What clinicians and other stakeholders needs to know about special populations (for GFR estimation)

Workshop on drug dosing in Pediatric Patients with Renal Impairment
November 30th, 2023

Presented by:
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Schulich School of Medicine and Dentistry

Objectives

- Identify key special populations
- Understand the renal development and postnatal adaption of glomerular filtration rate (GFR)
- Understand the challenges of switching from pediatric to adult formulae
- Name two conditions where creatinine cannot be used for the estimation of GFR

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Definition of special populations

Definition of Special Populations

Patients with characteristics that render the usual approaches for estimation of GFR unusable e.g.,

- Not steady state
- Abnormal muscle mass
- Conditions that affect
  - body surface area calculation
  - change in metabolism
  - the biomarkers – i.e., CF with ++ inflammation

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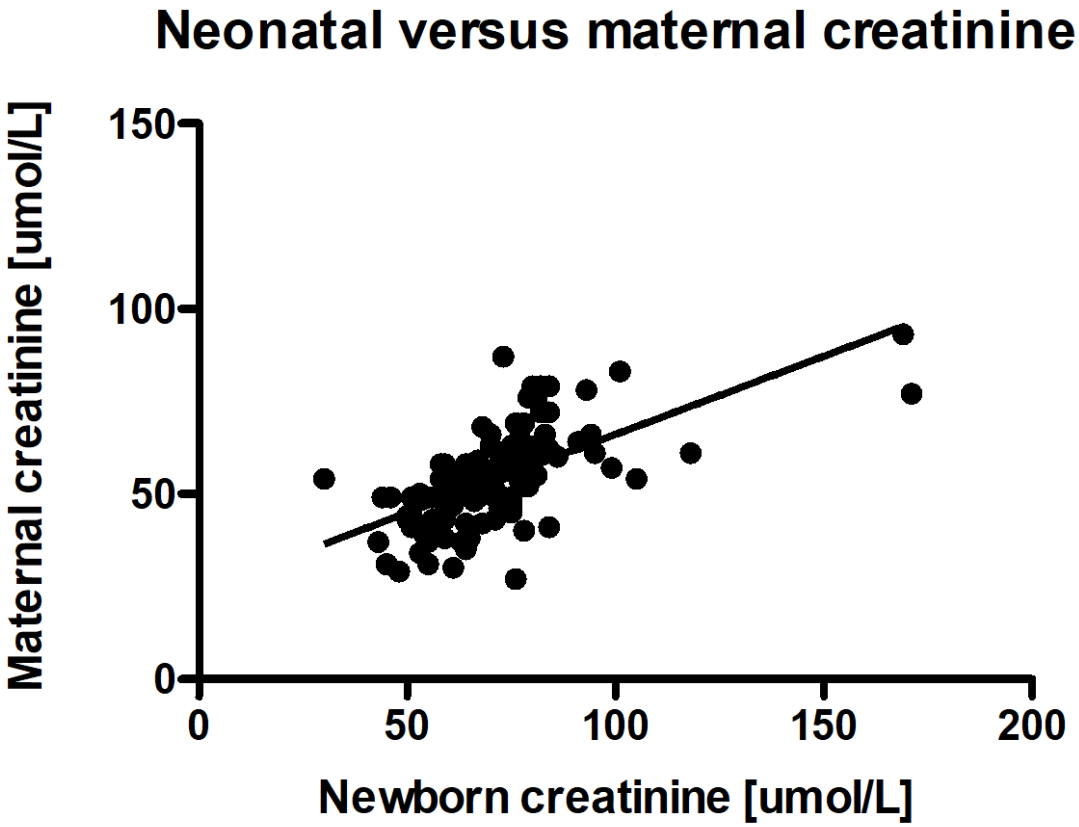
Newborns

How to measure GFR in Newborns?

a. Creatinine crosses the placenta. Even at 72 hours, there is a strong correlation between maternal and neonatal creatinine;
b. Very small amounts of Cystatin C cross the placenta (Nephrol Dial Transplant. 2012 Sep;27(9):3382-4);
c. Currently, beta trace protein appears not to cross the placenta (Clin Nephrol. 2014 Apr;81(4):269-76)
d. Carolyn Abitbol suggested to use renal volume as a surrogate GFR marker (J Pediatr. 2014 May;164(5):1026-1031)
e. Aminoglycoside levels (Curr Pharm Des. 2012;18(21):3114-8.)

Newborn and Premature Baby

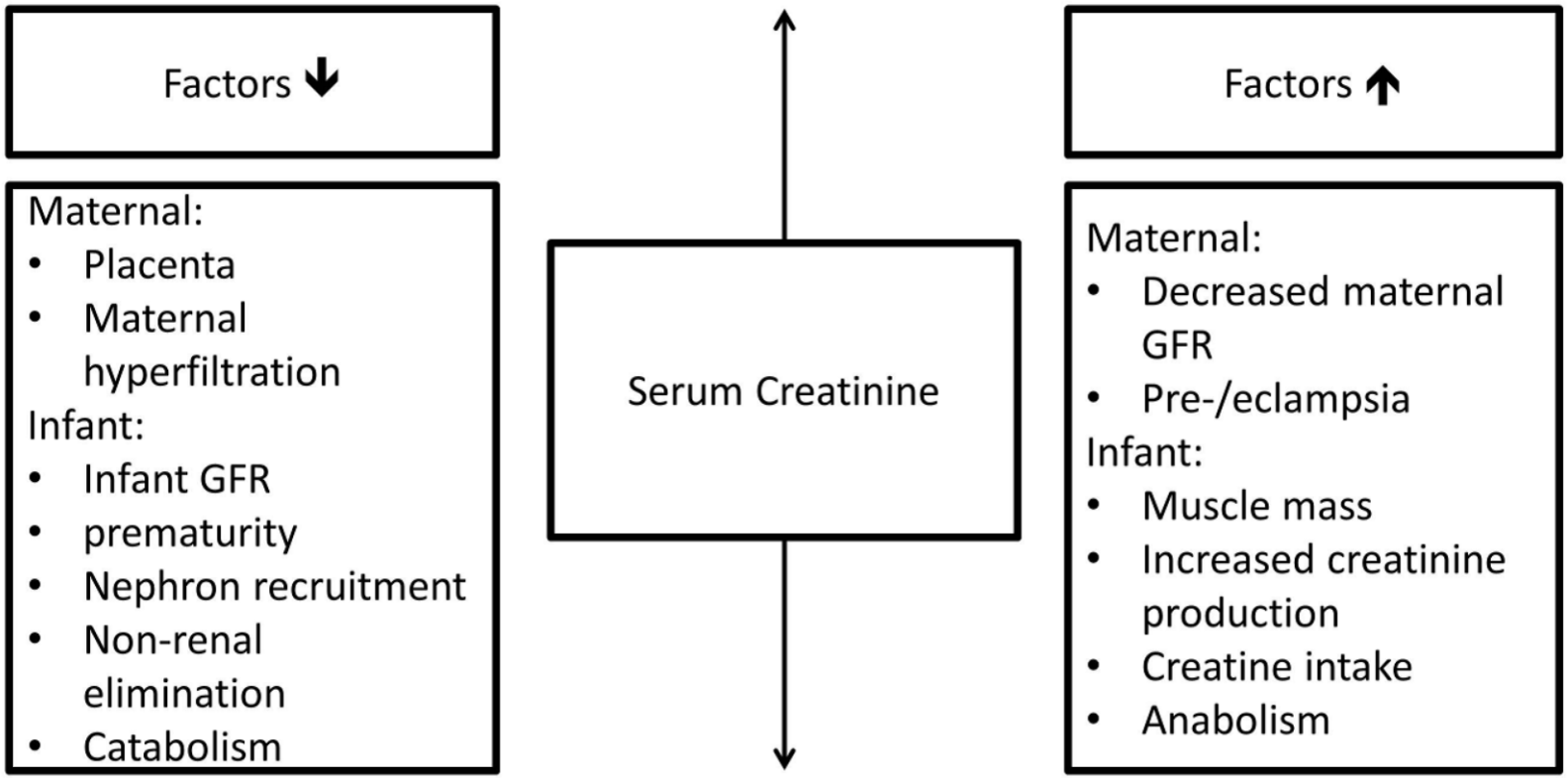
Creatinine reflects maternal values!



Even on day 3 of life, maternal and baby creatinine correlate r=0.287 p=0.003

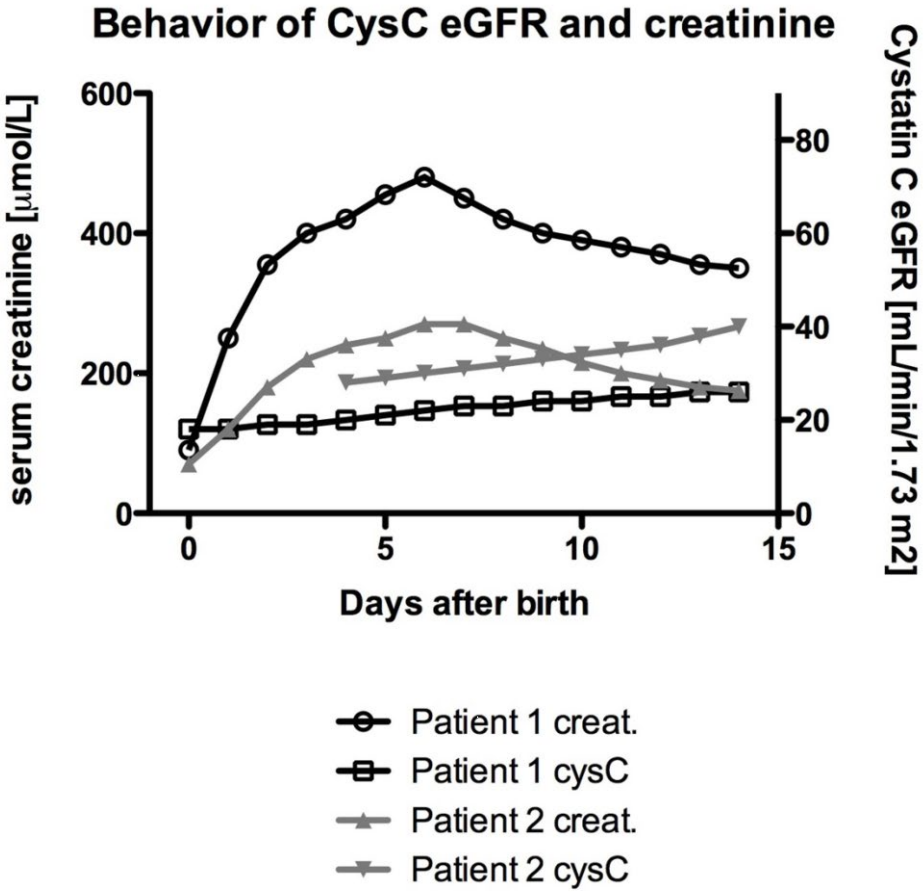
Bariciak E... Filler G, *Clin Biochem*. 2011 Sep;**44**:1156-9.

Factors influencing Neonatal Creatinine



Filler G et al. *Curr Opin Pediatr*. 2016 Apr;28(2):173-9. doi: 10.1097/MOP.0000000000000318.

Behavior of CysC and Creatinine in Neonates with Renal Dysplasia

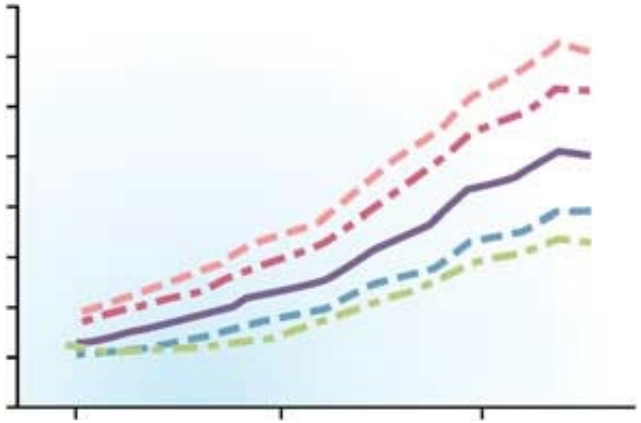


Filler G et al. *Curr Opin Pediatr*. 2016 Apr;28(2):173-9. doi: 10.1097/MOP.0000000000000318.

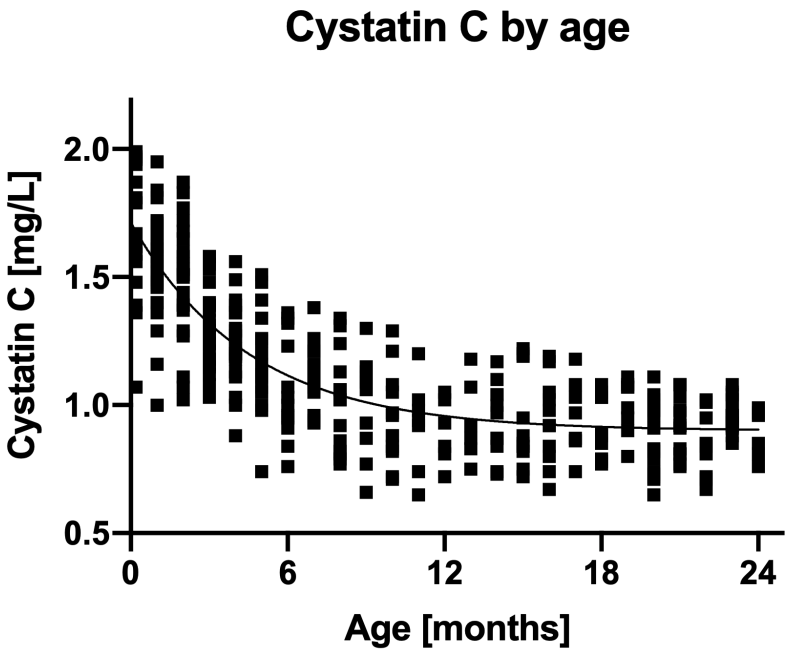
3

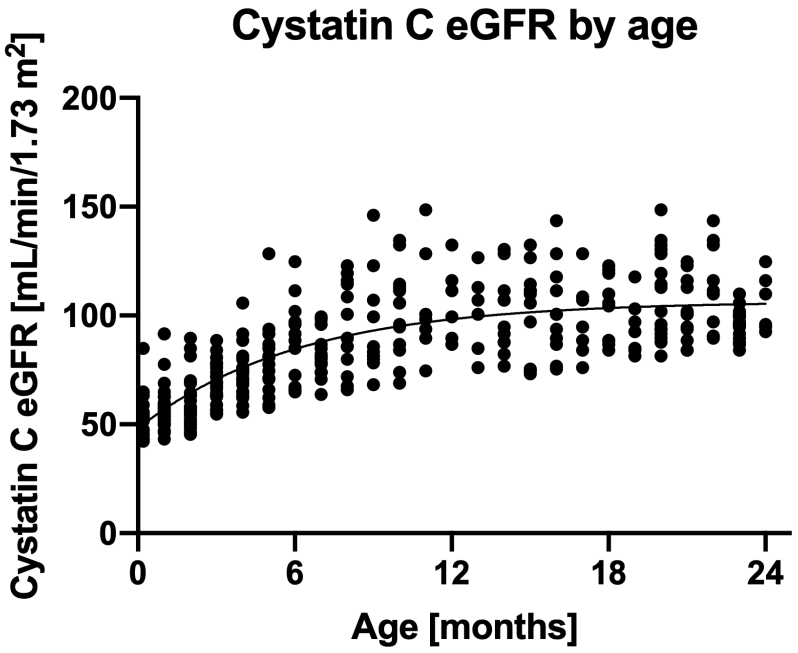
Infants and Toddlers

Postnatal Adaptation of GFR



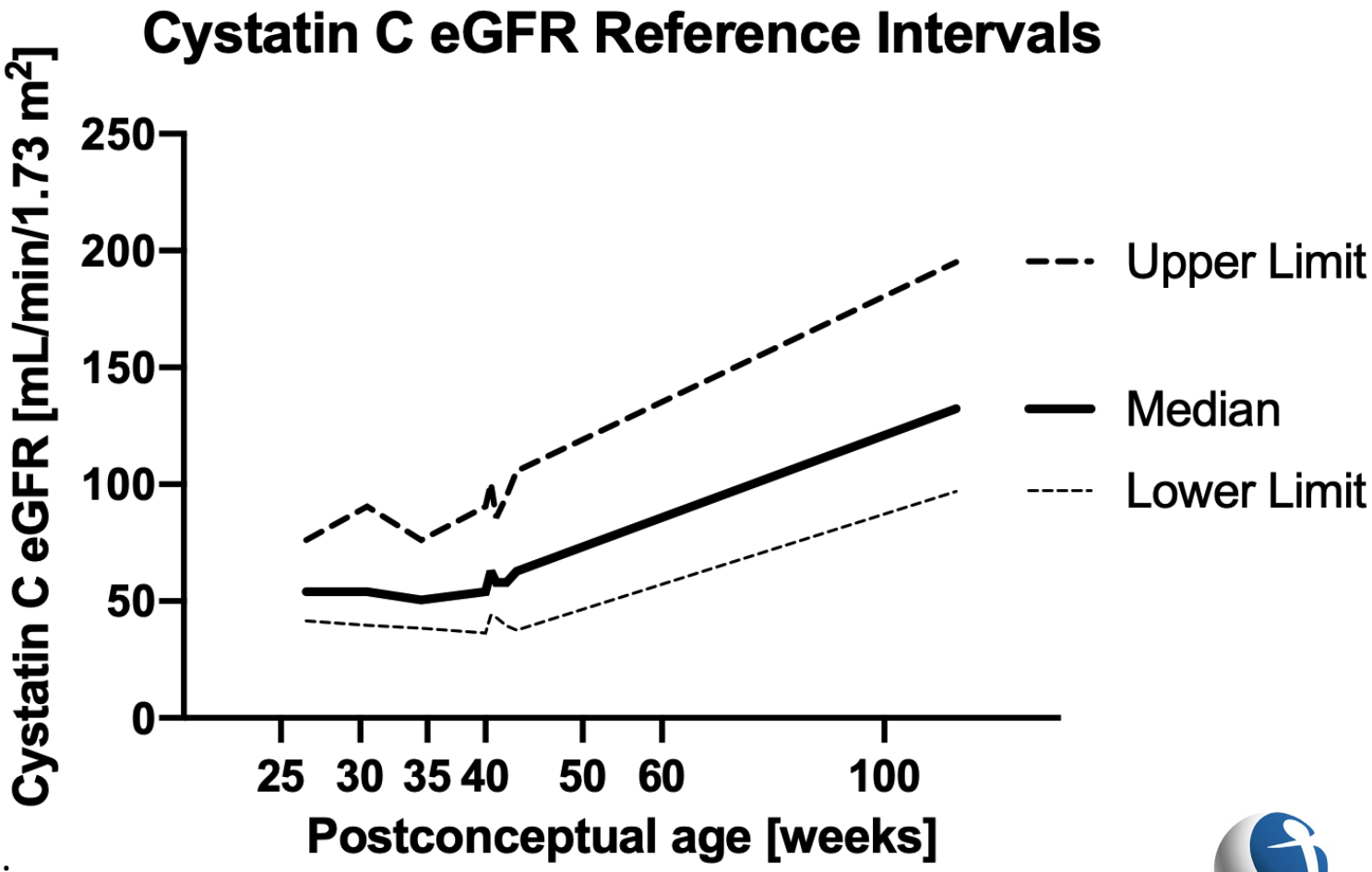
Filler G. *Kidney Int*, 2011 Sep;80:567-8. doi: 10.1038/ki.2011.172





Filler G et al. *Acta Paediatr.* 2021 Mar; 110(3):773-780. doi: 10.1111/apa.15557.

CysC eGFR in preterm/term infants



Filler G et al. *Acta Paediatr.* 2021 Mar; 110(3):773-780. doi: 10.1111/apa.15557.

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4

Abnormal legs

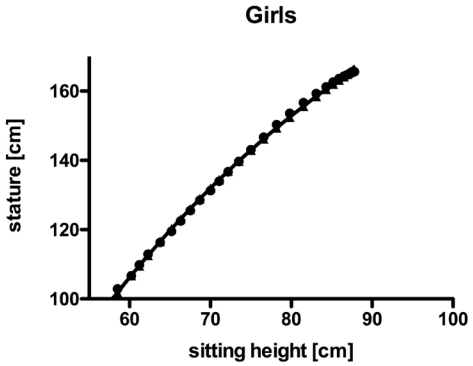
BSA calculation with abnormal legs

- You need an accurate height for BSA calculation

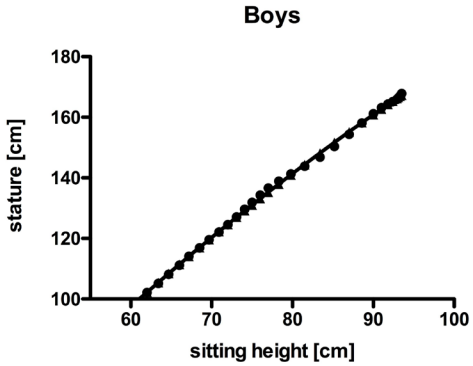
- Calculate stature either on sitting or knee height
  - For girls, Stature = 239+(241.7+239)*(1-EXP(-0.0211*sitting height[cm])
  - For boys, Stature = -84.1+(399.4+84.1)*(1-EXP(-0.00785*sitting height[cm])

Pediatr Nephrol. 2018 Nov;33(11):2037-2046. doi: 10.1007/s00467-017-3852-8.

BSA estimation with abnormal legs

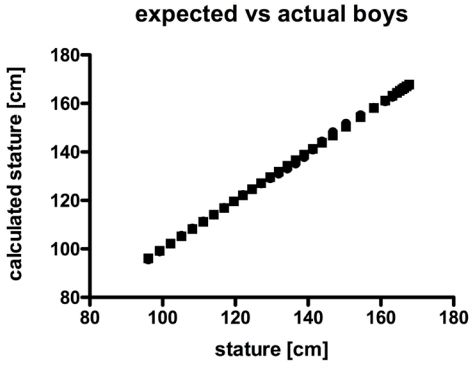


One-phase association
Best-fit values
Y0 -239.0
Plateau 241.7
K 0.02110
Tau 47.40
Half-time 32.85
Span 480.7



One-phase association
Best-fit values
Y0 -84.10
Plateau 399.4
K 0.007850
Tau 127.4
Half-time 88.29
Span 483.5

Number of XY Pairs 31
Spearman r 0.9991
95% confidence interval 0.9981 to 0.9996
P value (two-tailed) < 0.0001
P value summary ****
Exact or approximate P value? Gaussian Approximation
Is the correlation significant? (alpha=0.05) Yes



Number of XY Pairs 31
Spearman r 1.000
95% confidence interval 1.000 to 1.000
P value (two-tailed) < 0.0001
P value summary ****
Exact or approximate P value? Gaussian Approximati
Is the correlation significant? (alpha=0.05) Yes

Filler G et al. *Pediatr Nephrol.* 2018 Nov;33(11):2037-2046. doi: 10.1007/s00467-017-3852-8.

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Measuring the Knee Height

Distance from the posterior surface of the thigh (proximal to the patella) to the sole of the foot with the knee is bent at a 90^{o} angle.

- White boys Stature = 40.54 + (2.22 knee height)
  [R^2] = .96; RMSE = 4.16; CV = 2.79.
- Black boys Stature = 39.60 + (2.18 knee height)
  [R^2] = .95; RMSE = 4.44; CV = 2.99.
- White girls Stature = 43.21 + (2.15 knee height)
  [R^2] = .95; RMSE = 3.84; CV = 2.63.
- Black girls Stature = 46.59 + (2.02 knee height)
  [R^2] = .94; RMSE = 4.25; CV = 2.91.

Chumlea WC et al. *J Am Diet Assoc* 94:1385-1388, 1391 DOI: 10.1016/00 8223(94)92540-2

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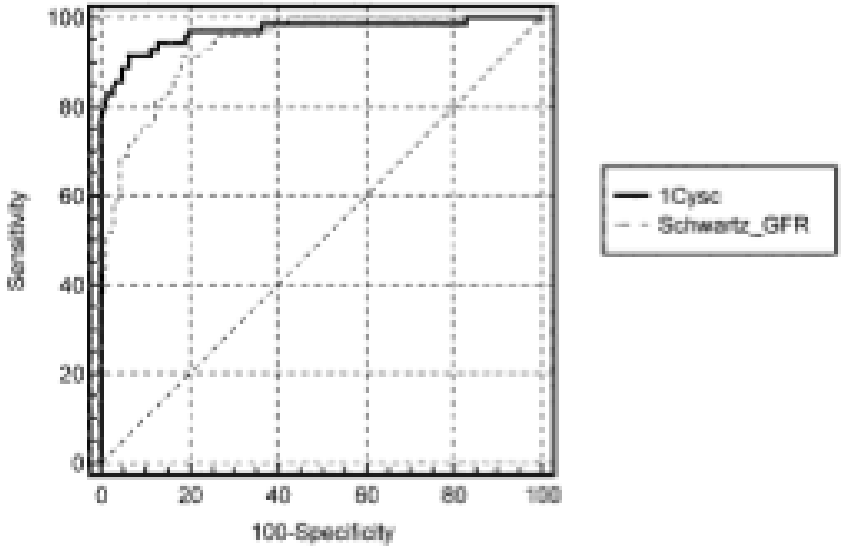
Spina bifida

CysC in Spina Bifida

- Improved performance with Cystatin C compared to Schwartz estimates
- Similar findings by Morgan C (Pediatr Nephrol. 2008;23(2):329-32)
- A Swedish group recently found Cystatin C still insensitive in comparison to nuclear medicine scans (J Urol. 2008;179(6):2407-9.)



ROC plots. Difference in areas 0.034, standard error 0.015, 95% confidence interval 0.005 to 0.062, p = 0.024. *Cysc*, cystatin C. *GFR*, glomerular filtration rate.

Pham-Huy A et al. *J Urol.* 2003;169:2312-2315 doi: 10.1097/01.ju.0000060205.23406.13.

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Muscular dystrophy

Muscular Dystrophy

- eGFR formulae using serum creatinine difficult to interpret in patients with muscular dystrophy.

- Formulae such as the Filler, Larsson or Zapitelli based on cystatin C-only appear to be more reliable in these patients.

Filler G et al. *Pediatr Nephrol.* 2018 Nov;33(11):2037-2046. doi: 10.1007/s00467-017-3852-8.

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Other populations

High Muscle Mass

- May lead to underestimation of eGFR using creatinine, but cystatin C is more accurate.
- Acute, strenuous exercise can temporarily decrease true GFR
- Creatine falsely elevates serum creatinine, but true GFR is unaffected. Consider cystatin C-only based eGFR estimation.

Oncology Patients

- May have normal renal function pre-treatment, but chemotherapy may negatively affect the renal function.
- Chemotherapeutic agents are often renally excreted, and they have narrow therapeutic windows.
- Neither the creatinine- nor cystatin C-based equations accurately measure GFR after chemotherapy.
- Nuclear GFR measurements may be more appropriate for these patients.

Cystic Fibrosis

Para-meter	Simple Schwartz Cr	Univariate Schwartz 2012 Cr	Univariate Schwartz 2012 Cys C	Univariate Schwartz 2012 BUN	Bivariate Schwartz 2012 Cr + CysC	Bivariate Schwartz 2012 Cr + BUN	Bivariate Schwartz 2012 CysC + BUN	Multi-variate Schwartz 2012 all	Multi-variate Schwartz 2012 Final	Böken-kamp 1998	Filler 2003	Grubb 2005	Zappitelli 2006 CysC	Zappitelli 2006 CysC + Cr	Bouvet 2006
Number of XY Pairs	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
Pearson r	0.6608	0.6596	0.1781	0.2449	0.5815	0.6315	0.2645	0.5965	0.6841	0.1764	0.1869	0.1963	0.1841	0.5048	0.1685
95% confidence interval	0.2639 to 0.8663	0.2619 to 0.8658	-0.3310 to 0.6069	-0.2673 to 0.6492	0.1399 to 0.8302	0.2165 to 0.8532	-0.2478 to 0.6611	0.1623 to 0.8372	0.3030 to 0.8766	-0.3326 to 0.6058	-0.3228 to 0.6126	-0.3141 to 0.6186	-0.3255 to 0.6108	0.03178 to 0.7931	-0.3571 to 0.6131
P value (two-tailed)	0.0039	0.0040	0.4941	0.3434	0.0143	0.0065	0.3050	0.0115	0.0025	0.4983	0.4725	0.4503	0.4795	0.0388	0.5327
Significant	**	**	ns	ns	*	**	ns	*	**	ns	ns	ns	ns	*	ns
Within 10%	47.1%	11.8%	5.9%	23.5%	23.5%	64.7%	41.2%	41.2%	41.2%	29.4%	35.3%	0.0%	41.2%	58.8%	23.5%

Wallace A, et al., *Can J Kidney Health Dis*. 2020 Jan 15:7:2054358119899312. doi: 10.1177/2054358119899312.

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Young adults

RESEARCH ARTICLE Open Access

Low agreement between modified-Schwartz and CKD-EPI eGFR in young adults: a retrospective longitudinal cohort study

Michael Webster-Clark[1], Byron Jaeger[3], Yi Zhong[2], Guido Filler[4,6*], Ana Alvarez-Elias[5], Nora Franceschini[1] and Maria E. Díaz-González de Ferris[2]

Abstract

Background: While there is a great deal of research updating methods for estimating renal function, many of these methods are being developed in either adults with CKD or younger children. Currently, there is limited understanding of the agreement between the modified new bedside Schwartz estimated glomerular filtration rate (eGFR) formula and the adult CKD-EPI formula in adolescents and young adults (AYAs) with chronic kidney disease (CKD) measured longitudinally.

Methods: Longitudinal cohort study of 242 patients (10–30 years) with CKD, followed retrospectively in a single tertiary centre as they transitioned from the paediatric- to adult-focused settings. The study population came from a longitudinal cohort of AYAs undergoing healthcare transition at the STARx Program at the University of North Carolina, in the South-Eastern USA, from 2006 to 2015. We calculated and compared the eGFR using the new bedside Schwartz formula and the CKD-EPI eGFR. Measurements were repeated for each age in years. Agreement was tested using Bland & Altman analysis. Subgroup analysis was performed using the following age groups 10–15, 15–20, 20–25 and 25–30 years, glomerular and non-glomerular causes of CKD and height z-score.

Results: Using repeated measures, concordance between the new Schwartz and CKD-EPI eGFR was low at 0.74 (95% C.I. 0.67, 0.79) at the lowest age range of 10–15, 0.78 (95% C.I. 0.71, 0.84) at age 15–20, 0.80 (0.70, 0.87) at ages 20–25, and 0.82 (95% C.I. 0.70, 0.90) at age 25–30. Discordance was worse in males and largest in the 10–15 year-old age group, and in patients with stunted growth.

Conclusions: The Schwartz and CKD-EPI equations exhibit poor agreement in patients before and during the transition period with CKD-EPI consistently yielding higher eGFRs, especially in males. Further studies are required to determine the appropriate age for switching to the CKD-EPI equation after age 18.

Keywords: CKD, eGFR, CKD-EPI, Schwartz formula, Paediatric to adult transition

Low Agreement modified Schwartz and CKD-EPI

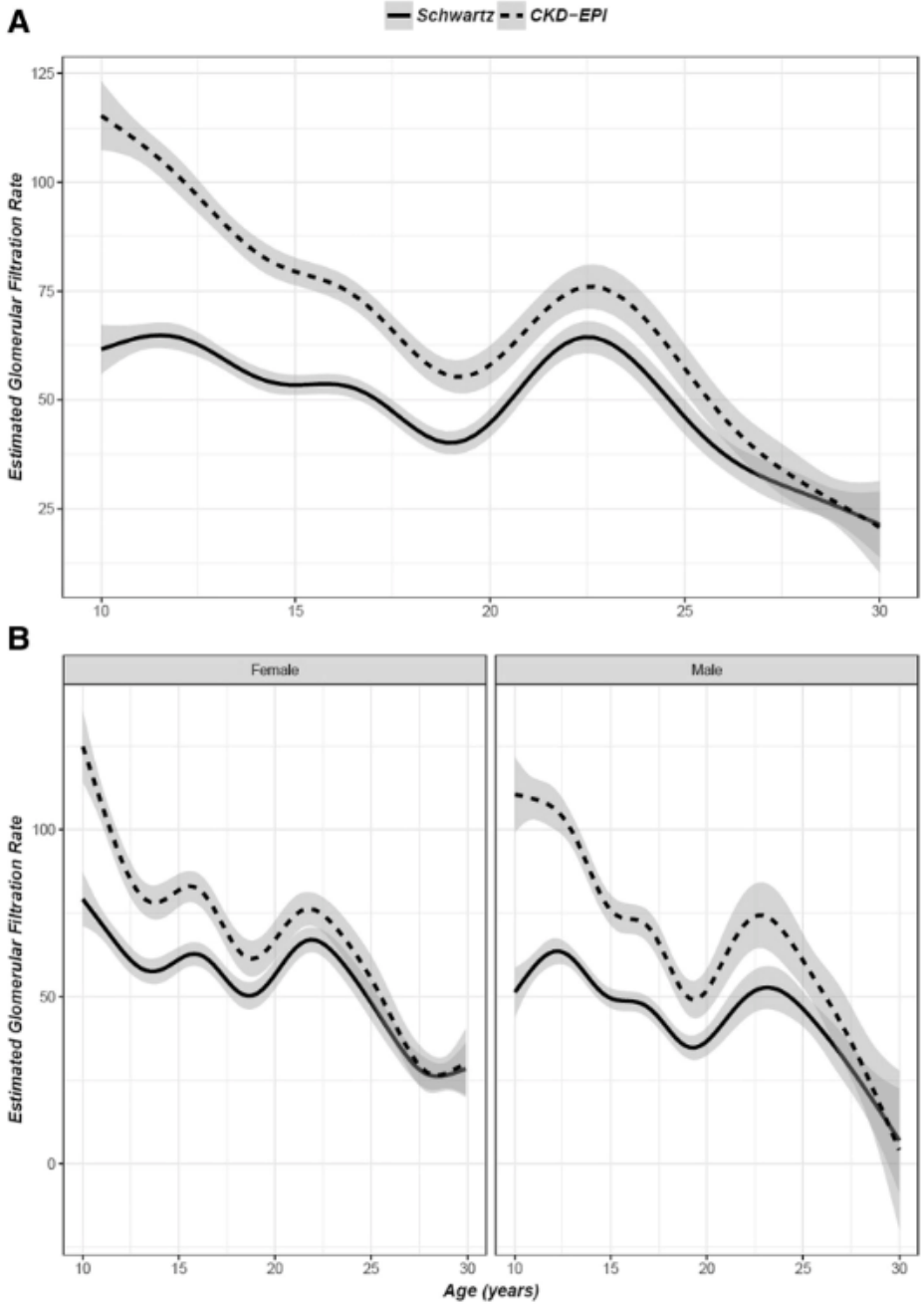
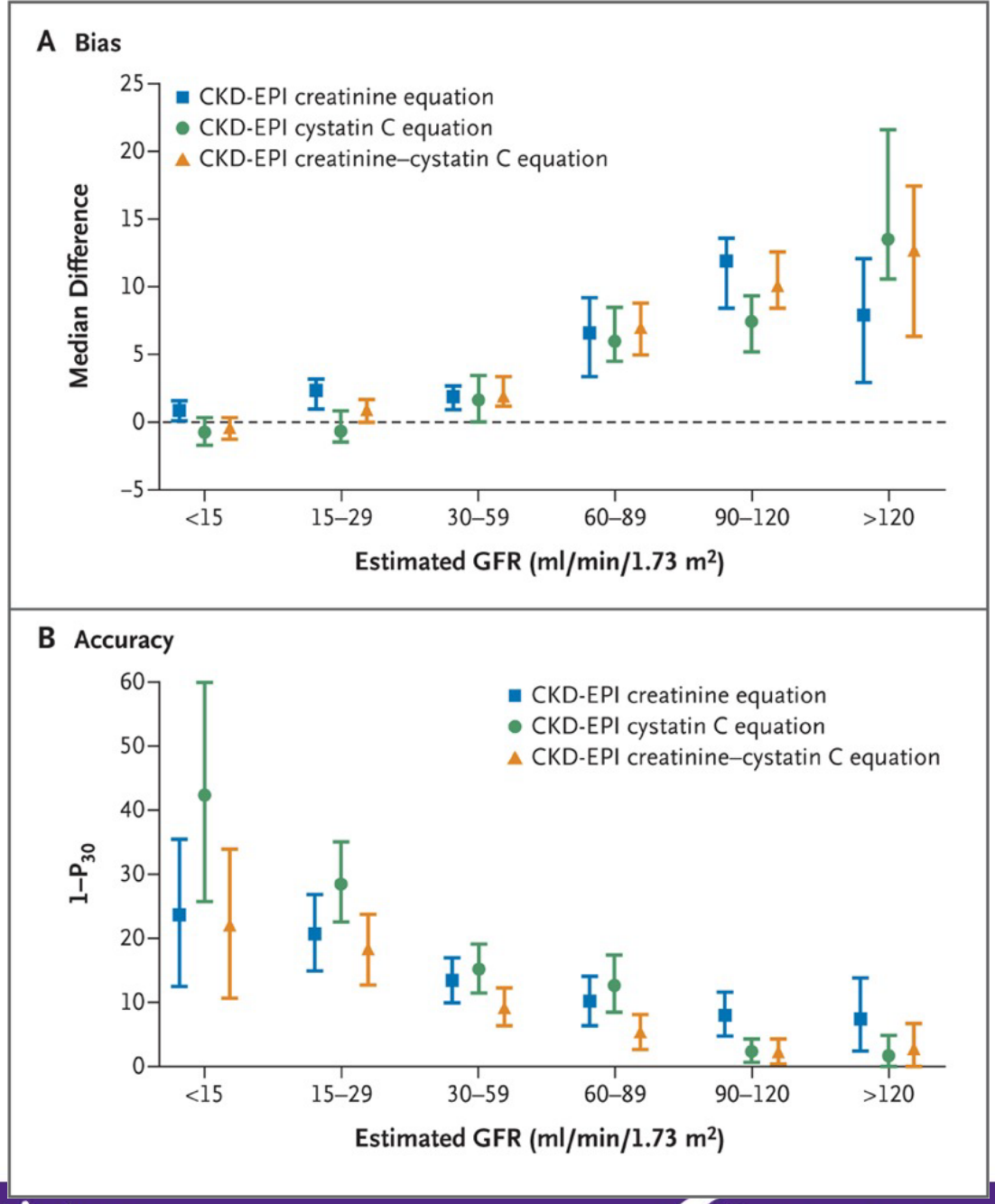
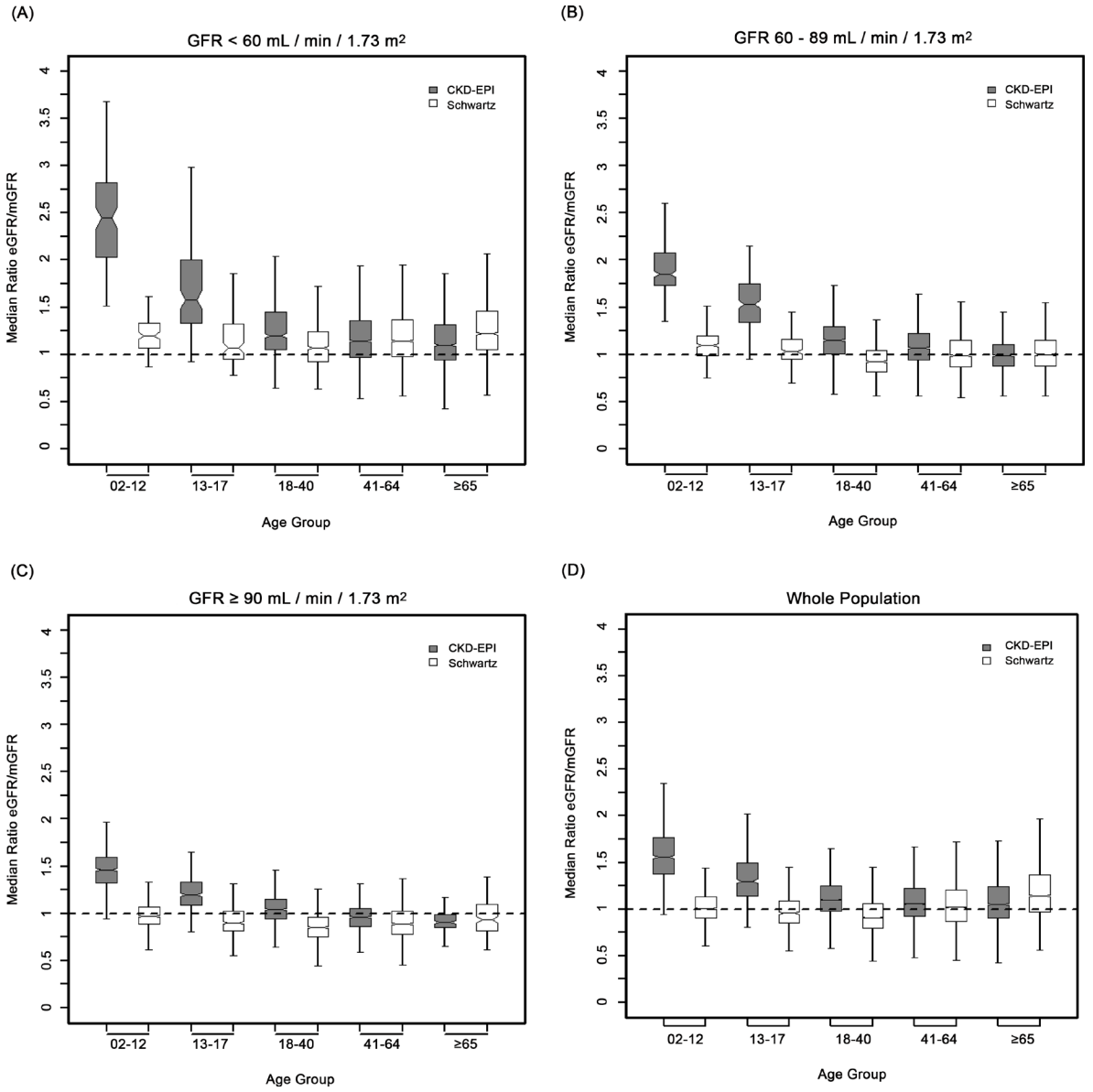


Fig. 1 Estimated Glomerular Filtration Rates by Age and Estimating Equation. Legend: These figures describe trends in eGFR over time based upon the CKD-EPI equation (dashed line) or the Schwartz equation (solid line). Panel **a**) describes the overall population trajectory, while Panel **b**) depicts separate trajectories for males (on the right) and females (on the left)



Helmersson-Karlqvist J et al.
Sci Rep. 2021 Mar 15;11(1):5882.
doi: 10.1038/s41598-021-85370-8.

Low Agreement modified Schwartz and CKD-EPI



Selistre L et al. *PLoS Med.* 2016 Mar 29;13(3):e1001979. doi: 10.1371/journal.pmed.1001979.

Pediatric Nephrology
https://doi.org/10.1007/s00467-023-06185-5

ORIGINAL ARTICLE

Limitations of U25 CKiD and CKD-EPI eGFR formulae in patients 2–20 years of age with measured GFR > 60 mL/min/1.73 m^2—a cross-sectional study

Guido Filler[1,2,3] · Fateh Ahmad[4] · Vipin Bhayana[4] · Maria E. Díaz González de Ferris[5] · Ajay P. Sharma[1]

Received: 2 July 2023 / Revised: 22 September 2023 / Accepted: 26 September 2023

Abstract

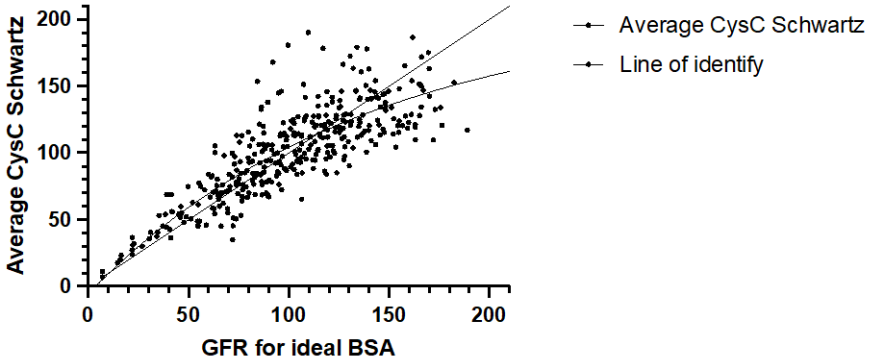
Background When applying Pierce U25 formula for estimating glomerular filtration rate (eGFR), we observed a higher proportion of eGFR < 90 mL/min/1.73 m^2 (chronic kidney disease (CKD) stage 2). We compared agreement and accuracy of the Pierce U25 (ages 2–25), Pottel (ages 2–100), and CKD-EPI (ages 18–100) formulae to GFR measurements.

Methods Post hoc analysis of the three eGFRs compared to 367 ^{99}m technetium-diethylene-triamine penta-acetic acid (^{99}Tc DTPA) GFR measurements (240 patients) using 3 sampling points and Brockner/Mørtensen correction (body surface area calculation based on ideal weight) on simultaneous serum creatinine and cystatin C measurements.

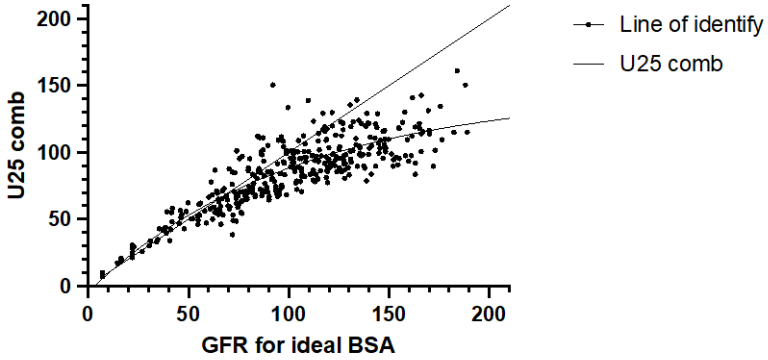
Results Overall, the U25 formula performed well with a Spearman r of 0.8102 (95% confidence interval 0.7706 to 0.8435, $p < 0.0001$) while diagnostic accuracy was low in patients with normal mGFR. The U25 formula reclassified 29.5% of patients with normal mGFR as CKD stage 2; whereas the average of the modified Schwartz formula based on serum creatinine and the Filler formula based on cystatin C, only over-diagnosed CKD stage 2 in 8.5%, 24.5% within 10% and 62.7% within 30%. We therefore combined both. The average Schwartz/Filler eGFR had 36.5% of results within 10%, 84.7% within 30%, and normal mGFR accuracy was 26.8%, 63.9% for 10% and 30%, respectively, outperforming the CKD-EPI and Pottel formulae.

Conclusions The Pierce U25 formula results correlated well with mGFR < 75 mL/min/1.73 m^2. Over the entire GFR range, accuracy was better for patients with a higher mGFR, when averaging the combined Schwartz/Filler formulae. More work is needed to prospectively confirm our findings in other centers.

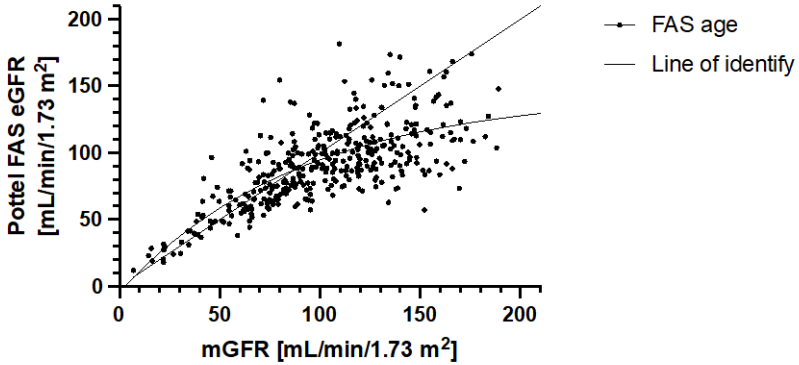
New CysC-Schwartz



U25 [U25 comb]



FAS age



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Summary special populations

Summary

- While serum-creatinine-based eGFR estimation is widely used, in special populations it may yield misleading measurements.
- Special populations are often patients with comorbidities that require closer attention to their kidney function.
- Wrong eGFR interpretation has significant implications.
- Special populations require alternative methods for accurate kidney function measurement.

Pediatric Nephrology
https://doi.org/10.1007/s00467-017-3852-8

EDUCATIONAL REVIEW

Educational review: measurement of GFR in special populations

Guido Filler[1,2,3,4] · Misan Lee[1]

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Abstract

Importance Changes in kidney function are typically followed by the sequential estimation of glomerular filtration rate (eGFR). Formulae for eGFR work well on a population basis, but there are well-known conditions where they do not work.

Objective The purpose of this review is to summarize the existing literature on special populations in the pediatric age range and provide recommendations on how to estimate GFR in these populations.

Findings The reliability of creatinine depends on muscle mass, while cystatin C (not widely available) is limited by inflammation and changes in protein catabolism. Various dietary factors can alter eGFR. Renal function in neonates changes drastically every day, and there are currently no satisfactory reference intervals for routine pediatric use. Gender effects and conditions such as wasting disease and obesity require alternative ways to obtain eGFR. In oncology patients, chemotherapy may negatively affect renal function, and nuclear GFR measurements may be necessary. For body builders, high muscle mass may lead to underestimation of eGFR using creatinine.

Conclusions and relevance Clinicians should be aware of special populations that may yield misleading eGFRs with conventional creatinine-based formulae, and that the alternative methods may be more appropriate for some populations.

Keywords Spina bifida · Newborn · Wasting disease · eGFR · Gender · Diet · Oncology

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Thank You