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Brief Report

First Report on the Percentiles of the Glomerular Filtration Rate in Iranian Children Using the 2009 Schwartz Equations

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Abstract

The glomerular filtration rate (GFR) is widely considered the best overall index of renal function. The Schwartz equations are designed for measuring the GFR in children between 1 and 16 years of age. In the present study, we investigated the percentiles of the GFR in a general population of Iranian children with no known renal disease via the 2009 Schwartz equations (updated and combined equations). Between 2010 and 2011, we selected 687 children aged 7–16 years from the Iranian province of Isfahan. Blood samples were analyzed for blood urea nitrogen, creatinine, and cystatin C. For each child, we calculated the GFR using 2 Schwartz equations. The Wilcoxon test was applied to examine the differences in the estimated GFRs between the equations. To determine the correlation between the GFRs obtained via the updated and combined Schwartz equations in the boys and the girls and also for the correlation between age and the GFR, we performed the Pearson or Spearman correlation coefficients. The statistical analyses were conducted using MedCalc, version 12.1.4.0 (MedCalc Software, Mariakerke, Belgium). The mean GFR was 100.06±19.80 mL/min/1.73 m^2 based on the updated equation and 96.10±18.44 mL/min/1.73 m^2 according to the combined equation. No significant differences were observed between these equations in estimating the GFRs. The correlation analysis for determining the association between age and the GFR estimated by the updated (r=0.05, P=0.1) and combined (r=0.06, P=0.09) Schwartz equations was not statistically significant. In conclusion, in the current study we showed that the updated and combined Schwartz equations exhibited high concordance in estimating GFR values in this age group.

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Keywords: ● Glomerular filtration rate ● Pediatrics ● Cystatin C, ● Iran

What's Known

- There is scarce information on normal glomerular filtration rate (GFR) values in children.
- • There are no data about the percentiles of the GFR in Iranian children.

What's New

- Updated and combined Schwartz equations had high concordance in estimating GFR values in Iranian children aged 7–16 years.
- There was no correlation between age and GFR values. GFR values remained relatively constant in this age group.
- This paper presents the 5th, 25th, 50th, 75th, and 95th GFR percentiles in Iranian children aged 7–16 years.

Introduction

The glomerular filtration rate (GFR) is widely deemed the best overall index of renal function. The urinary clearance of inulin is the gold standard method for measuring the GFR; however, this method is time-consuming, expensive, and complicated as it requires continuous intravenous infusions and collection of urine samples. Other methods use radiolabeled isotopes or nonradioactive contrast agents such as Cr51-EDTA, iohexol, and iothalamate; nonetheless, not only can these methods be difficult to perform but also they are invasive and not available in all laboratories or hospitals.[1] Thus, the GFR is commonly estimated by measuring serum creatinine and applying creatinine-based GFR equations in daily clinical practice. In recent years, cystatin C, a 13-kD proteinase inhibitor, has also been suggested as a novel marker of renal function. Several studies have suggested that cystatin C is a more sensitive marker than serum creatinine in finding GFR changes.[2,3]

For more than 3 decades, the original Schwartz equation, GFR=k×body length (cm)/serum creatinine (mg/dL), was the most widely used GFR equation in children.[4] This equation was developed using the Jaffe method for the measurement of serum creatinine. In 2009, Schwartz et al.[5] developed an updated version of their original equation drawing upon an enzymatic method (isotope dilution mass spectrometry) for the measurement of serum creatinine. Aside from this equation, they also proposed a novel GFR equation: the combined Schwartz equation, which is based on serum creatinine, blood urea nitrogen (BUN), and cystatin C.[5] The Schwartz equations are designed for children between 1 and 16 years of age. These equations have been previously validated in a general population of children with normal GFR values.[6,7]

In the existing literature, there is a dearth of data on normal GFR values in children. Particularly, there is no information on the percentiles of the GFR in a general population of Iranian children. In the present study, for the first time, we investigated the GFR percentiles of Iranian children using two 2009 Schwartz equations. The Schwartz equations were selected for the current study as they are the most widely used GFR equations for children worldwide.

Patients and Methods

Study Design and Population

The data used in the present study were obtained from a baseline survey of "Childhood and Adolescence Surveillance and PreventIon of Adult Non-communicable disease" (CASPIAN Study). The third phase of this nationwide school-based health survey was conducted between 2009 and 2010 among 5028 Iranian students aged 7–18 years who were selected by multistage random cluster sampling from urban and rural areas of 27 provinces of Iran. The sample size was determined using the paired continuous data equation. The inclusion criteria consisted of age between 7 and 16 years, having no known renal disease, and presenting no evidence of urinary tract infection at the time of sampling.

Multistage random cluster sampling was applied as follows: first, 3 educational areas, among the total number of 6 educational areas in the city of Isfahan, were selected by simple random sampling. Next, the study sample size was divided into 3 clusters. Then, all the primary and junior high schools located in the 3 selected educational areas were listed and half of them were selected by simple random sampling as well. Thereafter, the sample size for each cluster was divided by k (number of the students in each school), and the proportion of the samples for each school was defined. Finally, an approximately equal number of boys and girls were chosen at each grade of schools as a sampling framework by simple random sampling. For randomization, in each step of sampling we used random number sequences generated by computer. The details of the data collection and sampling of the CASPIAN studies are characterized elsewhere.[8] The present paper describes the findings on 712 children from Isfahan, as was the case in our previous report on chronic kidney disease screening in children residing in this area.[9] We excluded 25 children between 16 and 18 years of age. Thus, a total of 687 children aged 7–16 years were included in the present study. In brief, the study objectives and protocol were explained comprehensively to the students and their parents and a written informed consent was obtained from all the participants before enrollment in the study. The demographic and clinical data of the eligible students, including age, sex, height, weight, and blood pressure, were obtained. Fasting blood samples were taken and centrifuged for 10 minutes at 3000 rpm within 30 minutes of venipuncture in Isfahan's central provincial laboratory, where the biochemical analyses were performed. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (approval code: 298613).

Biochemical Measurements and GFR Estimation

Serum creatinine and BUN were measured by enzymatic methods on a Hitachi 917 auto-analyzer. Serum cystatin C was measured via the particle-enhanced immunoturbidimetric method (Dako, Glostrup, Denmark).[10] The validity of the enzymatic method in the measurement of creatinine and also the validity of the immunoturbidimetric method in the measurement of cystatin C have been approved previously.[5,10] In order to determine the reliability of the measurements of creatinine and cystatin C in our study, a single laboratory technician analyzed 40 samples of 40 children labeled with 2 different names twice for creatinine and cystatin C. The correlation of the results was 0.7 for creatinine and 0.75 for cystatin C, both of which were acceptable. Probable confounding factors for the measurement of BUN, creatinine, and cystatin C were eliminated via simultaneous measurements by the same technician for all the samples. The accuracy rate in the measurements of creatinine and cystatin C was 0.4 mg/dL and 0.2 mg/L, respectively. For each child, we estimated the GFR using the 2 following equations:

The updated Schwartz equation[5]:

GFR (ml/min/1.73 m^2)=0.413×Height (cm)/ Serum Creatinine (mg/dl)

The combined Schwartz equation[5]:

GFR (ml/min/1.73 m^2)=39.1×(Height (m)/Creatinine (mg/dl))$^{0.516}$×(1.8/Cystatin C (mg/L))$^{0.294}$×(30/BUN(mg/dl))$^{0.169}$×(1.099)$^{\text{ifmale}}$×(Height (m)/1.4)$^{0.188}$

Statistical Analysis

The Wilcoxon test was applied to examine the differences in the estimated GFRs between the equations. We determined the age- and gender-specific 5th, 25th, 50th, 75th, and 95th percentiles of the GFR values based on each equation. The correlations between the GFR values obtained by the updated and combined Schwartz equation and the correlations between the GFR values and the age of the children were examined using the Person or Spearman tests, as appropriate. The statistical analyses were performed using MedCalc, version 12.1.4.0 (MedCalc Software, Mariakerke, Belgium).

Results

A total of 687 children, comprising 375 (54.58%) males and 312 (45.41%) females, were studied for the GFR analysis. The median of age was 12 years (range=7–16 y). The mean height was 142.6±12.6. The mean values of serum creatinine, cystatin C, and BUN were 0.67±0.11, 0.85±0.34, and 12.19±4.07, correspondingly.

The mean GFR was 100.06±19.80 mL/min/1.73 m^2 based on the updated Schwartz equation and 96.10±18.44 mL/min/1.73 m^2 based on the combined Schwartz equation. The Wilcoxon test revealed no significant differences between these equations in estimating the GFR (P=0.22). We determined the percentiles of the estimated GFRs for each equation. Table 1 shows the age- and gender-specific 5th, 25th, 50th, 75th, and 95th percentiles of the GFR values based on the updated and combined Schwartz equations. Figure 1 depicts the box-and-whisker plots of the GFR values estimated by the updated and combined Schwartz equations. The Wilcoxon test showed no significant differences between the equations in estimating the GFR in the boys (Z=1.57, P=0.14) and the girls (Z=1.19, P=0.23). On the other hand, a high level of correlation was observed between the equations in the boys (r=0.92, P=0.0001) and the girls (r=0.95, P=0.0001). Finally, there was no significant correlation between age and the GFR estimated by the updated (r=0.05, P=0.1) and combined (r=0.06, P=0.09) Schwartz equations.

Discussion

In the current study, we presented the percentiles of the GFR in a general population of Iranian children using 2 recently developed Schwartz equations. To the best of our knowledge, this is the first study on the percentiles of GFR values in children without known renal dysfunction in the Middle East. The knowledge about GFR percentiles may be of interest to pediatricians in evaluating renal function in children.

In the literature, there are only a few studies on normal GFR values in children. Blake et al.[11] reported reference ranges for the GFR in children using 51Cr-EDTA measurements. Their study comprised 27 children aged 2–17 years with normal 99mTc-DMSA results. The mean GFR in the index study was 109.5 mL/min/1.73 m^2. However, the mentioned study did not present percentiles for the GFR values for different ages and sexes. The mean of GFR in our study was 100.06±19.80 by the updated Schwartz equation and 96.10±18.44 by the combined Schwartz equation. The mean GFR in our study is comparable with that in the study of Blake and colleagues.[11] Nevertheless, the aforementioned study employed a reference method for the measurement of the GFR in children, which may have augmented the accuracy of their results. Nonetheless, it should be considered that it is difficult to obtain a reference GFR for children since ethical considerations may preclude the enrollment of healthy children with no known renal disease in studies that would expose them to radioactive radiations to determine the reference GFR. Instead, we enrolled a larger sample in our study and determined their GFR using 2 Schwartz equations as these equations are more widely used than the reference GFR methods in daily clinical practice. In a similar study conducted on Japanese children aged

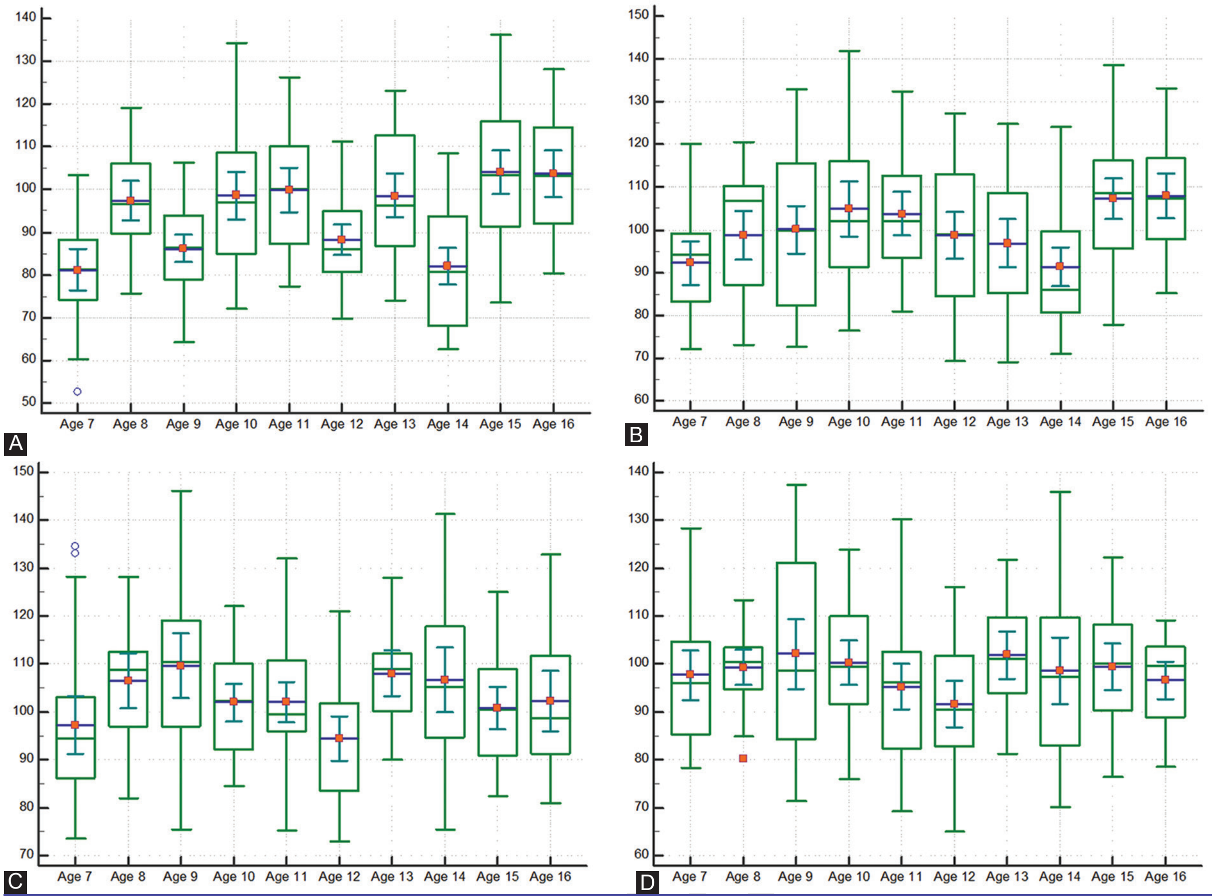

Figure 1: Box-and-whisker plots of the glomerular filtration rate (GFR) values (mL/min/1.73 m^2) based on the updated Schwartz equation in the boys (A) and the girls (B) and the combined Schwartz equation in the boys (C) and the girls (D).

between 3 months and 16 years, the percentile of the GFR was determined without the use of a reference method.[12]

The 2009 Schwartz equations were developed in 349 American children aged 1–16 years with measured GFRs between 15 and 75 mL/min/1.73 m^2. Since then, the external validity of these equations has been evaluated in several studies. For instance, Staples et al.[6] compared the estimated GFR using the updated Schwartz equation with the measured GFR using iothalamate clearance in a population of 503 children with a mean GFR of 110.6 mL/min/1.73 m^2. They found a good agreement between the GFRs estimated by this equation and the GFRs measured by iothalamate clearance in their studied sample. In another study, Bacchetta et al.[7] reported that the updated Schwartz equation was accurate in children with moderate renal impairment and normal GFRs. The United States National Kidney Disease Education Program (NKDEP) has recently suggested the updated Schwartz equation as the "best creatinine-based GFR equation for all children."[13]

In the present study, we observed no correlation between age and GFR values within the age range of 7–16 years. This observation may indicate that GFR values remain relatively constant in this age group in Iranian children. Our observations are similar to previous studies in different populations.[14] For instance, in a study among Japanese children, Uemura et al.[12] showed that the GFR remained relatively constant after infancy until the age of 16 in this population.

In the current study, we showed that both Schwartz equations were highly in concordance in predicting GFR values in children aged 7–16 years. The updated equation is only based on the values of serum creatinine and height. It can, therefore, be easily applicable and cost- beneficial in daily clinical practice in comparison with the more complicated combined equation.

The findings of the current study must be interpreted in view of its limitations, first and foremost among which is its relatively small number of patients. Moreover, we included only children between 7 and 16 years of age and our results may, thus, not be applicable to all Iranian children. The present study is the first report on the percentiles of the GFR in a general population of Iranian children via the Schwartz equations. Further studies with larger sample sizes are warranted to obtain more representative results.

Table 1: Age- and gender-specific 5th, 25th, 50th, 75th, and 95th percentiles of the GFR values based on the updated and combined Schwartz equations

Age	Sex	n	5th percentile	25th percentile	50th percentile	75th percentile	95th percentile
GFR values based on the updated Schwartz equation							
7 y	Boys	27	60.45	74.06	81.45	88.62	101.15
	Girls	32	79.56	85.87	96.88	105.32	127.31
8 y	Boys	29	76.75	90.11	96.58	105.54	117.27
	Girls	22	81.98	93.83	100.28	103.50	112.41
9 y	Boys	47	67.79	80.05	87.37	94.83	104.94
	Girls	34	72.66	84.31	99.65	121.27	136.23
10 y	Boys	39	73.90	84.54	97.03	108.92	132.25
	Girls	34	77.81	91.72	100.02	110.12	122.94
11 y	Boys	32	78.68	87.89	101.01	110.78	124.83
	Girls	47	73.09	83.28	97.50	103.33	128.94
12 y	Boys	42	70.85	80.04	85.64	94.83	109.13
	Girls	36	66.69	82.34	90.05	100.85	114.72
13 y	Boys	35	75.45	85.34	96.38	113.11	121.11
	Girls	22	82.99	92.68	100.41	109.72	120.03
14 y	Boys	46	63.32	67.08	80.07	93.79	106.73
	Girls	31	71.94	82.62	97.30	110.12	134.60
15 y	Boys	49	75.89	91.73	103.53	115.64	134.21
	Girls	30	77.45	90.32	100.74	108.28	121.19
16 y	Boys	29	81.03	90.76	101.89	111.53	126.00
	Girls	24	79.98	88.01	99.35	103.20	128.54
GFR values based on the combined Schwartz equation							
7 y	Boys	27	73.25	83.15	94.30	99.41	116.21
	Girls	32	74.84	87.17	95.02	103.76	133.2
8 y	Boys	29	74.54	88.18	106.69	110.13	116.19
	Girls	22	83.53	94.69	108.41	112.54	127.98
9 y	Boys	47	74.64	84.37	101.18	118.66	131.66
	Girls	34	76.63	97.05	111.37	119.08	145.84
10 y	Boys	39	77.91	91.15	102.07	116.32	140.66
	Girls	34	85.20	92.26	103.00	110.13	120.47
11 y	Boys	32	82.23	94.40	102.90	113.57	130.42
	Girls	47	78.42	95.87	100.06	112.19	130.67
12 y	Boys	42	70.52	83.04	98.20	113.05	125.79
	Girls	36	73.88	82.98	94.17	100.44	119.08
13 y	Boys	35	70.05	84.81	96.76	109.10	123.78
	Girls	22	90.86	98.38	108.75	112.19	127.16
14 y	Boys	46	71.18	80.32	85.33	99.71	122.24
	Girls	31	76.17	94.40	105.31	118.39	140.23
15 y	Boys	49	79.29	95.94	108.75	115.64	137.73
	Girls	30	83.78	90.86	101.18	109.10	120.32
16 y	Boys	29	85.94	96.76	106.34	112.88	131.34
	Girls	24	81.56	90.63	97.74	109.78	130.09

GFR: Glomerular filtration rate

Conclusion

In conclusion, in the current study we presented the 5th, 25th, 50th, 75th, and 95th percentiles of GFR values in a general population of Iranian children aged 7–16 years. The updated and combined Schwartz equations showed high concordance in estimating GFR values in this age group. The GFR values remained relatively constant in this age group.

Conflict of Interest: None declared.

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