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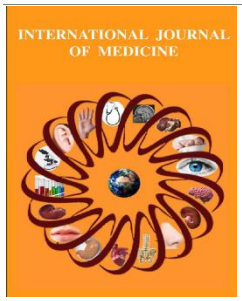

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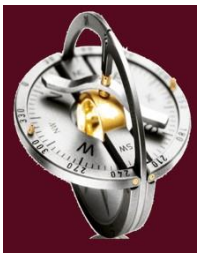

Research Article

Early Prediction of Acute Kidney Injury: A Comparative Study of Serum Cystatin C and Serum Creatinine

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Abstract

Background: Acute kidney injury (AKI) is a common clinical syndrome associated with high morbidity, mortality, and long-term risk of chronic kidney disease. Conventional biomarkers such as serum creatinine rise late after renal injury and are influenced by several non-renal factors, limiting their utility for early detection. Serum cystatin C, a low molecular weight cysteine protease inhibitor, has emerged as a promising early biomarker, independent of age, sex, and muscle mass. ***Objectives***: To compare the diagnostic performance of serum cystatin C and serum creatinine in the early prediction of AKI among patients admitted with predisposing conditions, using RIFLE criteria for classification. ***Methods***: This prospective case–control study was conducted at SSG Hospital, Vadodara, Gujarat, over eight months. Sixty patients with AKI risk factors were enrolled: 37 developed AKI and 23 served as controls. Serum creatinine (Jaffe's method) and serum cystatin C (ELISA) were measured daily. Statistical analysis was performed using SPSS 20.0 and MedCalc 12.5, applying Chi-square, Fisher's exact, Pearson correlation, and Kappa statistics. ***Results***: AKI incidence was 61%, predominantly in males (70%) and younger adults (<40 years). Major etiologies were complicated malaria (18.9%), gastroenteritis, and snake bite. Serum cystatin C identified AKI earlier in 29.7% of cases, compared to creatinine in 24.3%, while both rose simultaneously in 46%. Correlation between cystatin C and creatinine at 24 hours was moderate (r = 0.493; p = 0.032). ***Conclusion***: Serum cystatin C is a more sensitive and earlier marker than serum creatinine for AKI detection, particularly in infectious etiologies. Incorporating cystatin C into diagnostic protocols may enable earlier intervention and improved outcomes in resource-limited settings.

Keywords: Cystatin C, Creatinine, Acute Kidney Injury, RIFLE criteria.

Introduction:

Acute kidney injury (AKI) is a clinical syndrome characterized by an abrupt decline in renal function, resulting in the accumulation of nitrogenous waste products and disturbances in fluid, electrolyte, and acid–base balance. It occurs in diverse clinical settings, ranging from community-acquired illnesses to hospital-based complications. Globally, the reported incidence of AKI varies widely, and mortality rates remain alarmingly high, ranging from 30% to 90% depending on etiology and the severity of illness [1]. AKI not only contributes to immediate morbidity and mortality but also predisposes survivors to chronic kidney disease (CKD) and end-stage renal disease (ESRD), thereby placing a long-term socioeconomic burden on patients and healthcare systems [2].

Traditionally, clinicians have relied on serum creatinine, blood urea nitrogen, and urine output to diagnose AKI. While these parameters are universally available and cost-effective, they have considerable limitations. Serum creatinine, for example, rises only after significant nephron damage has occurred and is influenced by age, sex, muscle mass, and hydration status [3]. Furthermore, its elevation lags 24–48 hours behind the actual renal insult, delaying the diagnosis and limiting opportunities for early intervention [4]. Blood urea is even less reliable, as it is affected by dietary protein intake, liver function, and catabolic state. Such shortcomings necessitate the search for more sensitive and specific biomarkers capable of detecting kidney injury at an earlier stage.

Cystatin C, a low molecular weight cysteine protease inhibitor produced by all nucleated cells, has emerged as a promising alternative. Its production is constant, and unlike creatinine, its levels are unaffected by age, sex, muscle mass, or diet [5]. Cystatin C is freely filtered at the glomerulus and reabsorbed and catabolized by the proximal tubule, making it a reliable marker of glomerular filtration rate [6]. Multiple studies have reported that serum cystatin C rises earlier than creatinine following kidney injury and correlates better with severity, recovery, and prognosis [7,8].

The epidemiology of AKI shows marked regional differences. In developed countries, AKI is predominantly hospital-acquired, occurring in elderly patients with sepsis, multi-organ failure, or exposure to nephrotoxic drugs and contrast media. In contrast, in developing countries such as India, AKI frequently affects younger adults and is commonly community-acquired. Infectious diseases such as malaria, gastroenteritis, leptospirosis, and septicemia, along with envenomation and poisoning, are leading causes [9,10].

Given these differences, there is a compelling need to evaluate the role of newer biomarkers in resource-limited, high-burden settings. This study was conducted to compare the performance of serum cystatin C and serum creatinine in predicting early AKI among patients admitted with predisposing conditions, using RIFLE criteria to classify severity.

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Materials and Methods

Study Design and Setting

This prospective case–control study was carried out in the Department of Medicine, Sir Sayajirao General (SSG) Hospital, Vadodara, Gujarat.

The hospital functions as a tertiary care referral center, catering to a wide catchment area that includes both urban and rural populations. The study was conducted over an eight-month period.

Sample Size and Grouping

A total of 60 patients were enrolled. Among these, 37 patients who developed AKI during hospitalization formed the case group, and 23 patients without AKI served as controls. Recruitment was consecutive, based on eligibility, and informed consent was obtained from all participants or their relatives.

Inclusion Criteria

- Patients admitted with one or more risk factors for AKI were eligible. Risk factors included:
- Complicated malaria (Plasmodium falciparum and mixed infections),
- Dengue fever,
- Acute gastroenteritis,
- Snake bite,
- Septicemia,
- Cirrhosis of liver,
- Eclampsia,
- Use of nephrotoxic drugs such as aminoglycosides, amphotericin B, acyclovir, and NSAIDs,
- Poisonings (organophosphorus compounds, pesticides, chemicals),
- Patients on ventilatory support, and
- Acute cardiovascular events such as cardiogenic or hypovolemic shock.

Exclusion Criteria

- Patients with known chronic kidney disease,
- Those receiving systemic glucocorticoid therapy,
- Patients with hypo- or hyperthyroidism.
- Exclusion of thyroid disorders was necessary as cystatin C concentrations can be influenced by thyroid dysfunction.

Ethical Considerations

Approval was obtained from the Institutional Ethics Committee of the medical college. Written informed consent was obtained from patients or their guardians, and patient confidentiality was strictly maintained.

Clinical Evaluation and Data Collection

- All patients underwent a detailed clinical history and thorough physical examination at admission. Demographic details including age, sex, occupation, and risk factors were recorded.
- Baseline laboratory investigations included:
- Complete blood count,
- Renal function tests (blood urea, serum creatinine, electrolytes),
- Liver function tests,
- Random blood sugar,
- Viral markers (HIV, HBsAg, HCV),
- Urine analysis,
- Chest radiography,
- Electrocardiogram, and
- Abdominal ultrasonography.
- Additional investigations such as CT scan, echocardiography, or blood cultures were performed where clinically indicated.

Measurement of Biomarkers

- Serum creatinine was estimated by the Jaffe's method using automated analyzers.
- Serum cystatin C was measured using a specific ELISA-based immunoassay kit.

Both biomarkers were measured daily until a ≥50% rise from baseline was observed.

Definition and Classification of AKI

AKI was defined according to RIFLE criteria[4].
Risk: 1.5-fold increase in serum creatinine or GFR decrease >25%,
Injury: 2-fold increase in serum creatinine or GFR decrease >50%,
Failure: 3-fold increase in serum creatinine or GFR decrease >75%, or serum creatinine ≥4 mg/dL.
Parallel cut-offs were applied to cystatin C to classify AKI severity.

Data Management

All data were entered into a pretested case record form and transferred to Microsoft Excel (2010). Data were password-protected and anonymized.

Statistical Analysis

Data were analyzed using IBM SPSS version 20.0 and MedCalc version 12.5. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. The following statistical tests were applied:

- Chi-square test for categorical data,
- Fisher's exact test when expected frequencies were small,
- Pearson correlation coefficient to assess relationship between serum creatinine and cystatin C levels at 24 hours,
- Kappa statistics to evaluate agreement between creatinine and cystatin C in diagnosing AKI across study days.
- A p-value <0.05 was considered statistically significant

Results

A total of 60 patients were included, of whom 37 developed AKI and 23 served as controls. Results are presented as demographics, etiological profile, biomarker comparison, and severity assessment.

Table 1. Sex-wise distribution of patients

Gender	Total (N=60)	Cases (N=37)	Controls (N=23)
Male	43 (72%)	26 (70%)	17 (74%)
Female	17 (28%)	11 (30%)	6 (26%)

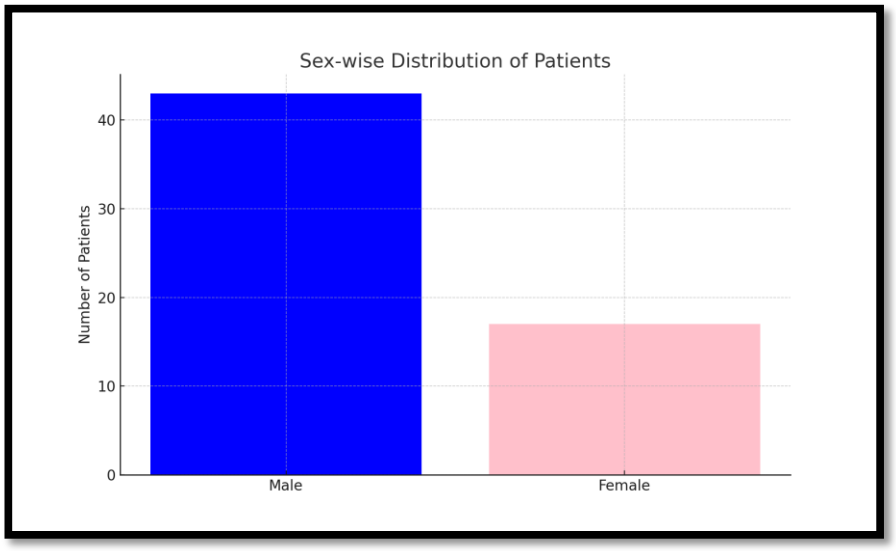


Table 2. Age-wise distribution of patients

Age group	All patients (N=60)	AKI cases (N=37)	Controls (N=23)
<30	15 (25%)	8 (21.6%)	7 (30.4%)
30–39	15 (25%)	9 (24.3%)	6 (26.1%)
40–49	8 (13.3%)	3 (8.1%)	5 (21.7%)
50–59	7 (11.7%)	7 (18.9%)	0 (0%)
60–69	7 (11.7%)	4 (10.8%)	3 (13.0%)
≥70	8 (13.3%)	6 (16.2%)	2 (8.6%)

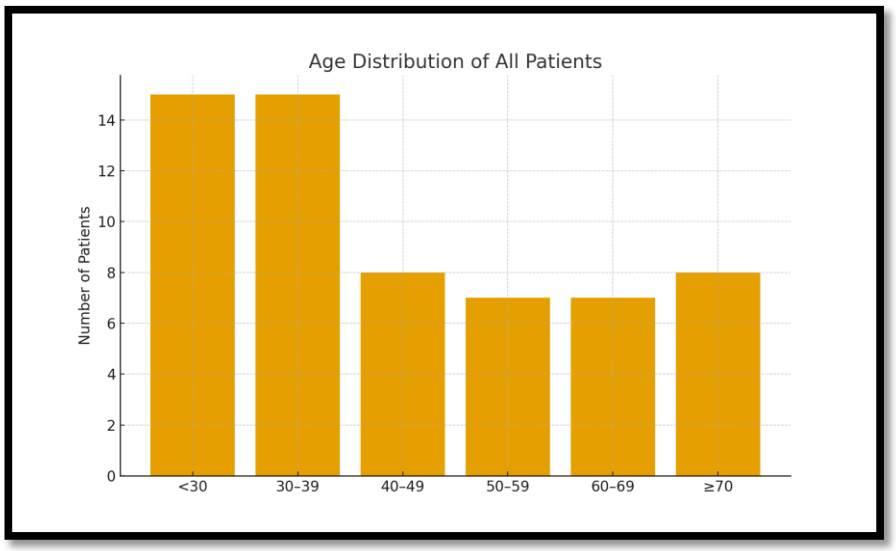


Table 3. Causes of AKI in cases (N=37)

Etiology	Frequency	Percentage (%)
Malaria	7	18.9
Snake bite	3	8.1
Gastroenteritis	3	8.1
Septicemia	3	8.1
Seizures	3	8.1
UTI/Pyelonephritis	2	5.4
CVA	2	5.4
Cardiogenic shock	2	5.4
Hyperosmolar coma	2	5.4
Poisoning	2	5.4
Others	8	21.6

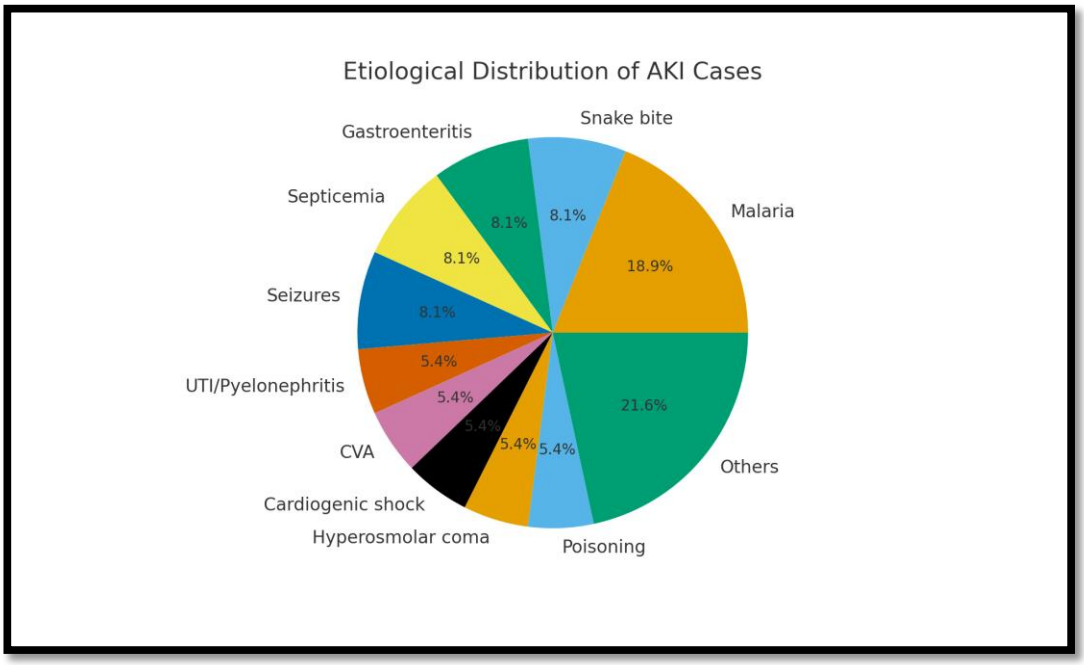
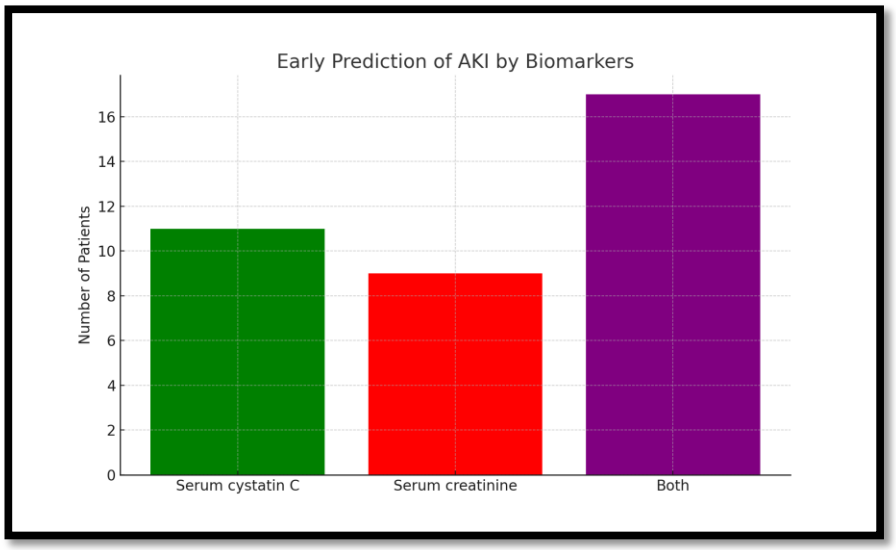


Table 4. Early prediction of AKI among cases (N=37)

Predictor	Frequency	Percentage (%)
Serum cystatin C	11	29.7
Serum creatinine	9	24.3
Both	17	46.0



Discussion

Acute kidney injury (AKI) is a complex syndrome with significant clinical, economic, and social implications. In this study, we evaluated the utility of serum cystatin C compared with serum creatinine in detecting AKI in patients with predisposing risk factors. Our findings confirm that cystatin C is a more sensitive marker for early diagnosis of AKI and provides better assessment of severity when staged according to RIFLE criteria.

Comparison with Previous Literature

The present study observed an overall AKI incidence of 61% among at-risk patients, consistent with earlier Indian studies highlighting the high burden of community-acquired AKI. Kaul et al. (2012) reported gastroenteritis, malaria, and septicemia as leading causes of AKI in India [10], while Prakash et al. (2013) documented changing trends over 26 years, with infections remaining the dominant etiology.[11] Our study corroborates these findings, identifying complicated malaria as the most common cause, followed by gastroenteritis, snake bite, and septicemia.

International data present a different epidemiological profile. Cerdá et al. (2008) emphasized that AKI in developed nations predominantly affects elderly, critically ill patients, often linked with hospital-acquired sepsis, surgery, or nephrotoxic drugs [12]. In contrast, our study confirms that AKI in India primarily affects younger individuals (30–39 years), reflecting the demographic vulnerability to community-acquired infectious diseases.

With regard to biomarkers, our findings align with Balajinathan et al. (2012), who compared cystatin C and creatinine in snake bite patients and demonstrated the superiority of cystatin C for early detection [9]. Similarly, Nejat et al. (2010) showed that cystatin C predicted AKI earlier than creatinine in 15% of intensive care patients, though both markers rose simultaneously in a subset [6]. In our study, cystatin C identified AKI earlier in 29.7% of patients, creatinine in 24.3%, while both rose together in 46%. This supports the diagnostic superiority of cystatin C, though overlap with creatinine remains.

Demographic and Etiological Insights

The male predominance (70% of AKI cases) is consistent with Indian data [9,10]. This may reflect greater male exposure to occupational and environmental hazards such as infections, toxins, and snake bites, along with delayed healthcare-seeking behavior. In contrast, Western

studies show a more balanced gender distribution [13].

Age distribution in our study revealed that young adults (≤40 years) were most affected, with 45.9% of cases occurring below 40 years. This echoes findings by Prakash et al. (2013), who noted a predominance of younger patients in Indian cohorts [11]. The socioeconomic implications are considerable, as AKI in productive age groups contributes to loss of workforce and increased healthcare costs.

Complicated malaria accounted for 18.9% of cases, followed by gastroenteritis and snake bite. While this aligns with Indian epidemiology, it contrasts with Western cohorts where sepsis, nephrotoxins, and cardiac surgery predominate [13]. The continued prominence of malaria underscores the need for public health measures in endemic regions.

Biomarker Performance

The diagnostic lag of serum creatinine is well established, as it increases only after 24–48 hours of renal insult [3]. In this study, cystatin C identified AKI earlier in nearly one-third of cases and demonstrated superior staging accuracy in malaria, septicemia, stroke, and gastroenteritis. Interestingly, in snake bite–associated AKI, both biomarkers performed similarly, suggesting etiology-specific variability.

The Pearson correlation between cystatin C and creatinine at 24 hours was moderate ($r = 0.493$, $p = 0.032$), closely matching the correlation reported by Balajinathan et al. (2012; $r = 0.473$) [9]. This indicates that cystatin C is best used as a complementary biomarker rather than a complete replacement for creatinine in clinical settings.

Clinical Implications

The clinical relevance of cystatin C lies in its potential for earlier intervention—allowing clinicians to withdraw nephrotoxic agents, optimize hemodynamics, and prevent progression to dialysis-dependent renal failure. Given the dominance of infectious causes in India, cystatin C may be particularly valuable in malaria- and sepsis-related AKI, which are prone to rapid deterioration.

Strengths and Limitations

Strengths of this study include its prospective design and use of standardized RIFLE criteria. Importantly, it provides region-specific epidemiological data on AKI in India. Limitations include the relatively small sample size, single-center setting, and cost barriers to widespread cystatin C testing. Moreover, thyroid function was not universally screened, which may have introduced bias, as cystatin C levels can be altered in thyroid disorders.

Future Directions

Larger multicenter studies are required to validate cystatin C's role across diverse patient populations. Cost-effectiveness analyses are essential to justify its routine use in resource-limited settings. Furthermore, combining cystatin C with other biomarkers such as neutrophil gelatinase–associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) may improve diagnostic accuracy and prognostic value.

Conclusion

Cystatin C proved superior to creatinine in early prediction of AKI, especially in malaria and septicemia. Incorporating cystatin C into diagnostic protocols may enhance early detection and outcomes. Further multicenter research is needed to validate these results and examine cost-effectiveness**.**

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