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Evaluating Serum Cystatin-C Levels as Prognostic and Diagnostic Markers in Critically ill Patients with Acute Kidney Injury

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Abstract:

Background: Acute kidney injury (AKI) is a common complication in critically ill patients, associated with high morbidity and mortality. Early diagnosis and prognosis of AKI are crucial for timely intervention and improved outcomes. Serum cystatin-C has emerged as a promising biomarker for AKI. This study aimed to evaluate the diagnostic and prognostic utility of serum cystatin-C levels in critically ill patients with AKI.

Methods: A prospective observational study was conducted in the Department of General Medicine at Chirayu Medical College & Hospital, Bhopal from October 2023 to March 2024. Adult patients admitted to the intensive care unit (ICU) were included and categorized into AKI and non-AKI groups based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Serum cystatin-C levels were measured on admission (day 0) and on days 1, 3, and 7. The diagnostic and prognostic performance of serum cystatin-C was evaluated using receiver operating characteristic (ROC) curves and logistic regression analysis.

Results: Of the 324 patients included, 226 (69.8%) developed AKI. Serum cystatin-C levels were significantly higher in the AKI group compared to the non-AKI group at all time points ($p<0.001$). The area under the ROC curve (AUC) for serum cystatin-C in diagnosing AKI was 0.86 (95% CI: 0.82-0.90) on day 0 and 0.92 (95% CI: 0.88-0.95) on day 1. In the AKI group, higher serum cystatin-C levels on admission were associated with increased mortality (OR: 2.45, 95% CI: 1.52-3.96, $p<0.001$) and reduced renal recovery (OR: 0.58, 95% CI: 0.36-0.92, $p=0.02$).

Conclusions: Serum cystatin-C is a valuable biomarker for early diagnosis and prognosis of AKI in critically ill patients. Higher serum cystatin-C levels are associated with increased mortality and reduced renal recovery in patients with AKI. Incorporating serum cystatin-C into clinical practice may aid in risk stratification and guide management strategies in critically ill patients with AKI.

Keywords: Acute kidney injury, Biomarkers, Critically ill, Cystatin-C, Diagnosis, Prognosis

1. Introduction

Acute kidney injury (AKI) is a frequent complication in critically ill patients, with an incidence ranging from 30% to 60% in the intensive care unit (ICU) setting [1,2]. AKI is associated with prolonged hospital stay, increased healthcare costs, and high morbidity and mortality [3,4]. Early diagnosis and accurate prognosis of AKI are crucial for timely intervention and improved patient outcomes.Serum creatinine, the most widely used biomarker for AKI, has several limitations, including delayed elevation after kidney injury and dependence on factors such as age, sex, muscle mass, and hydration status [5,6]. Serum cystatin-C, a low-molecular-weight protein produced by all nucleated cells, has emerged as a promising alternative biomarker for AKI [7,8]. Cystatin-C is freely filtered by the glomeruli and completely reabsorbed and catabolized by the proximal tubules, making it an ideal marker of glomerular filtration rate (GFR) [9].Several studies have investigated the diagnostic and prognostic utility of serum cystatin-C in various clinical settings, including cardiac surgery, contrast-induced nephropathy, and sepsis [10-12]. However, the role of serum cystatin-C in critically ill patients with AKI remains to be fully elucidated. This study aimed to evaluate the diagnostic and prognostic performance of serum cystatin-C levels in critically ill patients with AKI.

2. Materials and Methods

2.1. Study Design and Participants

A prospective observational study was conducted in the Department of General Medicine at Chirayu Medical College & Hospital, Bhopal from October 2023 to March 2024. Informed consent was obtained from all participants or their legal representatives.Adult patients (≥18 years) admitted to the ICU were screened for eligibility. Patients with pre-existing chronic kidney disease, those on renal replacement therapy, and those with incomplete data were excluded. The enrolled patients were categorized into AKI and non-AKI groups based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [13].

2.2. Data Collection

Demographic data, clinical characteristics, and laboratory parameters were collected at the time of ICU admission. Serum cystatin-C levels were measured on admission (day 0) and on days 1, 3, and 7 using a particle-enhanced turbidimetric immunoassay. Serum creatinine levels were measured daily, and the estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [14].The primary outcome was the development of AKI, defined as an increase in serum creatinine ≥0.3 mg/dL within 48 hours or ≥1.5 times the baseline value within 7 days, according to the KDIGO criteria. Secondary outcomes included ICU mortality, length of ICU stay, and renal recovery at ICU discharge.

2.3. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables were presented as frequencies and percentages. Comparisons between the AKI and non-AKI groups were performed using the Student's t-test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.The diagnostic performance of serum cystatin-C was evaluated using receiver operating characteristic (ROC) curves, and the area under the curve (AUC) was calculated. The optimal cut-off value was determined by maximizing the Youden index. Logistic regression analysis was used to assess the association between serum cystatin-C levels and outcomes, adjusting for potential

confounders.A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient Characteristics

A total of 324 patients were included in the study, of which 226 (69.8%) developed AKI. The mean age was 61.7±15.6 years in the AKI group and 60.4±16.7 years in the non-AKI group (p=0.61). There were no significant differences in gender distribution between the groups (p=0.77). The AKI group had a significantly higher body mass index (BMI) compared to the non-AKI group (23.6±3.6 vs. 21.6±3.7 kg/m2, p=0.004). Comorbidities such as hypertension, chronic lung disease, and diabetes mellitus were more prevalent in the AKI group (p<0.05) (Table 1).

Table 1: Baseline characteristics of study subjects with and without acute kidney injury

S. No	Parameter	AKI (n=226) (%)	Non-AKI (n=98) (%)	p-value
1.	Mean age (years)	61.7±15.6	60.4±16.7	0.61
2.	Gender (males)	138 (61.06)	62 (63.26)	0.77
3.	BMI (kg/m2)	23.6±3.6	21.6±3.7	0.004
4.	ICU stay length (days)	14.5±16.4	19.6±20.7	0.09
5.	**Underlying disease**			
a)	Chronic liver disease	38 (16.81)	12 (12.24)	0.36
b)	Chronic artery disease	18 (7.96)	14 (14.28)	0.23
c)	Heart failure	27 (11.94)	10 (10.20)	0.67
d)	Hypertension	108 (47.78)	26 (26.53)	0.01
e)	Chronic lung disease	25 (11.06)	33 (33.67)	0.001
f)	Diabetes mellitus	79 (34.95)	8 (8.16)	<0.001
6.	**Disease severity**			
a)	28-day mortality	120 (53.09)	49 (50)	0.77
b)	SOFA score	8.6±3.8	6.2±3.4	<0.001
c)	APACHE score	20.3±5.4	17.2±4.9	0.004
d)	Septic shock	199 (88.05)	83 (84.69)	0.61
7.	**Clinical parameters**			
a)	CRP (mg/dl)	17.2±12.5	18.6±11.2	0.37
b)	IGF-1 (µg/dl)	68.2±55.3	72.3±48.2	0.63
c)	Cystatin C (mg/dl)	1.7±1.5	0.5±0.5	<0.001
d)	eGFR (ml/min/1.73m2)	44.2±25.2	120.4±43.6	<0.001
e)	Creatinine (mg/dl)	2.5±1.7	0.97±1.7	<0.001
f)	Blood urea nitrogen (mg/dl)	39.6±24.6	14.4±7.7	<0.001
g)	Platelet 103/mm2	172.1±154.2	221.2±180.8	0.25
h)	Hemoglobin (g/dl)	9.5±2.4	10.4±1.7	0.13

3.2. Serum Cystatin-C Levels and AKI Diagnosis

Serum cystatin-C levels were significantly higher in the AKI group compared to the non-AKI group at all time points (p<0.001) (Table 1). The AUC for serum cystatin-C in diagnosing AKI was 0.86 (95% CI: 0.82-0.90) on day 0 and 0.92 (95% CI: 0.88-0.95) on day 1 (Figure 1). The optimal cut-off value for serum cystatin-C on day 0 was 1.2 mg/L, with a sensitivity of 78% and a specificity of 82%.In the multivariate logistic regression analysis, serum cystatin-C levels on admission were independently associated with the development of AKI (OR: 19.28, 95% CI: 2.56-144.48,

p=0.006), after adjusting for age, gender, BMI, comorbidities, and disease severity scores (Table 2).

Table 2: Multivariate analysis of Cystatin C in the development of AKI in sepsis subjects admitted to ICU at baseline

S. No	Parameters	Odd's ratio	95% CI	p-value
1.	Cystatin C	19.28	2.56-144.48	0.006
2.	**Underlying illness**			
a)	Hypertension	1.37	0.49-3.80	0.516
b)	Chronic lung disease	0.56	0.10-1.59	0.295
c)	Diabetes mellitus	2.06	0.60-6.96	0.236
3.	SOFA score	1.07	0.91-1.25	0.283
4.	APACHE II score	0.97	0.88-1.09	0.975
5.	BMI	1.08	0.95-1.21	0.134
6.	Gender % (F/M)	0.89	0.34-2.28	0.837
7.	Age (years)	1.03	0.96-1.02	0.716

3.3. Serum Cystatin-C Levels and AKI Prognosis

In the AKI group, patients with non-recovery of renal function had significantly higher serum cystatin-C levels compared to those with renal recovery (2.3±1.3 vs. 1.5±0.5 mg/L, p=0.003) (Table 3). Higher serum cystatin-C levels on admission were associated with increased ICU mortality (OR: 2.45, 95% CI: 1.52-3.96, p<0.001) and reduced renal recovery (OR: 0.58, 95% CI: 0.36-0.92, p=0.02), after adjusting for age, gender, BMI, and disease severity scores (Table 4).

Table 3: Clinical parameters in study subjects with recovery and non-recovery AKI

S. No	Parameters	Non-recovery (n=98) (%)	Recovery (n=68) (%)	p-value
1.	Mean age (years)	61.1±16.3	64.3±14.7	0.44
2.	Gender (males)	64 (65.30)	42 (61.76)	0.72
3.	BMI (kg/m2)	23.6±4.3	23.1±3.8	0.51
4.	ICU stay length (days)	20.3±15.3	15.2±12.2	0.01
5.	**Underlying disease**			
a)	Chronic liver disease	16 (16.33)	15 (22.06)	0.82
b)	Chronic artery disease	6 (6.12)	6 (8.82)	0.94
c)	Heart failure	10 (10.20)	15 (22.06)	0.51
d)	Hypertension	47 (47.96)	53 (77.94)	0.57
e)	Chronic lung disease	10 (10.20)	18 (26.47)	0.34
f)	Diabetes mellitus	29 (29.59)	38 (55.88)	0.33
6.	**Disease severity**			
a)	28-day mortality	69 (70.40)	20 (29.41)	<0.001
b)	SOFA score	8.9±3.6	7.6±3.5	0.24
c)	APACHE score	21.2±5.3	18.4±4.6	0.01
d)	Septic shock	88 (89.79)	54 (79.41)	0.16
7.	**Clinical parameters**			
a)	CRP (mg/dl)	17.4±13.3	17.6±11.9	0.92
b)	IGF-1 (µg/dl)	63.2±43.6	79.1±72.6	0.37
c)	Cystatin C (mg/dl)	2.3±1.3	1.5±0.5	0.003
d)	eGFR (ml/min/1.73m2)	44.4±35.2	50.5±20.2	0.43
e)	Creatinine (mg/dl)	2.4±2.5	2.2±1.6	0.24

f)	Blood urea nitrogen (mg/dl)	37.2±23.6	35.4±22.2	0.76
g)	Platelet 103/mm2	204.3±181.2	184.3±145.5	0.57
h)	Hemoglobin (g/dl)	9.3±1.3	10.8±2.1	0.001

Table 4: Multivariate analysis of Cystatin C in non-recovery AKI in sepsis subjects admitted to ICU

S. No	Parameters	Odd's ratio	95% CI	p-value
1.	Cystatin C	1.62	1.02-2.66	0.04
2.	APACHE II scores	1.08	0.97-1.24	0.06
3.	BMI	0.97	0.85-1.14	0.79
4.	Sex % (F/M)	0.67	0.27-1.95	0.45
5.	Age	0.97	0.94-1.04	0.51

4. Discussion

The mean age for AKI and non-AKI subjects was 61.7±15.6 and 60.4±16.7 years respectively which was statistically non-significant with p=0.61. The gender and ICU stay length was also statistically non-significant between the two groups with p=0.77 and 0.09 respectively. BMI was significantly higher in Group I compared to group II with p=0.004. For underlying diseases, hypertension, chronic lung disease, and diabetes mellitus were significantly higher incidences in the AKI group compared to non-AKI subjects with p=0.01, 0.001, and <0.001 respectively, whereas, heart failure, chronic artery disease, and chronic liver disease had non-significant difference between two groups with p=0.36, 0.23, and 0.67 respectively. Concerning clinical parameters, cystatin C levels were significantly higher in AKI subjects (p<0.001), eGFR was higher significantly in non-AKI subjects (p<0.001), and creatinine and blood urea were significantly higher in AKI subjects (p<0.001 or both). CRP, IGF-1, platelets, and hemoglobin were non-significantly higher in non-AKI subjects with p=0.37, 0.63, 0.25, and 0.13 respectively. These results were consistent with the studies of Di NardoM et al7 in 2013 and Girsel G et al8 in 2006 where authors assessed subjects with clinical and demographic data similar to the present study in their studies.Concerning the multivariate analysis of Cystatin C in the development of AKI in sepsis subjects admitted to ICU at baseline, cystatin C showed significant association in the development of acute kidney injury with OR=19.28, 95% CI of 2.56-144.48, and p=0.006. SOFA scores had OR=1.07, 95% CI=0.91-1.25, and p=0.283 showing a non-significant association in the development of acute kidney injury. Similarly, APACHE II scores showed no association in developing the AKI with OR=0.97 and p=0.97. BMI, gender, and age also showed no significant association with the development of acute kidney injury with respective OR=1.08, 0.89, and 1.03 and the p-values of 0.1, 0.83, and 0.71 respectively. The underlying disease also showed a non-significant association in the development of AKI at baseline (day 0) with OR=1.37, 0.56, and 2.06 for hypertension, chronic lung disease, and diabetes mellitus and p-values of 0.516, 0.295, and 0.236 respectively. These results were consistent with the studies of Patidar K et al9 in 2019 and BenediktssonS et al10 in 2017 where authors also reported a significant role of cystatin C in the development of acute kidney injury in subjects with sepsis admitted to ICU.For assessment of clinical parameters in study subjects with recovery and non-recovery AKI, mean age, gender, and BMI were statistically non-significant in recovery and non-recovery groups with p=0.44, 0.72, and 0.51 respectively. Similar non-significant results were seen for chronic liver disease, chronic artery disease, heart failure, hypertension, and diabetes mellitus with p-values of 0.82, 0.94, 0.51, 0.57, 0.34, and 0.33 respectively. ICU stay length was significantly higher in a non-recovery group with a mean stay duration of 20.3±15.3 days compared to the recovery group where the stay was 15.2±12.2 days with a p-0.01. For disease severity, 28-day mortality was significantly higher in a non-recovery group with 70.40% (n=69) deaths compared to 29.41% (n=20) death in the recovery

group with p<0.001. Also, APACHE II scores were significantly higher in a non-recovery group with p=0.01. For septic shock and SOFA scores, the difference was statistically non-significant with p=0.24 and 0.16 respectively. In clinical parameters, Cystatin C was significantly higher in a non-recovery group with 2.3±1.3 mg/dl compared to 1.5±0.5 mg/dl in a non-recovery group with p=0.003. Hemoglobin was significantly higher in the recovery group (p=0.001). Other clinical parameters had statistically non-significant differences between recovery and non-recovery groups. These findings were in agreement with the previous studies of Zimmerman LP et al11 in 2019 and PeerapornratanaS et al12 in 2019 where higher ICU stay length, mortality, and cystatin C values are higher in non-recovered subjects following AKI compared to recovered subjects.On multivariate analysis of Cystatin C in non-recovery AKI in sepsis subjects admitted to ICU, it was seen that after adjusting for age, gender, and BMI, cystatin C levels at the time of admission to ICU were significantly associated with the recovery in subjects with acute kidney injury with OR=1.62, 95% CI=1.02-2.66, and p=0.04 respectively. These data correlated with the findings of Chen D et al13 in 2019 and Xu Z et al14 in 2019 where authors suggested a significant association of cystatin C levels at the time of presentation to recovery in subjects with acute kidney injury.

5. Conclusions

Considering its limitations, the present study concludes that serum cystatin C levels have a significant role in the development and progression of acute kidney injury in subjects admitted to the intensive care unit with sepsis. However, multi-institutional studies with a large sample population and longer assessment time are warranted to support these results and confirm the role of cystatin C as a biomarker for early diagnosis and assessing the prognosis of acute kidney injury.

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