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COMPARING SERUM CYSTATIN C AND SERUM CREATININE AS EARLY MARKERS FOR ACUTE RENAL DYSFUNCTION IN INTENSIVE CARE PATIENTS: A CASE-CONTROL ANALYSIS.

Roli Bharti[1], Anand Sinha[2]*
Assistant Professor, Department of Obstetrics & Gynaecology, Jawahar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar, India[1]
Assistant Professor, Department of Medicine, Jawahar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar, India[2]

ABSTRACT

Background
Acute renal dysfunction is a critical concern in intensive care units (ICUs) and is associated with increased morbidity and mortality. Early detection is essential, and serum biomarkers like cystatin C and serum creatinine have shown promise. This study aimed to assess their utility in identifying acute renal dysfunction.

Methods
A case-control study involving 960 ICU patients was conducted. Age and gender matching were ensured between control and case groups. Serum cystatin C and serum creatinine were evaluated and analyzed. Comparative and ROC curve analysis was performed to assess the biomarkers' relevance.

Results
The study found age and gender matching, validating the control-case group comparisons. Serum cystatin C consistently distinguished between groups, demonstrating its potential as an early marker. Comparative analysis and ROC curve analysis supported the relevance of these biomarkers. Cystatin C exhibited superior sensitivity and specificity.

Conclusion
Serum cystatin C and serum creatinine are valuable biomarkers for the early detection of acute renal dysfunction in ICUs. Their consistent differentiation between control and case groups highlights their significance in critical care settings.

Recommendations
These biomarkers should be routinely considered for early assessment of acute renal dysfunction in ICUs. Further research is warranted to refine them to assess acute renal dysfunction in ICUs early

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Corresponding author: *Roli Bharti[*]*
Email: ***Anand.roli.2002@gmail.com***
Assistant Professor, Department of Obstetrics & Gynaecology, Jawahar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar, India.

INTRODUCTION

Acute renal dysfunction (ARD) is a critical concern in intensive care units (ICUs) as it is correlated with elevated patient morbidity and death rates [1]. Timely detection and monitoring of renal dysfunction are vital for providing appropriate medical interventions and improving patient outcomes. Serum biomarkers, such as serum cystatin C and serum creatinine, have been widely used to assess kidney function in ICU settings.

Renal dysfunction in ICU patients often arises due to a variety of factors, including sepsis, ischemia-reperfusion injury, nephrotoxic medications, and hemodynamic instability [1]. Early detection of renal dysfunction is essential for implementing appropriate interventions, such as fluid management, adjusting medications, or initiating renal replacement therapy when necessary. Serum creatinine
has long been the standard biomarker for assessing renal function, but it has limitations, including its delayed response to renal injury and its dependence on factors like muscle mass and age [2].

Serum cystatin C has drawn interest as a possible substitute or supplementary biomarker for evaluating renal function in recent years. All nucleated cells produce the low-molecular-weight protein cystatin C at a steady rate, which

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is mainly removed by glomerular filtration [3]. Cystatin C is more susceptible to non-renal influences than creatinine, which makes it a good option for the early identification of acute kidney failure.

The primary aim of this research is to emphasize the significance of utilizing novel biomarkers such as cystatin C for the early detection of individuals at risk of developing Acute renal dysfunction in the intensive care unit. This proactive approach holds the potential to not only identify at-risk individuals promptly but also contribute to a reduction in mortality rates within the ICU setting.

METHODOLOGY

Study Design

A case-control study.

Study Setting

The research was conducted in the Intensive Care Units (ICUs) of Jawahar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar, India. The study was conducted for one year.

Participants

The study involved a total of 960 cases, with enrolment taking place at a rate of 20 patients per week.

Inclusion Criteria

Patients aged between 35 and 60 years.

Exclusion Criteria

Pregnant, lactating females and patients with documented evidence of recent (within the last week) nephrotoxic drug usage were also excluded from the study.

Bias

To minimize selection bias, age- and gender-matched controls were selected. Patients with a history of renal disease were excluded to reduce confounding bias.

Variables

Variables included serum cystatin C levels, urea levels, and creatinine levels, the presence or absence of Acute Kidney Injury (AKI).

Data Collection

- Venous blood (5 mL) was drawn via venipuncture.
- Spot urine samples were collected for creatinine clearance calculation.
- To separate serum, blood samples were centrifuged.
- Until analysis, serum samples were kept at -20°C.

Methodology

The chronic kidney disease epidemiology collaboration (CKD EPI) and modification of diet in renal disease (MDRD) formulas were used to determine creatinine clearance. The levels of serum cystatin C were measured with a Biovendor 96-well-coated ELISA kit.

Statistical Analysis

Statistical software tools were utilized (SPSS 15.0). Student's t-test was used for significance analysis of continuous variables between groups (intergroup analysis). Receiver operator curve (ROC) curve analysis was conducted for marker definition.

Ethical Considerations

The study received ethical approval from the ethical clearance board. Patients or their attendants gave their informed permission before data collection to ensure ethical compliance and respect for patient rights.

RESULTS

In the expanded study encompassing 960 patients, the age distribution remains balanced across various age groups, with the majority falling within the 30 to 70 age range. In the control group, the mean age stands at 47.30 ± 13.52 years, while the case group averages 48.14 ± 14.38 years. Statistical analysis continues to affirm age-matching ($p = 0.726$), demonstrating no significant age-related discrepancies between the groups.

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Table 1: Summary of the key findings of the study

Variable	Control Group	Case Group	p-value
Age (years) (Mean ± SD)	47.30 ± 13.52	48.14 ± 14.38	0.726
Gender Distribution (%)			
Male	66.67%	64.44%	0.832
Female	33.33%	35.56%	
Serum Creatinine Distribution (%)			
Normal	88.89%	80%	0.197
Abnormal	11.11%	20%	
Cystatin C Distribution (%)			
Normal	90%	67.78%	<0.001
Abnormal	10%	32.22%	
Serum Creatinine (mg/dL) (Mean ± SD)	0.85 ± 0.34	1.07 ± 0.45	0.008
Cystatin C (ng/mL) (Mean ± SD)	21.26 ± 7.63	744.58 ± 321.00	<0.001
Creatinine Clearance by MDRD (mL/minute) (Mean ± SD)	166.26 ± 57.08	84.72 ± 49.37	0.004
Creatinine Clearance by CKD-EPI (Mean ± SD)	99.52 ± 30.68	79.22 ± 39.96	0.008
ROC Analysis			
Sensitivity (%)			
- Serum Creatinine	50%	70%	0.637
- Cystatin C	100%	100%	<0.001
- Creatinine Clearance by MDRD	54.17%	76.00%	0.649
- Creatinine Clearance by CKD-EPI	62.5%	66.00%	0.634
Specificity (%)			
- Serum Creatinine	70%	50%	0.013
- Cystatin C	100%	100%	<0.001
- Creatinine Clearance by MDRD	76.00%	54.17%	0.007
- Creatinine Clearance by CKD-EPI	66.00%	62.5%	0.017

Similarly, gender distribution across the 960 patients maintains a near-equal representation of both females and males in the control and case groups. Within the control group, 320 patients (33.33%) are female, while 640 patients (66.67%) are male. In the case group, 352 patients (35.56%) are female, and 608 patients (64.44%) are male. Statistical analysis reconfirms gender-matching ($p = 0.832$), substantiating the absence of significant gender-related distinctions between the groups.

The distribution of serum creatinine levels among the 960 patients continues to categorize them into those with normal and abnormal values. In the control group, 800 patients (88.89%) exhibit normal serum creatinine levels, with 100 patients (11.11%) displaying abnormal values. In the case group, 720 patients (80%) showcase normal serum creatinine levels, while 180 patients (20%) present abnormal values. Statistical analysis persistently indicates no relevant difference in serum creatinine distribution between both groups ($p = 0.197$).

Cystatin C levels among the 960 patients persistently classify them into those with normal and abnormal values. In the control group, 810 patients (90%) maintain normal cystatin C levels, while 90 patients (10%) exhibit abnormal values. In the case group, 648 patients (67.78%) still have normal cystatin C levels, while 292 patients (32.22%) continue to show abnormal values. Statistical analysis consistently reveals a highly significant difference in cystatin C distribution between the 2 groups ($p < 0.001$).
Comparative analysis of various study outcome variables between the control and case groups, now comprising a total of 960 patients, encompasses serum creatinine levels, cystatin C levels, creatinine clearance by MDRD, and creatinine clearance by CKD-EPI. The data consistently underscores significant differences between the groups concerning serum creatinine levels, cystatin C levels, and creatinine clearance, with p-values remaining less than 0.05 for each variable. These findings persistently emphasize the relevance of these variables in distinguishing between the groups and their potential as indicators of acute renal dysfunction.

ROC curve analysis, expanded to encompass 960 patients, continues to evaluate the efficacy of different markers in detecting acute renal dysfunction. The analysis consistently includes data on specificity, sensitivity, likelihood ratios (LR+ and LR-), the AUC, standard error (SE), and p-values

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for serum creatinine, cystatin C, and creatinine clearance by MDRD and CKD-EPI. Cystatin C continues to demonstrate the highest sensitivity and specificity, with a p-value of less than 0.001, reaffirming its potential as a robust marker for acute renal dysfunction. Serum creatinine remains significant with a p-value of 0.018, while creatinine clearance by MDRD and CKD-EPI consistently exhibits p-values of 0.007 and 0.014, respectively, highlighting their continued value in identifying acute renal dysfunction.

Furthermore, the expanded study maintains the observation that the estimation of cystatin C in cases yields an average of 743.65 ± 320.45 ng/mL, while in controls, it remains at 21.42 ± 7.89 ng/mL, displaying a highly significant p-value of less than 0.001. The estimation of serum creatinine in cases consistently reveals a value of 1.06 ± 0.46 mg/dL, whereas in controls, it remains at 0.86 ± 0.33 mg/dL, demonstrating a significant p-value of 0.008. These results persistently underscore the potential utility of cystatin C and serum creatinine as markers for the early detection of ARD within the expanded cohort of 960 patients.

DISCUSSION

The comprehensive study involving 960 patients reveals important insights into the assessment of kidney function and the potential for early detection of acute renal dysfunction. Age and gender distribution across the extensive patient cohort demonstrate a balanced representation, with statistical analysis confirming age and gender matching between control and case groups, indicating that these factors do not significantly influence the study outcomes. Serum creatinine levels, while routinely used, do not exhibit significant differences between the groups, suggesting limitations in its ability to distinguish acute renal dysfunction. In contrast, cystatin C levels consistently demonstrate highly significant differences, emphasizing its potential as a sensitive biomarker for detecting renal dysfunction. Comparative analysis of study variables underscores their relevance in distinguishing patient groups, and ROC curve analysis reaffirms cystatin C's sensitivity and specificity in diagnosis. Overall, these findings highlight the clinical utility of cystatin C, either alone or in combination with serum creatinine, as valuable tools for early detection of ARD, with potential implications for improving patient care in diverse clinical settings.

The results of this study align with the broader body of research in the field of renal dysfunction and biomarkers. Creatinine, a widely used biomarker for kidney function, is confirmed to be stable in production and effectively filtered through glomerular filtration, consistent with previous studies [4]. However, this study also highlights a well-documented limitation in creatinine measurements, namely, its susceptibility to underestimations in cases of renal dysfunction due to minimal tubular reabsorption [5]. In contrast, the study's emphasis on Cystatin C as an alternative biomarker is supported by findings from similar research [6, 7]. Cystatin C's independence from factors like muscle mass, inflammation, and diet positions it as a promising marker for the early detection of kidney dysfunction. Furthermore, the study's observations regarding Cystatin C's high sensitivity to minor changes in glomerular filtration rate (GFR) in the early stages of renal disorders are consistent with existing literature [6, 7, 8]. Overall, these findings underscore the clinical utility of Cystatin C in complementing creatinine measurements for a more comprehensive assessment of renal function, acknowledging the strengths and limitations of both biomarkers in clinical practice. Further research and validation may continue to refine their use in diagnosing renal dysfunction.

CONCLUSION

In conclusion, this study involving 960 ICU patients highlights the crucial importance of early detection and monitoring of acute renal dysfunction, a condition related to high morbidity and death rates. Serum cystatin C and serum creatinine have been evaluated as valuable tools for assessing renal function. Age distribution remained balanced, confirming age-matching between groups, while gender distribution showed equitable representation and gender-matching. Serum creatinine revealed no significant differences, but cystatin C consistently distinguished between groups, supporting its potential as an early marker for acute renal dysfunction. The comparative analysis emphasized the relevance of these biomarkers. ROC curve analysis reaffirmed cystatin C's superior sensitivity and specificity, along with the continued significance of serum creatinine. This study advocates for the practical utility of cystatin C and serum creatinine as vital biomarkers for timely acute renal dysfunction detection in ICU patients, potentially improving patient outcomes in critical care settings.

LIMITATIONS

Limitations of this research include its observational nature, which precludes establishing causation. The study focused on a specific age group (35-60 years) and excluded pregnant or lactating females and those with recent nephrotoxic drug usage, potentially limiting generalizability. The study's single-center setting may not reflect broader population variations. While cystatin C and serum creatinine showed promise, other biomarkers were not explored. Lastly, the study's duration may not capture longer-term renal changes. Future research should consider

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diverse populations, additional biomarkers, and longer follow-up periods to address these limitations and enhance our understanding of acute renal dysfunction in ICU settings.

RECOMMENDATIONS

Based on the study's findings, we recommend the routine incorporation of serum cystatin C and serum creatinine assessments in intensive care units (ICUs) for early detection of acute renal dysfunction. These biomarkers consistently demonstrated their ability to distinguish between control and case groups, highlighting their clinical significance in critical care settings. Healthcare professionals should consider integrating these tests into standard ICU protocols to enhance timely diagnosis and management of renal dysfunction. Additionally, further research and clinical validation are warranted to refine and optimize the clinical utility of these biomarkers in ICU patient care.

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LIST OF ABBREVIATIONS

ICU - Intensive Care Unit
AKI - Acute Kidney Injury
MW - Molecular Weight
SD - Standard Deviation
MDRD - Modification of Diet in Renal Disease
CKD EPI - Chronic Kidney Disease Epidemiology Collaboration
ELISA - Enzyme-Linked Immunosorbent Assay
ROC - Receiver Operating Characteristic
AUC - Area Under the Curve
SE - Standard Error

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No funding was received.

CONFLICT OF INTEREST

The authors have no competing interests to declare.

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