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Original Research Article

A Clinical Study of Serum Cystatin-C Levels in Acute Kidney Injury

Ramesh[1], Somasekhar Patil[2]

[1]Associate Professor, Department of General Medicine, Prathima Institute of Medical Sciences, Naganoor, Karimnagar.
[2]Associate Professor, Department of General Medicine, Prathima Institute of Medical Sciences, Naganoor, Karimnagar

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Corresponding author: Dr. Somasekhar Patil
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Abstract

Background: A 45%–60% increase in mortality is linked to acute kidney injury. Dialysis can stop progression and lower mortality in individuals with acute renal damage with early identification and beginning. The conventional measure for AKI detection, serum creatinine, has significant drawbacks. The ability of cystatin C to diagnose AKI and whether it can do so earlier than serum creatinine was studied prospectively in this study.

Methods: Patients at risk of developing AKI history of preceding Acute Diarrhoeal disease (ADD), and febrile illness with symptoms suggestive of AKI were selected. Patients having one or more risk factors for CKD and patients already having CKD are excluded. Also, patients with a history of alcohol abuse and chronic smoking were excluded since these can interfere with the measurement of cystatin C.

Results: The estimation of levels of serum cystatin C showed early elevation of serum cystatin C on the second day in 77% of cases which increased to 94% on the third day and progressed to 100% on day 4 in patients with AKI depicted in table 5. The estimation of cystatin C in the remaining n=15 cases who did not progress to AKI revealed that n=13 cases had normal levels of serum cystatin C and increased in n=2 cases which were found to be transient and came back to normal levels at day 4.

Conclusion: Serum Cystatin C is an excellent early biomarker for the detection of AKI. This biomarker can also accurately distinguish between prerenal and intrinsic AKI. The results of the current showed that elevated levels of serum cystatin c are produced earlier than the other conventional renal functional markers. Cystatin c is also less likely to be influenced by age, gender muscle mass, and ethnicity.

Keywords: Acute kidney injury, serum cystatin C, serum creatinine, blood urea

Introduction

Acute kidney injury (AKI) is characterized by a sudden (within 48 hrs) decline in kidney function, as well as an increase in serum creatinine of at least 0.3 mg/dl, a percentage increase of at least 50% from baseline, or confirmed oliguria of at least 0.5 ml/kg/hr for at least 6 hours. [1] There are several potential causes for it. The incidence ranges from 5% for patients across the hospital to 25% for those in the intensive care unit. It has a worse clinical outcome and a high death rate between 45%

and 60%. [2] Delays in diagnosis and in starting dialysis are to blame for the poor result. The lack of a reliable biomarker to anticipate the onset of AKI contributes to the delay in starting hemodialysis. Despite their acknowledged limitations, Scr level and urine output are currently the accepted indicators of reduced kidney function. They are ineffective for the early identification of AKI due to their low sensitivity and specificity and the fact that renal damage takes time to cause a change in creatinine levels. [3] Therefore, it is crucial to have a reliable biomarker that can predict the emergence of AKI following renal injury. Numerous research is examining the effectiveness of more recent biomarkers for the detection of AKI, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and cystatin C. 2 Because it is generated at a largely consistent rate and released into the plasma, cystatin-C is regarded as an excellent biomarker of kidney function. [4] Glomeruli filter out >99% of the water. Minimal protein binding is present. A 13 kDa endogenous cysteine proteinase inhibitor is called cystatin-C. Numerous studies have assessed cystatin c it functions as an endogenous marker of kidney function in populations at risk for or suffering from chronic kidney disease, and they have found that cystatin-C is more accurate than serum creatinine levels at differentiating between normal and impaired kidney function. [5, 6] Recent studies have suggested many new plasma and urine indicators for the early detection of AKI and associated clinical effects in a range of clinical situations. [7, 8] Cystatin C among them seems to be a helpful AKI detection marker. [9] All nucleated cells consistently generate this low molecular weight cysteine proteinase constitutively. It is completely reabsorbed in the proximal tubule without being secreted after being freely filtered by the renal glomeruli. Thus, GFR is the main factor affecting cystatin C serum levels. Urine often does not contain considerable quantities of cystatin C. [10] In patients undergoing cardiac surgery or who are critically unwell, elevated urine levels of cystatin C may suggest tubular dysfunction independent of GFR and may be an early signal of AKI. [11, 12] Serum cystatin C (SCysC) performs at least as well as serum creatinine in the general population, and even outperforms SCr in some patient groups, according to several pieces of research examining SCysC as a GFR marker. [13] In the contexts of critical care [14], cardiac surgery [15], and radiocontrast injection [16] SCysC has also been recommended as an early biomarker of AKI. In this study, we assessed cystatin c-potential as a biomarker for AKI in individuals who were at high risk of acquiring the condition. Additionally, we compared the diagnostic precision of cystatin-C with serum creatinine level in predicting AKI, and we also looked at the relationship between cystatin-C level and AKI severity and outcome.

Material and Methods

This cross-sectional observational study was conducted in the Department of General Medicine, Prathima Institute of Medical Sciences, Naganoor, Karimnagar. Institutional Ethical committee permission was obtained for the study. Written consent was obtained from all the participants of the study after explaining the nature of the study in the local language.

Inclusion criteria

1. Patients at risk of developing AKI.
2. Males and females
3. Aged 20 years and above
4. Admitted to Medical Wards of PIMS
5. Willing to participate in the study

Exclusion criteria

1. Patients with diabetes mellitus
2. Patients with systemic hypertension, CAD
3. Patients with CKD
4. Patients with chronic NSAID abuse

5. Patients with drug intake affecting renal functions
6. Chronic smoking, alcoholism

Patients at risk of developing AKI history of preceding Acute Diarrhoeal disease (ADD), febrile illness with symptoms suggestive of AKI were selected. Patients having one or more risk factors for CKD and patients already having CKD are excluded. Also, patients with a history of alcohol abuse and chronic smoking were excluded since these can interfere with the measurement of cystatin C. The proforma sheet contained information about the social, economic, and medical profile of the patient. Additionally, the history of AKI symptoms, such as a reduction in urine production, was noted, as well as the number of hours that each symptom lasted. The patient's baseline clinical check-up was completed. Vital signs were noted baseline research was completed. All patients underwent an abdominal USG to evaluate the size and texture of the kidneys and rule out CKD.

On the day of admission, the levels of serum creatinine and cystatin were tested. The development of AKI was then monitored for each of them. Daily measurements of serum creatinine were taken, and the progression of AKI was determined using the AKIN group's suggested staging method, which states that *Stage 1:* represents an increase in serum creatinine of 150–200% from baseline or less than 0.3 mg/dl. *Stage 2:* is defined as an increase in serum creatinine of 200–300% from baseline. *Stage 3* is defined as a rise in serum creatinine of greater than 30% from the starting point or as a rise in serum creatinine of at least 4 mg/dl.

The day the AKI criteria were fulfilled according to serum creatinine was noted as day -I. We used either the rise in serum creatinine of ≥ 0.3 mg/dl or ≥ 150 to 200 % from baseline to diagnose AKI. patients who did not develop AKI served as controls. In controls, serum creatinine was measured for a minimum of 5 days starting from the enrolment. Also, the duration of stay in the hospital is noted for all patients and the number of dialyzes needed for those who developed AKI was also recorded.

Statistical analysis: The endpoint was the day that AKI was identified by serum creatinine. Cystatin C levels were out of the ordinary that day when this was compared to them. The student's 't' test was used to compare the mean serum cystatin C levels between those who got AKI and people who did not.

Results

A total of n=50 cases were included in the study, and we found AKI developed in n=35 cases and according to the AKIN staging of AKI which was detected by an increase in serum creatinine of ≥ 0.3 mg/dl or ≥ 150 to 200% raise from the baseline values. Among these n=35 cases, the serum cystatin C levels were found to increase from day 1 in n=34 cases, and in n=1 case found serum cystatin C levels were normal on day 1 and developed AKI subsequently. These patients had normal serum creatinine levels on day 1 and the development of AKI according to serum creatinine levels (day 1) was either on day 2 or day 3.

Table 1: Development of Acute Kidney injury in the cases of the study

Development of AKI	Frequency	Percentage
Yes	35	70
No	15	30
Total	50	100

Among the n=50 cases included in the study, n=24 were males and n=26 were females. Among the n=35 cases developing AKI n=20 were males and n=15 were females. Indicating that males have a greater tendency to develop AKI as compared to females.

Table 2: Distribution of cases in the study based on the duration of symptoms

Duration of Symptoms (in Hours)	Frequency	Percentage
5 hrs or less	12	24.00
> 5 hours	38	76.00
Total	50	100.00

Based on the duration distribution of the cases included in the study out of n=50 cases n=12(24%) were less than 5 hours in duration and n=38(76%) cases were greater than 5 hours in duration depicted in table 2. The detailed hourly distribution of cases revealed most of the cases were at 6 hours n=12(24%) followed by a duration of 7 hours n=9(18%) and at 8 hours n=8(16%). The hourly distribution of cases in the study has been depicted in figure 1.

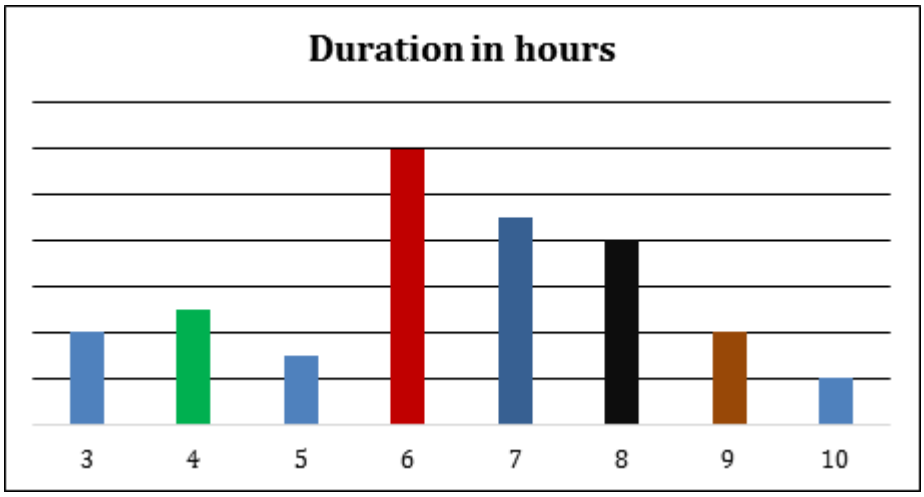

Figure 1: Duration distribution of the cases in the study

The estimation of serum cystatin C was found to be normal in n=34 cases and elevated in n=1 case who later developed AKI.

The levels of creatinine recorded in cases that progressed to AKI have been depicted in table 3. A critical analysis of table 3 indicated on day 1 the values of serum creatinine were normal in all 100% of cases and on the second day 94% of the cases in the study were showing elevated serum creatinine levels and on the third day, 97% had elevated serum creatinine levels.

Table 3: Showing the levels of creatinine recorded in cases that progressed to AKI

Serum creatinine	Abnormal >1.5 mg/dl	Normal < 1.10 mg/dl
Day 1	00	35
Day 2	33	02
Day 3	34	01
Day 4	35	00
Day 5	35	00

The estimation of blood urea has been depicted in table 4 it showed blood urea remained normal on the first and the second day in patients who progressed to AKI and subsequently on the fourth day 83% of cases showed elevated blood urea levels and progressed to 100% cases on the fifth day.

Table 4: Showing the levels of blood urea recorded in cases that progressed to AKI

Blood urea	Elevated > 40.0 mg/dl	Normal < 30.0 mg/dl
Day 1	00	35
Day 2	00	35
Day 3	08	27
Day 4	29	06
Day 5	35	00

Table 5: Showing the levels of cystatin C recorded in cases that progressed to AKI

Serum Cystatin C	Elevated > 1.15 mg/dl	Normal < 1.0 mg/dl
Day 1	00	35
Day 2	27	08
Day 3	33	02
Day 4	35	00
Day 5	35	00

The estimation of levels of serum cystatin C given in table 5 showed early elevation of serum cystatin C on the second day 77% of cases which increased to 94% on the third day and progressed to 100% on day 4 in patients with AKI depicted in table 5. The estimation of cystatin C in the remaining n=15 cases who did not progress to AKI revealed that n=13 cases had normal levels of serum cystatin C and increased in n=2 cases which were found to be transient and came back to normal levels at day 4.

Discussion

A person's body's muscle mass and dietary habits have a substantial impact on how much creatinine is produced. The renal tubules produce creatinine, which is also filtered by the glomeruli. This tubular secretion, which accounts for 20% of the kidney's overall creatinine excretion, can rise when GFR falls. These characteristics all help to explain why serum creatinine concentration might not be a reliable indicator for determining GFR accurately, especially at lower rates. [17] This study demonstrates that serum cystatin C functions as a reliable indicator of AKI. Additionally, compared to the traditional renal function marker blood creatinine, serum cystatin C enables the identification of AKI development one to two days earlier. Six hours after an acute renal insult, serum cystatin C levels were observed to be increased. The body's steady mechanism of producing cystatin C is unaffected by renal issues, elevated protein catabolism, or dietary considerations. Additionally, unlike creatinine, it does not alter with aging or muscle mass. Due to its biochemical properties, it may be freely filtered in the renal glomerulus and then processed and reabsorbed by the proximal tubule. Because of these factors, serum cystatin C has been recommended as the optimal endogenous GFR marker. [18-21] However, even accounting for creatinine clearance, only a small number of studies show that growing older is independently related to increased blood cystatin C levels. [22] In the current study, it was found that serum cystatin C levels >1.10 mg/dl, or the level above the normal range, have a higher sensitivity for prediction of AKI. It was found that serum cystatin C was more sensitive than serum creatinine in detecting AKI. These findings have clinical significance since they allow for the prevention of AKI development by allowing for the early diagnosis of AKI. More than half (60%) of the patients in the AKI group had normal creatinine readings, but they also had increased cystatin C levels and were in the creatinine blind zone. All AKI patients also exhibited abnormal cystatin C. This supports the fact that blood cystatin C levels are increased far in advance of an increase in serum creatinine levels. When detecting early renal

impairment that is overlooked by relying solely on blood creatinine, serum cystatin C has better sensitivity. A study by H Rosenthal et al., [23] found serum cystatin C a superior marker of rapidly reduced glomerular filtration after nephrectomy in kidney donors compared to creatinine serum cystatin c detects rapid GFR decrease one to two days earlier than creatinine. Cystatin c is an early and accurate marker to detect rapid GFR decreases as in ARF. C Briguari et al., [24] found that in patients with chronic kidney disease cystatin c seems to be a reliable marker for early diagnosis and prognosis of contrast-induced acute injury. Qiang Li et al., [25] found that cystatin c is more sensitive than serum creatinine in assessing renal function at an early shock. The serum cystatin c was a better marker for kidney functions as compared to serum creatinine levels in ICU patients. There is concern that the inflammatory process in sepsis may affect serum cystatin c estimation. However, J Martensson et al., [26] have shown that sepsis has no impact on the level of cystatin c in plasma during the first week in ICU. Peralta A et al., [27] found that adding cystatin c to a combination of creatinine and albumin creatinine ratio measures improved the predictive accuracy for all-cause mortality in end-stage renal diseases.

Conclusion

In conclusion, serum cystatin c is an excellent early biomarker for the detection of AKI. This biomarker can also accurately distinguish between prerenal and intrinsic AKI. The results of the current showed that elevated levels of serum cystatin c are produced earlier than the other conventional renal functional markers. Cystatin c is also less likely to be influenced by age, gender muscle mass, and ethnicity. The use of serum cystatin C-based GFR may be more effective and accurate for initiating treatment early and leading to a positive result in cases of AKI.

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