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Original Article

Biochemistry Section

Comparison of Estimated Glomerular Filtration Rate from Venous and Umbilical Cord Blood in Preterm and Low-birth-weight Neonates using Creatinine and Cystatin-C: A Case-control Study

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ABSTRACT

Introduction: Premature and Low-Birth-Weight (LBW) neonates demonstrate underdeveloped organs, including low nephron counts, rendering them susceptible to renal impairment subsequently. Therefore, early and accurate detection of kidney dysfunction is important for management. Traditionally, serum creatinine is used for estimating Glomerular Filtration Rate (GFR), which maternal levels and neonatal muscle mass may influence. Therefore, cystatin-C, a non protein-bound, low-molecular-weight marker, is tested for this study for the early detection of renal dysfunction.

Aim: To identify creatinine or cystatin-C as a better marker in premature and LBW neonates.

Materials and Methods: This case-control study was conducted from June to October 2022 at the SRM Medical College Hospital, Tamil Nadu, India. The participants were from Chengalpattu district, including 63 rural and 47 suburban pregnant women. The primary inclusion criteria were neonates diagnosed as premature and LBW, with a sample size of 53 neonates per group. A 3-5 mL of venous and cord blood samples of neonates were collected, serum was separated and stored at -20°C to estimate creatinine, cystatin-C levels and GFR. The results were expressed as mean values, and statistical significance was assessed using the Student's t-test, with a p-value <0.05 considered statistically significant.

Results: Cystatin-C were found to be 1.9±0.8 mg/dL and significantly higher in cord blood samples in comparison with the control. The cystatin-based eGFR value was found to be 91.4±43.2 mL/min and 149±35.4 mL/min for venous and cord blood samples, respectively. Whereas only cystatin-C was statistically significant in venous blood samples. However, GFR based on creatinine and cystatin-C was significantly decreased in both venous and cord blood samples.

Conclusion: The AUC for cystatin-C in cord blood samples was found to be 0.7, indicating its reliability compared to creatinine. Moderate accuracy observed indicates the need for a larger number of samples for the establishment of a diagnostic marker. Thereby, for cystatin-C to be used as a marker for renal dysfunction further validation is required.

Keywords: Diagnostic marker, Premature birth, Renal dysfunction

INTRODUCTION

According to the World Health Organisation (WHO) globally, preterm birth accounts for 13.4 million babies in the year 2020; and the associated complications have led to approximately 900000 deaths in 2019 [1]. A preterm infant is a baby born at less than 37 weeks of gestation, and a LBW infant (LBW) is a baby with a birth weight of less than 2500 grams. Normal growth and development are affected due to LBW and prematurity, which could lead to a higher risk of developing diseases like Chronic Kidney Disease (CKD), Hypertension (HTN) [2] or cardiovascular disease in childhood and adulthood [3]. Preterm birth is a high-risk factor for perinatal morbidity and mortality [4]. Globally, prematurity is responsible for 10% of neonatal mortality, or approximately 500,000 deaths per year [5]. The incidence of premature birth in India is 14.5%. The health status of preterm, LBW, and gestational age newborns admitted to the Neonatal Intensive Care Unit (NICU) requires continuous monitoring [6].

Nephrogenesis continues even during 36 weeks of gestation, and preterm birth may reduce the nephron number, specifically in cases of acute kidney injury. The interrupted organogenesis observed in preterm birth could result in low nephron endowment, endothelial dysfunction, proteinuria and hypertension [7]. The GFR is the commonly used kidney function marker, and it was found to be low in preterm neonates with kidney injury. A long-term study on LBW infants showed that a deterioration of renal function with a tendency to obesity was observed [8]. GFR usually decreases in neonates and increases gradually with age, reaching a maximum of 20 mL/min/1.73 m^2 at one month [9]. Preterm and LBW newborns are at increased risk of developing CKD [10]. Therefore, early and accurate estimation of GFR is important [11]. GFR can be estimated from clearance parameters such as inulin, serum creatinine, and serum cystatin-C [12]. Among these, cystatin-C is considered to be more stable and unaffected by other factors, making it an ideal marker [13]. Another study shows that an average blood loss of 10 mL/kg of neonatal blood occurs on the first day of life, which underscores the use of umbilical cord blood for diagnostics [14]. Umbilical cord blood, which is normally discarded, can be used as an alternative to venous blood for use as markers for risk assessment in adult life [15].

A study performed on participants between the ages of 35 and 54 years shows that the early events in life could act as predictors for hypertension and kidney function. A study-showed that there was an independent association between prematurity and increased blood pressure, while LBW indicated kidney dysfunction [16]. Umbilical cord blood can also be used as the earliest sample of newborns, helping in the early detection of disease [17]. Moreover,

studies of cystatin-C-based eGFR in neonatal cord blood samples are limited [18].

Therefore, this study aimed to find a better marker in GFR estimation by comparing Cystatin-C with the conventional marker, creatinine.

The primary objective of this study was-to estimate and compare the GFR in premature and LBW neonates using serum creatinine and cystatin-C levels for early identification of renal dysfunction, and the secondary objectives were to compare GFR estimates obtained from cord blood and venous blood samples and evaluate the correlation between creatinine- and cystatin-C-based GFR values.

MATERIALS AND METHODS

This case-control study was conducted at SRM Medical College Hospital and Research Centre, Kattankulathur, Tamil Nadu, India, from June 2022 to October 2022. Ethical approval for the study was obtained (Ethics clearance number: 8390/IEC/2022), and informed consent was taken from participants who donated umbilical cord blood samples. This study included 110 premature and LBW neonates as 'cases' (Group I) and normal birth-weight neonates as 'controls' (Group II).

Sample size: The sample size was calculated using the prevalence (p) of 16.4% from the National Family Health Survey-4 conducted by the Indian Institute of Population Sciences [19]. The sample size was calculated using the Cochran formula:

$$n=z^2\times p\times(1-p)/d^2$$

where: z-Confidence level (95%),

p-Proportion of the population and

d-Absolute precision.

$n=(1.96)^2\times16.4\times83.6/(10)^2=53$

Although the estimated sample size was 53 per group, considering a non-response rate of 5%, the final sample size was 55 per group.

Inclusion criteria for case: Pregnant women aged 21-28 years from Chengalpattu district, including 63 from rural and 47 from suburban areas, and their neonates were recruited. Cord blood and venous blood samples of 55 neonates diagnosed as premature and LBW were included in the study. The neonates born less than 37 gestational weeks were considered as preterm and less than 2500 g were considered as LBW neonates [19].

Exclusion criteria for case: Full-term neonates with normal birthweight and neonates with other illnesses were excluded from the study.

Inclusion criteria for control: Only neonates from uncomplicated pregnancies with APGAR scores of 9 and 10 at 1 and 5 minutes, respectively, were included as controls [20]. The neonates born between 39-41gestational weeks and a birthweight of 2750 to 3000 gm were included. The neonates in the study were not sex matched for this study.

Exclusion criteria for control: Mothers with complications of pregnancy, like preeclampsia and gestational diabetes mellitus, were excluded.

Study Procedure

From the recruited neonates, three mL venous blood sample was collected for the determination of serum creatinine and cystatin-C. A 3-5 mL of cord blood of neonates were collected from the labour ward and transported to the Department of Biochemistry, Central laboratory in less than 24 hours for analysis. The cord blood and venous blood samples were centrifuged at 3000 rpm for 15 minutes to collect serum, which was then transferred and frozen at -20°C for subsequent batch analysis. The serum samples were then estimated for creatinine by Jaffe's Kinetic method using creatinine-detect kit (Catalogue No. 1797, Thermo Scientific) and cystatin-C by the Immunoturbidimetry method in the Auto-analyser Beckman-Coulter AU480 using cystatin diagnostic kit (Proton Biologicals, India). Glomerular filtration was estimated using Schwartz (creatinine-based) and CKiD (cystatin-C-based) formulae.

Creatinine-based Formula for eGFR calculation in term neonates [21]:

$eGFR\ mL/min/m^2 = \{0.45 \times height\ (cm)\} \div serum\ creatinine\ (mg/dL)$

A creatinine-based prediction model for eGFR in preterm and LBW neonates without renal disease was published by Brion LP et al., working with Schwartz, hypothesised that low muscle mass in low- and preterm neonates would overestimate their eGFR based on the equation. The authors concluded that a lower constant of 0.33 should be used for preterm and LBW neonates [22].

Creatinine-based Formula for eGFR calculation in preterm and LBW neonates:

$eGFR\ mL/min/m^2 = \{0.33 \times height\ (cm)\} \div serum\ creatinine\ (mg/dL)$

Based on the pregnancy category, eGFR values obtained using the Zappitelli and CKiD equations were comparable in preterm births [23].

Cystatin-C-based Formula for eGFR calculation by the CKD in Children (CKiD) formula:

$eGFR\ mL/min/m^2 = 70.69 \times Cystatin\text{-}C\ (mg/dL) - 0.931$

STATISTICAL ANALYSIS

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) Statistics version 20.0. The collected data were summarised and presented as mean values with their corresponding standard deviations (Mean±SD). Comparisons between cases and controls were performed using the Student's t-test for independent samples to assess statistical significance in continuous variables. Pearson's correlation coefficient was used to assess the relationship between renal biomarkers and estimated GFR (eGFR). A p-value <0.05 was considered statistically significant.

RESULTS

Pregnant women aged 21-28 years from Chengalpattu district, including 63 from rural and 47 from suburban areas, and their neonates were recruited [Table/Fig-1].

Parameters	Case (n=55)	Control (n=55)	p-value
Birth weight in grams, Mean±SD	2077±337	3157±300	<0.001
Gestational age in weeks, Mean±SD	34.1±1.8	39.3±0.8	<0.001
Length in cm, Mean±SD	43.2±2.8	47.8±1.8	<0.001
APGAR 1' Median (IQR)	8 (8-9)	8 (8-9)	0.34
APGAR 5' Median (IQR)	9 (8-9)	9 (9-9)	0.33
Maternal PIH, n (%)	5 (9.1%)	-	-
Maternal diabetes, n (%)	12 (21.8%)	-	-
Serum bilirubin in mg%, Mean±SD	14.01±3.4	12.7±3.5	0.07
TSH on day-3 in mIU/mL, Mean±SD	4.42±2.7	4.26±2.68	0.75

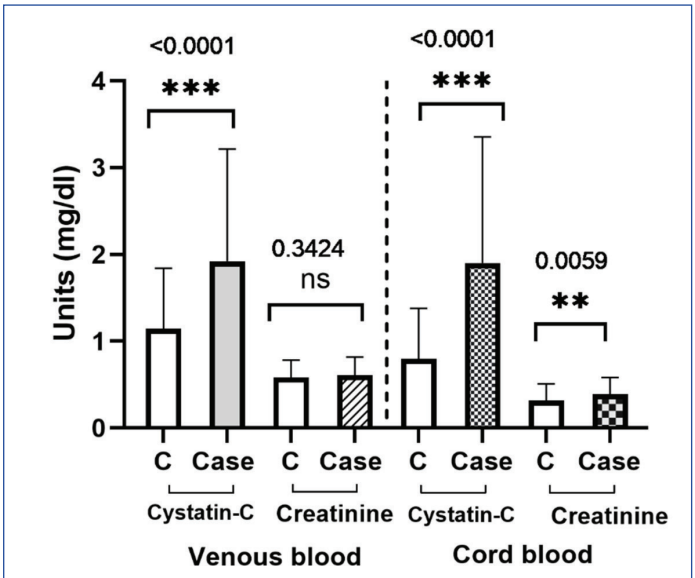
[Table/Fig-1]: Baseline characteristics of study population.
Student's t-test was applied; SD: Standard deviation; IQR: Interquartile range; PIH: Pregnancy induced hypertension; TSH: Thyroid stimulation hormone

In venous serum samples, cystatin-C levels were significantly higher in cases, with a corresponding significant reduction in cystatin-C-based eGFR (p-value - 0.0001), indicating impaired renal function. In cord blood samples, significantly higher cystatin-C (p-value-0.001), and creatinine levels (p-value- 0.006) and significantly lower eGFR values estimated from both biomarkers were compared with controls (p-value <0.01 and p-value <0.0001) [Table/Fig-2-4].

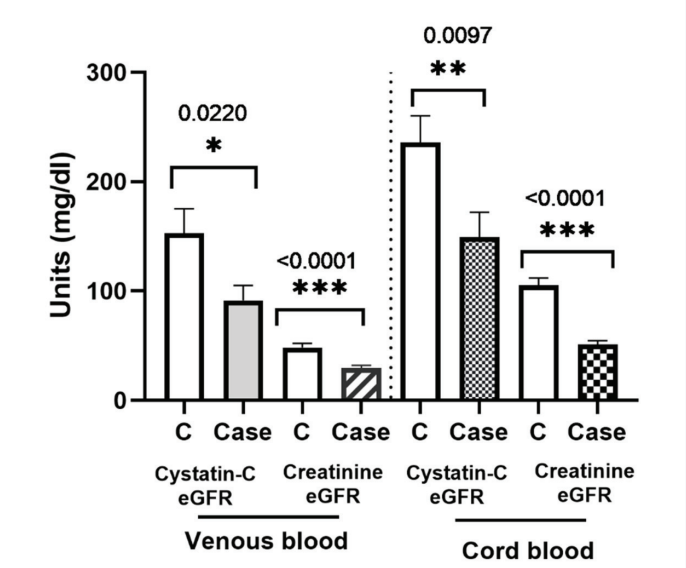
Cystatin-C levels showed a positive correlation with cystatin-C-based eGFR (r=0.4, p-value=0.0001) and with venous cystatin-C concentrations (r=0.5, p-value=0.0001) [Table/Fig-5]. The cord blood cystatin-C resulted in the highest AUC of 0.7, among

Parameters	Normal range	Case (n=55)	Control (n=55)	p-value	t value
Venous blood					
Cystatin-C (mg/dL)	0.9-2.2	1.9±0.8	1.14 ± 0.6	0.0001*	5.558
Cystatin-C-based eGFR (mL/min)	30-60	91.4±43.2	152.5±37.6	0.02*	2.307
Creatinine (mg/dL)	0.6-1.2	0.6±0.2	0.5±0.1	0.34	0.9515
Creatinine-based eGFR (mL/min)	20-40	29.7±4.1	48.3±10.6	0.0001*	4.131
Cord blood					
Cystatin-C (mg/dL)	0.9-2.2	1.9±1.4	0.7±0.5	0.0001*	7.406
Cystatin-C-based eGFR (mL/min)	30-60	149±35.4	235.7±55.3	0.01*	2.609
Creatinine (mg/dL)	0.6-1.2	0.3±0.1	0.2±0.1	0.006*	2.778
Creatinine-based eGFR (mL/min)	20-40	51±6.1	105±7.9	0.0001*	7.027

[Table/Fig-2]: Comparison between the Cystatin-C, creatinine, and eGFR in preterm and Low Birth Weight (LBW) neonates.
A t-test was used



[Table/Fig-3]: The difference in the Cystatin-C and Creatinine values between the case and control in venous blood samples of the premature neonates.



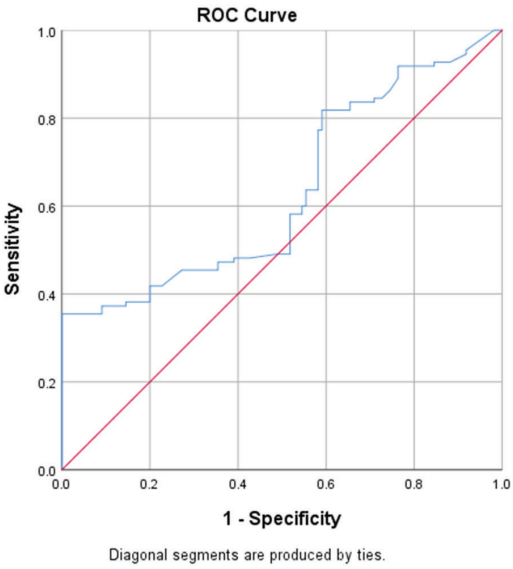
[Table/Fig-4]: The difference in eGFR estimated from Cystatin-C and Creatinine values between the case and control in cord blood samples of the premature neonates.

other studied indices, representing only a fair accuracy compared to venous cystatin-C (AUC 0.6) and serum creatinine (AUC 0.5).

The ROC was performed for cystatin-C, eGFR based on cystatin-C and creatinine, GFR based on creatinine for both venous and cord blood, to assess the sensitivity and specificity towards the estimation of GFR in premature neonates. However, in case of venous blood Cyst-C (sensitivity -47%, specificity-35%), GFR- cystatin-C

Cord \ Serum	Mean (Venous blood)	Mean (Cord blood)	r value	p-value
Cystatin-C (mg/dL)	1.9±0.8	1.9±1.4	0.5	0.0001*
Cystatin-C-based eGFR (mL/min)	91.4±43.2	149±35.4	0.4	0.0001*
Creatinine (mg/dL)	0.6±0.2	0.3±0.1	0.1	0.28
Creatinine-based eGFR (mL/min)	29.7±4.1	51±6.1	-0.05	0.5

[Table/Fig-5]: Correlation between venous blood and cord blood parameters of eGFR based on Cystatin-C and creatinine.



[Table/Fig-6]: ROC curve of serum cystatin-C showing a cut-off value of 1.51 mg/dL with 47% sensitivity and 35% specificity.

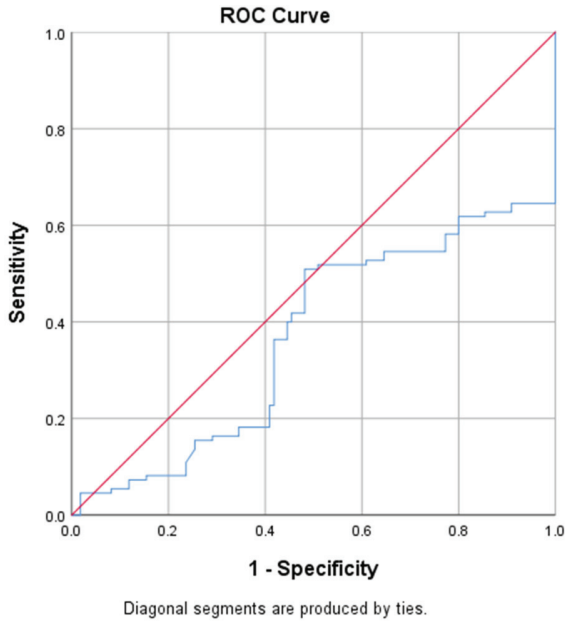
(sensitivity -51%, specificity-50%), and creatinine (sensitivity - 38%, specificity- 40%), serum creatinine GFR (sensitivity - 20%, specificity- 60%). The cut-off for serum cystatin-C was 1.51 mg/dL (AUC: 0.6; CL 95%:0.5-0.7; p-value:0.001) with 47% sensitivity and 35% specificity as indicated in [Table/Fig-6].

The cut-off for serum cystatin-C-based eGFR was 50 mL/min (AUC: 0.3; CL 95%:0.2-0.4; p-value: 0.001) with 51% sensitivity and 50% specificity as indicated in [Table/Fig-7].

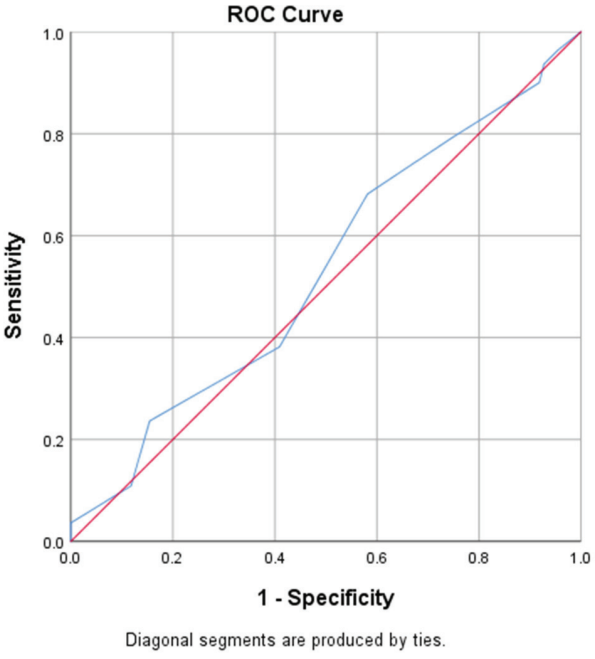
The cut-off for serum creatinine was 0.65 mg/dL (AUC: 0.5; CL 95%:0.4-0.6; p-value: 0.4) with 38% sensitivity and 40% specificity as indicated in [Table/Fig-8].

The cut-off for serum creatinine-based eGFR was 33.3 mL/min (AUC: 0.1; CL 95%:0.1-0.2; p-value: 0.0001) with 20% sensitivity and 60% specificity as indicated in [Table/Fig-9].

The cut-off for cord blood cystatin-C was 1.4 mg/dL (AUC: 0.7; CL 95%: 0.6-0.7; p-value: 0.0001) with 52% sensitivity and 15% specificity as indicated in [Table/Fig-10].



[Table/Fig-7]: ROC curve of serum cystatin-C based eGFR at a cut-off of 50 mL/min showing 51% sensitivity and 50% specificity.



[Table/Fig-8]: ROC curve of serum creatinine at a cut-off of 0.65 mg/dL showing 38% sensitivity and 40% specificity.

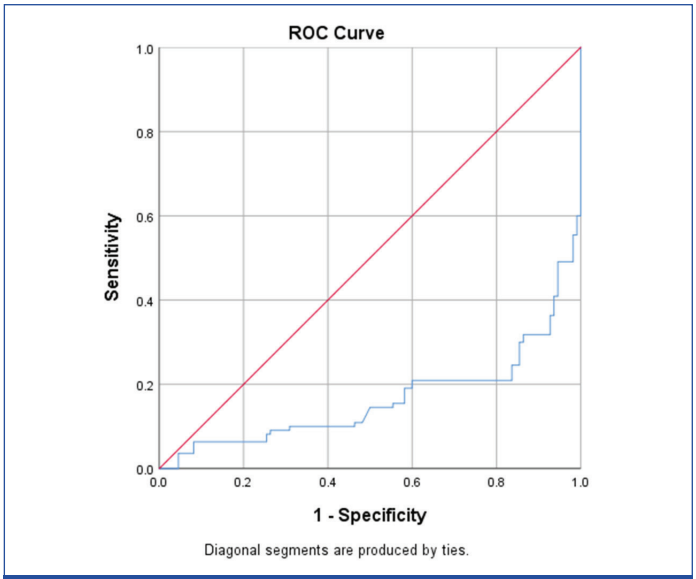
The cut-off for cord blood cystatin-C eGFR was 54 mL/min (AUC: 0.3; CL 95%: 0.2-0.3; p-value: 0.0001) with 46% sensitivity and 77% specificity as indicated in [Table/Fig-11].

The cut-off for cord blood creatinine was 0.55 mg/dL (AUC: 0.6; CL 95%:0.5-0.6; p-value: 0.004) with 22% sensitivity and 10% specificity as indicated in [Table/Fig-12].

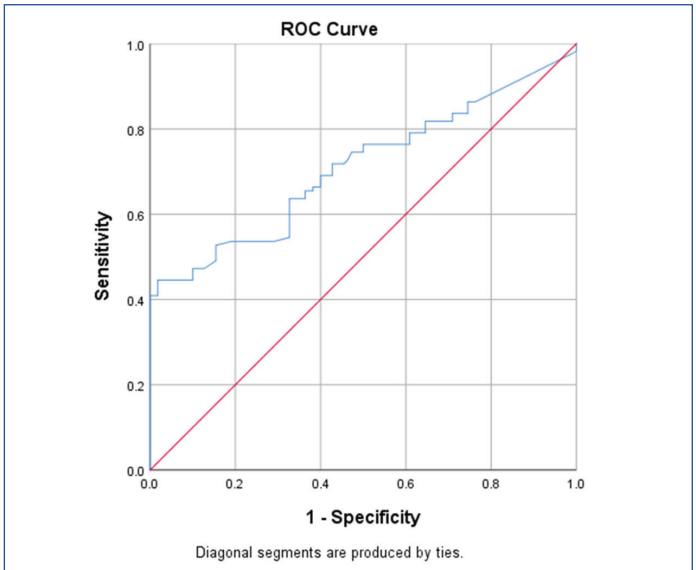
The cut-off for cord blood creatinine-based eGFR was 55.5 mL/min (AUC: 0.2; CL 95%: 0.1-0.2; p-value: 0.0001) with 27% sensitivity and 69% specificity as indicated in [Table/Fig-13].

DISCUSSION

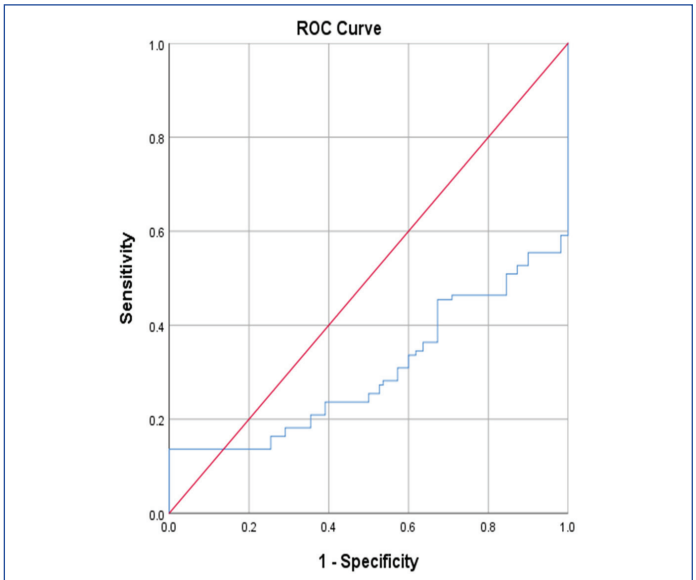
The traditional serum creatinine-based eGFR was compared to eGFR based on Cystatin-C to serve as a biomarker in premature and LBW neonates. It is important to know the early deviation in the laboratory findings is that it gives insight into renal disease. But there are certain limitations to the traditional methods for assessing GFR. These methods typically involve measuring the kidney's clearance ability for



[Table/Fig-9]: ROC curve of serum creatinine based eGFR at a cut-off of 33.3 mL/min showing 20% sensitivity and 60% specificity.

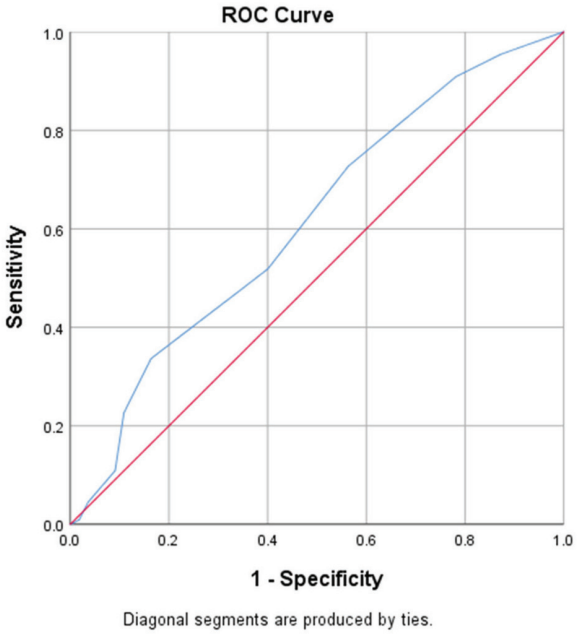


[Table/Fig-10]: ROC curve of cord blood cystatin-C at a cut-off of 1.4 mg/dL showing 52% sensitivity and 15% specificity.

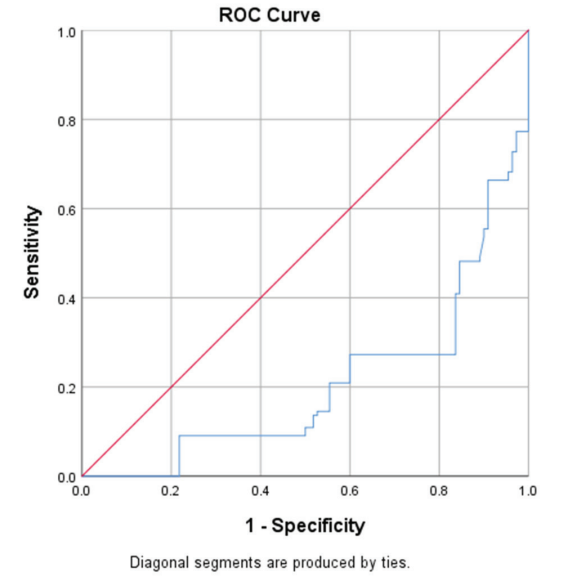


[Table/Fig-11]: ROC curve of cord blood cystatin-C based eGFR at a cut-off of 54 mL/min showing 46% sensitivity and 77% specificity.

both endogenous substances and exogenous substances such as urea and creatinine, inulin, Cr51-EDTA, 99mTc-labelled Diethylene Triamine Penta Acetic Acid, and others. The advantages of using



[Table/Fig-12]: ROC curve of cord blood creatinine at a cut-off of 0.55 mg/dL showing 22% sensitivity and 10% specificity.



[Table/Fig-13]: ROC curve of cord blood creatinine-based eGFR at a cut-off of 55.5 mL/min showing 27% sensitivity and 69% specificity.

cystatin-C as a marker are the continuous production and free filtration without any contributing factor like the muscle mass [24].

In this study of 110 neonates, the cystatin-C-based eGFR and creatinine-based eGFR were found to be lower (<90 mL/min) in LBW neonates in venous and umbilical cord blood. Although traditionally, the elevated serum levels of creatinine were considered unreliable, the concern about this is increasing as a predictor of progressive kidney disease [25].

Similar results of lower eGFR in preterm vs normal babies were noted in another study with values ranging 60.10±17.53 vs 75.89±9.1 mL/min/1.73 m^2 [20]. Although the mean serum cystatin-C was found to be 1.9±1.2, that falls well within the normal range 0.80-2.20 mg/L, a higher value of mean serum cystatin-C was observed in the LBW; a similar result was reported by Dorum S et al., in preterm neonates in Istanbul [26]. Serial measurements of Systolic Blood Pressure (SBP) in Preterm-Very LBW (PT-VLBW) reported by Wickland J et al., found that they had low eGFR (estimated by cystatin-C) at both 1-3 and 10-13 years [27]. Finney H et al., also stated that cystatin-C is a more reliable marker for continuous assessment and a predictor of GFR in infants and younger populations [28]. The preterm group was not classified based on weight and days of birth, eGFR is a dependent variable on these factors. Therefore, the mean value presented doesn't fall within the normal range in the present study.

A study that assessed whether lipocalin and cystatin-C could be used as endogenous markers of GFR in preterm infants found that it is a promising tool for detecting acute kidney injury. This review also emphasises the importance of simultaneous detection and the need for reference values in premature infants [29]. Although several studies emphasise the importance of cystatin-based GFR estimation, similar to the findings in the current study. When the newborns affected by perinatal hypoxia/asphyxia were studied for the cystatin C and creatinine levels in venous and cord blood samples. The ROC of cystatin-C from cord blood with a cut-off of 1.67 mg/L and 1.69 mg/L showed sensitivity of 82-84% and specificity of 90-94%, indicating its diagnostic reliability [30].

In this prospective cohort study of critically-ill children, the area under the ROC curve for serum cystatin at different time points ranged between 78-94% sensitivity while creatinine showed 50-69.2% only. The cut-off was 0.645 mg/L for CysC and 30 µmol/L; thus, revealing the accuracy of cystatin-C to be more accurate than creatinine [31]. Bahar A et al., showed that no significant difference was observed between cord blood and venous blood tested on day 3 (1.36±0.35 mg/L and 1.35±0.33 mg/L, respectively) [32]. Similar to the level of significance that was higher p-value <0.001 for creatinine, cystatin showed a statistical significance of p-value <0.05; the study on neonates with congenital abnormalities also reported the same [33]. In another study that was conducted in neonates using cord blood and venous blood also revealed that cystatin-C was more sensitive than creatinine in comparison with creatinine (Cr) and Schwartz's estimated clearance [34]. This indicates that cystatin can still be used as a prognostic marker in neonates. The difference between the values is because of the k value and the height of the neonates considered in the equation since the cases are preterms and the controls are normal neonates.

While correlation and ROC are measures of two different properties, such as the strength of linear association between values, and to measure the discrimination at given thresholds. In the preset study, although there was a moderate correlation between serum creatinine, eGFR, and the study variable, there was a lot of overlap between the groups, and hence poor sensitivity and specificity despite moderate correlation.

The study highlights the importance of continuous monitoring and taking preventive measures for assessment of renal function in preterm and LBW newborns, who are especially vulnerable to persistent renal complications such as CKD. Based on this stratification, the clinicians will be able to take preventive measures to better manage their treatment plan and medications.

Incorporating the measurement of cystatin-C as a standard neonatal care protocol in preterm births could drive the potential to establish an early biomarker-driven approach for the risk stratification of renal disorders. With the assessments, a comprehensive understanding of renal development and functionality could be achieved through the integration of additional biomarkers and developing a cost-effective point of care testing method.

Limitation(s)

The major limitation of this study was that it was conducted only in a single centre, while a multicentred study would have yielded reliability. A discrepancy in the results, indicating low specificity of 15%, underscores the limitations of creatinine as a standalone marker for renal function assessment in neonates, according to the limited samples studied. Additionally, the broad categorisation of preterm newborns, which may restrict the accuracy and reliability of the results, was also the limitation. If the study could have been extended as a longitudinal study, the effectiveness of the marker through different stages of growth could have been understood.

CONCLUSION(S)

This study evaluated the renal function in premature and LBW neonates in comparison to the normal-weight neonates. When cystatin-C and creatinine were used as biomarkers to predict the development of any renal problems, renal underdevelopment was seen in eGFR scores. When compared to creatinine, there was a positive correlation between cystatin-C and cystatin-C-based eGFR in cord blood. Therefore, among the studied indices, cystatin-C in cord blood could be used as a better marker than creatinine since it is a marker for renal function. However, it could be a superior marker subject to validation through gestation and age-specific assessment parameters. These considerations could expedite early detection and devise interventional strategies.

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