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Determination of glomerular filtration rate using cystatin C in healthy Nigerian newborns

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ABSTRACT

Background: The value of Cystatin C as a biomarker of Glomerular filtration rate (GFR) among African newborns is unknown, due to paucity of studies, restricting the measurement of GFR in this population of newborns to creatinine clearance despite its limitations. This study was therefore conducted to estimate GFR from serum Cystatin C in a population of Nigerian newborns and explored the relationship with anthropometrics.

Methods: This was a cross-sectional, analytical study. A total of 60 healthy preterm and 30 healthy term babies were recruited at a tertiary hospital in North-central, Nigeria. Serum Cystatin C was determined using ELISA according to standard methods. Anthropometric measurements were done with standard methods. The GFR was estimated using Zappitelli's equation. Data were analyzed using SPSS Version 20, and **p-value < 0.05** was considered significant.

Results: Mean serum Cystatin C was 1.20 ± 0.33 (range 0.80–2.20) mg/L with comparable values in males and females (1.19 ± 0.35 vs 1.15 ± 0.31 mg/L, $p = 0.481$). Mean serum Cystatin C among preterm babies were higher than term babies (1.31 ± 0.36 vs 1.01 ± 0.11 mg/L, $p = < 0.001$). Mean estimated GFR was 65.36 ± 16.9 ml/min/1.73² and was comparable in males and females (64.39 ± 17.95 vs 66.52 ± 15.76 ml/min/1.73 m², $p = 0.555$). Estimated GFR was lower among preterm than term babies (60.10 ± 17.53 vs 75.89 ± 9.1 ml/min/1.73 m², $p = < 0.001$). Serum cystatin C and estimated GFR moderately correlated with gestational age and anthropometrics (length, occipitofrontal circumference and weight).

Conclusions: Serum cystatin C as a biomarker GFR among newborns is low compared with most studies done out of Africa. The serum cystatin C and estimated GFR correlated with the gestational age and anthropometric parameters. The findings relationship between the serum Cystatin C, estimated GFR and anthropometrics among the newborns suggested a need for more studies.

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Glomerular filtration rate; cystatin C; Nigerian; newborns

1. Introduction

The best method of assessment of renal function in children, including neonates is the measurement of the glomerular filtration rate (GFR) [1]. Serum creatinine has been the leading endogenous biomarker of GFR up till recent when researchers have identified other biomarkers such as cystatin C [2]. Indeed, some nephrologists now preferred cystatin C due to many limitations associated with creatinine [3]. For instance, the serum levels of creatinine in newborns is a reflection of maternal serum value up to 72 hours after birth, making the creatinine unreliable in the first 48–72 hours of life [4]. In preterm babies, there is an increased level of serum creatinine due to back secretion into the circulation by the immature kidney tubules [5]. Furthermore, jaundice is a common clinical condition in the newborns that tends to affect serum creatinine measured with the Jaffe reaction method [5]. Also, there is significant variation in the levels of day to day creatinine [6]. In contrast, cystatin

C is a non-glycated basic protein with a molecular weight of 13.3 kDa and functions as an inhibitor of cysteine proteinase [4]. Cystatin C is produced by all nucleated cells at a constant rate and freely filtered in the glomerulus. After glomerular ultrafiltration, complete endocytosis and metabolism of cystatin C take place at the apical brush border of the proximal renal tubules [3]. Consequently, the clearance of serum cystatin C reflects GFR, while the appearance of it in the urine reflects renal tubular dysfunction [3]. Furthermore, cystatin C does not cross the placenta, thus reflecting newborns actual value at birth [6]. It is also not affected by neonatal conditions such as jaundice [5].

A recent systematic review and meta-analysis by Quix *et al* showed that serum cystatin C is superior to serum creatinine (Cr) as a biomarker of estimation GFR [7]. Similarly, the review of methods of assessment of glomerular filtration rate in the neonates by Filler and colleagues concluded that cystatin C is a more suitable

marker for the assessment of renal functions in the newborns compared with creatinine and as such called for more studies using Cystatin C [8].

Although there are studies that had estimated GFR using Cystatin C among the newborns, these were carried out predominantly among the Caucasians. From the available literature, the only African study was a recent assessment of estimated GFR using serum Cystatin C among newborns in Lagos, Nigeria, which excluded the preterm babies and relationships with anthropometrics were not explored [9]. Bearing in mind the role of racial and gender profile variation in renal profiles, direct extrapolation from the relatively few Caucasian studies may be erroneous. Hence, this study set to determine the serum Cystatin C and estimated glomerular filtration rate (eGFR) using Zappitelli's equation among healthy preterm and term babies in a population of Nigerian newborn babies and examined the relationships with anthropometrics (weight, length and occipitofrontal circumference).

2. Methods

This study was a cross-sectional, analytical study carried out between 15th January- April 30 2017 at the Post-natal ward and Neonatal Intensive Care Unit (NICU) of the University of Ilorin Teaching Hospital (UITH), Ilorin, North-Central part of Nigeria. The Post-natal ward provides routine care to all the term newborns delivered at the labor ward of the hospital before discharge home. The NICU routinely provides care for all the preterm babies delivered at the labor ward of UITH. It can manage between thirty and forty newborns at a time, with an annual admission rate of 1300–1500 newborns [10].

The minimum sample size was calculated from the formula for comparison of two independent sample means [11]. The power for the study was set at the level of 80%, while type one (α) error level was 0.05. The minimum detectable differences (d) in the mean glomerular filtration rate was 5 ml/min/1.73 m². A pooled standard deviation of 6.73 ml/min/1.73 m² from 5.7 ml/min/1.73 m² and 9.22 ml/min/1.73 m² earlier reported by Adedoyin et al [12] among preterm and term babies respectively in UITH, was used to estimate the minimum sample size of 30 per group.

For the preterm babies, two subgroups of 28–33 weeks and 34–36 weeks gestations had a sample size of 30 each. For each recruited baby, the assessment of the gestational age (GA) was by both the mother's last menstrual date and the new Ballard score [13]. However, in a situation where the mother was unsure of her date, the new Ballard score was used for the gestational age assessment. The classification of the newborns was further done according to weight and GA using Lubchenco chart [14].

The study consecutively recruited healthy newborns (delivered with Apgar score of 7 and above, with stable vital signs at delivery and time of recruitment); appropriate for gestational age as assessed by Lubchenco chart and less than or equal to 24 hours. However, excluded were newborns with abnormal renal functions. Also, the study excluded newborns delivered outside the Hospital's labor ward; parents or caregivers declined consent; congenital malformations or features suggestive of chromosomal abnormalities; babies that were sick; babies delivered to mother with a history of fever, chorioamnionitis, diabetes, pregnancy-induced hypertension, or thyrotoxicosis, history suggestive of receiving nephrotoxic drugs within 24 hours before delivery (example: gentamycin) and history of renal failure.

A pre-tested semi-structured proforma was used to obtain relevant information while a general physical examination including anthropometric measurements (occipitofrontal circumference, weight and length) and systemic examinations were done at the recruitment in a well illuminated and warm environment by the principal investigator.

Each of the recruited newborns had 1.5 ml of venous blood sample collected for the determination of serum cystatin C. From each sample; serum was harvested after centrifuged at 3000 rpm for 15 minutes, transferred into a cryovial bottle and frozen at –70°C for subsequent batch analysis.

The serum cystatin C was analyzed using Human cystatin C Enzyme-Linked ImmunoSorbent Assay (ELISA) kit (SL057Hu), SunLong Biotech Co Ltd., China. The sensitivity of the assay kit was 0.05 ng/ml with a limit of detection of 0.3 ng/ml. The Kit also has intra-assay and inter-assay coefficient of variation of <10% and <12% respectively and used principle of Sandwich-ELISA to assay the concentration of cystatin C. A set of standards (serial dilution of standard of 27 ng/ml provided to obtain concentrations of 18 ng/ml, 12 ng/ml, 6 ng/ml, 3 ng/ml and 1.5 ng/ml) was used to generate a standard curve with a coefficient of variation of R² = 0.9928. The study determined the concentration of Cys-C in the samples by comparing the optical density (OD) of the samples to the standard curve earlier generated.

Ethical approval was obtained from the Ethical Review Committee of the University of Ilorin Teaching Hospital (NHREC/02/05/2010), while parents/caregivers gave written informed consent.

3. Data analysis

The information from the study proforma was entered into an excel spreadsheet and subsequently exported into SPSS version 20 for analysis. Logarithm transformation of cystatin C and estimated GFR were carried out before

the analysis due to non-normal distribution. Mean was used to summarize continuous variables (normal distribution) while Student's t-test and analysis of variance (ANOVA) with post hoc (Tukey-Kramer) where applicable, was used to compare two means and more than two means respectively. The GFR was estimated using the Zappitelli's equation ($eGFR = 75.94 \times Cys^{-1.17}$) [15], which have been found to have a better accuracy compared with the Filler's formula [16]. Furthermore, compared with the eGFR obtained from the Zappitelli's equations were other cystatin based equations (Filler's equation [17], Chronic Kidney Disease in Children (CKiD) equation [18] and Grubb's equation [19]). Pearson's correlation statistics were used to assess the relationship between cystatin C, GFR and anthropometric parameters. For all the statistical tests, significant value for *p*-value was less than 0.05.

4. Results

This study involved a total of 90 healthy newborns; males were 42 (47%), while females were 48 (53%). The mean age at recruitment was 5.6 ± 0.9 hours. The mean weight was 2347.11 ± 717.8 gram. The mean length was $45.51 \text{ cm} \pm 4.5 \text{ cm}$, while the mean occipitofrontal circumference was $32.34 \pm 3.0 \text{ cm}$. The birth weight, length and occipitofrontal circumference were significantly higher among term babies compared with preterm babies, $p < 0.001$ (Table 1)

The overall mean serum cystatin C was 1.20 ± 0.33 (range 0.80–2.20) mg/L. The mean serum cystatin C in males was 1.19 ± 0.35 mg/L, which was not different from that of females, 1.15 ± 0.31 mg/L, ($p = 0.481$). The mean serum Cystatin C among preterm babies were significantly higher than term babies (1.31 ± 0.36 vs 1.01 ± 0.11 mg/L, $p = < 0.001$). Furthermore, the mean serum Cystatin C among gestational age (28–33 weeks) were significantly higher compared to late preterm babies (34–36 weeks) and term babies (37–42 weeks) as shown in Table 1.

The overall mean Cystatin C based GFR was $65.36 \pm 16.9 \text{ ml/min/1.73}^2$. The mean estimated GFR in males was $64.39 \pm 17.95 \text{ ml/min/1.73 m}^2$, which was comparable to that of females $66.52 \pm 15.76 \text{ ml/min/1.73 m}^2$ ($p = 0.555$). The estimated GFR was lower among very preterm babies compared with term babies, (60.10 ± 17.53 vs $75.89 \pm 9.1 \text{ ml/min/1.73 m}^2$, $p = < 0.001$) Furthermore, the mean estimated GFR

was lower among very preterm babies (28–33 weeks) compared with late preterm (34–36 weeks) and term babies as shown in Table 1.

The overall mean eGFR from Zappitelli's equation was comparable with eGFR obtained using CKiD equation (65.36 ± 16.9 vs $63.76 \pm 13.7 \text{ ml/min/1.73 m}^2$, $p = 0.486$). However, the values from eGFR using the Filler's and Grubb's equations were higher compared with values obtained from Zappitelli's formula (82.14 ± 20.9 vs $65.36 \pm 16.9 \text{ ml/min/1.73 m}^2$; $p = < 0.001$ and 101.97 ± 37.2 vs $65.36 \pm 16.9 \text{ ml/min/1.73 m}^2$; $p = < 0.001$ respectively). Based on the gestation categories, the values of eGFR obtained using Zappitelli's equation, and CKiD equation was comparable among the preterm babies. In contrast, the eGFR from Zappitelli's equation was higher than the values obtained using CKiD equation (67.33 ± 12.7 vs $75.89 \pm 9.06 \text{ ml/min/1.73 m}^2$, $p = 0.004$) in the term babies as shown in Table 2.

The serum cystatin C and eGFR correlated with gestational age and anthropometrics. In term of strength, both were moderately correlated (cystatin C and GFR) with gestational age with a coefficient of -0.688 and 0.631 , respectively ($p < 0.001$) as shown in Table 3. The serum Cystatin C was moderately (negative) correlated with birth weight, length and occipitofrontal circumference with $r = -0.592$, -0.580 and -0.607 respectively). The eGFR was moderately (positive) with birth weight, length and occipitofrontal circumference with $r = 0.560$, 0.583 and 0.570 respectively) as shown in Table 3.

5. Discussion

This current study assessed both the serum Cystatin C and estimated the GFR among neonates delivered at a tertiary health facility in Nigeria, and it involved both preterm and term babies compared with the earlier study that excluded the preterm infants. Although the mean serum Cystatin C (1.20 ± 0.33 (range 0.80–2.20) mg/L obtained fall within the reported reference range, it is low compared to the values of $1.54 \pm 0.28 \text{ mg/l}$ at birth in Spain [20] and $1.96 \pm 0.44 \text{ mg/l}$ among Chinese newborns [21]. However, similar to the value obtained in this study is $1.27 \pm 0.30 \text{ mg/l}$ in Turkey [22]. The differences in the values of serum cystatin C in this study compared with others studies may be due to a number of reasons; this study recruited apparently healthy newborns compared with the study in Spain that included babies

Table 1. General characteristics, serum cystatin C and estimated GFR among the newborns.

Variable	28-33 weeks	34-36 weeks	37-42 weeks	F	P
Gender (M:F)	30 (14:16)	30 (16:14)	30 (12:18)		
Age (Hours)	2.04 ± 0.4^a	5.07 ± 0.6^b	16.48 ± 0.2^c	35.907	<0.001
Birth Weight (Kg)*	1600.00 ± 314.5^a	2385.7 ± 498.4^b	3055.67 ± 368.4^c	98.921	<0.001
Length (cm)*	41.28 ± 3.3^a	46.39 ± 3.0^b	48.87 ± 3.3^c	43.396	<0.001
OFC (cm)*	29.37 ± 2.2^a	32.96 ± 2.1^b	34.7 ± 1.7^c	54.755	<0.001
Serum Cystatin C (mg/L)*	1.46 ± 0.38^a	1.10 ± 0.19^b	1.0 ± 0.11^b	31.178	0.001
Estimated GFR (ml/min/1.73 m ²)*	51.00 ± 15.90^a	69.19 ± 14.21^b	75.89 ± 9.06^b	27.816	< 0.001

OFC- occipitofrontal circumference; Tukey-Kramer showed that data with similar alphabets were not significantly different from each other (a, b, c); * Mean $\pm$ SD

Table 2. Comparison of estimated GFR (eGFR) using different cystatin-based equations.

Gestational age	GFR Mean $\pm$ SD (Zappitelli's equation.) ml/min/1.73m ²	GFR Mean $\pm$ SD (Filler's equation.) ml/min/1.73m ²	Zappitelli's equation vs Filler's equation. <i>p</i>	GFR Mean $\pm$ SD CKiD* equation.) ml/min/1.73m ²	Zappitelli's equation vs CKiD* equation <i>p</i>	GFR Mean $\pm$ SD (Grubb's equation.) ml/min/1.73m ²	Zappitelli's Equation vs Grubb's equation <i>P</i>
28-33 weeks (n = 30)	51.00 $\pm$ 15.9	70.27 $\pm$ 21.0	<0.001	55.95 $\pm$ 14.0	0.205	81.35 $\pm$ 35.7	<0.001
34-36 weeks (n = 30)	69.19 $\pm$ 14.2	88.54 $\pm$ 17.4	<0.001	67.99 $\pm$ 11.1	0.719	112.90 $\pm$ 33.0	<0.001
37-42 weeks (n = 30)	75.89 $\pm$ 9.1	87.62 $\pm$ 19.5	0.005	67.33 $\pm$ 12.7	0.004	111.65 $\pm$ 35.0	<0.001
28-42 weeks (n = 90)	65.36 $\pm$ 16.9	82.14 $\pm$ 20.9	<0.001	63.76 $\pm$ 13.7	0.486	101.97 $\pm$ 37.2	<0.001

Zappitelli's equation eGFR = $75.94/(\text{cystatin C})^{1.17}$ Filler's equation eGFR = $91.62 \times (\text{cystatin C})^{-1.123}$ *Chronic Kidney Disease in Children (CKiD) equation eGFR = $70.69 \times \text{cystatin C (mg/L)}^{-0.931}$ Grubb's equation eGFR = $84.69 \times (\text{cystatin C})^{-1.680} \times 1.384$ **Table 3.** The correlation between serum cystatin C, gestational age, anthropometric parameters and GFR.

Variable	Serum Cystatin C mg/L		Estimated GFR ml/min/1.73 m ²	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Gestational age	-0.688	<0.001	0.631	<0.001
Birth weight	-0.592	<0.001	0.560	<0.001
Length	-0.580	<0.001	0.583	<0.001
OFC	-0.607	<0.001	0.570	<0.001

r - Pearson's correlation coefficient. OFC-Occipitofrontal circumference.

with different pathologies. Also, the present study comprises of AGA term and preterm babies compared with the Chinese that involved preterms and very low birth weight babies. The differences may also partly due to the differences in the methods of assays for the determination of cystatin C. The three methods [Enzyme linked immunosorbent assay (ELISA), particle-enhanced nephelometric immunoassay (PENIA) and particle-enhanced turbidimetric immunoassay (PETIA)] of determination of serum cystatin C tend to give slight variation in results. The current study used the ELISA technique, while the other studies used the PENIA method. Besides, the possibility of racial difference in Cystatin C level may also partly account for the observed differences. Köttgen et al [23] in the United States of America demonstrated the existence of variation in the values of Cystatin C obtained among the major ethnic groups, (lower value of mean serum Cystatin C among non-Hispanic black and Mexican American individuals compared with their white counterparts). Also, studies among adult Ivoirians [24] and Nigerians [25] have also reported variations in the values of Cystatin C compared with the Caucasian values.

The values of mean serum Cystatin C was higher among preterms (28–33 weeks) compared with the term neonates. This finding is similar to the observation by Dorum et al [22]. On the contrary, Bahar et al [26] reported no differences in the values of serum Cystatin C between preterm and term babies. It is worthy of note that work of Bahar et al [26] has a relatively small number of preterm babies which could account for the inability to detect the differences between the preterm and term babies. This present study also did not find any difference in the mean serum level of Cystatin C between males and females babies and affirmed the findings of previous studies that Cystatin C is independent of genders [22,26].

The mean GFR from this present study is similar to values (61.17 ± 30.45 ml/min/1.73 m²) documented in Turkey [22]. The similarities in Turkey and present studies could be because preterm babies constitute a larger part of both works. In contrast, the mean GFR is higher compared with values (52.72 ± 8.39 ml/min/1.73 m²) among term babies reported from Slovenia [27]. The differences with respect to the above study could be due to the

differences in the study population and methods of determination of serum cystatin C. The mean GFR (61.17 ± 30.45 ml/min/1.73 m²) is higher than the value from the Nigeria study 38.18 (31.84–61.34) ml/min/1.73 m² [9]. Although both the present study and earlier Nigeria study used ELISA, no explanation could be offered for the higher values obtained in this work. This observation further raised the issue of the need for standardization in Cystatin C assay methods as suggested by Yata et al [28].

The eGFR derived from Zappitelli's formula was similar to the values obtained with the CKiD equation. This finding is similar to the observation by Abitbol et al [29] in the United States, who validated both Zappitelli's and CKiD equations in a group of preterm and term babies. Both Grubb and Filler's had higher values for the eGFR in the newborns. It is worthy of note that the only Nigerian study also observed higher values for Filler's equation. A validation study by Deng et al [21] in China among Pediatric patients showed that the Grubb's formula had a significant bias with the tendency for overestimation of eGFR and could have accounted for the high value in this study. The finding of higher values for eGFR using the Filler's and Grubb's equations further raised the issue of overestimation of glomerular filtration and may be inappropriate in the newborns.

This study showed that serum Cystatin C declined with increasing gestational age, which is consistent with the finding of Dorum et al [22]. In contrast, studies from Italy [30], and Slovenia [31] found no significant correlation between the gestational age and serum cystatin, although both studies excluded preterm babies that were less than 34 weeks. This present study also found a negative correlation between the anthropometric parameters and serum Cystatin C. This suggested that Cystatin C may not be independent of anthropometric indices as earlier documented by some researchers [21,22]. In keeping with this finding is a recent study that involved a large cohort of children (4,305 children) in the Netherlands that demonstrated the influence of body composition on both the value of serum Cystatin C and estimated GFR [32].

The present study also showed a moderate positive correlation of GFR with gestational age and anthropometric parameters. Whereas studies with inulin [33] and serum creatinine [34] demonstrated the correlation between gestational age and GFR, most studies done using Cystatin C have reported contrary findings [35,36]. This finding also suggested the need to consider a new formula for estimate GFR in the newborns that will incorporate anthropometric indices. Indeed, in support of the observation of the influence of anthropometrics on the GFR found in this study, is the demonstration of the reliability of Cystatin C based formula that incorporates the kidney volume and body surface areas for determining GFR among

newborns [27]. Hence, the observation of a positive correlation between GFR and anthropometric parameters in this study calls for further studies.

6. Conclusion

In conclusion, the values of serum cystatin C and eGFR appeared low compared with most studies done out of Africa. The Zappitelli's equation and CKiD formula had similar values for eGFR. Also, both the serum cystatin C and estimated GFR correlated with the gestational age and anthropometric parameters. The findings from this study also suggest a possible relationship between the serum Cystatin C, estimated GFR and anthropometrics among the newborns and the need for more studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

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