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Original Research Article

A Study of Serum Cystatin C and Serum Creatinine as Markers in Early Prediction of Acute Kidney Injury Patients Requiring Intensive Care in a Tertiary Care Centre

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Conflict of interest: Nil

Abstract:

Introduction: AKI is a common complication in patients admitted to the ICU with a prevalence rate of 30% and mortality rate between 30% and 90% depending upon various causes. Serum Creatinine (S.Cr) inaccurately estimates GFR due to tubular secretion and reabsorption of creatinine and can be affected by age, sex, muscle mass, drugs and diet. Serum Cystatin C (S.Cys C) is a marker which is independent of the above factors and the present study is to estimate S.Cr and S.Cys C in patients who are admitted to Intensive Care Unit with predisposing factors of AKI.

Objectives: 1. To study Serum Cystatin C and Serum Creatinine in subjects with AKI in ICU patients.
2. To study Serum Cystatin C and Serum Creatinine for the estimation of eGFR in ICU.

Methods and Material: 86 patients with age above 18 years, who were admitted to ICU with predisposing factors of AKI between January 2021–December 2021 were taken by universal sampling and subjected to S.Cr and S.Cys C testing in order to establish their role as markers in early detection of AKI.

Statistical Analysis: The data was entered into Microsoft excel spread sheet. The qualitative variables were coded. The collected data was summarized and presented as frequencies, proportion, mean and standard deviation, depending on the quantitative or qualitative variables. Analysis was performed using SPSS 22 version.

Results: Among the 86 patients, 26 patients who developed AKI, 70% had high Cystatin C on day 1 with normal serum creatinine and the remaining patients had high levels of both Cystatin C and creatinine at the same time.

Conclusions: Serum Cystatin C can be taken as an early marker in critically ill patients to predict the development of AKI as majority of those who developed AKI did show an early rise in levels of Cystatin C even prior to the raise in Serum Creatinine levels.

Keywords: Acute Kidney Injury, Serum Cystatin C, Serum Creatinine, ICU.

Introduction

Acute kidney injury (AKI) commonly is encountered in various patient populations including critically ill patients, those after cardiac surgery, and those receiving contrast agents. These patients usually have a worse clinical outcome than their non-AKI counterparts . Adverse outcomes include prolonged hospitalization, need for renal replacement therapy, development of chronic kidney disease, and increased mortality rate. [1,2] The poor outcome is caused in part by the lack of a timely and accurate biomarker to predict the occurrence of AKI. Currently, serum creatinine (SCr) level and urine output are the standard indicators of decreased kidney function despite their known limitations.They have limited sensitivity and specificity and creatinine level change is delayed in response to kidney impairment, thus limiting their usefulness in the early detection of AKI [3].Therefore, the need for an accurate and timely biomarker to predict AKI

development after renal insult is essential. About 1 in 5 hospitalized patients get AKI. This number approximately doubles for patients in the ICU setting. Severely ill patients with AKI who are in the hospital have the highest chance of death, up to 50%. [1-4] Approximately 1 in 10 patients who have AKI need dialysis: A significant number of those patients will die in the hospital and approximately 20% of survivors will continue to need dialysis after they are sent home from the hospital. Among survivors needing dialysis after having AKI, some will need to stay on dialysis permanently. [4-6] About one third of patients who have AKI will develop CKD within 2 to 5 years of having AKI. This risk increases with more severe and repeated episodes of AKI. [7 -11]

Patients who live after having AKI have higher chances for stroke and heart disease (e.g., heart attack, heart failure). [12,13] Cystatin C(cys C), a 13-kDa endogenous cysteine proteinase inhibitor ,is a member of the family of proteins that has an important role in intracellular catabolism of various peptides and proteins. CystatinC is considered to be a good biomarker of decreased kidney function because it is produced at a relatively constant rate and released into plasma5(2)99% is filtered by glomeruli and there is no significant protein binding. Therefore the present study was undertaken to identify the earlier marker of AKI and thereby reducing the morbidity and mortality of AKI.

Hence our study aims to determine the overall prevalence of AKI among ICU hospitalised COVID 19 patients and also to assess the mortality pattern and its relation to the above mentioned contributory factors.

Subjects and Methods:

Source of data: Blood samples of the subjects admitted to the ICU were collected between January 2015 - December 2015. A primary source of information technique with observational method was adopted on blood samples collected.

Inclusion criteria: Subjects older than 18 years of both gender admitted in intensive care units, at risk of developing Acute kidney injury (hemodynamically unstable subjects, subjects with SIRS and those receiving nephrotoxic drugs)

Exclusion criteria: Subjects with hypothyroidism or hyperthyroidism, those receiving glucocorticoids, cimetidine and trimethoprim, patients if at admission have Acute kidney injury with serum creatinine > 1.4 mg/dl, those at admission having urine output <0.5 ml/kg/hr and also the patients having established renal disease

Method of collection: 86 subjects admitted to intensive care units of who met inclusion and exclusion criteria were taken after explaining the purpose of the study and After taking informed written consent.

Detailed history, clinical examination and the relevant investigations were done as per pre-structured proforma.

In the selected 86 subjects, Serum Cystatin C and Serum Creatinine were measured by nephelometry and modified Jaffe's method respectively on first two consecutive days and thereafter only Serum Creatinine till the last day of hospital stay.

The subjects were classified according to the analyte that first increased.

Class A- Those with cystatin c increased first

Class B- Those with creatinine increased first

Class C- Those with both cystatin c and creatinine increased at the same time.

Class D- Those with both parameters normal

GFR also calculated using cystatin c and creatinine according to the following Formulas.

Cockcroft-Gault formula

Using Serum Creatinine as

$$\frac{\text{140-age x weight in kg x 0.85 if female}}{\text{72 x S.creatinine (mg/dl)}}$$

Using Serum Cystatin C as

$$\frac{\text{Serum cystatin c(mg/dl)}}{100}$$

Statistical Analysis: Sample size was calculated as 84 using the formula $n= 4PQ/d^2$, where P is the prevalence, Q is 1-P and d=10%=0.01(margin of error). Both descriptive and inferential statistics were employed for data analysis.

The Descriptive statistics procedure displays univariate summary statistics for several variables in a single table and calculates standardized values.

Variables can be ordered by the size of their means alphabetically, or by the order in which the researcher selects the variables. The descriptive statistics like frequencies, percentages, mean, standard deviation have been employed. Inferential statistics like Chi-square test, goodness-of-fit test, Crosstabs (Cramer's V) were employed.

Ethical consideration: The study received approval by the Institutional research review board.

Results

Population Characteristics: Among the 86 subjects chosen for the study, 60 were male and 26 were female with a male to female ratio of 3:1. Majority of the subjects were in the 31-40 age groups with mean age of 40 in both genders. Out of

86 subjects taken for study, 26 (30.2%) developed AKI during the hospital stay with AKI to Non-AKI ratio of 1:2.3.

Table 1: Distribution of study participants as per the presence of AKI

Category	Number of Subjects	Percentage
Patients who developed AKI	26	30.2%
Patients who did not develop AKI	60	69.8%
Total	86	100%

Majority of the subjects who developed AKI were in the age group of 41-50yrs and equally distributed in both the gender.

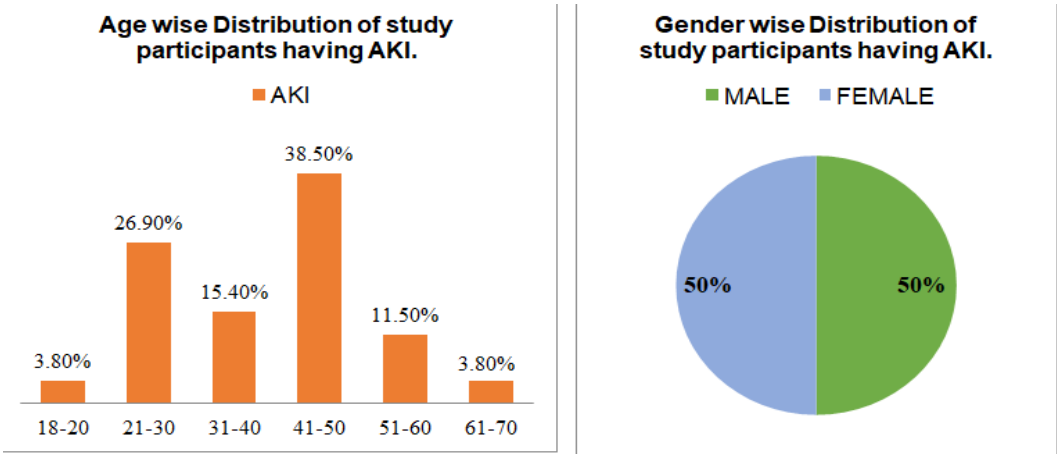

Figure 1: Age & Gender wise Distribution of study participants having AKI

Table 2: Distribution of study participants based on etiological causes in AKI

Diagnosis	Category		Total
	AKI	NON-AKI	
Sepsis	12 (46%)	17 (28%)	29 (34%)
OP compound consumption	1 (4%)	0	1 (1%)
Dengue	2 (8%)	13 (22%)	15 (17%)
RHD	2(8%)	1 (2%)	3 (3%)
Myocardial Infarction	3 (12%)	8 (13%)	11 (13%)
DKA	0	2 (3%)	2 (2%)
RTA	2 (8%)	13 (22%)	15 (17%)
SHOCK	4 (15%)	6 (10%)	10 (12%)
TOTAL	26	60	86

Majority of the subjects who developed AKI were with sepsis followed by shock

Table 3: Distribution of study participants based on Class in AKI

Class	Category		Total
	AKI	NON-AKI	
A	18 (69%)	2 (3%)	20 (23%)
B	0	0	0
C	8 (31%)	0	8 (9%)
D	0	58 (97%)	58 (67%)
TOTAL	26	60	86

Majority of the subjects who developed AKI belongs to class A that means in most of the AKI subjects the parameter which got increased first was Cystatin C followed by Creatinine with a time interval of 1-2 days and the rest belongs to Class C (those with both Cystatin C and Creatinine increased at the same time). This confirms the finding that Serum Cystatin C is elevated much before Serum Creatinine levels start raising.

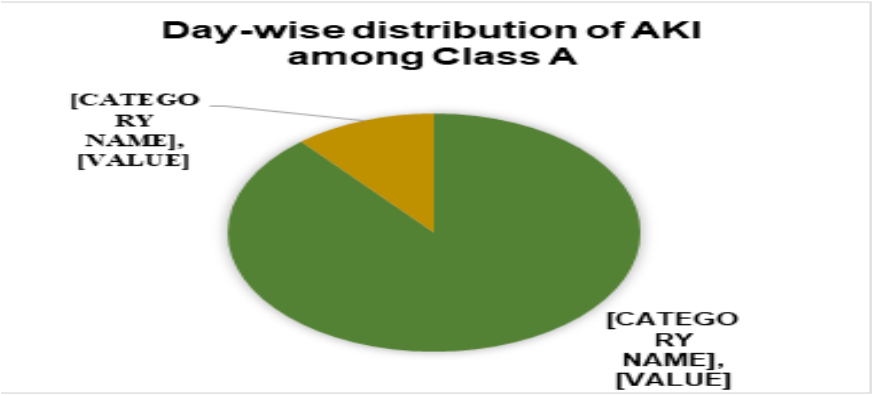

Figure 2: Day-wise distribution of AKI among Class A after the elevation of Serum Cystatin C

Among the Class A patients, 88.9% of them developed AKI on the second day (next day after the elevation of Cystatin C) and the remaining 11.1% on the third day (two days after the elevation of Cystatin C)

Table 4: Mean Cystatin C and Serum Creatinine in AKI subjects

Variable	Value (mg/dl)	Standard deviation (SD)
Mean S.Cystatin C	4	2.8
Mean S.Creatinine	1.4	1.15

In the patients who developed AKI, the mean serum cystatin c and serum creatinine was found to be 4mg/dl with a standard deviation of 2.8 and 1.4mg/dl with a standard deviation of 1.15 respectively.

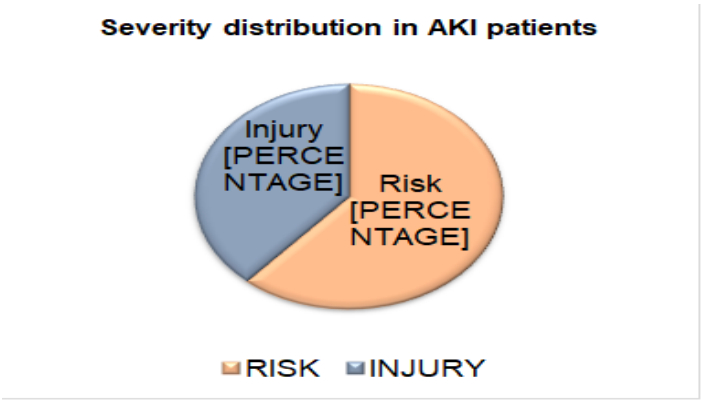

Figure 3: Severity distribution in AKI patients as per RIFLE Criteria

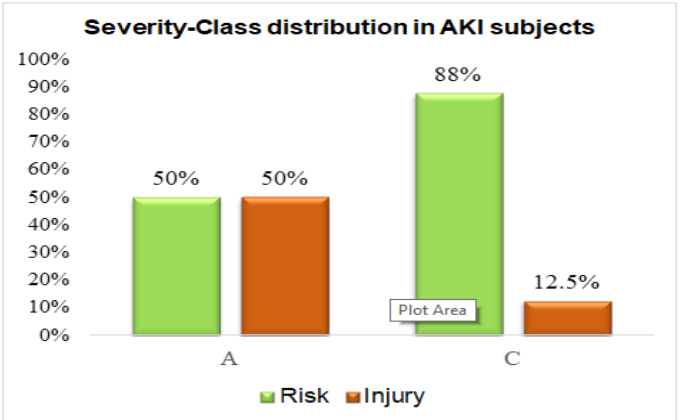

Figure 5: Severity-class distribution in AKI subjects

AKI subjects were staged according to RIFLE, and it was found out that majority of them were in the Risk stage and the rest were in the Injury group and it showed that estimation of Cystatin C along with Creatinine enabled to detect more AKI at the earliest.

Table 5: Correlation between GFR calculated with Cystatin C and Creatinine on day 1.

	GFR C1	GFR Cr1
GFR C1 (Pearson Coefficient)	1	0.690
GFR Cr1 (Pearson Coefficient)	0.690	1

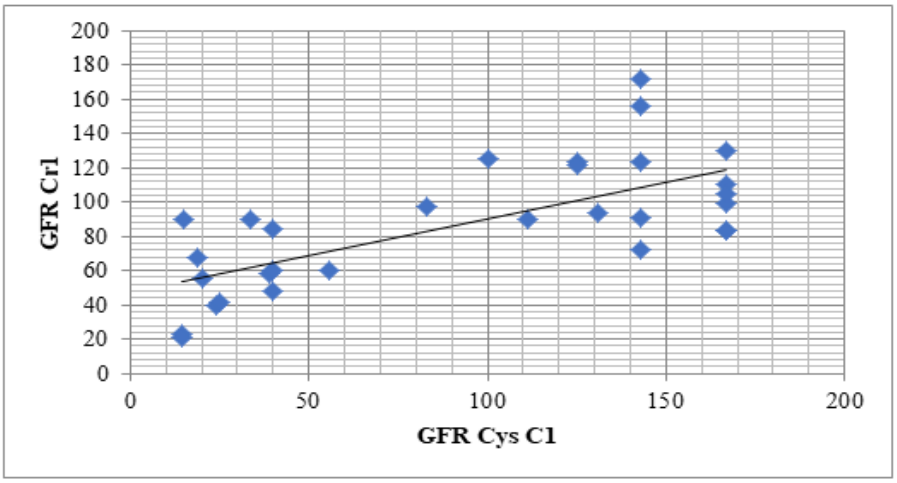

Figure 6: Correlation between GFR calculated with Cystatin C and Creatinine on day 1

Table 6: Correlation between GFR calculated with Cystatin C and Creatinine on day 2.

	GFR C2	GFR Cr2
GFR C2 (Pearson Coefficient)	1	0.771
GFR Cr2 (Pearson Coefficient)	0.771	1

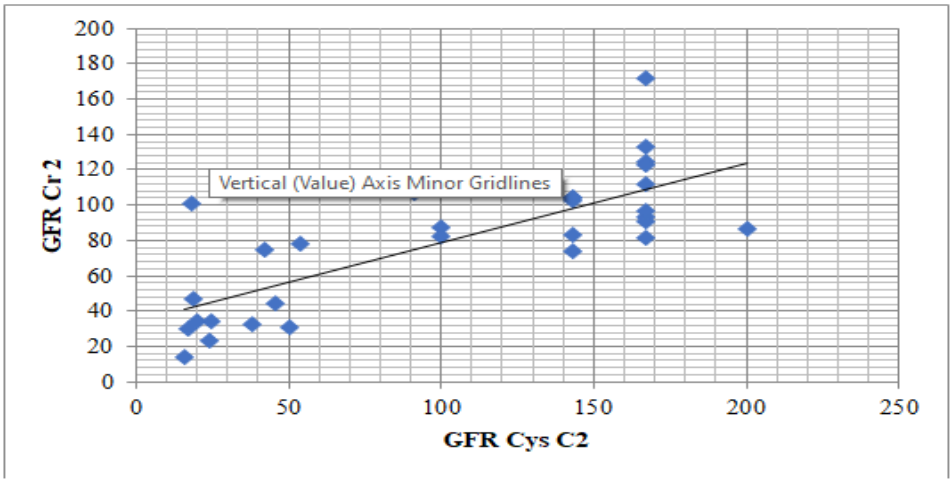

Figure 7: Correlation between GFR calculated with Cystatin C and Creatinine on day 1

GFR was estimated on two consecutive days with Cystatin C and Creatinine and it showed that there is no much difference between GFR calculated with Cystatin C and Creatinine and statistically correlation is significant at the 0.01 level.

Discussion

Acute kidney injury commonly is encountered in various patient populations especially in critically ill patients admitted to ICU. Hence this study concentrates on critically ill patients admitted to ICU who are at risk of developing AKI. [15,17] Therefore, we need an early biomarker which can predict the occurrence of AK at an early stage.

Serum Cystatin C production is more predictable and it could meet most of the ideal filtration biomarker criteria with less inter-individual variation although it is modestly influenced by hyperthyroidism, drugs, low grade chronic inflammation. [18,19]

Among the 86 subjects chosen for the study, 60 (69.8%) were males and the remaining were females 26(30.2%). Majority were in the age group of 31-40 years with mean age of 40 years in both sexes. Out of 86 subjects, 26 subjects (30.2%) developed AKI during the hospital stay and among subjects with AKI one in-hospital mortality occurred.

Majority of subjects who developed AKI were in the age group of 41-50 years (38.5%) and were equally distributed in both males and females. Serum Cystatin C was elevated in all subjects who developed AKI. In 69.8% of subjects with AKI, it was found to be elevated on day 1 whereas serum creatinine in them remained normal on day 1 and day 2 also with a time interval of 1-2 days before serum creatinine started rising (class A).

In the rest of the subjects, it got elevated along with serum creatinine at the same time (class C). The mean serum cystatin C and serum creatinine in AKI subjects were 4mg/dl and 1.4mg/dl respectively. All the AKI subjects were in the early stage of AKI with 61.5% in Risk group and the remaining 38.5% were in the Injury group of RIFLE classification.

Correlation between GFR calculated using cystatin c and creatinine had shown that there is no much difference between both and the correlation is statistically significant with a p-value of <0.05.

In the present study, out of 86 patients 70% were males and 30% were females with a male to female ratio of 2.3:1 which is comparable to a study conducted by A.R. Shoukath et al from Karnataka in which 66% were males and 34% were females with a male to female ratio of 1.94:1.20 In a study conducted by Murty et al from Delhi, there were 77.7% were males and 22.3% were females with a male to female ratio of 3.5:1 21and in a study from New Zealand by Villa et al 68% were males and 32% were females. [22]

In the present study, out of 86 patients 26(30.2%) were developed AKI during the hospital stay with a AKI to Non-AKI ratio of 1:2.3 whereas in a study conducted by A.R. Shoukath et al from Karnataka it was 1.3:1 and in a study by Herget et al it was 1.1:1. In the present study, among the patients who developed AKI male to female distribution was equal in both whereas in a study by A.R. Shoukath et al and Herget et al a male predominance was seen with a male to female ratio of 1.8:1 and 1.9:1 respectively. In the present study 70% of patients who developed AKI had high serum cystatin c on day 1 with normal Serum Creatinine and it was comparable to 85.7% in a study by A.R. Shoukath et al. In a study by Herget et al it was 100%.

In the present study, there were 2(2.3%) patients with high cystatin c who did not develop AKI which is comparable to 1% in a study by A.R. Shoukath et al. In the present study, the mean Serum Cystatin C and Serum Creatinine was 4mg/dl and 1.4mg/dl respectively whereas the mean Serum Cystatin C and Serum Creatinine was 3.14mg/dl and 1.86mg/dl respectively in a study by A.R. Shoukath et al and it was 1.27mg/dl and 1.6mg/dl in a study by Ronwald et al.

Conclusion

We studied 86 ICU subjects, out of that 26 developed AKI during the hospital stay and one in-hospital mortality. Majority of the patients who developed AKI had high serum cystatin c on day 1 with normal serum creatinine. Serum cystatin C raised 1-2 days prior to serum creatinine.

This study concludes that serum cystatin c is an early marker of AKI than serum creatinine in detecting the risk of developing AKI in critically ill patients.

From October 1, 2020 to December 31, 2020,520 patients were admitted to JSS hospital with a diagnosis of COVID-19 present on admission or made during the hospitalization. The baseline characteristics of patients at hospital admission are provided in Table 1. A total of 112 patients (21.5%) were treated with mechanical ventilation at some point during the hospitalization. Among the 520 patients, 52 (10%) died, 61 (11.7%) were discharged to home or to a rehabilitation facility, and 85 (16.3%) were still in treatment.

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