Comparison of the performance of the updated Schwartz, combined Schwartz and the Grubb glomerular filtration rate equations in a general pediatric population.

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Background

Glomerular filtration rate (GFR) is widely accepted as the best overall indicator of renal function [1]. The reference methods for the measurement of GFR require determination of renal clearance of exogenous substances such as inulin, Cr51-EDTA, iohexol and iothalamate. These methods are invasive, expensive and hard to employ in daily clinical practice; therefore GFR is routinely estimated by measuring serum concentration of endogenous markers of renal function [2]. Serum creatinine is the most commonly used endogenous marker for assessment of GFR worldwide. However, in recent years a novel marker of renal function, cystatin C, is suggested as a more sensitive marker than serum creatinine in GFR assessment [3, 4].
The original Schwartz equation (developed in 1976) was the most popular GFR equation for children below 18 years of age in the past three decades [5]. This equation was developed with creatinine measured by Jaffé reaction [5]. However, during these years the laboratory methods for the measurement of serum creatinine has been widely replaced with new enzymatic method (isotope dilution mass spectrometry). The original Schwartz equation is believed to overestimate GFR when creatinine is measured by enzymatic methods [2]. Accordingly, in 2009, Schwartz et al.[6] proposed an updated version of their original equation that was developed based on enzymatic method of creatinine measurement. In addition to their 'updated' equation, they also developed a new GFR equation which is based on serum levels of creatinine, blood urea nitrogen (BUN), and, cystatin C (named as the 'combined' Schwartz equation) [6]. Both 2009 Schwartz equations are derived from a cohort of children with mild to severe chronic kidney disease (CKD) and their performance in general children is not well determined [2, 6].

Beside the equations proposed by Schwartz et al., there are several other cystatin C based GFR equations in pediatrics. Among the existing equations, only the equation proposed by Grubb et al. [7] is developed with a cystatin C measurement method similar to the method used in 2009 Schwartz et al. study [6]. This methodological similarity has made the comparison between these equations possible. In this study we made a side-by-side comparison of the performance of the updated Schwartz, the combined Schwartz and the Grubb equations in a relatively large number of healthy children with no known renal disease. Our aim was to investigate how these equations perform relative to each other in estimating GFR and categorizing individuals in CKD or non-CKD groups in this population.

Methods

Study design and population
The data used in this study were obtained from a baseline survey of "**C**hildhood and **A**dolescence **S**urveillance and **P**revent**I**on of **A**dult **N**on-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 present paper, describes the findings of 712 school students from Isfahan, a large province located in central parts of the country. A detailed description about the procedure of data gathering and sample collection of the Caspian studies has been characterized elsewhere [8]. In brief, after complete explanation of the study objectives and protocol for the students and their parents, a team of trained nurses collected demographic and clinical features of the eligible subjects including age, sex, height, weight and blood pressure. Fasting blood samples were drawn from participants and centrifuged for 10 min at 3000 rpm within 30 min of venipuncture in Isfahan central provincial laboratory, where biochemical measurements were done. Written informed consent was obtained from parents/caregivers, and oral assent from the students before enrollment in the study. The study was approved by institutional review boards, and adhered to the tenets of Helsinki declaration.

Biochemical analysis and GFR estimation
Serum creatinine and BUN were measured by enzymatic methods on a Hitachi 917 auto-analyzer. Serum cystatin C was measured by particle-enhanced immunoturbidimetric method (Dako, Glostrup, Denmark) [9]. A cystatin C level lower than 1.38 mg/l is suggested as normal in general population [10].
To calculate GFR for each subject, we applied the following equations:
The 'updated' Schwartz equation [6]. $GFR(ml/min/1.73\ m^2) = 0.413 \times Height\ (cm)/Serum\ Creatinine\ (mg/dl)$
The 'combined' Schwartz equation [6]. $GFR(ml/min/1.73\ m^2) = 39.1 \times (Height\ (m)/Creatinine\ (mg/dl))^{0.516} \times (1.8/CystatinC\ (mg/L))^{0.294} \times (30/BUN\ (mg/dl))^{0.169} \times (1.099)^{if\ male} \times (Height\ (m)/1.4)^{0.188}$
The Grubb equation [7].
According to the estimated GFR by each equation, participants were categorized as CKD group (defined as GFR<60 mL/min/1.73 m^2) or non-CKD group (defined as GFR>60 mL/min/1.73 m^2).

Statistical analysis
Continuous values are expressed as mean SD and categorical variables are presented as numbers (percentage). The level of agreement in estimating GFR between equations was examined using Bland-Altman analysis [11]. Based on this statistical method, the limits of agreement were determined by the mean difference 1.96 SD of the percentage of changes. Weighted kappa statistics was used to assess the agreement between equations in categorizing individuals as CKD or Non-CKD. Statistical analyses were carried out using SPSS software version 19.0 (SPSS, Chicago, IL, USA) and MedCalc version 12.1.4.0 (MedCalc Software, Mariakerke, Belgium). P <0.05 was considered the significance threshold.

Results

Of 712 included Persian children, 377 (52.9%) were male. The mean age was 12.2 2.4 years (range: 7-18), and the mean body mass index was 18.2 3.8 kg/m^2. Detailed demographic and clinical characteristics of the participants are presented in table 1. Mean GFR was 99.65 19.71 ml/min/1.73 m^2 by combined Schwartz equation, 99.66 19.74 ml/min/1.73 m^2 by updated Schwartz equation, and 168.04 81.63 ml/min/1.73 m^2 by Grubb equation. Figure 1 shows the distribution of estimated GFRs by each equation. The Grubb equation showed a considerably wider distribution of values at both upper and lower levels of GFR values in comparison with the Schwartz equations. Such a difference in GFR distribution was due to the larger standard deviation of GFR values estimated by the Grubb equation. Figure 2 shows the Bland-Altman plots for the agreement between GFR values by each equation. We found a high level of agreement between the combined Schwartz and updated Schwartz equations (mean difference: 0 12.74 ml/min/1.73 m^2). Agreements between the combined Schwartz and Grubb equations (mean difference: -68.4 68.34 ml/min/1.73 m^2), and between the updated Schwartz and Grubb equations (mean difference: -68.4 75.98 ml/min/1.73 m^2) were poor.
The frequency of CKD was 7%, 1.7% and 1.3%, based on the Grubb, combined Schwartz and updated Schwartz equations, respectively. Table 2 shows the overlaps of individuals categorized as CKD or non-CKD based on each equation and also the corresponding weighted kappa coefficients quantifying Inter- and intra-rater reliability assessments .The weighted kappa statistics revealed a very good agreement between two Schwartz equations in categorizing individuals in CKD or non-CKD groups (κ = 0.85; 95% CI: 0.69–1). On the other hand, the Grubb equation showed fair agreement with two Schwartz equations in categorizing individuals as CKD or non CKD (table 2).

Table 1. Demographic, biochemical and renal characteristics of the study participants.

	Mean	SD	Median	Range
Age *(years)*	12.2	2.4	12	7-18
Height *(cm)*	148.6	13.0	152	125-183
BMI *(kg/m²)*	18.2	3.8	18.1	12.34-36.85
Systolic blood Pressure *(mm Hg)*	102.2	13.3	100	70-145
Diastolic blood Pressure *(mm Hg)*	65.1	10.5	65	35-95
Blood urea nitrogen *(mg/dl)*	12.1	4.0	11	5-33
Serum creatinine*(mg/dl)*	0.6	0.1	0.7	0.4-1.2
Serum cystatin C *(mg/L)*	0.8	0.3	0.8	0.45-2.6
Estimated GFR *(ml/min per 1.73 m²)*				
Combined Schwartz equation	**99.6**	**19.7**	**98.7**	**50.1-189.8**
Updated Schwartz equation	**99.6**	**19.7**	**98.5**	**57.4-182.7**
Grubb equation	**168.0**	**81.6**	**154.1**	**17.0-448.3**

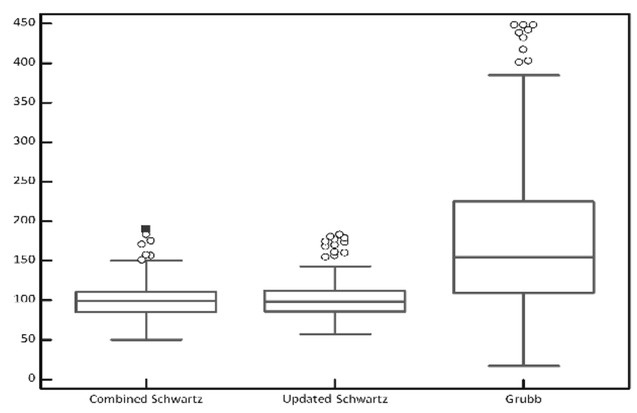

Figure 1. The Box-and-Whisker plots of the distribution of the estimated GFR by different equations. The Box-and-Whisker plots display the 25th, 50th, and 75th percentile by the lines at the bottom, middle, and top of the box. The brackets show the 95% range

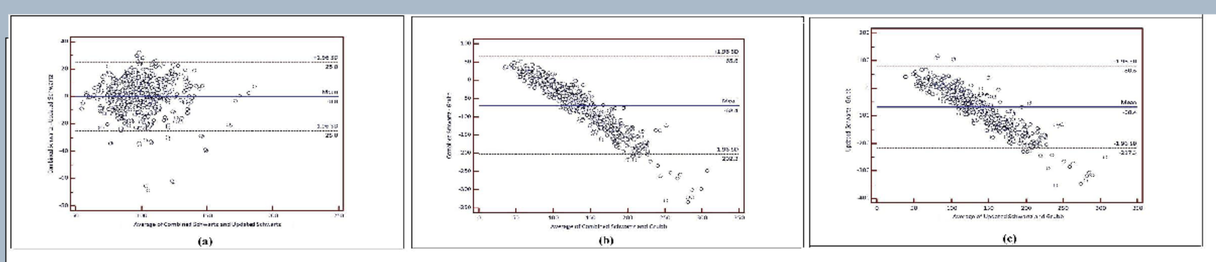

Figure 2. Bland-Altman plots of comparison between equations in estimating GFR. A: comparison between combined Schwartz and updated Schwartz equations. B: comparison between combined Schwartz and Grubb equations. C: Comparison between updated Schwartz and Grubb equations. The continuous line shows the mean difference between two equations and the dash lines show the limits of agreement defined as mean 1.96 SD.

Table 2. Overlaps of CKD or non-CKD individuals based on the study equations and weighted kappa coefficients quantifying Inter- and intra-rater reliability assessment (n=712).

combined Schwartz equation	updated Schwartz equation		combined Schwartz equation	Grubb equation		updated Schwartz equation	Grubb equation	
	Non-CKD	CKD		Non-CKD	CKD		Non-CKD	CKD
Non-CKD	**700(98.3%)**	0	Non-CKD	**660(92.7%)**	40(5.6%)	Non-CKD	**660(92.7%)**	43(6%)
CKD	3(0.4%)	**9(1.3%)**	CKD	2(0.3%)	**10(1.4%)**	CKD	2(0.3%)	**7(1%)**

Weighted Kappa statistics		
Equations	Kappa	95%CI
Combined Schwartz vs Updated Schwartz	0.85	0.69-1
Combined Schwartz vs Grubb	0.3	0.15-0.45
Updated Schwartz vs Grubb	0.22	0.08 0.36

Note: The bold numbers (percents) show overlaps in defining CKD or non-CKD. CKD was defined as GFR<60 mL/min per 1.73 m^2. Weighted kappa, < 0.20 poor agreement; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 good; 0.81-1.00 very good.
Abbreviation: CKD: Chronic Kidney Disease; CI: Confidence Interval.

Conclusions

In this study, we compared the performance of updated Schwartz equation, combined Schwartz equation and the Grubb equation in a sample of general pediatric population. Based on our findings, two 2009 Schwartz equations are in high concordance in estimating GFR and defining individuals as CKD or non-CKD. On contrary, there is a limited agreement between the Schwartz equations and the Grubb formula.
In general, a favorable degree of agreement in estimated GFR values (Bland-Altman analysis) and a very good agreement in defining CKD and non-CKD (weighted kappa statistics) were observed between the updated Schwartz and the combined Schwartz equations. These findings may suggest that there is no systematic deviation between these equations and they can be used interchangeably in daily clinical practice. The updated equation only requires the values of serum creatinine and height, and therefore is simpler than the combined equation. The updated equation can be considered more accessible and cost-benefit in daily pediatric practice and also in large CKD screening programs.
In our study, the Grubb equation appeared to be highly inconsistent with two Schwartz equations. In order to better understand the sharp contrast between Grubb and Schwartz equations we bring an example. A 12-year old boy of average height (160 cm) with a serum creatinine level of 0.8 mg/dl, cystatin C level of 0.7 mg/L and a BUN of 10, would have a GFR estimates of about 100 ml/min/1.73 m^2 by the combined Schwartz equation; whereas his GFR would be estimated as high as 213 ml/min/1.73 m^2 by the Grubb equation. Such overestimations by the Grubb equation resulted in a higher mean GFR value for Grubb equation in comparison with the Schwartz equations in our study. A similar observation was found by Fadrowski et al. [12] who compared the performance of these equations in a large number of American adolescents aged 12 to 17 years. In their study, the median GFR estimated by the updated Schwartz, combined Schwartz, and Grubb equations were 96.6, 96.6 and 130.1 ml/min/1.73 m^2 respectively. Similar to the findings of Fadrowski et al.[12], in our study the median GFR by the updated Schwartz and the combined Schwartz equations were almost equal (98.5 and 98.7 ml/min/1.73 m^2 respectively), while the Grubb equation showed a considerably higher median GFR (154.1 ml/min/1.73 m^2) (table 1).
From another point of view, when applying Grubb equation, all children over 14 years of age with a cystatin C level greater than 1.23 mg/L will be diagnosed as CKD (GFR<60 ml/min/1.73 m^2); whereas this is not reproducible when using the Schwartz equations. As a consequence, in our study the Grubb equation yielded a higher prevalence of CKD in comparison with the Schwartz equations. Such apparent discrepancies between the Schwartz and the Grubb equations are probably due to the differences in the characteristics of the sampled populations of the Schwartz et al. [6] and the Grubb et al. [7] studies. It is well established that the demographic and clinical status of the population that one GFR equations is derived from, significantly affects the accuracy of the obtained equation [13, 14].

During the past decade, several other creatinine- and/or cystatin C-based GFR equations have been proposed for children (e.g. Zappitelli et al. [15]; Bouvet et al. [16]; Filler et al. [17]; and. Leger et al [18]). However, all of such equations are originated from specific patients with various types of kidney diseases, and therefore their extrapolation to the general pediatric population is a matter of debate [2, 19]. Furthermore, differences in cystatin C assay methods used in these studies have made the comparison between the existing equations difficult. It is important to note that the equations by Schwartz et al. [6] and Grubb et al. [7] are developed using particle-enhanced turbidimetric immunoassay (PETIA) for cystatin C measurement. On the other hand, the majority of other exiting cystatin C based equations used particle-enhanced nephelometric immunoassay (PENIA) method [15-18]. Since we aimed to investigate the performance of the combined Schwartz equation, we used PETIA assay for cystatin C measurement in our study. With respect to the lack of a uniform reference standard for the calibration of PETIA and PENIA assays at present time [12], from several existing equations we were able to include only the Grubb equation for comparison in this study.
The updated Schwartz equation is validated in children with normal renal function [20]. The United States National Kidney Disease Education Program (NKDEP) has suggested this equation as the "best creatinine based-GFR equation for all children" [21].Nevertheless, at present time a global consensus on an ideal GFR equation in children does not exist. In 2002, the National Kidney Foundation (KDOQI) recommended the use of the original Schwartz equation in all children [22]. However, due to dramatic changes in laboratory assay methods and considering several new GFR equations introduced during the past decade, there is an essential need for updating KDOQI guidelines and reaching a global agreement on an all-purpose GFR equation for children. Further studies with a reference GFR are warranted to investigate the accuracy of existing equations in healthy children with normal renal function.
The main limitation of our study was lack of a gold-standard measurement of GFR for study subjects. Given this, we were not able to determine the most accurate equation in our population. However, one should acknowledge that it is cumbersome to obtain reference GFR in such a large population with healthy renal function. The lack of reference GFR is a common limitation present in other similar works as well [12, 23-25].
In conclusion, in this study we demonstrated a high concordance and agreement between two 2009 Schwartz equations in estimating GFR and defining CKD individuals in general pediatric population. The updated equation is more easily implemented in daily clinical practice. More studies with reference GFR are needed to evaluate the accuracy of existing GFR equations in children with normal renal function.

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