on Cobas 121and analyser with ISE. Serum Troponin I was measured using Enzyme enhanced Chemiluminiscence method on Immulite 1000.

Statistical Analysis

Statistics analysis was performed by using Graph Pad Prism software. Quantitative variables were expressed as the mean and SD and were normally distributed. Continuous variables were compared by using the independent t test. Qualitative data were displayed as a percentage and compared by using chi square test. The receiver operating characteristic (ROC) curve was generated for pre-operative serum Cys C. The area under the ROC curve (AUC) was measured to evaluate the predictive performance of the serum Cys C level for PORD. An AUC value of 1.0 signified a perfect biomarker, and a value of 0.5 signified it was no better than what would be expected by chance. The optimal cut-off value was the value that had the highest combined sensitivity and specificity. A two sided p value of < 0.05

was considered statistically significant. P value of < 0.05 was considered statistically significant.

RESULTS

The study subjects were divided into two groups: Group I who developed PORD and Group II who did not develop PORD which also served as control group. Table 1 presents the comparison of demographic and anthropometric characteristic in both the groups. The PORD group had significantly higher age compared to the control group (non-PORD group) (p <0.0001). No significant difference could be observed in BMI of both the groups. Table 2 depicts the comparison of biochemical parameters in PORD and non PORD group. In the pre-operative patients of either groups there was No significant difference in serum creatinine value however serum Cys C showed a significant rise in subjects who developed PORD post CABG compared to the non- PORD group (p < 0.0001). Mean GFR based upon serum creatinine and Cys C was significantly lower in PORD group as compared to the non-PORD group but the difference was more significant when Cys C based GFR was used (p < 0.0001) in comparison to the GFR based upon serum creatinine (p < 0.05). Table 3 and Fig. 1 illustrates the ROC analysis of serum Cys C for predicting PORD after CABG. The best predictive performance was achieved preoperatively with an AUC value of 0.82. The optimal cut-off value was 2.15 mg/L (sensitivity, 72.73 %; specificity, 100 %). Figure 2 indicates the trend of value of serial measurement of serum potassium and troponin I levels in groups with and without PORD pre operatively, and at interval of 6 hrs, 12 hrs, 24 hrs, 36 hours post operatively. There was no significant difference pre operatively and serial measurements post operatively in either groups. The serum potassium levels increased post operatively 6 hrs after the procedure, however 24 hrs after the procedure the values returned to baseline preoperative value in either group while troponin I levels increased post operatively 6 hrs after the procedure, however 24 hrs after the procedure the values did not return to baseline preoperative value in either group. Table-4 shows the CKD classification of patients in groups with and without PORD based on serum creatinine and serum Cys C. The analysis clearly show that when creatinine is used for AKD grading of patients, in both groups, more patients were in grade 1 but when Cys C was used for AKD grading, the more number of patients shifted from grade 1 to grade 2, 3 and 4.

Table 1: Baseline demographic characteristics of study population

Sr. No.	Characteristics	Group-1 PORD-YES	Group-2 PORD-NO	P Value
1	Gender Males n (%)	81.8%	86.3%	>0.99 NS
2	Age (yrs) (mean ±SD)	69.32 ± 7.0	56.64 ± 6.5	<0.0001***
3	BMI(kg/m) (mean ± SD)	27.39 ± 2.8	26.84 ± 3.3	0.5609 NS

Table 2: Comparison of biochemical parameters in study population

Sr. No.	Characteristics	Group-1 PORD-YES (mean ±SD)	Group-2 PORD-NO (mean ±SD)	P Value
1	Pre-operative Serum creatinine (mg/dl)	1.209 ± 0.33	1.177 ± 0.3	0.7508 NS
2	Pre-operative Serum Cys C (mg/L)	2.499 ± 0.54	1.877 ± 00.18	<0.0001***
3	Albumin creatinine ratio (ACR)	1.091 ± 0.29	1.045 ± 0.21	0.5608 NS
4	e-GFR using serum creatinine (**ML/MIN/1.73M^2**)	98.91± 46.91	136.5± 55.99	0.0202*
5	e-GFR using serum Cys C (**ML/MIN/1.73M^2**)	36.23± 15.41	65.5± 17.21	<0.0001***
6	serum K baseline (pre-operative) (mEq/L)	4.895 ± 0.51	4.936 ± 0.66	0.8215 NS
7	serum K (post-operative 6 hours)	6.055 ± 0.32	6.195 ± 0.38	0.1991 NS
8	serum K (post-operative12 hours)	5.036 ± 0.64	5.141 ± 0.66	0.6012 NS
9	serum K (post-operative24 hours)	4.495 ± 0.69	4.491 ± 0.71	0.9831 NS
10	serum K (post-operative36 hours)	4.105 ± 0.64	4.041 ± 0.67	0.7500 NS
11	serum troponin I baseline (ng/ml)	0.7364 ± 0.39	0.6318 ± 0.30	0.3322 NS
12	serum troponin I (post-operative 6 hours) (ng/ml)	16.54 ± 2.80	16.1 ± 3.35	0.6391 NS
13	serum troponin I (post-operative 12 hours) (ng/ml)	23.12 ± 4.74	22.01 ± 3.73	0.3957 NS
14	serum troponin I (post-operative 24 hours) (ng/ml)	12.95 ± 2.65	12.3 ± 2.38	0.3914 NS
15	serum troponin I (post-operative 36 hours) (ng/ml)	8.38 ± 2.36	7.58 ± 2.55	0.2872 NS

Table 3: ROC analysis of baseline serum Cys C and serum Creatinine for prediction of post-operative renal disease

Sr No	parameters	Cut off	Area under the curve	Sensitivity	95% CI	Specificity	P value
1	Serum Cys C (mg/L)	2.15	0.8233	72.7 %	0.6869 to 0.9598	100 %	0.0002

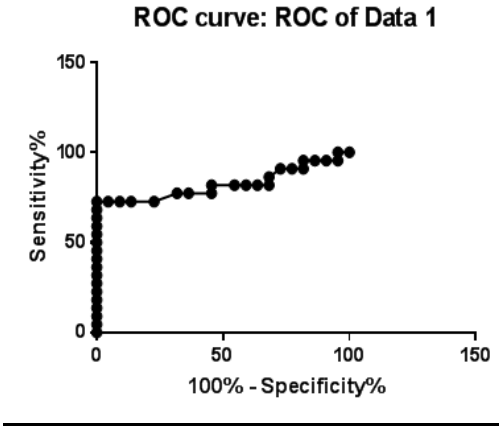

Figure 1: The receiver operating characteristic analysis of serum Cys C for the prediction of AKI at preoperative stage

Table 4: CKD classification of patients in groups with and without PORD based on serum creatinine and serum Cys C

	CKD- GRADE 1	CKD-GRADE 2	CKD-GRADE 3	CKD-GRADE 4
	In group with PORD			
Based upon serum creatinine	11	6	5	
Based upon serum Cys C	2	10	10	
	In group without PORD			
Based upon serum creatinine	18	2	2	0
Based upon serum Cys C	2	15	4	1

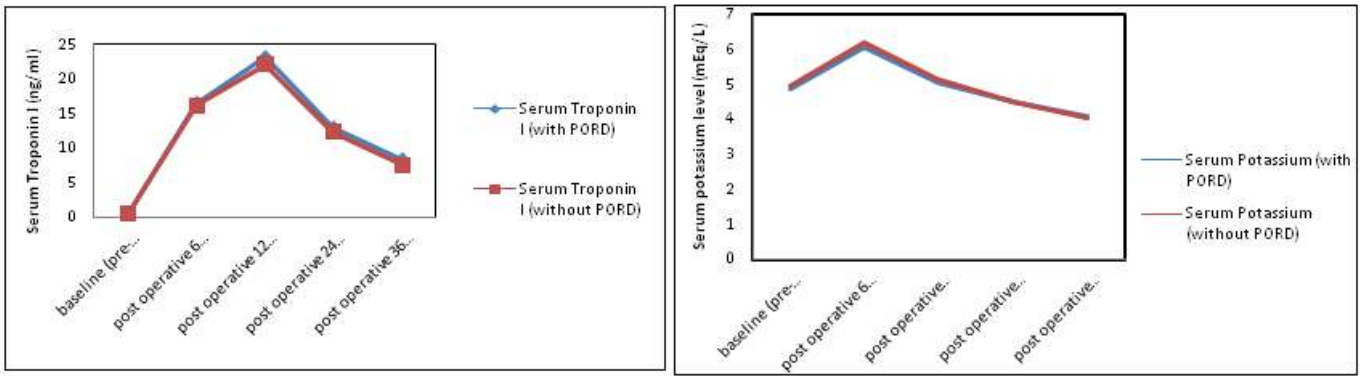

Figure 2: Illustration of the trends of pre-and postoperative serum potassium and troponin I levels in groups (with and without PORD)

DISCUSSION

Present study was formulated to determine the predictive value of serum CysC over serum creatinine as an index of decreased renal function after coronary artery bypass grafting. Until recently estimation of serum creatinine concentration is considered most useful determinant for AKI and widely used to assess renal dysfunction. However serum creatinine concentration estimation may not be ideal marker as creatinine is an inaccurate measure of GFR. Serum creatinine levels are dependent on its generation from muscle mass, which many times may be reduced in the post-operative set up and elderly subjects undergoing CABG. Table 1 indicates that the patients belonging to study Group I who progressed to PORD following CABG were mainly the older age group (69.32). Significantly high serum Cys C values in PORD group indicate that Cys C is a better marker to predict PORD where difference in serum creatinine values in both the group was less significant compared to Cys C in older patients. Further the GFR was more significantly lower in PORD group when calculated using serum Cys C instead of serum creatinine (Table-2). Post-operative

renal dysfunction (PORD) leads to an increased risk of complications which may cause critical complications post cardiac surgery and increase hospital or ICU stay. High values of pre-operative serum Cys C and low GFR calculated by CysC are predictive of impending renal dysfunction and AKI post operatively, however Cys C cannot predict the underlying mechanism in development of AKI. The primary clinical tool for measurement of renal function is serum creatinine, which is insensitive for detection of moderate reduction in renal function and is affected by factors unrelated to renal function such as age, gender and lean muscle mass[9]. Creatinine based equations to estimate GFR have been derived to compensate for these non-renal factors but their precision when applied to elderly patients gives an incorrect of estimate of GFR as elderly persons have reduced muscle mass. Serum Cys C has consistently been shown superior to serum creatinine in predicting AKI following cardiac surgery.[10,11,7]. It also appears to offer prognostic value in post-operative settings predicting AKI and cardio renal syndrome type 1. Studies have indicated that when considering all available data, Cys C also appears to be a reliable marker of chronic renal dysfunction and Cys C is a dependable early predictor of AKI with only NGAL outperforming its predictive value in CKD. Studies have suggested that in clinical settings Cys C seems to identify a "preclinical state" of kidney dysfunction that is not detected by serum creatinine or creatinine based GFR[12]. Serum potassium levels increase drastically during surgical procedures owing to hypothermia, and many other factors like anaesthetic agents used which affects the hemodynamic processes. Serum Potassium levels return to baseline values 24 hours after surgery. Elevated troponin I levels indicate extent of myocardial injury during the procedure. Pre-operative serum Cys C measurement would be an effective tool to predict PORD or surgical outcomes. Furthermore Troponin I measurements can be performed along with Cys C measurement serially to assess degree of myocardial injury and possible PORD. Troponin I is a marker of choice to detect cardiac damage in patients with renal disease, however serial measurements of Troponin I post CABG procedure may help on assessing PORD**.** Further studies required to assess role of Cys C and troponin I as predictive value of PORD in patients undergoing CABG. Post CABG some amount of myocardial damage is inevitable, however whether the degree of damage is clinically significant and relevant or not needs to be further assessed.

CONCLUSION

Acute kidney injury is one of the most common complications following cardiac surgery, particularly in high-risk patients. Although, understanding of the pathophysiology of AKI has improved over time, significant improvement in the prognosis of patients with this serious complication is yet to be found. Strategies for prevention, diagnosis and treatment are still in development, with significant effort being put into advancing our knowledge and progressing beyond our current limitations. Cys C level in serum can be considered as a significant marker of reduction in GFR than serum creatinine in Subjects who developed PORD post CABG. Cys C can be measured from spot serum sample and has advantage over 24 hrs urine collection necessary to estimate creatinine clearance. It also has less inter individual variability when compared to serum creatinine. However Cys C measurement alone cannot explain mechanism of AKI and index of kidney injury. Measurement of serum Cys C along with cardiac Troponin I and other routine biochemical tests can be useful to improve the strategies for myocardial protection, to assess degree of damage to myocardium following CABG procedure and predicting surgical and adverse outcomes in the form of PORD.

LIMITATIONS: Post-operative serum Cys C values could not be assessed.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

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