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Serum cystatin C concentration levels as a marker of acute renal failure in critically ill patients – A cross section study

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Abstract: *Objective:* The objective of the present study was to assess serum cystatin C concentration levels as a marker of ARF in critically ill patients. *Method:* This was a randomized cross sectional study done on 100 patient admitted in ICU at Basaveshwar Teaching and General Hospital (BTGH). It included the patient with normal serum creatinine who are at risk of developing failure, and excluded the patient with acute and chronic renal failure, Sr. Cystatin C and Sr. Creatinine levels were determined at admission and these were considered as the first reading of Sr. Creatinine and Sr. Cystatin C. Sr. Creatinine and Sr. Cystatin C were repeated after the patient developed ARF and was considered as second reading and results were analyzedand were compared to know which was earlier marker for acute renal failure and due consideration was given to age, gender, occupation, history, physical examination along with special attention to symptoms of the patient. *Result:* The present one year cross sectional study was conducted on patients admitted in the Medical Intensive Care Unit of BTGH, Gulbarga, during the period of January 2011 to May 2012.In the present study out of 100 patients, 66 (66%) were male and 34 (34%) were female. The male: female ratio was 1.94:1. In this study, out of 100 patients, there were 26 (26%) patients each in the age group of 18 to 30 years and more than 60 years. There were 36 (36%) patients each with primary gastrointestinal and respiratory disease and 12 (12%) patients with snake bite. In the present study 56 (56%) patients developed ARF. The mean age of patients with ARF was 50.25 ± 17.85 years. Themean Sr. Creatinine and Sr. Cystatin C values in ARF were 1.86 mg/dL and 3.14 mg/L respectively. The mean Sr. Creatinine and Sr. Cystatin C values in patients without ARF were 0.68 mg/dL and 0.73 mg/L respectively. In the present study among patients who developed ARF 39.29%, 53.57% and 7.14% patients have satisfied R_{Creat} (50 to 99%), I_{Creat} (100 to 199%) and F_{Creat} (≥ 200%) criteria respectively. Among patients with category R_{Creat} rise of Sr. cystatin C was ≥ 100% and 57.14% patients had 100 to 199% rise in Sr. cystatin C levels and among 42.86% patients a rise of more than or equal 200% was noted. The sensitivity, specificity, PPV, NPV of Sr.creatinine for second reading was 78.57%, 100%, 100%, 78.57% respectively and the sensitivity, specificity, PPV, NPV for second reading of Sr. Cystatin C was 100% (100%for all parameters) Sr. Creatinine was normal in some patients with ARF whereas Sr. Cystatin C was above the normal value in all ARF patients indicating that Sr. Cystatin C is more reliable marker than Sr. Creatinine. *Conclusion:* This study concludes that Sr. Cystatin C is early and more reliable marker of ARF than Sr. Creatinine in critically ill patients.

Keywords: Sr.Cystatin C, Creatinine, RIFLE, Acute Renal Failure.

Abbreviations: *BTGH:* Basaveshwar Teaching and General Hospital. *MRMC:* Mahadevappa Rampure Medical College. *P:* Prevalence. *ABG:* Acid Blood-Gas Analysis. *RBS:* Random Blood Sugar. *PPV:* Positive Predictive Value. *NPV*: Negative Predictive Value.

Introduction

Acute Renal Failure (ARF) is a common complication in patients admitted to the intensive care unit (ICU). It is common in hospitalized patients, with a mortality rate between 30% and 90% depending upon various causes [1]. ARF is often due to multifactorial etiology in critically ill patients. Increasing use of nephrotoxic drugs, invasive procedures, intravascular catheters and major surgical procedures (cardiovascular and abdominal surgeries) predispose patient to sepsis and renal failure [2].

Acute renal failure is the abrupt loss of renal function sufficient to decrease urinary elimination of nitrogenous waste (urea nitrogen and creatinine) although there is consensus about this general definition, few

agree on the magnitude of the rise in serum creatinine necessary to ascribe a diagnosis of ARF. The differences in the definition plus variances in the methods of patients accrual, population analyzed, categorization of causes, render development of broad based over view of ARF difficult. The high mortality of patients with ARF is not explained entirely by comorbid conditions. Recent data indicate that ARF per seincrease the risk of development of multiple non renal conditions that lead to death and disability. The relative importance of factors contributing to ARF will be different depending on the underlying pathology and patient characteristics. A patient population of young trauma patients developing ARF can probably not be compared with older patients with ischemic and congestive heart disease developing ARF after cardiac surgery. The large differences in mortality for patients with ARF, as reported in recent trials (varying between 28 and 83%) can possibly be explained by differences in patient population [3-4].

In clinical practice, the detection of ARF, which is characterized by a rapid decline of the glomerular filtration rate (GFR), is based on increase in serum creatinine (Sr. Creatinine). However, there are major limitations to the use of creatinine for estimating GFR. Minor changes of Sr. Creatinine, as typically seen early in acute renal failure, may already reflect substantial decline in GFR. Sr.Creatinine inaccurately estimates GFR due to tubular secretion and reabsorption of creatinine [5]. Sr. Creatinine can be affected by age, sex, muscle mass, drugs and diet [6].

The early and accurate detection of acute renal failure is crucial to prevent its progression, and thereby, to potentially improve its outcome. Hence there is a need of an early and more reliable marker of ARF which can detect minor GFR reduction and which is not affected by age, sex, muscle mass, drugs and diet. Many international studies [3-4] say that Serum Cystatin C (Sr. cystatin C) is one such marker,but there is lack of Indian studies regarding Sr. Cystatine C levels as a marker of acute renal failure in critically ill patients. Hence the present study was undertaken to assess whether Sr. Cystatin C is an early and more reliable marker of ARF.

Material and Methods

The present study was conducted on patients admitted in the Medical Intensive Care Unit of BTGH, Gulbarga during the period of January 2011 to June 2012.

Study design: Eighteen months Cross sectional study.

Study period: The present study was conducted during January 2011 to June 2012.

Source of data: Patients admitted in the Medical Intensive Care Unit of BTGH, Gulbarga.

Samplesize: A total of 100patients admitted in the Medical Intensive Care Unit of BTGH, Gulbarga.

Samplingprocedure: Although reliable statistics on the prevalence of ARF amongst different tropical countries are not available, statistics based on referrals to dialysis units suggest that the condition is more common in the tropics. Kaufman recently reported a 0.1% incidence of community acquired intrinsic ARF from the US [7]. This contrasts with data from a institute, a large referral hospital in North India, where 1.5% of all hospital admissions were referred to the Nephrology services for management of moderate or severe ARF [8].

As this is a cross sectional study sample size was calculated by the following formula:

$$N=4PQ/D^2$$

Where *N:* Sample size. *P:* Prevalence of the disease which was taken as 50% (approx. from the studies conducted [7-10]) as no records were available regarding the study. *Q:* 100-P (prevalence). *D:* Absolute error taken as 15%.

Selection criteria:

Inclusion: Patients at risk of developing ARF (all patients of medical intensive care unit without Co-Exisiting/known acute or chronic renal failure).

Exclusion: Acute and Chronic Renal Failure.

Procedure: The study was approved by the Ethical and Research Committee of Mahadevappa Rampure Medical College (M.R.M.C) Gulbarga. Based on the selection criteria patients admitted in Medical Intensive Care Unit were screened for eligibility.

The patients with normal Sr. Creatinine that is ≤ 1.3 mg/dl and willing to participate were included in the study after obtaining their informed consent. Patients with acute or chronic renal failure that is Sr. Creatinine > 1.3 mg/dl were excluded from the study [5]. Demographic data like age, gender, address and occupation was recorded on predesigned and pretested proforma. At admission detailed history was taken in all patients and thorough general physical and systemic examination was carried out with special attention to the symptoms of the patients. Clinical diagnosis was made depending on history and examination.

Vital signs: Temperature, pulse rate, blood pressure, respiratory rate, oxygen saturation were monitored hourly.

Intake and output charting: Meticulous fluid chart consisting of amount and type of intravenous fluid given and accurate urine output charting was maintained in all the patients. Most of the patients were catheterized as they were critically ill. All base line investigations as per the predesigned and pretested proforma like complete blood count, liver function test, renal function test, urine routine and microscopy were done.

Sr. TSH, X-ray chest, Complete blood count, liver function tests, urine routine and microscopy, was done at admission and repeated when required, ultrasound abdomen, ABG and blood sugar level were done to make an etiological diagnosis were done at admission. S. Cystatin C levels were determined at admission and these were considered as the first reading of Sr. Creatinine and Sr. Cystatin C. Sr. Cystatin C was done by serum nephelometry method. Any value above 0.95mg/l was considered high. Further Sr. Creatinine was done daily for five days in all the patients to know whether the patient has developed ARF.

Acute Renal Failure was defined as an abrupt decrease in renal function (over hours to days) sufficient to result in retention of nitrogenous waste products (blood urea nitrogen and creatinine) in the body. There is no consensus regarding the magnitude of elevation of Sr. Creatinine or blood urea nitrogen sufficient to ascribe a diagnosis of ARF. In this study ARF is detected according to first three RIFLE (the Risk of renal dysfunction, Injury to the kidney, Failure of the kidney function, Loss of kidney function and End Stage Renal Disease) criteria of the GFR domain.

First three RIFLE criteria of GFR domain are; [11]

- R-criteria is raise in creatinine by ≥50%
- I-criteria is raise in creatinine by ≥100%
- F-criteria is raise in creatinine by ≥200%

Once there was increase in Sr. Creatinine of more than or equal to fifty percentage from baseline, Sr. Cystatine C levels were repeated. The values of Sr. Creatinine and Sr. Cystatin C on this day were considered as the second readings. The percentage rise of Sr. Creatinine and Sr. Cystatin C were calculated. Patients were categorized depending upon the percentage rise of sr. Creatinine into R (creat), I (creat) and F (creat) in accordance to first three RIFLE criteria of the GFR domain. Similarly the patients with rise in Sr. Cystatin C ≥ 50%. ≥100% and ≥ 200% were categorized as R(cyst), I(cyst) and F (cyst). In the patients who didnot develop ARF, Sr. Cystatin C was done on day 5. These patients were considered as controls.

Statistical methods: The data was tabulated and analyzed using rates, ratios, percentages. The comparison was done using chi-square test and student-ttest. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Results

The present one year cross sectional study was conducted on patients admitted in the Medical Intensive Care Unit of B.T.G.H, Gulbarga, during the period of January 2011 to June 2012. A total of 100 patients were studied. The data obtained was tabulated and analyzed as below.

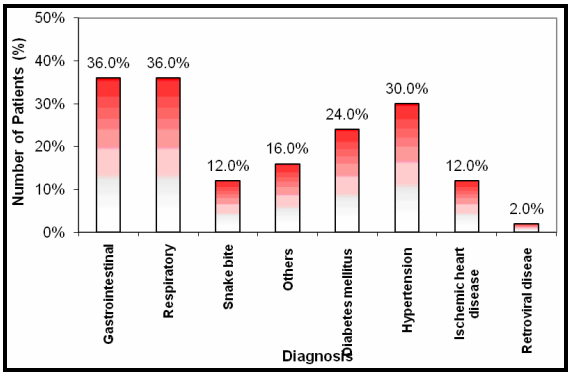
Table-1: Age distribution		
Age group (Years)	Distribution (n=100)	
	Number	Percentage
18 – 30	26	26.00
31 – 45	24	24.00
46 – 60	24	24.00
> 60	26	26.00
Total	**100**	**100.00**

In this study, out of 100 patients, there were 26 (26%) patients each in the age group of 18 to 30 years and more than 60 years, and 24 (24%) patients each in the age group of 31 to 45 years and 46 to 60 years.

Table-2: Sex distribution		
Gender	Distribution (n=100)	
	Number	Percentage
Male	66	66.00
Female	34	34.00
Total	**100**	**100.00**

In the present study out of 100 patients, 66 (66%) were male and 34 (34%) were female. The male: female ratio was 1.94:1.

Graph-1: Primary diagnosis according to the system involved and associated conditions



In the present study, there were 36 (36%) patients each with primary gastrointestinal and respiratory disease and 12 (12%) patients with snake bite.

Table-3: Sex distribution in ARF and Non ARF patients				
Sex	ARF (n=56)		Non ARF (n=44)	
	Number	Percentage	Number	Percentage
Male	36	64.29	30	68.18
Female	20	35.71	14	31.82
Total	**56**	**100.00**	**44**	**100.00**
x^2=0.083		DF=1		p=0.773

In the present study, there were 36 (64.29%) males and 20 (35.71 %) females in the patients with ARF. Among those who did not develop ARF 30 (68.18%) were males and 14 (31.82%) were females suggesting equal distribution of gender in both groups.

Table-4: Comparison of rise in Sr. creatinine levels and Sr. Cystatin C levels from admission to 2nd reading among patients with ARF				
Criteria (Percentage Rise)	Sr. Creatinine (n=56)		Sr. Cystatin C (n=56)	
	No.	%	No.	%
R (50 to 99%)	22	39.29	0	0.00
I (100 to 199%)	30	53.57	32	57.14
F (≥ 200%)	4	7.14	24	42.86
Total	**56**	**100.00**	**56**	**100.00**

In the present study among patients who developed ARF 39.29%, 53.57% and 7.14% patients have satisfied R_{Creat} (50 to 99%), I_{Creat} (100 to 199%) and F_{Creat} (≥ 200%) criteria respectively. Among patients with category R_{Creat} rise of Sr. cystatin C was ≥ 100% and 57.14% patients had 100 to 199% rise in Sr. cystatin C levels and among 42.86% patients a rise of more than or equal 200% was noted.

Table-5: Comparison of accuracy of Sr. Creatinine and Sr. Cystatin C				
	Sr. Creatinine		Sr. Cystatin	
	1st reading	2nd reading	1st reading	2nd reading
Sensitivity	0%	78.57%	85.71%	100%
Specificity	100%	100%	95.45%	100%
PPV	0%	100%	96.00%	100%
NPV	44%	78.57%	84.00%	100%

In this study the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of Sr. Creatinine for first reading was 0%, 100%, 0%, 44% respectively and the sensitivity, specificity, PPV, NPV for first reading of Sr. Cystatin C was 85.71%, 95.45%, 96% and 84% respectively. The sensitivity, specificity, PPV, NPV of Sr. Creatinine for second reading was 78.57%, 100%, 100%, 78.57% respectivelyand the sensitivity, specificity, PPV, NPV for second reading of Sr. Cystatin C was 100%.

Discussion

This study was conducted on 100 patients admitted in the Medical Intensive Care Unit of BTGH, Gulbarga. In this study, out of 100 patients 66(66%) patients were males and 34 (34%) patients were females with a male to female ratio of 1.94:1.These findings were comparable to a study conducted on patients admitted in ICU by villa et al [11] in which out of 100 patients, 68 (68%) were males and 32 (32%) were females. In the present study, out of 100 patients, 56 (56%) patients developed ARF based on RIFLE criteria [11] between one to three days of admission and 44 (44%) did not develop ARF. This was comparable to a studyconducted by Herget et al [5] on 85 ICU patients, 44 (51.7%) patients developed ARF and 41(48.3%) patients did not develop ARF.

In the present study out of 56 ARF patients, there were 36 (64.29%) males and 20 (35.71 %) females. Among those who did not develop ARF that is 44 patients 30 (68.18%) were males and 14 (31.82%) were females suggesting equal distribution of gender in both groups. In a study by Herget et al [5] 66 and 34 percentage were males and females respectively among patients with ARF and among those who did not develop ARF 61% and 39% were male and females respectively suggesting equal distribution of gender in both groups. In this study the Sr. Creatinine during the first reading was normal in all i.e. 100 patients (inclusion criteria is normal creatinine). This finding was comparable to the study conducted by Hoste et al [12] in which the first reading of Sr. Creatinine was normal in all patients. In this study second reading of Sr. Creatinine was normal in 56(56%) patients and high in 44 (44%) patients. Second reading of Sr.Creatinine was within normal limit in 12 patients with ARF that is, inspite of ≥ 50% rise in Sr.Creatinine

Inthis study the first reading of Sr. Cystatin C was normal in 50 (50%) patients and high in 50 (50%) of patients that is out of 56 ARF patients, 48 (85.71%) patients had high Sr. Cystatin C levels at admission which is one to three days prior to rise in Sr. Creatinine. However one patient with high Sr. Cystatin C at admission did not develop ARF. This was comparable to a study by Herget et al [5] where in all patients of ARF, Sr. Cystatin C had raised one to two days earlier to S.Creatinine. In the present study the second reading of Sr. Cystatine C was normal in 44 (44%) patients and high in 56 (56%) patients that is second reading of Sr. Cystatin C was high in all ARF patients. In this study among patients who developed ARF the mean percentage raise in Sr. creatinine levels in R_{Creat} category was 69.67% ± 11.33% whereas mean percentage raise in Sr. Cystatin C were noted as 134.90% ± 24.18%. Similarly in those with category I_{Creat} (100 to 199%) mean percentage raise in Sr. Creatinine levels was 135.93% ± 26.65% whereas mean rise in Sr. Cystatin C was recorded as 222.46% ± 43.88% suggesting significant raise in Sr. Cystatin C compared Sr. Creatinine ($p<0.001$). However among patients with F_{Creat} (percentage rise ≥ 200%) comparison could not be done as there were only two patients.

In the present study the mean Sr. Creatinine and Sr. Cystatin C values in patients with ARF were 1.86 mg/dL and 3.14 mg/L respectively. The mean Sr. creatinine and Sr. Cystatin C values in patients without ARF were 0.68 mg/dL and 0.73 mg/dL respectively. In a study conducted by Ronwald et al [13], on 150 patients the mean Sr.Cystatine C levels were 1.27±0.44 and 0.92±0.23 mg/L in ARF and non ARF patients respectively. In this study the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of Sr. Creatinine for first reading was 0%, 100%, 0%, 44% respectively and the sensitivity, specificity, PPV, NPV for first reading of Sr. Cystatin C was 85.71%, 95.45%, 96% and 84% respectively. The sensitivity, specificity, PPV, NPV of Sr. Creatinine for second reading was 78.57%, 100%, 100%, 78.57% respectively and the sensitivity, specificity, PPV, NPV for second reading of Sr. Cystatin C was 100%.

In a study conducted by Hoste et al [12] Sr. Creatinine proved a very insensitive screening test for the early detection of renal dysfunction in ICU patients. The limitations of the study were smaller sample size and urine output criteria was not included in the diagnosis of ARF because many patients were on diuretics at admission. As high doses of diuretics may lead to dehydration following

which pre-renal failure sets in due to reduced intravascular volume leading to decreased GFR and consequently raised s.creatinine levels. Also preadmission normal baseline Sr. Cystatin C and Sr. Creatinine were not available with many patientsbut patients whose creatinine was less than 1.3mg/dl even though they were eldery diabeitic and hypertensive were included in the study (i.e with good blood sugar and diabetic control,) hence thisstudy was limited to monitoring of patients from entry to the ICU and cannot be readily used to assess the status of patients on entry to the ICU. Lack of a 'gold standard' independent measure of GFR such as an inulin or radioisotope clearance, prevented from commenting on whether Sr. Cystatin C or Sr Creatinine correlated more accurately with a true decrease in GFR.Though none of the patients were a known case of thyroid diseaseand Sr. TSH levels were normal in all patients, thyroid disease couldnot be ruled out and the variation of Sr. Cystatin C in relation to thyroid disease could not be analyzed. Though none of the patients were on steroids, the effect of cortisol on Sr. Cystatine C levels could not be analyzed as Sr. Cortisol levels were not measured. Further a large multicentric study is required to confirm these results.

Conclusion

In our study of 100 ICU patients, 56 patients developed Acute Renal Failure during the hospital stay. The first reading of Sr. Cystatin C in patients with ARF was high in significant number of patients were as the first reading of Sr. Creatinine was normal in all the patients with ARF indicating that Sr. Cystatin C is an early marker of ARF. Further the second reading of Sr. Creatinine in patients with ARF was normal in 12 patients that is inspite of ≥ 50% rise in sr. Creatinine where as the second reading of Sr. Cystatin C was high in all patients with ARF. The percentage raise of Sr. Cystatin C was significantly greater than percentage raise of Sr. Creatinine in patients with ARF. This study concludes that Sr. Cystatin C is an early and more reliable marker of ARF than Sr. Creatinine in critically ill patients.

Table-6: Comparison between 1st reading and 2nd reading of Sr.Cystatin

Sr. Cystatin	
1st reading	**2nd reading**
85.71%	100%
95.45%	100%
96.00%	100%
84.00%	100%

Table-7: Comparison between 1st reading of Sr. Creatinine and 2nd reading of Sr. Cystatin

	Sr. Creatinine	**Sr. Cystatin**
	1st reading	**2nd reading**
Sensitivity	0%	100%
Specificity	100%	100%
PPV	0%	100%
NPV	44%	100%

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