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Original Article

Glomerular Filtration Rate Estimation Based on Cystatin C Formulas among Neonates

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ABSTRACT

Background: Glomerular filtration rate (GFR) is the best indicator to assess renal function; however, it is difficult to perform it, especially in neonates. Serum creatinine is the most commonly used marker of GFR; nevertheless, it has some limitations since it can be affected by factors other than renal function. Cystatin C, another endogenous marker used to estimate GFR, is not affected by non-renal factors. The results of some studies suggest that serum cystatin C levels are more accurate tests of kidney function than serum creatinine levels. This study aimed to estimate GFR with cystatin C-based formulas among neonates and determine the correlations between these methods and the Schwartz formula.

Methods: The population of this research consisted of 99 neonates whose serum creatinine and cystatin C levels were measured concurrently. Moreover, the glomerular filtration rate was estimated using the Schwartz formula and 14 cystatin C-based formulas separately.

Results: Based on the findings, all GFR values based on cystatin C formulas correlated significantly with each other ($P<0.05$); however, with one exception, none of these values correlated with Schwartz GFR ($P>0.05$). The only cystatin C formula that yielded values correlating with the Schwartz formula was CysCrEq, which used serum cystatin C and creatinine concomitantly.

Conclusion: It can be concluded that since all GFR values based on cystatin C correlated significantly and cystatin Cwasindependent of non-renal factors, cystatin C reflected the real GFR more accurately than serum creatinine. Nonetheless, further studies with gold standard techniques are required to verify the usefulness of cystatin C-based formulas.

Keywords: Creatinine, Glomerular filtration rate, Neonates, Schwartz formula

Introduction

Glomerular filtration rate (GFR) is measured by various methods (1). Although inulin clearance is the gold standard assay for GFR measurement in both mature and immature kidneys (2, 3), it is time-consuming, expensive, and cumbersome (2). Nuclear medicine scans are also considered accurate methods for GFR measurement; however, most clinicians do not recommend these scans in neonates (2). Serum creatinine is the most common renal marker for GFR estimation; nevertheless, serum creatinine in neonates reflects the maternal serum creatinine level rather than neonatal values in the first week after birth (1, 2, 4). In addition, serum creatinine level can be affected by factors other than renal function, such as birth weight, muscle mass, and renal tubule maturity, as well as the laboratory method of creatinine measurement (1, 5-7). Therefore, it is recommended to use more stable markers for GFR in neonates that are not affected by non-renal factors and do not pass through the placenta (8). Cystatin C is a potentially suitable factor that has been reported as a suitable marker for GFR estimation in children and adults (4, 9-13).

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Accordingly, the present study was designed to measure serum cystatin C levels among neonates and compare the GFR estimated with cystatin C-based formulas and the Schwartz formula.

Methods

The serum samples for this analytical cross-sectional study were obtained from 99 hospitalized neonates admitted to the neonatal department at Ali-AsgharChildren'sHospital in Tehran, Iran, from March-June 2018. The sample size was estimated using previous articles and a convenience sampling method was used to select the samples. The exclusion criteria were any structural abnormalities or neonatal syndromes. Informed consent was obtained from the parents of all neonates. Serum creatinine and cystatin C levels were measured in these neonates concurrently. The Jaffe reaction method was applied to measure the serum creatinine. To estimate GFR, the Schwartz formula (GFR=k×height/serum creatinine) was used, with a value of 0.41 and 14 different cystatin C-based formulas (Table 1).

The collected data were analyzed in SPSS software (version 13.0) using mean ± standard deviation for descriptive statistics and Spearman's rank correlation for the evaluation of the relationships between quantitative variables. All p-values were two-tailed, and P<0.05 was considered significant.

Table 1. Glomerular filtration rate formulas based on serum cystatin C level

Filler et al. (4)	GFR = 91.62 × (1/CysC)1.123
Le Bricon et al. (24)	GFR = [78 × (1/Cystatin C)] + 4
Hoek et al. (25)	GFR = 4.32 + (80.35 × 1/Cystatin C)
Larsson et al. (26)	GFR = 77.24 × Cystatin C-1.2623
Rule et al. (27)	GFR = 76.6 × Cystatin C-1.16
Bokenkamp et al. (1)	GFR = 137/cys C – 20.4
Larsson et al.2 (26)	GFR = 99.43 × cys C-1.2623
Grubb et al. (28)	GFR = 84.69× cys C-1.680×1.384
Bouvet et al. (29)	GFR = 63.2×((cr/96)-0.35)((cysC/1.2)-0.56)((BW/45)×0.30)((age/14)×0.40)
Zappitelli (New Bokenkamp) (30)	GFR =78.77/CysC +1.84
Zappitelli (New Filler) (30)	GFR = 79.04 × (1/CysC)1.156
Zappitelli (New Grubb) (30)	GFR = 79.2 × (1/CysC)1.157 × 1.002 for age of < 14 years
Zappitelli (CysEq) (11, 30)	GFR =75.94/[CysC1.17]
Zappitelli (CysCrEq) (30)	GFR = (43.82 × e0.003 × height)/(CysC0.635 ×SCr0.547 [mg/dL])

Results

In this research, 47 (47.47%) out of 99 neonates were female. The mean scores of age, birth weight, and height of all cases were estimated at 3.7±5.72 days, 2.569±704.30 g, and 46.9±4.05 cm, respectively. It was reported that 8(08.08%), 33 (33.33%), 58 (58.58%) of the subjects had respectively a bodyweight of < 1,500 g, 1,500-2,500 g, and >2,500 g. Based on the results, the mean scores of serum creatinine and serum cystatin C concentrations were obtained at 0.56 mg/dl (0.20-1.56 mg/dl) and 2.11 mg/l (0.75-22.00 mg/l) respectively. The information regarding the mean serum creatinine and cystatin C levels according to birth weight is summarized in Table 2.

Glomerular filtration rate was estimated separately using the Schwartz formula and 14 cystatin C-based formulas. Table 3 tabulates mean GFR and the ranges estimated with these equations. The correlation of GFR estimated was determined with the Schwartz formula and the cystatin C-based formulas. The correlation of GFR estimated with the Bouvet equation and other cystatin C formulas was significant; however, it

Table 2. Reference ranges of cystatin C levels in preterm and term neonates

Birth weight	Mean serum creatinine (Range)	Mean serum cystatin
<1,500 g	0.62±0.52 (0.3-1.9)	1.68±0.32
1,500–2,500 g	0.53±0.27 (0.2-1.57)	1.9±0.72
>2,500 g	0.67±0.65 (0.3-5.2)	2.27±2.7

Table 3. Mean and range of serum creatinine, cystatin C, and glomerular filtration rate based on Schwartz and cystatin C-based formulas

	Minimum	Maximum	Mean	Standard deviation
Creatinine	0.20	1.57	0.5637	0.26168
Cystatin C	0.75	22.00	2.1108	2.15701
Filler	2.85	126.56	51.87	23.7
Larsson	1.56	111.06	41.2996	21.39761
Larsson2	0.74	156.81	47.0969	31.39523
Bouvet	1.13	734.73	45.3	86.23270
Grubb	0.65	190.05	53.6958	38.28807
Rule	2.12	106.94	42.7024	20.19750
Hoek	7.97	111.45	52.2801	19.39648
Le Bricon	7.55	108.00	50.5574	18.82919
Bokenkamp	-14.17	162.27	61.3740	33.07178
New Filler	2.22	110.22	44.1360	20.79859
New Bokencamp	5.42	106.87	48.8571	19.01506
New Grubb	2.22	110.70	44.2954	20.89300
CysEq	2.04	106.33	42.1594	20.12469
CysCrEq	11.76	97.57	52.4884	17.16833

Table 4. Correlations between glomerular filtration rates calculated with the Schwartz and cystatin C-based formulas

		Schwartz	Bokencamp	Filler	Larsson	Larsson2	Grubb	Bouvet	LeBricon	Hoek	Rule	New Filler	New Bokencamp	CysEq	New Grubb	CysCrEq
Schwartz	Pearson correlation	1	0.057	0.050	0.042	0.026	0.021	-0.130	0.057	0.057	0.048	0.048	0.057	0.047	0.048	0.620
	P-value		0.582	0.600	0.680	0.801	0.836	0.204	0.582	0.582	0.641	0.640	0.582	0.645	0.640	0.000
Bokenkamp	Pearson correlation	0.057	1	0.990	0.997	0.988	0.985	0.276	1.000	1.000	0.999	0.999	1.000	0.999	0.999	0.794
	P-value	0.582		0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Filler	Pearson correlation	0.090	0.904	1	0.872	0.835	0.824	0.315	0.904	0.904	0.884	0.885	0.904	0.883	0.884	0.793
	P-value	0.382	0.000		0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Larsson	Pearson correlation	0.042	0.997	0.990	1	0.997	0.995	0.264	0.997	0.997	1.000	1.000	0.997	1.000	1.000	0.774
	P-value	0.680	0.000	0.000		0.000	0.000	0.009	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Larsson2	Pearson correlation	0.026	0.988	0.990	0.997	1	1.000	0.250	0.988	0.988	0.994	0.994	0.988	0.995	0.994	0.749
	P-value	0.801	0.000	0.000	0.000		0.000	0.013	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Grubb	Pearson correlation	0.021	0.985	0.990	0.995	1.000	1	0.247	0.985	0.985	0.992	0.992	0.985	0.992	0.992	0.742
	P-value	0.836	0.000	0.000	0.000	0.000		0.014	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Bouvet	Pearson correlation	-0.130	0.276	0.270	0.264	0.250	0.247	1	0.276	0.276	0.268	0.268	0.276	0.268	0.268	0.182
	P-value	0.204	0.006	0.007	0.009	0.013	0.014		0.006	0.006	0.008	0.008	0.006	0.008	0.008	0.075
Le Bricon	Pearson correlation	0.057	1.000	0.990	0.997	0.988	0.985	0.276	1	1.000	0.999	0.999	1.000	0.999	0.999	0.794
	P-value	0.582	0.000	0.000	0.000	0.000	0.000	0.006		0.000	0.000	0.000	0.000	0.000	0.000	0.000
Hoek	Pearson correlation	0.057	1.000	1.000	0.997	0.988	0.985	0.276	1.000	1	0.999	0.999	1.000	0.999	0.999	0.794
	P-value	0.582	0.000	0.000	0.000	0.000	0.000	0.006	0.000		0.000	0.000	0.000	0.000	0.000	0.000
Rule	Pearson correlation	0.048	0.999	0.884	1.000	0.994	0.992	0.268	0.999	0.999	1	1.000	0.999	1.000	1.000	0.782
	P-value	0.641	0.000	0.000	0.000	0.000	0.000	0.008	0.000	0.000		0.000	0.000	0.000	0.000	0.000
New Filler	Pearson correlation	0.048	0.999	0.885	1.000	0.994	0.992	0.268	0.999	0.999	1.000	1	0.999	1.000	1.000	0.782
	P-value	0.640	0.000	0.000	0.000	0.000	0.000	0.008	0.000	0.000	0.000		0.000	0.000	0.000	0.000
New Bokencamp	Pearson correlation	0.057	1.000	0.904	0.997	0.988	0.985	0.276	1.000	1.000	0.999	0.999	1	0.999	0.999	0.794
	P-value	0.582	0.000	0.000	0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000		0.000	0.000	0.000
CysEq	Pearson correlation	0.047	0.999	0.883	1.000	0.995	0.992	0.268	0.999	0.999	1.000	1.000	0.999	1	1.000	0.781
	P-value	0.645	0.000	0.000	0.000	0.000	0.000	0.008	0.000	0.000	0.000	0.000	0.000		0.000	0.000
New Grubb	Pearson correlation	0.048	0.999	0.884	1.000	0.994	0.992	0.268	0.999	0.999	1.000	1.000	0.999	1.000	1	0.782
	P-value	0.640	0.000	0.000	0.000	0.000	0.000	0.008	0.000	0.000	0.000	0.000	0.000	0.000		0.000
CysCrEq	Pearson correlation	0.620	0.794	0.793	0.774	0.749	0.742	0.182	0.794	0.794	0.782	0.782	0.794	0.781	0.782	1
	P-value	0.000	0.000	0.000	0.000	0.000	0.000	0.075	0.000	0.000	0.000	0.000	0.000	0.000	0.000	

was not strong ($r<0.5$). It was revealed theGFR estimates had strong correlations with other cystatin C formulas ($r>0.7$). Among GFR values from cystatin C-based formulas, none of them, except one, correlated with the Schwartz GFR ($P>0.05$). The only cystatin C formula to yield a value that correlated with GFR obtained with the Schwartz formula was CysCrEq, which uses serum cystatin C and creatinine concomitantly. Table 4 summarizes the correlation coefficients for all formulas.

Discussion

Cystatin C is produced by all nucleated cells in the body and its free form is filtered by glomeruli and completely catabolized by proximal tubular cells (10). Therefore, its serum level reflects kidney function (14). The results of studies have shown cystatin Cto as a sensitive and specific marker of renal function among adults and children(6, 15, 16). To the best of our knowledge, few studies have investigated the reference values for cystatin C in neonates, particularly preterm newborns (2, 3), and to date, cystatin C-based formulas have not been used to estimate GFR.

Cystatin C as a GFR marker in neonates has some advantages (17, 18), including its independence from gestational age, gender, muscle mass, nutrition, hydration status, and maternal serum cystatin C level (15, 19, 20). Furthermore, it does not pass through the placenta, and there is no interference of laboratory values with serum cystatin, bilirubin, hemoglobin, and ketone (1, 8). On the other hand, there are some limitations in using cystatin C as a neonatal GFR marker. For instance, it is an expensive test, it is still unclear how immature kidneys handle it, and few studies have compared GFR estimated with cystatin C against gold standard tests. Giovanni et al. measured inulin clearance in 20 preterm neonates and found a significant relationship between reciprocal cystatin C and inulin clearance (3). Moreover, the findings of some studies have shown that thyroid function and corticosteroid therapy affect serum cystatin values (5, 21).

The results of some previous studies reported the range of serum cystatin C values among

Table 5. Reference values of cystatin C in neonates in different studies

Study	Sample size	Serum cystatin C Mean	Serum cystatin C Range	Neonate age	Gestational age
Ibrahim (11)	90	1.20 mg/l	0.80–2.20 mg/l	5.6 hours	Term
Armangil (31)	108	1.8 mg/l	1.1–2.3 mg/l	First day of life	32.5±2.6 week
Armangil (31)	108	1.65 mg/l	1.0–2.1 mg/l	Third day of life	32.5±2.6 week
Bokenkamp (32)	23	2.16	1.64–2.59 mg/l	0-3 days	Term
Bokenkamp (32)	14	2.02	1.52–2.40 mg/l	3-30 days	Term
Harmoinen (20)	58	1.88 mg/l	1.07–2.86 mg/l	0-7 days	<37 week
Harmoinen (20)	50	1.70 mg/l	1.24–2.32 mg/l	0-7 days	>37 week
Bahar (33)	14	1.49 mg/l	0.98–2.30 mg/l	Third day of life	<37 week
Bahar (33)	84	1.32 mg/l	0.78–2.40 mg/l	Third day of life	≥37 week
Finney (19)	16	1.48 mg/l	0.65–3.37 mg/l	First day of life	24–28 week
Finney (19)	14	1.65 mg/l	0.62–4.42 mg/l	First day of life	29–38 week
Finney (19)	50	1.37 mg/l	0.81–2.32 mg/l	0-3 months	Term
Treiber (22)	75	1.97 mg/l	1.38–3.23 mg/l	Umbilical cord	34–41 week
Treiber (22)	75	1.93 mg/l	1.28–2.66 mg/l	Third day of life	34–41 week

healthy term and preterm neonates(22, 23). The reference ranges published to date are shown in Table 5. To the best of our knowledge, few studies have focused on GFR estimation with cystatin C-based formulas in neonates. The difficulty in establishing a reliable GFR formula for neonates can be attributed to the very large dispersion in serum cystatin C concentrations found thus far(13). In the present study,14 different cystatin C-based formulas available for children and adults were used to estimate GFR. According to the results of the present research, most estimated GFR values with these formulas had a highly significant correlation in neonates. The main finding of our study, however, is the absence of any correlation between GFR based on the Schwartz formula and equations that use cystatin Clevel. If in this study, it was possible to measure GFR with a gold standard test, the researchers could search for significant correlations between measured GFR and cystatin C-based GFR. Due to the fact that serum creatinine reflects maternal values in the first week after birth, whereas cystatin Codes do not pass through the placenta, and consequently, is not affected by this confounding factor, cystatin C-based equations are likely to reflect neonatal GFR more accurately than the Schwartz equation (10, 11, 22-36). It is suggested to perform further studies with gold standard tests to determine the accuracy of cystatin C as a GFR marker in neonates.

According to the results of a study performed by Kandasamy et al., serum cystatin C was not significantly associated with neonatal birth weight; nevertheless, serum creatinine was associated with this parameter. However, it was reported that measuring GFR based on serum creatinine could delay the diagnosis of acute kidney damage among newborns with lower birth weights(6). According to El-Gammacy et al., acute kidney injury can be predicted by measuring cystatin C in infants on day 3 after birth (12).

Conclusion

The results of this study showed significant correlations amongGFR values calculated with all cystatin C-based formulas. Since cystatin C levels are independent of non-renal factors, this marker may reflect the real GFR more accurately than serum creatinine. However, it is recommended that this marker be compared against gold standard techniques to determine whether it is a better marker to measure GFR.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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