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ORIGINAL ARTICLE

STUDY OF SERUM CYSTATIN C TO DETECT EARLY ACUTE KIDNEY INJURY IN ADDITION TO ROUTINE RENAL FUNCTION TESTS IN ACUTELY ILL PATIENTS

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ABSTRACT:
Early diagnosis of Acute Kidney Injury in Emergency department is a challenging task. Current diagnostic criteria for AKI poorly recognize early renal dysfunction & may cause delayed diagnosis. We evaluated the use of serum cystatin C for the early and accurate diagnosis of AKI in patients hospitalized in Intensive care unit. Our estimation of kidney function of estimated glomerular filtration rate is clinically dependent on equations like Cockgroft formula which has a inverse relation to Serum Creatinine and its incorrect and late evaluation makes our approach incorrect thus delaying the patients recovery. Serum Creatinine is also dependent on parameters of age, sex, Body mass index & thus leads to an inaccurate measurement of kidney function. Serum Creatinine is limited as a marker of kidney dysfunction in the settings and may be inaccurate in several situations, such as in patients with low muscle mass or with fluid overload or high muscle mass or age. New biomarkers have the potential to identify earlier patients with AKI and in the future potentially intervene to modify outcomes. Equations combining serum cystatin C and Serum Creatinine perform better than the equations using either cystatin C or SCr alone, especially in situations where CKD needs to be confirmed. Combining creatinine, cystatin C and urine albumin to creatinine ratio improves risk stratification for kidney disease progression and mortality.
Key words: Acute kidney injury, Creatinine, Cystatin C

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INTRODUCTION

Acute kidney injury (AKI) is a condition that substantially increases morbidity and mortality. Although novel biomarkers are being used in practice, the diagnosis of AKI is still made with surrogate markers of GFR, such as serum creatinine (SCr), urine output and creatinine based estimating equations. Fortunately, understanding the early stress response of the kidney to acute injuries has revealed a number of potential biomarkers. Biomarkers of AKI that are capable of early detection, risk stratification, and prognostication would represent a tremendous advance in the care of this highly vulnerable population. [5]

Acute kidney injury (AKI) is a common and serious condition, the diagnosis of which depends on serum creatinine, which is a delayed and unreliable indicator of AKI. Fortunately, understanding the early stress response of the kidney to acute injuries has revealed a number of potential biomarkers. Biomarkers of AKI that are capable of early detection, risk stratification, and prognostication would represent a tremendous advance in the care of this highly vulnerable population. [5]

Clinically applicable AKI biomarkers should be (a) non-invasive, using easily accessible samples such as blood or urine; (b) rapidly measurable using standardized clinical assay platforms; (c) sensitive to facilitate early detection, with a wide dynamic range and cut-off values that allow for risk stratification; (d) specific for AKI, to differentiate intrinsic AKI from pre-renal azotemia and chronic kidney disease; (e) predictive of clinical outcomes such as need for dialysis, length of hospital stay, and mortality; (f) able to guide initiation of therapies; and (g) facilitate monitoring the response to interventions Fortunately, understanding the early stress response of the kidney to acute injuries has revealed a number of proteins that inform early pathophysiology, and serendipitously, represent potential biomarker. [5]

Attention has been focused on the development of "early" biomarkers, enabling diagnosis of AKI long before creatinine levels start to increase. Logically, a combination of biomarkers could enhance diagnostic accuracy, but validation of current individual candidate biomarkers is still underway. Actually, more than ten promising biomarkers for AKI have been identified. The most relevant substances are neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule-1 (KIM-1), beta-2 microglobulin (β_2M), and interleukin-18 (IL-18). [6]

Cystatin C is a protease inhibitor that is released into the blood, filtered through the glomerulus, and completely reabsorbed in the proximal tubule. In chronic kidney disease, cystatin C was found to better predict glomerular function than serum creatinine. In cardiac surgery patients, a 50% increase in cystatin C could predict AKI 48 h before changes in serum creatinine or creatinine clearance suggested renal dysfunction. In practice, however, NGAL is still an earlier biomarker than cystatin C. [6]

METHODOLOGY

Patient selection

Outpatient department of Dr DY Patil hospital. The Study period of patients was from May 2014 to April 2016. They were registered when admitted under ICU department. At the time of registration the patients with exclusion criteria were not enrolled for study.

Inclusion criteria

Patients more than 18yrs of age.

Patients admitted in ICU suspected to have Acute Kidney Injury.

Exclusion criteria

Patients below 18yrs of age.

On Chronic Glucocorticoid Therapy.

Previously Diagnosed AKI/CKD.

Sampling technique: Simple random sampling

Written informed consent was taken from the participants. Patients admitted to ICU and having inclusion criteria were included in the study. Pre designed questionnaire schedule consisting of standard questions related to socio demographic factors, family history, addiction among family members, and so on, were interviewed. In addition, questionnaire also included questions on past and present Medical history and health seeking behaviour.

Following main domains were covered in questionnaire:

1. Clinical examination
2. Routine RFTs
3. Serum cystatin C

Data analysis:

The collected data was compiled in Microsoft Excel 2010 and analyzed using SPSS (Statistical Programme for Social Sciences) software 15 version, OpenEpi Software Version 2.3.

Ethics

Institute Ethical committee's approval was taken prior to the study.

AIM

Identify role of serum Cystatin C as a biomarker for increased risk of acute kidney Injury in acutely ill patients

OBJECTIVES

- Assess Serum Cystatin C and other Routine RFT's (sr.urea, sr.creat, urine, sr.electrolytes) in acutely ill patients needing ICU stay for 3 days within 24hrs of admission.
- Monitor renal status of study subjects till clinical stabilisation from acute illness or drop of renal function
- Compare the 2 groups (cystatin c vs non cystatin c) with respect to incidence of Acute kidney injury, demographic data & biochemical investigations.

RESULTS

Serum Cystatin C and other routine RFT were sent within 24 hours of admission in Intensive care unit.Patients were assessed on age their muscle mass and the associated disease which has been mentioned in the tables in the result. Diabetes and hypertension were the predominant illness associated with the patients which aggregated to atotal of 26%.All patients enrolled had a creatinine value of less than 1.2 which was the upper limit of normancy of serum creatinine.Patients with normal values of creatinine had a significant high value of serum cystatin C more than 0.95 and there was a total of 30 patients. In our study, all patients had normal Serum Creatinine levels and Mean count was 0.98 + 0.12.In clinical practice [115], the detection of AKI, which is characterized by a rapid decline of the GFR, is based on an increase of serum creatinine. However, there are major limitations to the use of creatinine for estimating GFR. Serum creatinine dont accurately reflect GFR during the nonsteady state of ARF by underestimating GFR. Thus, minor changes of creatinine, as typically seen early in ARF, may already reflect substantial declines in GFR. Furthermore, serum creatinine inaccurately estimates GFR due to tubular secretion and reabsorption of creatinine, and nonrenal factors that may apply to ARF patients who are predominantly critically ill.

Association between cystatin C and Serum creatinine

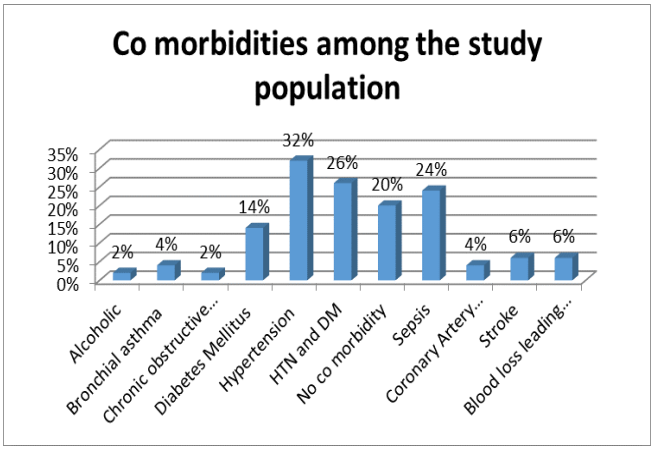
Showed significant difference between Cystatin C and Serum creatinine (p=0.01)**.** Similar results were seen in study by Murthy et al[113], where they showed that there was a significant difference between both (p=0.001)

Table 1: Age wise distribution among the study population (Mean age was 53.52 + 12.79 years)

Age	Percentage
18-30 years	6%
31 to 50 years	36%
51 to 70 years	48%
>70 years	10%
Total	100%

Table 1 shows the age wise distribution, where majority 48% patients were in age group of 51 to 70 years, followed by 36% in 31 to 50 years of age group, followed by 10% were in more than 70 years and only 6% less than 30 years.

Graph 1: Co morbidities among the study population



Graph 1 shows Co morbidities among the study population, where it was seen that majority 32% had HTN, 26% had HTN and DM, 20% had no co morbidities, 14% had DM, 4% had Bronchial Asthma and 2% each Alcoholic and COPD respectively, 24% had sepsis, 4% had coronary artery disease, 6% had stroke and 6% blood loss leading to AKI.

Table 2: Distribution of sepsis among the Diabetic population

Parameter	Number of Patients	Percentage
Diabetic with sepsis	7	35%
Diabetic without sepsis	13	65%
Total	20	100%

Table 3: Distribution of sepsis among the Hypertensive population

Parameter	Number of Patients	Percentage
HTN with sepsis	15	51.72%
HTN without sepsis	14	48.27%
Total	29	100%

Table 3 shows Personal history among the study population, where majority 51.72 % had HTN with sepsis and 48.27% had HTN without sepsis.

Table 4: Cystatin C levels among the study population

Cystatin C	Frequency	Percentage
0.53 to 0.95	20	40%
>0.95	30	60%
Total	50	100%

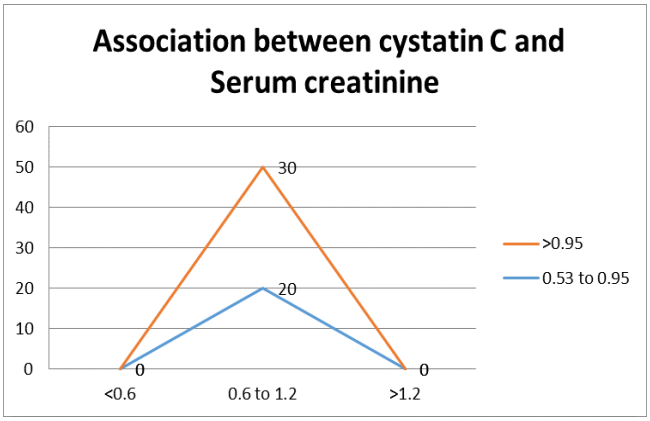
Mean levels were 1.34+ 0.77

Table 5: Association between cystatin C and Serum creatinine

Cystatin C/serum creatinine	<0.6	0.6 to 1.2	>1.2	Total
0.53 to 0.95	0	20	0	20
>0.95	0	30	0	30
Total	0	50	0	50

Applying chi square test, p=0.01, as p value is <0.05 which shows significance.

Graph 2: Association between cystatin C and Serum creatinine



Statistical significance was seen in cystatin C levels and Serum creatinine.

Table 6: Association between gender and cystatin C levels

Cystatin C/gender	Male	Female	Total
0.53 to 0.95	13	7	20
>0.95	16	14	30
Total	29	21	50

P value= 0.2, shows no significance

DISCUSSION

In our study, majority 48% patients were in age group of 51 to 70 years, followed by 36% in 31 to 50 years of age group, followed by 10% were in more than 70 years and only 6% less than 30 years. Mean age was 53.52 + 12.79 yearsIn a study by Murty et al [113] mean age was 53.8+ 17.9 In our study, majority 58% were males and only 42%

were females.In a study by Murty et al [113]77.75% were male

Majority 22 had swelling of feet, followed by 21 had breathlessness, followed by 4 had Hematuria, followed by 3 had Oligouria and only 1 had Polyuria.In our study, majority 32% had HTN, 26% had HTN and DM, 20% had no co morbidities, 14% had DM, 4% had BA and 2% each AL and COPD respectively.

Study by Zand F et al [120] showed that co morbid problems were history of hypertension 11.3%, smoking 45.7%, drug abuse 18.3%, diabetes mellitus 2.7%, and history of nephrotoxic drug consumption 8.7%.

In our study, all had normal Serum Creatinine levels and Mean count was 0.98 + 0.12

In clinical practice [115], the detection of AKI, which is characterized by a rapid decline of the GFR, is based on an increase of serum creat. However, there are major limitations to the use of creatinine for estimating GFR. Serum creatinine dont accurately reflect GFR during the nonsteady state of ARF by underestimating GFR. Thus, minor changes of creatinine, as typically seen early in ARF, may already reflect substantial declines in GFR. Furthermore, serum creatinine inaccurately estimates GFR due to tubular secretion and reabsorption of creatinine, and nonrenal factors that may apply to ARF patients who are predominantly critically ill.

Association between cystatin C and Serum creatinine

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Similar results were seen in study by Murthy et al[113], where they showed that there was a significant difference between both (p=0.001)

CONCLUSION

Early diagnosis of AKI, particularly in severely ill patients, remains difficult. Creatinine-based measurements prove to be little helpful. Serum creatinine levels start to increase when most of the kidney function is already lost and a steady state has been reached. Creatinine clearance also remains a late and indirect marker of AKI. Currently, much attention goes to biomarkers that are able to detect AKI in an earlier phase of development.

Most promising are NGAL, cystatin C, KIM-1, β2M, and IL-18. Apart from a role in diagnosis, some markers (e.g., NGAL) also may have benefit in assessing eventual unwarranted renal effects of toxins, ischemic events, and infusion fluids. Validation of those kidney markers in various conditions of AKI is actually ongoing. However, clinical studies on biomarkers are still scarce, particularly in critically ill patients, and sensitivity and specificity of individual biomarkers remain unacceptably low. Development of biomarker kits that combine markers with different characteristics may increase diagnostic accuracy. Large multicentric randomized studies are imperative to confirm whether the use of biomarkers can influence course and treatment of AKI. Finally, linking the assessment of biomarker specificity and sensitivity to creatinine-based criteria should be abandoned. An early and goal-directed therapy for AKI by using offensive strategies that are "covered" and directed by early and serial evaluation of biomarkers probably is the ultimate method to combat excessive "renal" mortality in the ICU. In our study we conclude that cystatin C can be used as an important biomarker to diagnose early for AKI.

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