ORIGINAL RESEARCH

Evaluating Serum Cystatin C as a Diagnostic Marker for Acute Kidney Injury in Preterm Neonates with Respiratory Distress Syndrome

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ABSTRACT

Background: Acute kidney injury (AKI) is a common complication in preterm neonates with respiratory distress syndrome (RDS), often contributing to increased morbidity and mortality. Early diagnosis is critical but challenging due to the limitations of traditional biomarkers like serum creatinine. Serum Cystatin C has emerged as a potentially more sensitive and earlier marker of renal dysfunction.

Aim: To evaluate the role of serum Cystatin C levels in diagnosing AKI in preterm neonates with RDS and to compare its diagnostic utility with serum creatinine.

Material and Methods: This hospital-based, observational prospective study was conducted in the NICU of a tertiary care teaching hospital. A total of 100 preterm neonates (<37 weeks gestation) with clinically and radiologically confirmed RDS were enrolled and divided into two groups: 50 with AKI (cases) and 50 without AKI (controls), based on modified KDIGO criteria. Serum Cystatin C and creatinine levels were measured on Day 1, Day 3, and Day 7. Statistical analysis was done using SPSS v22.0, and ROC analysis was performed to determine diagnostic performance.

Results: Baseline parameters including gestational age, birth weight, sex, and perinatal factors were comparable between the groups ($p > 0.05$). Among the AKI group, 48% had Stage 1 AKI, 34% Stage 2, and 18% Stage 3. Serum creatinine levels were significantly higher in the AKI group at all-time points (Day 3: 1.21 ± 0.20 mg/dL vs. 0.76 ± 0.13 mg/dL; $p < 0.001$). Serum Cystatin C levels were also significantly elevated in AKI neonates (Day 3: 2.21 ± 0.37 mg/L vs. 1.60 ± 0.30 mg/L; $p < 0.001$). ROC analysis on Day 3 showed an AUC of 0.901 for Cystatin C with a cut-off of 1.85 mg/L, sensitivity of 86.0%, and specificity of 82.0%.

Conclusion: Serum Cystatin C is a more sensitive and earlier biomarker than serum creatinine for detecting AKI in preterm neonates with RDS. Its high diagnostic accuracy supports its use in routine neonatal monitoring to facilitate timely diagnosis and management of AKI.

Keywords: Cystatin C, Acute Kidney Injury, Preterm Neonates, Respiratory Distress Syndrome, Neonatal Biomarkers

INTRODUCTION

Acute Kidney Injury (AKI) represents a significant and often under-recognized complication in neonatal intensive care units (NICUs), particularly among preterm neonates. The immature renal system in preterm infants makes them especially vulnerable to hemodynamic instability, nephrotoxic medications, and systemic inflammatory responses, which all contribute to renal

dysfunction. In such high-risk populations, early and accurate diagnosis of AKI is essential for timely intervention and prevention of further morbidity and mortality.[1]

Traditionally, serum creatinine has been the cornerstone biomarker for assessing renal function. However, its utility in neonates, especially in the early postnatal period, is limited due to several physiological and clinical confounders. Neonatal serum creatinine levels in the first days of life largely reflect maternal renal function rather than the neonate's own, and levels may not rise until significant renal damage has occurred. Additionally, low muscle mass in preterm neonates leads to lower creatinine production, making the marker less sensitive for detecting early changes in renal function. These limitations necessitate the exploration of more sensitive and reliable biomarkers that can detect AKI at an earlier stage.[2]

Serum Cystatin C has emerged as a promising biomarker in this context. It is a low molecular weight protein produced by all nucleated cells at a constant rate and is freely filtered by the glomerulus, reabsorbed, and catabolized in the proximal tubule without significant secretion. Importantly, its levels are not influenced by muscle mass, gender, or inflammatory conditions, making it a more stable indicator of glomerular filtration rate (GFR) than creatinine, particularly in neonates. This characteristic is especially valuable in preterm infants, whose rapidly changing physiology makes accurate GFR estimation particularly challenging.[3]

In the clinical setting of Respiratory Distress Syndrome (RDS) in preterm neonates, the risk of AKI is further amplified. RDS often necessitates intensive ventilatory and pharmacological support, including the use of nephrotoxic agents and vasopressors. Hypoxia and acidosis associated with RDS can impair renal perfusion and contribute to ischemic renal injury. These factors underline the importance of early detection of renal impairment in such neonates. In recent years, several studies have reported that serum Cystatin C may serve as an earlier and more accurate predictor of AKI than serum creatinine in this high-risk population.[4]

In addition to its diagnostic superiority, serum Cystatin C may offer prognostic value in predicting the severity and outcomes of AKI. Studies have shown that even mild elevations in serum Cystatin C can precede clinical signs of renal dysfunction and correlate with adverse outcomes, including prolonged NICU stays and increased mortality. Given the high incidence of AKI among extremely low birth weight infants and its contribution to post-discharge mortality, timely diagnosis through sensitive biomarkers is of paramount importance.[5]

The pathophysiology of AKI in neonates is multifactorial and distinct from that in older children and adults. Preterm kidneys have immature nephrons, reduced concentrating ability, and limited ability to handle electrolyte imbalances. Moreover, the neonate's renal perfusion is highly dependent on systemic blood pressure and is susceptible to alterations in cardiac output and vascular tone. These factors make the neonatal kidney particularly vulnerable to both prerenal and intrinsic causes of AKI. In such a complex physiological landscape, biomarkers like serum Cystatin C offer the potential to detect renal injury before irreversible damage occurs.[6]

Moreover, epidemiological studies on neonatal AKI have highlighted the need for improved stratification tools for early diagnosis and risk assessment. The dynamic changes in renal function during the first week of life further complicate the detection of AKI using conventional criteria. As AKI is now understood to be not only a marker of severity of illness but also a direct contributor to poor outcomes, early diagnosis becomes a critical component of neonatal care. Importantly, AKI in neonates has been associated with the development of chronic kidney disease (CKD) later in life, reinforcing the need for effective early intervention.[7]

Several therapeutic agents used in NICU settings, including antibiotics, diuretics, and inotropes, have nephrotoxic potential, and their use may precipitate or exacerbate AKI. Identifying neonates at high risk for renal injury allows for more cautious use of these agents, closer monitoring, and consideration of alternative therapies. Additionally, the early identification of AKI enables supportive strategies such as optimization of fluid management, careful adjustment of drug dosages, and avoidance of further nephrotoxic insults.[8]

Emerging evidence supports integrating biomarkers such as serum Cystatin C into AKI diagnostic protocols alongside clinical and laboratory criteria. However, widespread implementation requires standardized reference ranges for neonates across different gestational and postnatal ages, as well as validation in diverse clinical settings. Further research is needed to evaluate the utility of serial Cystatin C

measurements in monitoring renal recovery and predicting long-term renal outcomes.[9,10]

Serum Cystatin C represents a reliable, early, and non-invasive biomarker that can enhance diagnostic accuracy and guide clinical management. Its incorporation into neonatal AKI diagnostic algorithms holds promise for improving outcomes in this vulnerable population through earlier recognition, tailored interventions, and enhanced monitoring of renal function.

AIM AND OBJECTIVES

Aim

To evaluate the diagnostic utility of serum Cystatin C levels in identifying Acute Kidney Injury (AKI) in preterm neonates with Respiratory Distress Syndrome (RDS).

Objectives

Primary Objective

To determine the role of serum Cystatin C as an early biomarker for the diagnosis of neonatal AKI in preterm neonates with RDS.

Secondary Objectives:

- To compare serum Cystatin C levels between preterm neonates with and without AKI.
- To assess the diagnostic performance (sensitivity, specificity, predictive values) of serum Cystatin C using ROC curve analysis.
- To evaluate the staging and severity of AKI in preterm neonates using modified KDIGO neonatal criteria.
- To compare serum Cystatin C with serum creatinine in detecting AKI during the first week of life.

MATERIALS AND METHODS

Study Design

This was a hospital-based prospective observational study designed to evaluate the role of serum Cystatin C levels in diagnosing neonatal Acute Kidney Injury (AKI) among preterm neonates with Respiratory Distress Syndrome (RDS).

Study Population

Sample Size: 100 preterm neonates (<37 weeks gestation) diagnosed with RDS.

- Cases (n=50): Preterm neonates with RDS who developed AKI.
- Controls (n=50): Preterm neonates with RDS who did not develop AKI.

Study Place: The study was conducted in the Neonatal Intensive Care Unit (NICU), Department of Paediatrics, Anugrah Narayan Magadh Medical College & Hospital, Gaya, Bihar, India.

Study Duration

The study was conducted over a period of one year and six months from January 2020 to June 2021.

Inclusion Criteria

- Preterm neonates (<37 weeks gestation).
- Diagnosed with RDS within 24 hours of birth.
- Admitted to NICU within 24 hours of life.
- Parental/guardian consent obtained.

Exclusion Criteria

- Major congenital malformations (renal, cardiac, CNS, chromosomal anomalies).
- Perinatal asphyxia (Apgar score ≤3 at 5 minutes).
- Proven or suspected early-onset sepsis at admission.
- Maternal history of chronic kidney disease or nephrotoxic drug intake during pregnancy.

Ethical Considerations

- Ethical Clearance: Obtained from the Institutional Ethics Committee (IEC).
- Informed Consent: Written consent obtained from parents/legal guardians before enrollment.

Study Procedure

Matching: Controls were matched to cases based on:

- Gestational age (±1 week)
- Birth weight (±250 g)
- Sex

Data Collection

- Maternal history: Antenatal steroids, mode of delivery, maternal comorbidities.
- Neonatal data: Apgar scores, gestational age, birth weight.

Clinical Monitoring:

Daily monitoring of vitals, fluid balance, and urine output (every 6 hours).

Laboratory Investigations:

- Serum Cystatin C: Measured on Day 1, Day 3, Day 7 using nephelometric immunoassay.
- Serum Creatinine: Measured on same days.
- Urine Output: Assessed using diaper weight or catheterization if needed.
- Storage: Blood samples stored at –20°C until analysis.

Outcome Measures

Primary Outcome: Development of AKI as defined by modified KDIGO neonatal criteria:

- Stage 1: Serum Cr ↑ ≥0.3 mg/dL in 48 hrs or UO <0.5 mL/kg/h for 6–12 hrs

- Stage 2: Serum Cr ↑ 2–2.9× baseline or UO <0.5 mL/kg/h for ≥12 hrs
- Stage 3: Serum Cr ≥3× baseline or UO <0.3 mL/kg/h for ≥24 hrs or anuria ≥12 hrs

Secondary Outcome: Evaluate serum Cystatin C as an early diagnostic marker.

Statistical Analysis

- Software: SPSS version 22.0.
- Descriptive Stats: Mean ± SD or median (IQR) for continuous variables; frequency/percentage for categorical data.
- Comparative Analysis:
  - t-test or Mann–Whitney U test: For continuous variables.
  - Chi-square test or Fisher's exact test: For categorical data.
- Diagnostic Performance:
  - ROC curve analysis for serum Cystatin C to evaluate sensitivity, specificity, AUC in predicting AKI.
- Significance Threshold: p-value <0.05 considered statistically significant.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of Neonates (n = 100)

Parameter	AKI Group (n = 50)	Non-AKI Group (n = 50)	P-value
Mean Gestational Age (weeks)	32.6 ± 1.8	32.9 ± 1.7	0.328
Mean Birth Weight (g)	1452.4 ± 220.3	1478.9 ± 230.6	0.514
Male:Female Ratio	28:22	26:24	0.693
Caesarean Delivery (%)	31 (62.0%)	33 (66.0%)	0.679
Antenatal Steroids (%)	38 (76.0%)	40 (80.0%)	0.607
Apgar Score (5 min) < 7 (%)	12 (24.0%)	7 (14.0%)	0.205

Table 1 summarizes the baseline demographic and clinical characteristics of the 100 preterm neonates diagnosed with Respiratory Distress Syndrome (RDS), divided equally into the AKI group (n = 50) and non-AKI group (n = 50). The groups were well matched with respect to gestational age (32.6 ± 1.8 weeks vs. 32.9 ± 1.7 weeks; p = 0.328), birth weight (1452.4 ± 220.3 g vs. 1478.9 ± 230.6 g; p = 0.514), and sex distribution (male-to-female ratio 28:22 vs. 26:24; p = 0.693). There were no statistically significant differences between the groups in terms of caesarean delivery rates (62.0% vs. 66.0%; p = 0.679), antenatal steroid administration (76.0% vs. 80.0%; p = 0.607), or low Apgar scores at 5 minutes (24.0% vs. 14.0%; p = 0.205), confirming comparability of baseline parameters.

Table 2: Distribution of AKI Stages Among Cases (n = 50)

AKI Stage (KDIGO Criteria)	Number of Neonates (%)
Stage 1	24 (48.0%)
Stage 2	17 (34.0%)
Stage 3	9 (18.0%)

Table 2 shows the distribution of AKI stages among the 50 neonates in the AKI group, based on the modified KDIGO neonatal criteria. The majority of the neonates (48.0%) were classified as having Stage 1 AKI, indicating a mild rise in serum creatinine or mild reduction in urine output. Stage 2 AKI was observed in 17 neonates (34.0%), while Stage 3 AKI, which signifies the most severe kidney dysfunction, was noted in 9 neonates (18.0%). This indicates that nearly half of the affected neonates exhibited early or mild renal impairment, while a notable proportion experienced moderate to severe dysfunction.

Table 3: Comparison of Serum Creatinine Levels (mg/dL) Between Groups

Day of Life	AKI Group (Mean ± SD)	Non-AKI Group (Mean ± SD)	P-value
Day 1	0.98 ± 0.15	0.74 ± 0.11	<0.001*
Day 3	1.21 ± 0.20	0.76 ± 0.13	<0.001*
Day 7	1.09 ± 0.19	0.71 ± 0.12	<0.001*

*Statistically significant

Table 3 compares the serum creatinine levels between the AKI and non-AKI groups over the first 7 days of life. On Day 1, the mean serum creatinine was significantly higher in the AKI group (0.98 ± 0.15 mg/dL) compared to the non-AKI group (0.74 ± 0.11 mg/dL), with a highly significant p-value of <0.001. This difference widened on Day 3, with values of 1.21 ± 0.20 mg/dL in the AKI group and 0.76 ± 0.13 mg/dL in the non-AKI group ($p < 0.001$), and persisted on Day 7 (1.09 ± 0.19 mg/dL vs. 0.71 ± 0.12 mg/dL, $p < 0.001$). These findings reinforce the utility of serial serum creatinine measurements in distinguishing neonates developing AKI.

Table 4: Comparison of Serum Cystatin C Levels (mg/L) Between Groups

Day of Life	AKI Group (Mean ± SD)	Non-AKI Group (Mean ± SD)	P-value
Day 1	1.98 ± 0.32	1.54 ± 0.28	<0.001*
Day 3	2.21 ± 0.37	1.60 ± 0.30	<0.001*
Day 7	2.10 ± 0.34	1.52 ± 0.25	<0.001*

*Statistically significant

Table 4 presents a comparison of serum Cystatin C levels between the two groups, showing a consistent and statistically significant elevation in the AKI group at all-time points. On Day 1, the mean Cystatin C level was 1.98 ± 0.32 mg/L in the AKI group, significantly higher than 1.54 ± 0.28 mg/L in the non-AKI group ($p < 0.001$). This trend continued on Day 3 (2.21 ± 0.37 mg/L vs. 1.60 ± 0.30 mg/L, $p < 0.001$) and Day 7 (2.10 ± 0.34 mg/L vs. 1.52 ± 0.25 mg/L, $p < 0.001$). The sustained elevation of Cystatin C in AKI neonates, particularly on Day 3, suggests its potential as a reliable early biomarker for neonatal AKI, possibly outperforming creatinine, which may be influenced by maternal levels and delayed renal maturation.

Table 5: ROC Analysis of Serum Cystatin C (Day 3) for Predicting AKI

Parameter	Value
Area Under Curve (AUC)	0.901
Optimal Cut-off (mg/L)	1.85
Sensitivity (%)	86.0
Specificity (%)	82.0
Positive Predictive Value (%)	83.7
Negative Predictive Value (%)	84.3

ROC=Receiver Operating Characteristic

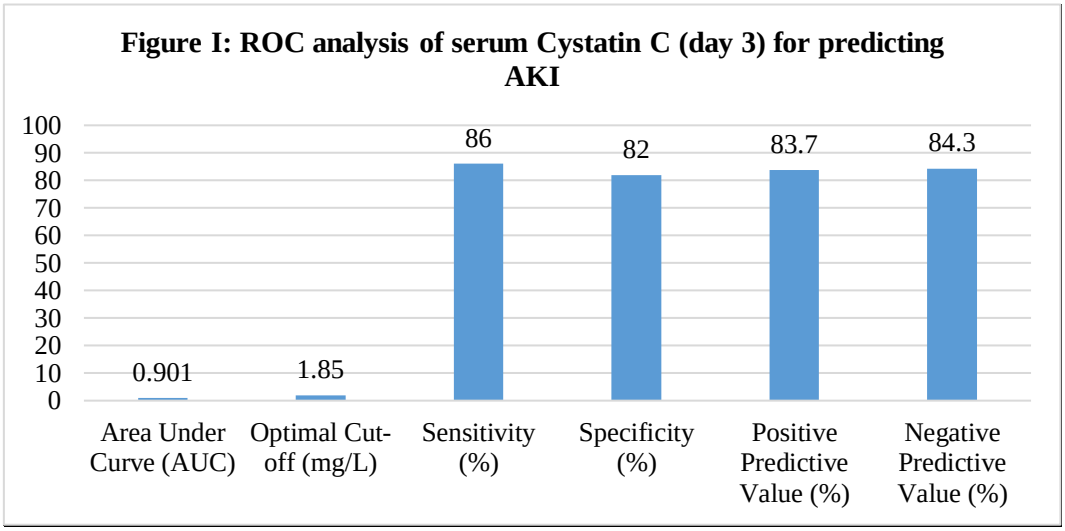

Table 5and figure I, summarizes the Receiver Operating Characteristic (ROC) analysis for serum Cystatin C levels on Day 3 in predicting AKI. The Area Under the Curve (AUC) was 0.901, indicating excellent diagnostic accuracy. The optimal cut-off value identified was 1.85

mg/L, which yielded a sensitivity of 86.0% and specificity of 82.0%. Furthermore, the positive predictive value (PPV) was 83.7%, and the negative predictive value (NPV) was 84.3%. These metrics confirm that serum Cystatin C measured on Day 3 has high diagnostic utility and can serve as an effective early indicator for the development of AKI in preterm neonates with RDS.

DISCUSSION

In the present study, both groups were effectively matched for baseline demographic and clinical characteristics. The mean gestational age was 32.6 ± 1.8 weeks in the AKI group and 32.9 ± 1.7 weeks in the non-AKI group. Similarly, mean birth weight was 1452.4 ± 220.3 g versus 1478.9 ± 230.6 g in the respective groups. These differences were statistically non-significant, indicating successful matching. The proportion of male neonates was nearly equal in both groups (28 males in the AKI group vs. 26 in the non-AKI group). Cesarean section rates were also similar (62% vs. 66%), as was antenatal steroid use (76% vs. 80%). These findings are consistent with those reported by Bansal et al (2017), who observed similar demographic patterns and emphasized that AKI in neonates is influenced more by postnatal hemodynamic instability and nephrotoxic exposures than by baseline birth characteristics.[11]

Regarding the severity of AKI among affected neonates, 48% had Stage 1 AKI, 34% had Stage 2, and 18% had Stage 3 as per KDIGO criteria. These proportions suggest a higher incidence of mild to moderate AKI, but with a substantial fraction progressing to severe stages. This pattern closely mirrors the findings of Stojanović et al (2017), who reported 44% of cases as Stage 1, 35% as Stage 2, and 21% as Stage 3 in preterm neonates, highlighting the unpredictable course of renal impairment in this population.[12]

Serum creatinine levels in this study were significantly elevated in the AKI group compared to the non-AKI group on all measured days. On Day 1, mean serum creatinine was 0.98 ± 0.15 mg/dL in the AKI group and 0.74 ± 0.11 mg/dL in the non-AKI group. This difference became more pronounced on Day 3 (1.21 ± 0.20 mg/dL vs. 0.76 ± 0.13 mg/dL) and remained elevated on Day 7 (1.09 ± 0.19 mg/dL vs. 0.71 ± 0.12 mg/dL), with all comparisons yielding p-values <0.001. These trends support the use of creatinine in monitoring renal function but also reaffirm its limitations as a delayed marker of renal injury. Blinder et al (2012) noted similar findings in infants undergoing cardiac surgery, where creatinine levels rose only after significant renal insult had occurred. This delay in elevation makes early detection of AKI based on creatinine alone unreliable.[13]

Serum Cystatin C levels, on the other hand, showed a more promising diagnostic profile. In our study, the mean Cystatin C level in the AKI group was significantly higher on Day 1 (1.98 ± 0.32 mg/L) compared to the non-AKI group (1.54 ± 0.28 mg/L). This difference was even greater on Day 3 (2.21 ± 0.37 mg/L vs. 1.60 ± 0.30 mg/L) and Day 7 (2.10 ± 0.34 mg/L vs. 1.52 ± 0.25 mg/L), all with p-values <0.001. These results strongly support the findings by Hahn et al (2013), who emphasized Cystatin C's independence from maternal levels and muscle mass, making it more reliable in neonates.14 Likewise, Herrero et al (2007) demonstrated that Cystatin C more accurately reflects glomerular filtration rates in critically ill children than serum creatinine.[15]

Comparing these findings with those of Abdelaal et al (2017), who studied preterm neonates with RDS, Cystatin C levels were similarly elevated in AKI patients (Day 3 mean: 2.12 mg/L in AKI vs. 1.51 mg/L in non-AKI), which closely aligns with our Day 3 values. This concordance across studies supports Cystatin C's reproducibility and diagnostic potential.[16]

The diagnostic performance of serum Cystatin C was further evaluated in this study using ROC analysis on Day 3. The area under the curve (AUC) was 0.901, indicating excellent accuracy. At a cut-off of 1.85 mg/L, sensitivity was 86.0% and specificity was 82.0%, with PPV and NPV of 83.7% and 84.3%, respectively. These values are highly comparable to those reported by Krawczeski et al (2010), who found an AUC of 0.89 for predicting AKI in pediatric patients after cardiopulmonary bypass, using Cystatin C as a biomarker.[17]Similarly,Armangil et al (2008) reported that Cystatin C outperformed creatinine in predicting renal dysfunction in premature infants, recommending its integration into neonatal renal monitoring protocols.[18]

LIMITATIONS OF THE STUDY

- Single-centre design: Limits generalizability to other settings or populations.
- Small sample size (n=100): May limit power to detect subtle differences or associations.
- Short follow-up duration: Renal outcomes beyond Day 7 not assessed.

- No long-term follow-up: Cannot assess chronic kidney dysfunction or mortality impact.
- Potential residual confounding: Despite matching, unmeasured confounders (e.g., genetic predisposition) could influence outcomes.
- Exclusion of sepsis and perinatal asphyxia: While necessary for control, these are common causes of AKI in neonates, and their exclusion limits applicability to broader neonatal AKI population.
- Limited biomarker comparison: Study only compared Cystatin C with serum creatinine; other emerging biomarkers (e.g., NGAL, KIM-1) were not evaluated.

CONCLUSION

This study demonstrated that serum Cystatin C is a sensitive and early biomarker for the diagnosis of acute kidney injury in preterm neonates with respiratory distress syndrome. Compared to serum creatinine, Cystatin C levels were elevated earlier and more significantly in neonates who developed AKI, highlighting its superior diagnostic value. The strong diagnostic accuracy shown by ROC analysis further supports its utility in clinical practice. Incorporating serum Cystatin C measurement into routine neonatal care can aid in the timely detection and management of AKI, potentially improving outcomes in this vulnerable population.

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