Study of Serum Cystatin-C Levels as a Biomarker and Urinary Microscopy in Severe Kidney Damage

Muddasir Indikar[1], Bheemashankar Tonsalli[2], Sandeep Patil[3], Deepa Sinnur[4], Santosh Patil[5]

[1]Department of Geriatric Medicine, [2]Consultant Gastroenterologist, [3]Department of Nephrology, [4]Department of Allied Health Sciences , [5]Department of Urology, BLDE (DU) Shri B.M.Patil Medical College Hospital and Research Centre Vijayapura, Karnataka, India.

Abstract

Background: Acute kidney injury (AKI) is a sudden loss of kidney function. It was formerly known as acute renal failure (ARF) traditionally, which has been described as a rapid loss of kidney function accompanied with dysregulation of extracellular volume and electrolytes, retention of urea and other nitrogenous waste products, and other symptoms. There is no reliable early detectable biomarker for AKI.

Aims and Objective: The aim of the research is to investigate the potential of Cystatin-C as a biomarker of AKI to forecast the need for renal replacement treatment in the later stages of ARF.

Materials and methods: This research included 50 individuals diagnosed with AKI who were hospitalized at a tertiary hospital during the period of December 2011 to August 2013. The study encompassed both outpatient and inpatient environments. Various tests like Serum creatinine, blood urea, Serum cystatin C, Urine routine, Serum electrolytes and Urine microscope were performed through blood and urine samples.

Results: Serum cystatin C levels and serum creatinine levels are statistically significant with p value of 0.02.

Conclusion: In conclusion, patients who experienced acute renal failure (ARF) displayed a notable increase in Serum Cystatin C levels. Furthermore, there was a statistically significant correlation between Serum Cystatin C levels and serum creatinine. Therefore, Serum Cystatin C emerges as a promising early predictive marker for acute kidney injury (AKI).

Keywords: AKI, Serum Cystatin-C, Biomarker

Introduction

Acute kidney injury (AKI), formerly known as acute renal failure (ARF)[1,2] refers to a swift decline in kidney function. Traditionally characterized by the sudden impairment leading to the retention of urea and other nitrogenous waste products, as well as the dysregulation of extracellular volume and electrolytes. AKI is characterized by any of the following criteria: A rise in Serum Creatinine by at least 0.3 mg/dl (26.5 µmol/l) within a 48-hour timeframe, an increase in serum creatinine to 1.5 times the baseline, acknowledged or presumed to have occurred within the preceding 7 days, Urine volume of 0.5 ml/kg/hrs sustained over 6 hours[2].

The term "acute kidney injury/impairment" has been suggested to cover the complete range of the syndrome, encompassing subtle alterations in renal function markers to the necessity for renal replacement therapy (RRT) [3].

Oliguria is characterized by a urine output of less than 1 mL/kg/h in infants, less than 0.5 mL/kg/h in children, and less than 400 mL or 500 mL[4] per 24 hours in adults, which is equivalent to 17 or 21 mL/hour. For instance, in an adult weighing 70 kg, this corresponds to 0.24 or 0.3 ml/hour/kg. Alternatively, the value of 0.5 mL/kg/h is commonly employed to define oliguria in adults as well [4]. Anuria is the absence of urine passage and is practically defined as the excretion of less than 100 milliliters of urine in a day[5]. Oliguria lasting for 12 hours or more demonstrated a sufficiently high likelihood ratio, validating its clinical utility and supporting its inclusion in the Risk, Injury, Failure, Loss, and End-Stage (RIFLE)-Injury urine output definition. However, adopting this cutoff would lead to the omission of a significant majority of cases of AKI-Cr. These findings hold importance as the identification of patients at

Address for Correspondence:

Dr. Muddasir Indikar

Assistant Professor, Department of Geriatric Medicine,

BLDE (DU) Shri B.M.Patil Medical College Hospital and Research Centre Vijayapura, Karnataka,India.

Email: drmuddasir12@gmail.com

risk of developing AKI-Cr is a crucial initial step for clinicians in determining the appropriate treatment for patients requiring specific intervention and those who can be observed. The critical significance of these distinctions is underscored by evidence indicating that fluid resuscitation may alleviate renal dysfunction[6], but caution is necessary as iatrogenic fluid overload can exacerbate outcomes[7] and affect the prognosis of AKI[8, 9]. Thus, the AKI concept, as defined by RIFLE, introduces a new paradigm. AKI is not synonymous with ATN, nor does it equate to renal failure. Instead, it incorporates both and extends to encompass other, less severe conditions. Indeed, as a syndrome, it involves patients who may not exhibit actual kidney damage but still experience functional impairment relative to physiological demand.

Early identification of at-risk patients is crucial as intervening only after the development of biochemical evidence of AKI (increased SCr) is likely to be tardy. Compounding these clinical challenges is the probability that the shift to renal dysfunction won't be sudden. This gradual transition from physiological salt and water retention to injury is evident in the limited diagnostic utility of urinary biochemistry for early AKI diagnosis in the ICU.

Both urine output and serum creatinine (SCr) are utilized as indicators of an acute change in glomerular filtration rate (GFR). The potential advantage of urine output over SCr lies in the swiftness of the response[10].

Traditionally, maintaining urine output has been considered equivalent to preserving renal function, and reductions in urine output often trigger various clinical interventions aimed at preventing or mitigating acute kidney injury (AKI) [1].

Oliguria shows a significant association with the development of new AKI-Cr; however, it's noteworthy that in most instances, episodes of oliguria are not subsequently accompanied by biochemical signs of renal injury. Consequently, relying solely on oliguria as a predictor of AKI-Cr is, at best, only moderately accurate.

Serum creatinine (SCr) is a byproduct of muscle cell breakdown and serves as a proxy for glomerular filtration efficiency. However, its predictive accuracy for renal injury is limited, especially in the early stages of acute kidney injury (AKI)[11].

The glomerular filtration rate (GFR) is widely acknowledged as the most comprehensive indicator of kidney function. The staging of patients with acute kidney injury (AKI) is facilitated by the RIFLE criteria, introduced by the Acute Dialysis Quality Initiative (ADQI) group [12]. In an individual with a serum creatinine concentration of 1.5 mg/dl, the estimated creatinine clearance (Clcr) experiences a linear decrease according to the Cockcroft-Gault (CG) equation. In contrast, the estimated glomerular filtration rate (eGFR) shows a curvilinear decline in the Modification of Diet in Renal Disease (MDRD) equation. Notably, the MDRD estimate of kidney function significantly increases for individuals aged 60 years and older, with the differences most pronounced in those with lower serum creatinine concentrations[13]. It is essential to consider these nuances when assessing kidney function in older individuals.

As per two epidemiology studies conducted in India over the past three decades have reported the distribution of medical, surgical, and obstetrical conditions resulting in acute renal failure (ARF) as 60%, 25%, and 15%, and 88%, 3.4% and 9%, respectively[14,15]. Notably, there are significant differences between the temperate and tropical zones. Patients in the tropics tend to be younger, with a mean age of 37.1 years, in contrast to around 72 years in the temperate zone. The tropics also face challenges in terms of treatment facilities, contributing to an increasing mortality rate. Intermittent peritoneal dialysis remains a primary treatment approach in several tropical areas. A reduction in Renal Blood Flow (RBF) can eventually result in ischemia and cellular death. This occurrence may take place prior to the onset of overt systemic hypotension and is commonly described as normotensive ischemic Acute Kidney Injury (AKI) [16, 17].

Numerous endogenous growth factors involved in the regeneration process following ischemic renal injury remain unidentified. Nevertheless, the exogenous administration of growth factors has demonstrated efficacy in alleviating and expediting recovery from Acute Kidney Injury (AKI)[18,19]. Resident dendritic cells (DCs) establish a continuous network throughout the entire kidney. The precise role of DCs in Acute Kidney Injury (AKI) remains unclear. However, subsequent to kidney ischemia-perfusion, resident dendritic cells release cytokines such as TNF and IL-6, as well as chemokines like MCP-1[20]. The renal vasculature exhibits heightened sensitivity to vasoconstrictor stimuli, including angiotensin II, endothelin (ET), and serotonin, as well as an increased responsiveness to renal nerve stimulation [21]. Among these vasoconstrictors, endothelin (ET) holds particular prominence. ET, a 21-amino acid peptide, stands as the most potent vasoconstrictor identified to date. Notably, the ET-1 gene undergoes upregulation during ischemia and reperfusion[22]. Monoclonal antibodies targeting ET or ET receptor antagonists have demonstrated efficacy in improving both renal function and histologic features in the context of renal ischemia-reperfusion injury [23, 24].

Unique features of tropical AKI include endemic malnutrition, a relative state of hypovolemia due to increased sweating and peripheral vasodilatation in hot climates, and the triggering of hemolytic crises in certain glucose 6-phosphate dehydrogenase-deficient ethnic groups exposed to specific drugs and toxins.

Regarding the pathophysiology of acute kidney injury (AKI), the driving force for glomerular filtration relies on the pressure gradient from the glomerulus to the Bowman space. Glomerular pressure, primarily determined by renal blood flow (RBF), is influenced by the combined resistances of renal afferent and efferent arterioles. Regardless of the AKI cause, reductions in RBF represent a common pathologic pathway leading to a decrease in glomerular filtration rate (GFR).

The novelty of this study lies in its investigation of Cystatin-C as a potential biomarker for acute kidney injury (AKI), particularly in forecasting the need for renal replacement treatment in later stages of acute renal failure (ARF). By analyzing a cohort of 50 individuals diagnosed with AKI, this research contributes fresh insights into the early detection and prognostic value of Serum Cystatin C levels. The study's findings reveal a statistically significant correlation between Serum Cystatin C levels and serum creatinine levels, underscoring the potential of Serum Cystatin C as an early predictive marker for AKI. This novel approach offers promising implications for improving patient outcomes through timely intervention and treatment. Overall, this study enriches the existing knowledge base on AKI biomarkers and provides valuable implications for clinical practice and future research in this field.

Materials and methods

Source of Data collection

This research took place in the medicine outpatient department (OPD) and inpatients (IPD) at K.R. Hospital Mysore during the period of December 2011 to August 2013. All participants in the study were informed about the research, and their informed written consent was obtained. The subjects included in the study were individuals diagnosed with AKI referred by a nephrologist.

Sampling method

This research employed a simple random sampling method who met the specified criteria. A total of 50 subjects, comprising both males and females, were recruited. Patient presenting with decreased urine output <0.5ml/kg/hrs. And Creatinine level >0.3mg/dl or 50% rise of serum creatinine from baseline value were included in the study. And patients with detected hypo or hyperthyroidism, thyroid replacement therapy, glucocorticoid therapy and acute on chronic CKD were excluded from study.

Procedure

Data was collected using a pretested proforma that met the objectives of the study. Detailed history and necessary investigations were undertaken. The purpose of the study was explained to the patients, and informed consent was obtained. Patients meeting the inclusion criteria were selected. Their blood samples were drawn to assess creatinine and cystatin C levels, and the rise of these levels in the serum above the normal range was evaluated. The analysis of data was conducted using the appropriate method, and ethical committee approval was obtained

Results

Table 1: Distribution of patients according to their age group (N = 50)

Age (in years)	No.	Percent
≤ 40	23	46.0
41-59	15	30.0
≥ 60	12	24.0
Range	18-80 years	
Mean age ± SD	47.03 ± 18.03	

In this study there were 23 patients (46%)' ≤40 years, 15 patients (30%) 41-59 years and 12 patients (24%) ≥60 years. There were 23 patients (46%)' ≤40 years, 15 patients (30%) 41-59 years and 12 patients (24%) ≥60 years (Table 1).

The total no. of males were 22 (44%) in number, females were 28 (56%) in number. And 29 (58%) patients have hypotension [blood pressure <90 mm hg], and 21 patients have normal blood pressure. 2 (4%) patients had Brown casts, 13 (26%) patients had Granular casts. And 35 (70%) patients had no casts in their urine. In this study 16 (32%) patients had oliguria, and 34 (68%) patients had normal urine Output. In this study 36 (72%) patients recovered, and 14 (28%) patients developed Acute renal failure(ARF). 42 (84%) patients had received conservative management, and 8(16%) patients underwent haemodialysis. 23(46%) patients had symptoms of 1day duration, 20(40%) within 2 days, and 7 (14%) patients had symptoms of 3 or more than 3 days. 19 (38%) patients had blood urea <40mg/dL, and 31 (62%) patients had blood urea of >40mg/dL. Out of 50 patients none of the patients had serum creatinine below 1 mg/dl and 24 patients had serum creatinine of 1-2 mg/dl, 20 patients had serum creatinine of 2-4 mg/dl and 6 patients had serum creatinine of > 4 mg/dl. 4 (8%) patients had normal cystatin C level, and 46 (92%) patients had elevated serum cystatin C level.

Table 2: Association of serum cystatin C of patients with their outcome (N = 50)

Serum Cystatin	Outcome of the patient		P Value
	Recovered (n=36)	ARF (n=14)	
Mean Value	3.27	7.87	0.02

In the present study out of 50 patients, the mean value of serum cystatin C levels were 3.27 mg/dl among patients who recovered and 7.87 mg/dl among patients who developed ARF (Table 2).

Table 3: Co-relation between serum creatinine and serum cystatin C (N = 50)

Co-relation Co-efficient	P Value
0.589	<0.001

The correlation coefficient of 0.589 indicates a moderate to strong positive correlation between the variables under study. The associated p-value of less than 0.001 suggests that this correlation is statistically significant, reinforcing the reliability of the relationship observed between the variables (Table 3).

Table 4: Association of blood urea of patients with their outcome (N = 50)

Blood urea	Outcome of the patient		P Value
	Recovered (n=36)	ARF (n=14)	
Normal	19	0	0.001
Elevated	17	14	

In this study 19 patients had normal blood urea, 31 patients had elevated blood Urea .14 0f 31 patients had ARF (Table 4).

Table 5: Association of age of patients with their outcome (N = 50)

Age (in years)	Outcome of the patient		P Value
	Recovered (n=36)	ARF (n=14)	
<40	17	6	0.443
40-60	12	3	
>60	7	5	

In this study, 23 patients were under the age of 40 years of which 6 patients had ARF. 15 patients were 40 to 60 years old of which 3 had ARF, and 12 patients were more than 60 years old of which 5 had ARF (Table 5).

Discussion

In the conducted study at K.R. Hospital, participants admitted to the Medical Emergency, Wards, and Medical Intensive Care Unit (MICU) displaying symptoms of Acute Kidney Injury (AKI), as confirmed by elevated serum creatinine levels or a documented history of reduced urine output, were enrolled based on predefined inclusion and exclusion criteria. Subsequently, spot urine samples and blood specimens were systematically collected from the participants. The collected samples underwent thorough analysis, with urine samples assessed for casts through routine examination, and blood samples examined for serum cystatin C levels.

The discussion in this study will be organized into distinct headings, addressing various aspects of the patient population. These include an examination of age-related patterns, the influence of sex, the status of blood pressure, findings from urine routine analyses, assessments of urine output, and an exploration of overall patient outcomes. Additionally, an in-depth analysis will be conducted to investigate the association between the serum cystatin C levels of patients and the ultimate outcomes they experienced. This structured approach aims to provide a comprehensive understanding of the interplay between these factors and the overall clinical picture, contributing valuable insights to the broader discourse on patient outcomes in the context of acute kidney injury.

Age

Table 6: Comparison of mean age of patients with other studies

Studies	Waikar et al[25]	Liano et al[25]	J.Prakash et al	Present study
Mean age	72	64	44.9	47

The investigations conducted by Waikar et al.[25] and Liano et al. revealed a higher mean age group when juxtaposed with the study conducted in India by J. Prakash et al. and the present study. Notably, the majority of participants in the current study fell within the age group of <40 years (46%), while 30% were in the age range of 41-59 years, and 24% were categorized in the age group of ≥60 years. This demographic distribution provides valuable insights into the age composition of the study cohort, contributing to a comparative understanding of age-related patterns in the context of the investigated parameters (Table 6).

In the current study, the female representation in the study population slightly exceeded that of males, with females accounting for 54% and males for 46%. This gender distribution aligns with findings from the investigation conducted by Waikar et al.[25], which similarly demonstrated an equal predisposition to acute kidney injury in both males and females. The parallel observations in gender distribution between these studies underscore the consistency in the prevalence of acute kidney injury across genders as documented in the scientific literature.

Blood pressure

Table 7: Comparison of blood pressure status in AKI patients with other studies

Blood Pressure	Bagshaw et al[26]	Present study
Hypotension	64.4%	58%
No hypotension	35.6%	42%

In the present study, 58% of patients exhibited hypotension upon admission, while 42% presented with normal blood pressure. These findings align with a study conducted by Bagshaw et al.[26] in 2005 across academic hospitals in America and Canada, where it was reported that 64.4% of patients with hypotension developed acute kidney injury within 24 hours after the onset of hypotension. The consistency in the prevalence of hypotension-associated acute kidney injury observed in both studies emphasizes the relevance of blood pressure status as a potential indicator for the development of kidney-related complications (Table 7).

Urine routine

Table 8: Comparison of granular casts in urine microscopy with other studies

Granular casts	Mark A et al[27]	Present study
Percent	63.4%	30%
ARF development among patients with granular casts	56.8%	46.15%

In the current study, 30% of patients exhibited casts in their urine microscopy, comprising 13 patients with granular casts and 2 patients with brown casts. Within the cohort of 15 patients displaying casts (granular and brown), 46.6% (7 patients) developed Acute Renal Failure (ARF). Specifically, among the 13 patients with granular casts, 46.15% (6 patients) developed ARF, while in the subset of 2 patients with brown casts, 50% (1 patient) developed ARF (Table 8).

Mark A et al.'s[27] study involving 197 patients revealed that 63.4% had granular casts in their urine, with 56.8% developing ARF, and 43.2% remaining unaffected. Another investigation by Mark et al. demonstrated that 47% of Acute Tubular Necrosis (ATN) patients and 40% of prerenal Acute Kidney Injury (AKI) patients exhibited urinary sediments. These findings contribute valuable insights into the association between specific urine sediment characteristics and the occurrence of ARF in diverse patient populations.

Urine output

Table 9: Comparison of oliguria with similar studies

Urine output	Macedo E et al[28]	Present study
Oliguria	55%	32%
No oliguria	45%	68%

In the current study, 32% of patients experienced oliguria, while 68% exhibited normal urine output. This distribution contrasts with findings from a study conducted by Macedo E et al.[28], which reported that 55% of patients had an episode of oliguria during their stay in the Intensive Care Unit (ICU). These observations contribute to our understanding of the prevalence of oliguria in the studied populations and provide comparative insights into urinary patterns among patients in different clinical settings (Table 9).

Additionally, the study also indicated that both oliguria lasting for more than 12 hours and oliguria consisting of three or more episodes were associated with elevated mortality rates. These insights contribute to a nuanced understanding of the potential implications of oliguria in the context of AKI, particularly in the critical care setting.

In a study conducted by Prowle JR et al.[29], it was observed that out of 32 patients with Acute Kidney Injury (AKI) admitted to the Intensive Care Unit (ICU), 23 patients developed oliguria.

Outcome of patients

Table 10: Comparison of outcome of patients with other studies

Outcome	Ahlstrom et al[30]	Present study
ARF	27%	28%
Recovered	73%	72%

In the current study, 72% of patients experienced recovery, while 28% developed acute renal failure (ARF). This outcome distribution aligns with a study conducted by Ahlstrom et al[30], which reported that ARF occurred in 28% of patients diagnosed with Acute Kidney Injury (AKI). These parallel findings contribute to the broader understanding of ARF incidence in the context of AKI across different study cohorts (Table 10).

Association of serum cystatin C of patients with their outcome

In the current study, 98% of patients exhibited elevated serum cystatin C levels, while 2% had normal levels. Among the 49 patients with elevated serum cystatin C levels, 69.5% experienced recovery, and 30.4% developed Acute Renal Failure (ARF).Furthermore, in this study involving 50 patients, the mean serum cystatin C levels were 3.27 mg/dL for those who

recovered and 7.87 mg/dL for those who developed ARF. The statistical analysis revealed a significant association between serum cystatin C levels and patient outcomes, with a p-value of 0.02.Moreover, the study found a statistically significant association between serum cystatin C levels and serum creatinine levels in predicting patient outcomes. These results contribute valuable insights into the potential prognostic value of serum cystatin C in predicting the outcomes of patients in the context of renal function.

The study conducted by Ahlstrom A et al.[30] demonstrated that serum cystatin C levels exhibited an excellent positive predictive value for Acute Renal Failure (ARF).

Additionally, research conducted by Zhang Z et al.[31] revealed that cystatin C levels serve as a promising biomarker in predicting Acute Kidney Injury (AKI). In contrast, urinary cystatin C levels exhibited only moderate diagnostic value in predicting AKI. These findings contribute to the understanding of the varying diagnostic efficacy of serum and urinary cystatin C levels in the prediction of AKI.

Table 11: Comparison of mean creatinine and cystatin C values with other studies

Biological Characteristic	Murthy M. et al[32]	Present study
Mean value of Serum creatinine	2.08±1.76	2.57±1.4
Mean value of Serum Cystatin	3.86±2.09	4.56±3.09
Pearson correlation co-efficient	0.735	0.589
p value	<0.01	<0.01
Correlation	Significant	Significant

The present study compares mean values of serum creatinine and cystatin C with those reported by Murthy et al.[32]. The mean serum creatinine in the present study is higher (2.57±1.4) compared to Murthy et al. (2.08±1.76). Similarly, the mean serum cystatin C value is also elevated in the present study (4.56±3.09) compared to Murthy et al. (3.86±2.09). Both studies found significant correlations between serum creatinine and cystatin C, with Pearson correlation coefficients of 0.589 in the present study and 0.735 in Murthy et al., and p-values less than 0.01, indicating statistically significant correlations in both studies (Table 11).

Association of serum potassium of patients with ARF

In this study, 26 patients exhibited normokalaemia, while 12 patients experienced hypokalaemia, and an additional 12 patients had hyperkalaemia. Among the 12 patients with hyperkalaemia, 10 developed Acute Renal Failure (ARF), and the statistical analysis demonstrated a significant association with a p-value of <0.001, indicating predictive value for ARF.

Conclusion

In conclusion, within the studied cohort of 50 patients diagnosed with Acute Kidney Injury (AKI), serum cystatin C exhibited a high degree of sensitivity, with elevated levels identified in 49 cases. The mean serum cystatin C levels were notably distinct between patients who experienced recovery and those who developed Acute Renal Failure (ARF), emphasizing its potential as a discriminative biomarker. The statistically significant elevation of serum cystatin C in ARF cases, coupled with its robust correlation with serum creatinine levels, underscores its diagnostic relevance. The observed significant predictive value, as indicated by the p-values for both serum cystatin C and serum creatinine, supports the utility of serum cystatin C as an early and valuable prognostic marker for AKI. These findings hold implications for enhancing early detection, risk assessment, and overall management strategies for patients at risk of AKI. The validation of the current findings and the elucidation of the precise role of serum Cystatin C (CysC) in Acute Kidney Injury (AKI) await larger-Scale Studies.

Recommendation

To enhance patient outcomes and further research on acute renal failure (ARF), several key actions are recommended based on this study's findings. Serum cystatin C levels should be routinely monitored in critically ill patients to identify those at higher risk of developing ARF. Regular urine microscopy should be performed to detect granular and brown casts, which are significant indicators of potential ARF development. Early stabilization of blood pressure is crucial, as many patients present with hypotension on admission. Age-specific management strategies should be developed to cater to different age groups, improving prevention measures and treatment protocols. The specific roles of granular and brown casts in ARF development need to be further investigated. Longitudinal studies should be conducted to track serum cystatin C levels over time, providing deeper insights into its role as a biomarker for kidney function. Comprehensive ARF management programs should be created in hospitals, incorporating routine monitoring and training on the importance of these biomarkers. By implementing these recommendations, the early detection and management of ARF can be improved, ultimately enhancing patient outcomes.

Acknowledgement

We extend sincere thanks to patients for participation, medical staff for support, colleagues for feedback, technicians for analysis, administrators for assistance, and gratitude to families and friends for encouragement throughout this study.

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Conflict of interest: Nil
Source of funding: Nil

Date received: Apr 17, 2024
Date accepted: Jun 30, 2024