Diagnostic accuracy of estimated glomerular filtration rate in pediatric oncology patients.

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ABSTRACT

Objective: To compare eGFR using different equations with 24-hour creatinine clearance

Methodology: We collected data of standardized 24-hour creatinine clearance of pediatric oncology patients for a period of one year and compared the efficiency of various equations for estimation of creatinine clearance with it. For error estimation we used mean relative prediction error (MRPE) and root mean square error (RMSE) and for accuracy estimation we used Lin's correlation.

Results: Out of 100 study participants, 57 were males and 43 were females. Mean age of the population studied was 11.8 while mean BMI was 13.95. Most common tumor reported was osteosarcoma. Out of 18 equations evaluated only 5 showed an accuracy of 0.80 or more, while SEM of none of the equation is near to the desired value (zero). Minimum SEM was found to be for Schwartz (2012) equation.

Conclusions: According to our study none of the equations in current clinical practices showed a good correlation with creatinine clearance adjusted according to body surface area.

Keywords: eGFR, creatinine clarence, renal function, pediatric oncology.

Introduction:

Chronic kidney disease (CKD) is one of the major global health issues with an annual incidence that is growing.[1] In certain individuals, CKD can proceed to stage 5 CKD/ kidney failure.[2] As a result, early discovery and precise GFR evaluation will aid in monitoring and managing the disease progression, which will improve the prognosis.[3]

In clinical practice, such as in the intensive care unit, following organ transplantation, or for medicine dose modification, correct assessment of the glomerular filtration rate (GFR) is often crucial to patients. There are several approaches for measuring GFR, all of which involve exogenous markers like inulin, iohexol, 51Cr-EDTA, or 99mTc-diethylenetriaminepentaacetic acid.[4,5] All of these indicators pass through the glomerulus without being reabsorbed or secreted by tubules. GFR measurement with the procedures outlined above can be difficult, intrusive, time-consuming, and expensive, and they are not available in all health-care institutions. To overcome these limitations, different formulae for estimating GFR based on serum creatinine (S. Creat) and/or serum cystatin C as a measure of renal function were devised.[2,6]

Although GFR is considered to be the best-known marker so far to assess renal function. Even so, it remains a challenge to measure it accurately and precisely as it exhibits both interindividual and intraindividual variability due to age, gender, and body size variations, as well as intraindividual variability related to hydration state, exercise, and protein intake.[5] An alternative way is to calculate it is using prediction models or monitoring the clearance of an ideal filtration marker. An ideal marker has no tubular secretion, reabsorption, or metabolism after free ultrafiltration at the glomerulus. It must also be removed solely by the kidneys.[7] Creatinine clearance (Cr. Cl) is measurement of creatinine in 24-hour urine sample in correlation of creatinine level in blood of patients.

Patients in pediatric oncology are given a variety of nephrotoxic chemotherapeutic and antibacterial drugs. As these drugs have a narrow therapeutic index and the drugs or their metabolites are mostly removed by the kidneys, a precise evaluation of renal function in these patients is critical for determining the best medication dosage.[8] Renal disease and kidney damage are extremely common in children, posing a substantial public health threat. Chronic kidney disease (CKD) has an incidence of 3.0–17.5 per million children and a prevalence of 14.9–118.8 per million children, with an upward trend.[9,10]

Several equations have been developed for estimation of eGFR in pediatrics with some based-on serum creatinine and others on both, serum creatinine and serum cystatin C. These include Schwartz, Counahan-Barratt, Updated Schwartz "bedside", $CKiD_{Cys\ C}$ (Schwartz "bedside" cystatin C), $CKiD_{Cr\ -\ Cys\text{-}C}$ (combined CKiD creatinine–cystatin C), Pottel and colleagues and $CKD\text{-}EPI_{Cr}$ (adult equation)[5,8]

In adults, it is established that certain equations estimate GFR better than others, but in pediatric oncology particularly in our population, no such work has been done to our best knowledge. We aim to compare different serum creatinine-based equations for the assessment of renal function in pediatric oncology patients. The major advantage of using these equations over currently used 24-hour creatinine clearance for measuring GFR is that we do not need 24 hours urine samples.

Objective:

To compare eGFR using different equations with 24-hour creatinine clearance.

Methodology:

This cross sectional study was conducted at Chemical Pathology department, Indus Hospital and Health Network using convenient probability sampling technique. Data was extracted from electronic medical records.

Sample size was calculated by using WHO sample size calculator. By using the accuracy of Flanders metadata equation in estimating GFR 31.4% (eGFR values within

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10% of measured GFR (mGFR) where mGFR is taken by estimating Creatinine clearance for body surface area based on 24-hours urine collection[8], margin of error 10% and confidence level 95%, the required sample size for this study was 83. We included 100 cases in our study. The study was approved by the institutional review board under Study IRB Number: IHHN_IRB_2022_09_028. A total of 100 tests of 24-hour creatinine clearance performed on the request of pediatric oncology department (inpatient as well as outpatient) during the study duration were taken for analysis. Patients with repeat testing were included if there was at least 3 months gap between sequential tests. All the patients were undergoing chemotherapy for at least a period of 6 months. The duration of the study was one year (1st December 2021 till 30th November 2022)

Statistical analysis:

Statistical package of social sciences (SPSS) version 23 and MS Excel was used to analyze the data. Results were expressed as mean and SD for quantitative variables. The ability of the identified eGFR equations to predict GFR was assessed in terms of bias, precision and accuracy, where precision assesses the correlation of two measurements and accuracy assesses the correctness of measurement series. Statistical package for social sciences (SPSS) version 23 was used to enter and analyze data. Mean error (ME) or standard error of the mean (SEM) were used to assess variability of mean value of test results, mean relative prediction error (MRPE) and root mean square error (RMSE) were used to assess standard deviation of residuals, all tests were calculated to estimate absolute bias, relative bias and precision, respectively. The ME (equation 1), MRPE (equation 2) and RMSE (equation 3) were calculated as follows(8).

Following Equations will be used for estimation of GFR (8, 15)

$$ME(\text{mL/min}) = \frac{1}{N}\sum_{i=1}^{n}(\text{eGFR} - \text{Cr Cl})_i$$

Eq. 1

$$MRPE\,(\%) = \frac{1}{N}\sum_{i=1}^{n}\left(\frac{\text{eGFR}-\text{Cr Cl}}{\text{Cr Cl}}\right)X100_i$$

Eq. 2

$$\text{RMSE(mL/min)} = \sqrt{\frac{1}{N}\sum_{i=1}^{n}(\text{eGFR} - \text{Cr Cl})^2}_i$$

Eq. 3

Additionally, Lin's concordance correlation coefficient (CCC) was calculated for accuracy testing

Equations used for calculation eGFR in the study are attached as annexure 1.

Results:

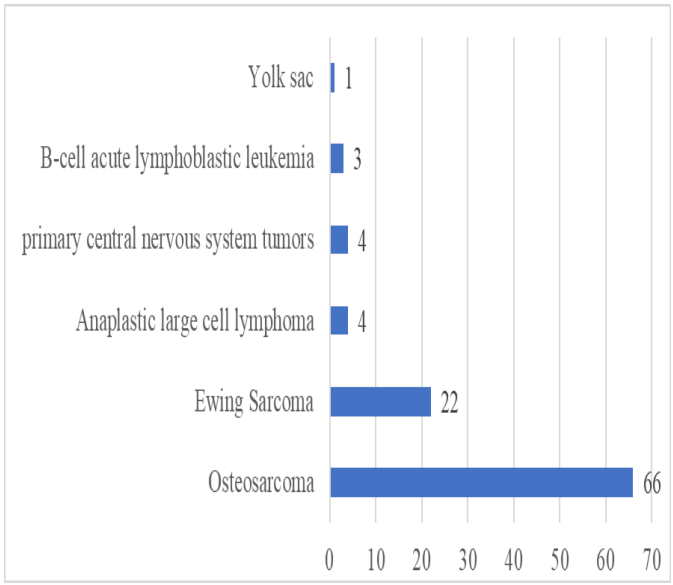
In our study population we had 57 males and 43 females. Mean age of was 11.8 while mean BMI was 13.95, as summarized in table 1.

Table 1: Basic demographics of study participants.

	Male (n=57)	Female (n=43)	Total (n=100)
Age (years)	11.07±3.755	12.81±3.679	11.80±3.786
Weight (cm)	29.39±12.435	28.18±8.299	28.83±10.794
Height (kg)	139.37±23.936	143.79±18.165	141.30±21.577
BMI (kg/m^2)	14.414±2.8399	13.396±2.2610	13.954±2.6464

Most frequent tumor type was found to be osteosarcoma followed by Ewing sarcoma. (Figure 1).

Figure 1: Frequency of various tumors in the study population.



The mean and SD for all the equations along with error estimation are summarized in table 2. As we can see the SEM of none of the equation is near to the desired value (zero). Minimum SEM was found to be for Schwartz (2012) (table 2)

Table 2: Error estimation for formulae included in the study.

Lin's Correlation (table 3) was applied to test accuracy of these equation and their agreement with the results obtained by the traditional mGFR or the Corrected creatinine clearance by body surface area. None of the equations showed good correlation with the creatinine clearance in pediatric population.

Table 3: Lin's correlation.

Precision ρ*	correlation of two measurements
Scale Shift ω**	reads increasing resistance values from left up to infinity
Effect Size υ $^+$	strength of relationship between two variables
Accuracy χ_a^{++}	correctness of measurement series
LCC#	Lin's Correlation coefficient

The scatter plots of the Lin's correlation are shown in figure 2.

As it can be seen from the Lin's correlation, Q(age) (for males), Q(height), Flanders, Pottel and Schwartz-Lyonare are the equations that showed comparatively better results than the others.

Discussion:

We identified 18 equations for the estimation of GFR in pediatric population based on creatinine only. Out of these only 5 showed an accuracy of 0.80 or more. Our results are somewhat comparable to the study conducted by Paez et al, who had compared with gold standard (mGFR). They suggested that Flanders metadata and univariate-Schwartz were the top two equations but still did not accurately calculate GFR.[8]

Paes et al postulated cause of failure to be the effect variation of drug levels at different occasions. In our study another limitation along with the reason stated was that we took 24-hour creatinine clearance in which sample collec-

tion errors and even hydration status may impact the results. Yet the strength of the study is that in our population such a study has never been conducted before with these number of equations and especially in pediatric oncology patients.

The majority of pediatric renal function equations were created in individuals with steady renal function. As a result, these equations should not be used in individuals suffering from acute renal injury. Furthermore, serum creatinine levels may be incorrect in people who are over or under hydrated.[11]

Interestingly most of the equations we used were intended for non-oncologic patients while four were specific to oncology cases, which also failed to yield a reliable result. This is in agreement with the studies published before as well.[12,14]

The peculiarity of our results was that in most of the previously published data the equations reported to be best were Flendes or Schwartz, but in our study, they were not the top scorers rather 3rd and 4th respectively. This might be attributed to the fact that we compared with 24-hour creatinine clearance while others used measured GFR.

Table 2: Error estimation for formulae included in the study

	Distribution		Error Estimation		
	Mean	SD	SEM	MRPE	RMSE
Creatinine clearance	84.02	2.85	---	---	---
Brandt (F)	1105.94	58.24	386.34	-4.68	724.79
Brandt (M)	638.07	38.21	291.01	-3.32	467.93
Counahan-Barratt	121.07	2.04	20.6	-0.44	47.99
Flanders	70.24	2.44	24.6	0.16	36.35
FM equation	113.2	2.1	21.25	-0.35	42.68
Geo et al	42.97	1.31	13.18	0.49	52.25
H-independent	37.53	1.43	14.44	0.55	55.99
Hoste	113.18	2.27	22.91	-0.35	42.36
Leger	53.26	1.6	16.19	0.37	43.71
Pottel et al	68.44	2.08	20.98	0.19	36.95
Q (age) F	-159.17	21.54	139.59	1.78	189.09
Q (age) M	74.48	4.04	30.76	0.5	60.42
Q (Height)	70.53	2.64	26.67	0.16	36.63
Schwartz	71.56	2.31	23.36	0.15	34.99
Schwartz (2012)	95.6	1.27	12.84	-0.14	30.38
Schwartz-bedside (2009)	116.28	1.96	19.78	-0.38	44.17
Schwartz-Lyon	64.69	2.09	21.12	0.23	37.03
U-Schwartz	63.16	2.05	20.71	0.25	38

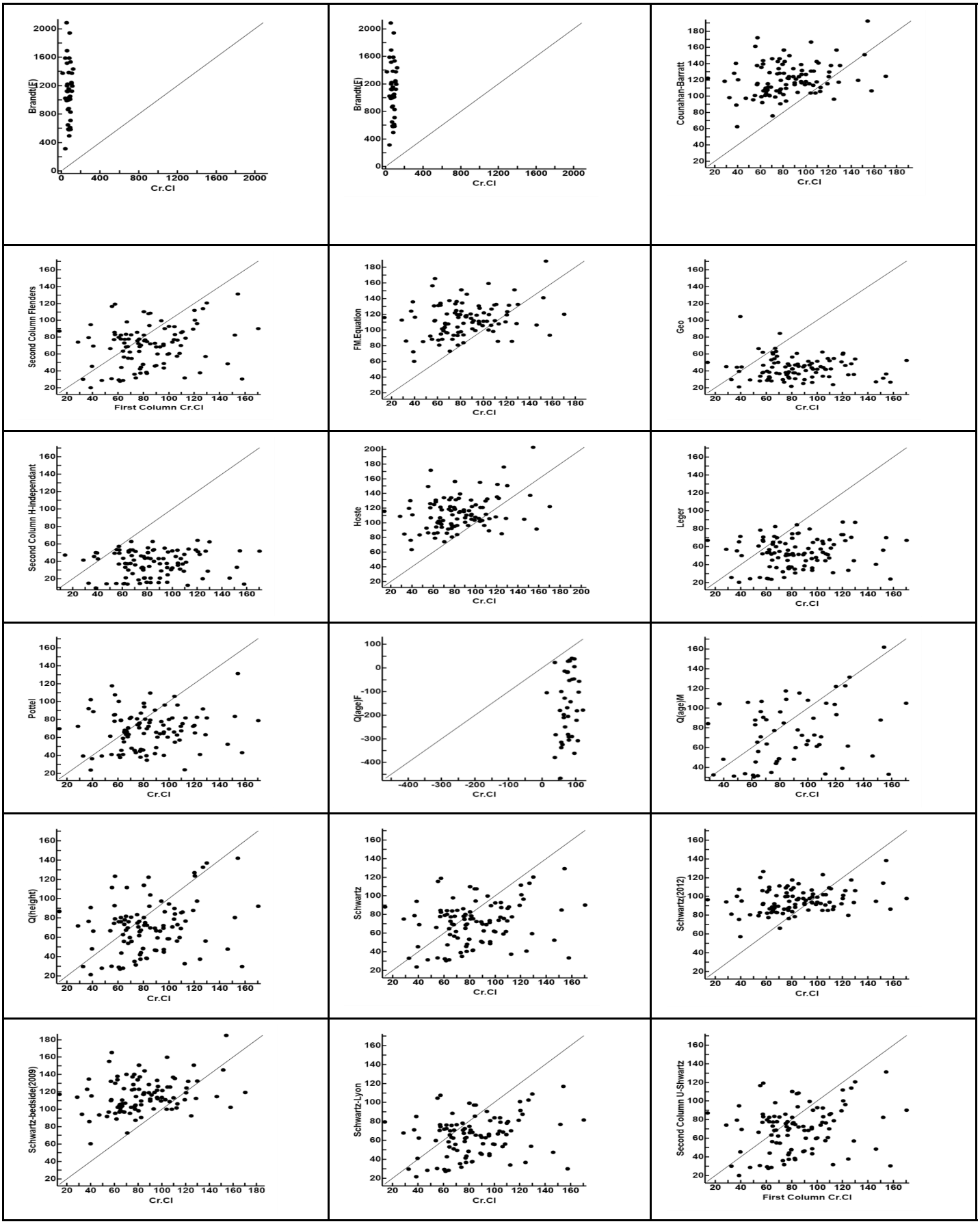
Conclusions:

Our study concluded that in the pediatric population, numerous equations for estimating GFR have been devised. Based on clinical data from a pediatric oncology cohort, none of those assessed in this study were found to be very reliable in predicting renal function on all occasions. According to our findings, the top equations identified in this investigation were the Q (age) for males and Q(height), followed by Schwart and Flanders metadata equation.

Table 3: Lin's correlation

	Precision ρ*	Scale Shift ω**	Effect Size u+	Accuracy Xa++	LCC#	Agreement##
Brandt (F)	-0.0564	17.902	11.2684	0.0138	0.008	Poor
Brandt (M)	0.2781	8.9843	5.6521	0.0487	0.0136	Poor
Counahan-Barratt	0.2634	0.7158	1.5219	0.4516	0.1189	Poor
Flanders	0.2049	0.855	0.5177	0.8724	0.1787	Poor
FM equation	0.2453	0.7384	1.1803	0.5737	0.1407	Poor
Geo et al	-0.0711	0.4581	2.1074	0.2824	-0.0201	Poor
H-independent	0.0639	0.502	2.2803	0.26	0.0166	Poor
Hoste	0.303	0.7961	1.1358	0.5984	0.1813	Poor
Leger	0.1241	0.5626	1.425	0.4576	0.0568	Poor
Pottel et al	0.111	0.7291	0.6339	0.7992	0.0887	Poor
Q (age) F	0.19	6.33	4.255	0.0813	0.0155	Poor
Q (age) M	0.3096	0.9495	0.4703	0.8993	0.2784	Poor
Q (height)	0.2396	0.9269	0.4868	0.8918	0.2137	Poor
Schwartz	0.2189	0.8117	0.4807	0.8792	0.1924	Poor
Schwartz (2012)	0.2653	0.4462	0.6027	0.6556	0.174	Poor
Schwartz-bedside (2009)	0.2634	0.6875	1.3523	0.5037	0.1327	Poor
Schwartz-Lyon	0.2189	0.7339	0.7839	0.7377	0.1615	Poor
U-Shwartz	0.1997	0.7198	0.8545	0.7044	0.1407	Poor

Fig 2: The scatter plots of the Lin's correlation.



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Author's Contribution:

Term	Author
Conceptualization	NM, FK, AMZ
Methodology	NM, FK, AMZ
Software	NM,
Validation	NM, FK, AMZ
Formal analysis	NM
Investigation	NM, FK, AMZ
Resources	FK
Data Curation	NM
Writing - Original Draft	NM
Writing - Review & Editing	NM, FK, AMZ
Visualization	NM, FK, AMZ
Supervision	FK, AMZ
Project administration	NM

Equation	Equation estimating GFR (mL/min)
Flanders metadata	$k \times \frac{\text{height (cm)}}{\text{serum creatinine (mg/dL)}} \times \frac{\text{BSA (m}^2\text{)}}{1.73\ \text{m}^2}$ $k = (0.0414 \times \ln(\text{age})\ (\text{years}) + 0.3018)$
Univariate-Schwartz	$\frac{42.3 \times \text{height (m)}}{\text{serum creatinine (mg/dL)}^{0.78}} \times \frac{\text{BSA (m}^2\text{)}}{1.73\ \text{m}^2}$
Height-independent	$\frac{107.3 \times Q}{\text{serum creatinine (mg/dL)}} \times \frac{\text{BSA (m}^2\text{)}}{1.73\ \text{m}^2}$ $Q = 0.0270 \times \text{age (years)} + 0.2329$
Rhodin-FFM	$\left(\frac{\text{FFM (kg)}}{70}\right)^{0.632} \times \frac{\text{PMA (weeks)}^{3.33}}{55.4^{3.33} + \text{PMA (weeks)}^{3.33}} \times 112$
Schwartz-Lyon	$\frac{37 \times \text{height (cm)}}{\text{serum creatinine (}\mu\text{mol/L)}} \times \frac{\text{BSA (m}^2\text{)}}{1.73\ \text{m}^2}$ (37 if males aged > 13 years) $\frac{33 \times \text{height (cm)}}{\text{serum creatinine (}\mu\text{mol/L)}} \times \frac{\text{BSA (m}^2\text{)}}{1.73\ \text{m}^2}$ (other children)
Rhodin-NFM	$\left(\frac{\text{NFM (kg)}}{70}\right)^{0.75} \times \frac{\text{PMA (weeks)}^{3.4}}{47.7^{3.4} + \text{PMA (weeks)}^{3.4}} \times 121$
Pottel-Belgium or Q (age)	$\frac{107.3 \times Q}{\text{serum creatinine (mg/dL)}} \times \frac{\text{BSA (m}^2\text{)}}{1.73\ \text{m}^2}$ Q=0.21+0.057 ×age (years)-0.0075 × age^2+0.00064 × age^3-0.000016 × age^4 (for boys) Q=0.23+0.034 ×age (years)-0.0018 × age^2+0.00017 × age^3-0.0000051 × age^4 (for girls)
Q (height	$\frac{107.3 \times Q}{\text{serum creatinine (mg/dL)}} \times \frac{\text{BSA (m}^2\text{)}}{1.73\ \text{m}^2}$ Q=3.94-13.4 ×height (m)+17.6 × height^2 (m)-9.84×height^3 (m) +2.04× height^4 (m) (for boys and girls)
Schwartz (16)	$\frac{36.5 \times \text{height (cm)}}{\text{serum creatinine (}\mu\text{mol/L)}} \times \frac{\text{BSA (m}^2\text{)}}{1.73\ \text{m}^2}$
Brandt ml=min	k=0.95 (males), 1.05 (females)
Bedside Schwartz ml/ min/1.73m^2	$0.413X \frac{hight\ (cm)}{SCr\ (\frac{mg}{dl})}$
Gao et al	0.68(Ht/Scr)^2-0.0008(Ht/Scr)^2+ 0.48X age-(21.53 in males or 25.68 in females)
Pottel et al	107.3/(Scr/Q) (Q=0.0270 X age+ 0.2329) (Cr in μmol/L)
Hoste et al	107.3/(Scr/Q) (Q= 3.94-13.4L+17.6L^2-9.84L^3+2.04L^4 (L in Meter)
FM equation	kL/Scr (k=0.0414×ln(Age)+0.3018)
Counahan-Barratt	0.43L (cm)/PCr (mg/dL)
Leger *et al.*	0.641[weight/Scr] + 16.063[height2/Scr] (ht in m)
Schwartz et al (ScrEq2012)(17)	$GFR_{Scr} = 42.3 \times \left(\frac{(H/100)}{(Ccr/88.4)}\right)^{0.79}$