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Comparison of the performance of different formulae to assess eGFR in children after allogenic hematopoietic stem cell transplantation

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Introduction There is an ongoing debate concerning the right formula to estimate GFR in pediatric oncological patients or recipients of hematopoietic stem cell transplantation.
Material and methods We did a retrospective analysis of renal function data before and up-to 3 years post hematopoietic stem cell transplantation (HSCT). We checked the accuracy and bias of eGFR based on Revised *Bedside* Schwartz equation 2009 (Schwartz 2009), Flanders Metadata (FLANDERS), CKiD U25 Creatinine (U25CREA), and CKiD U25 Cystatin C (U25CYSC) against Creatinine-Cystatin C-Urea-based CKiD Equation (Schwartz Combined 2012) as the reference.
Results We included 179 patients (67.0% female, 20.7% chronic kidney disease) aged 8.5 (5.5) years. Overall eGFR based on the U25CYSC formula performed best (baseline and 3-year follow up percentage of values outside the confidence limits 3.9, and 3.3%, respectively). One year after HSCT the best performance was offered by Schwartz 2009 formula (2.8% of outliers). No other studied formula in the overall analysis had the percentage of outliers less than 5%. FLANDERS had lowest and U25CYSC highest mean error (0.21 vs –22.53 ml/min/1.73 m^2, respectively). The root mean square error was lowest for FLANDERS (26.9) and highest for U25CYSC (32.36). Both 30% and 10% accuracy was highest for FLANDERS (91.06 and 42.46%, respectively), and lowest for U25CYSC (78.77 and 31.28%, respectively).
Conclusions There were small differences in accuracy between simpler eGFR formulae against the reference formula, however we observed differences in error. The U25CYSC offered best accuracy but largest error leading to underestimation of eGFR. Therefore, when applying given formula, one must be mindful of its potential limitations and potential inherent biases.

Key Words: renal function ‹› eGFR ‹› children ‹› HSCT

INTRODUCTION

The assessment of renal function is crucial in the practice of medicine at large. Both in adults and children, nephrologists, urologists, but also intensive care specialists, internists and specialists in other medical fields rely on its assessment. The assessment of kidney function is mainly based on its filtration status. Exact assessment of glomerular filtration rate (GFR) seems nearly impossible as the process of filtration occurs continuously in all nephrons, on average 1 million in each kidney, that daily filter approximately 180 liters of fluid [1]. Therefore, filtration is measured indirectly by clearance of endogenous or exogenous substances. However, the measurements enabling direct assessment of the renal clearance of endogenous substances are not easy to obtain as they

require, on top of drawing blood samples, collection of 24 hour urine samples [2–4]. These may be especially difficult to obtain when patient's collaboration is difficult to secure, i.e. in children, older adults with cognitive impairment, immobilized patients and persons with cognitive deficits irrespective of their age [4, 5]. Therefore, to estimate GFR (and thus obtain eGFR) in clinical practice we use the formulae linking age, body build, and serum concentrations of compounds that undergo renal clearance [6, 7].

The first such equation was published by Efferosome in 1957 [8]. Over the years not only new markers of filtration have been discovered [9–11], but new equations to estimate filtration rate were designed to better fit patients depending on their sex, age body size etc. and therefore, achieve more accurate result. By far the most widely used in clinical practice are Bedside Schwartz, MDRD an Cockcroft-Gault formula, but the number of equations mentioned in literature that are based on serum creatinine exceeds 50 [8], which means that none of them is offering perfect estimation of GFR.

In children estimation of renal filtration remains even more challenging due to various reasons [6, 12]. Pediatric patients present with wide age, drastically differing body-build, and intravascular volume [13–15]. Although several studies compared several methods to assess eGFR [7, 16], to the best of our knowledge the literature lacks in studies assessing prospectively wide spectrum of formulate before and after priming and subsequent pediatric hematopoietic stem cell transplantation (HSCT), especially as the number of long-term HSCT survivors is growing [17–19] with a range renal pathologies described as complications of the procedure [20, 21]. Therefore, we decided to assess, using the formula by Schwartz 2012 as a reference across wide age-range, in patients with and without chronic kidney disease (CKD), the performance of four widely used formulae to assess eGFR.

MATERIAL AND METHODS

We performed a retrospective analysis of data gathered at the at the Department of Clinical Immunology and Transplantation, Polish-American Pediatric Hospital, Jagiellonian University Medical College, Krakow, Poland, including pediatric patients who underwent allogenic HSCT between October 2008 and August 2019. Briefly, for current analysis we gathered information on patient's age, sex, height, body mass, presence of CKD, serum creatinine, cystatin-C and urea or blood urea nitrogen (BUN). We gathered data up to year 3 of follow-up as there were no new CKD cases after that time-point.

Table 1. *Equations used for calculation of eGFR in our study (based on [12])*

Name (text abbreviation)	eGFR calculation	Additional information
Revised *Bedside* Schwartz equation 2009 (Schwartz)	eGFR, ml/min/1.73 m^2 = k × height, cm/serum creatinine, mg/dl	k = 0.413
Creatinine-Cystatin C-based CKiD Equation (Schwartz 2012, Schwartz combined – *Reference method*)	eGFR = $39.8 \times [ht/Scr]^{0.456} \times [1.8/cysC]^{0.418} \times [30/BUN]^{0.079} \times [1.076^{male}]\ [1.00^{female}] \times [ht/1.4]^{0.179}$	eGFR (estimated glomerular filtration rate) = ml/min/1.73 m^2 BUN (blood urea nitrogten) = mg/dl cysC (cystatin C) = mg/l ht (height) = meters Scr (standardized serum creatinine) = mg/dl
Flanders Metadata (FLANDERS)	eGFR = k × height/serum creatinine, mg/dl	k = 0.0414 × ln[age] + 0.3018
CKiD U25 Creatinine (U25CREA)	eGFR = k × (height, m/sCr, mg/dl)	For males, k is calculated as: Age 1 to <12 years old: $39.0 \times 1.008^{(age-12)}$ Age 12 to <18 years old: $39.0 \times 1.045^{(age-12)}$ Age 18 to 25 years old: 50.8 For females, k is calculated as: Age 1 to <12 years old: $36.1 \times 1.008^{(age-12)}$ Age 12 to <18 years old: $36.1 \times 1.023^{(age-12)}$ Age 18 to 25 years old: 41.4
CKiD U25 Cystatin C (U25CYSC)	eGFR = k × (1 / cysC, mg/l)	For males, k is calculated as: Age 1 to <15 years old: $87.2 \times 1.011^{(age-15)}$ Age 15 to <18 years old: $87.2 \times 0.96^{(age-15)}$ Age 18 to 25 years old: 77.1 For females, k is calculated as: Age 1 to <12 years old: $79.9 \times 1.004^{(age-12)}$ Age 12 to <18 years old: $79.9 \times 0.974^{(age-12)}$ Age 18 to 25 years old: 68.3

Based on these data we calculated the following estimated Revised *Bedside* Schwartz equation 2009 (Schwartz 2009), creatinine-cystatin C-based CKiD Equation (Schwartz Combined 2012),
Flanders Metadata (FLANDERS), CKiD U25 Creatinine (U25CREA), CKiD U25 Cystatin C (U25CYSC) (Table 1) We then assumed, based on literature [9, 14, 21–23], that the method published by Schwartz in 2012 (Schwartz Combined 2012) utilizing apart from anthropometric parameters, creatinine, cystatin C and BUN offers highest accuracy [24]. We included the patients without eGFR missing data at baseline.

Statistical analysis

Data management and statistical analyses were done using SAS 9.4 (SAS Institute Inc. Cary, NC, USA) and R version 4.5.1 (R Core Team, 2025). To assess accuracy, we calculated the differences between each tested formula and the reference method, together with their 95% confidence intervals (CIs), and plotted these differences against the corresponding arithmetic means (Bland-Altman plots). We calculated the percentage of observations extending outside the 95% CI as a measure of precision. The Bland–Altman plots were created for each formula at four time points across the entire cohort, and separately for patients with and without CKD. Diagnosis of CKD was based on eGFR or proteinuria or urinary abnormalities or abnormalities detected in imaging studies [22]. For clarity, the latter plots were restricted to baseline and year 3 follow-up. Additionally, baseline plots were stratified by age tertiles to explore potential age-related variation.

Presence of over 5% observations outside the 95% CI was indicative of reduced precision. To further characterize individual-level variation, we calculated the mean error (ME) as the average difference between the tested and reference GFR values, and the root mean square error (RMSE) as the square root of the mean squared differences. Finally, we evaluated clinical accuracy by determining the proportion of estimates falling within ±30% and ±10% of the reference method.

Bioethical standards

We obtained a consent of the Jagiellonian University Committee for Ethics in Research (No. approval: 118.0043.1.16.2025) to perform the analysis.

RESULTS

The mean (SD) age of 179 patients with non-missing data for the baseline variables (67.0% female) was 8.5 (5.5) years. We obtained measurements at baseline, after 1, 2 and 3 years of follow-up. Of the total number of 179 patients 37 (20.7%) were diagnosed with CKD during follow-up. eGFR was routinely calculated based on Bedside Schwartz formula. Table 2 presents the median (p5-p95) values of eGFR based on the tested methods.

The analysis of accuracy

Overall, for the U25CYSC the percentage of observations outside the 95%CI for the difference with the reference formula were 3.9, 6.1, 8.0 and 3.3, respectively for the four timepoints. For U25CREA

Table 2. *Summary of eGFR values at baseline (median [P5–P95]) ml/min/1.73 m²*

Variable	Overall	CKD+	CKD–	Age Tertile 1 (0.0–5.0 years)	Age Tertile 2 (5.1–11.5 years)	Age Tertile 3 (11.6–20.8 years)	Schwartz Combined (2012) Tertile 1 (16.0–119.0)	Schwartz Combined (2012) Tertile 2 (119.0–148.0)	Schwartz Combined (2012) Tertile 3 (148.0–288.0)
U25CYSC	105.5 (59.3–166.9)	98.7 (37.4–157.9)	108.2 (65.6–170.4)	105.5 (58.9–166.7)	114.4 (67.5–157.3)	102.6 (39.8–161.5)	81.7 (34.2–110.4)	107.4 (73.8–146.4)	138.7 (102.5–201.8)
U25CREA	139.3 (74.5–223.5)	131.9 (62.1–196.4)	140.9 (79.3–229.8)	133.9 (74.4–234.2)	161.2 (94.6–209.5)	131.9 (59.9–223.9)	103.0 (60.7–148.7)	139.9 (104.3–219.8)	177.2 (133.5–234.2)
FLANDERS	131.0 (53.7–206.5)	116.0 (49.6–195.2)	134.0 (64.0–210.7)	109.0 (48.8–191.7)	151.5 (85.9–204.3)	133.0 (59.5–222.3)	89.0 (42.2–129.0)	134.0 (102.9–192.0)	168.0 (122.9–229.0)
Schwartz	135.0 (83.0–197.1)	135.0 (72.2–163.8)	134.0 (85.0–197.9)	125.0 (77.5–180.4)	142.5 (89.0–197.4)	122.0 (76.9–196.2)	111.5 (67.0–162.1)	136.0 (103.5–176.1)	155.0 (108.1–226.3)
Schwartz Combined (2012)	135.0 (60.5–187.4)	120.0 (47.0–181.4)	135.0 (80.2–186.9)	119.5 (55.8–180.5)	139.5 (89.8–188.4)	133.0 (45.0–187.8)	95.5 (44.7–116.1)	135.0 (120.0–147.0)	168.0 (150.9–251.2)

Schwartz Combined (2012) – eGFR based on creatinine, cystatin C, and BUN (Schwartz 2012); Schwartz – eGFR based on creatinine only (Schwartz 2009); FLANDERS – Fladers Metadata, U25CREA – CKiD U25 Creatinine, U25CYSC – CKiD U25 – Cystatin C

the percentages were 6.7, 6.1, 5.5, and 7.2. For FLANDERS the percentages were 7.3, 6.7, 7.4, and 5.9, and for Schwartz they were 6.1, 2.8, 6.1, and 5.9, respectively (Figure 1). In the analysis stratified by CKD status, U25CYSC performed the best offering narrowest 95% CI for the difference with the reference formula and the lowest percentage of values outside of the range (Figure 2). In the analysis stratified by tertiles of patient's age at baseline, U25CYSC offered narrowest 95% CI and lowest percentage outside the confidence limits. In the sensitivity analysis checking the interaction with the changing tertile of reference formula, the percentage of observations outside the confidence band ranged from 5.0 in the lowest tertile for U25CREA and FLANDERS to 6.7 for U25CYSC and Schwartz 2009. The percentage was 5.0 for all four measures in the mid-tertile of the reference formula and ranged from 5.1% for U25CYSC and FLANDERS to 10.2% for U25 Crea (Figure 3).

The analysis of error of measurement

For baseline measurements, FLANDERS had lowest and U25CYSC highest mean error (0.21 vs –22.53 ml/min/1.73 m^2, respectively). The RMSE was lowest for FLANDERS (26.9) and highest for U25CYSC (32.36). Both 30% and 10% accuracy was highest for FLANDERS (91.06 and 42.46%, respectively), and lowest for U25CYSC (78.77 and 31.28%, respectively). Table 3 contains detailed results for all assessment methods. These results were mirrored after stratification by tertiles of age distribution, with FLANDERS, Schwartz and U25CREA performing better than U25CYSC (Tables 4 and 5).

DISCUSSION

We found that in pediatric patients before and up-to 3 years after the allo-HSCT the performance of the four formulae to estimate GFR, that is U25CYSC, U25CREA, FLANDERS, and Schwartz 2009, when contrasted with formula by Schwartz (2012) display variable consistency and agreement. Overall, we found that for the U25CYSC formula there was a good consistency of measurements. However, it tended to underestimate eGFR as measured with the Schwartz 2012 formula. FLANDERS, was closest to the reference formula and Schwartz 2009 and U25CREA performed in that regard slightly worse than FLANDERS but better than U25CYSC. This

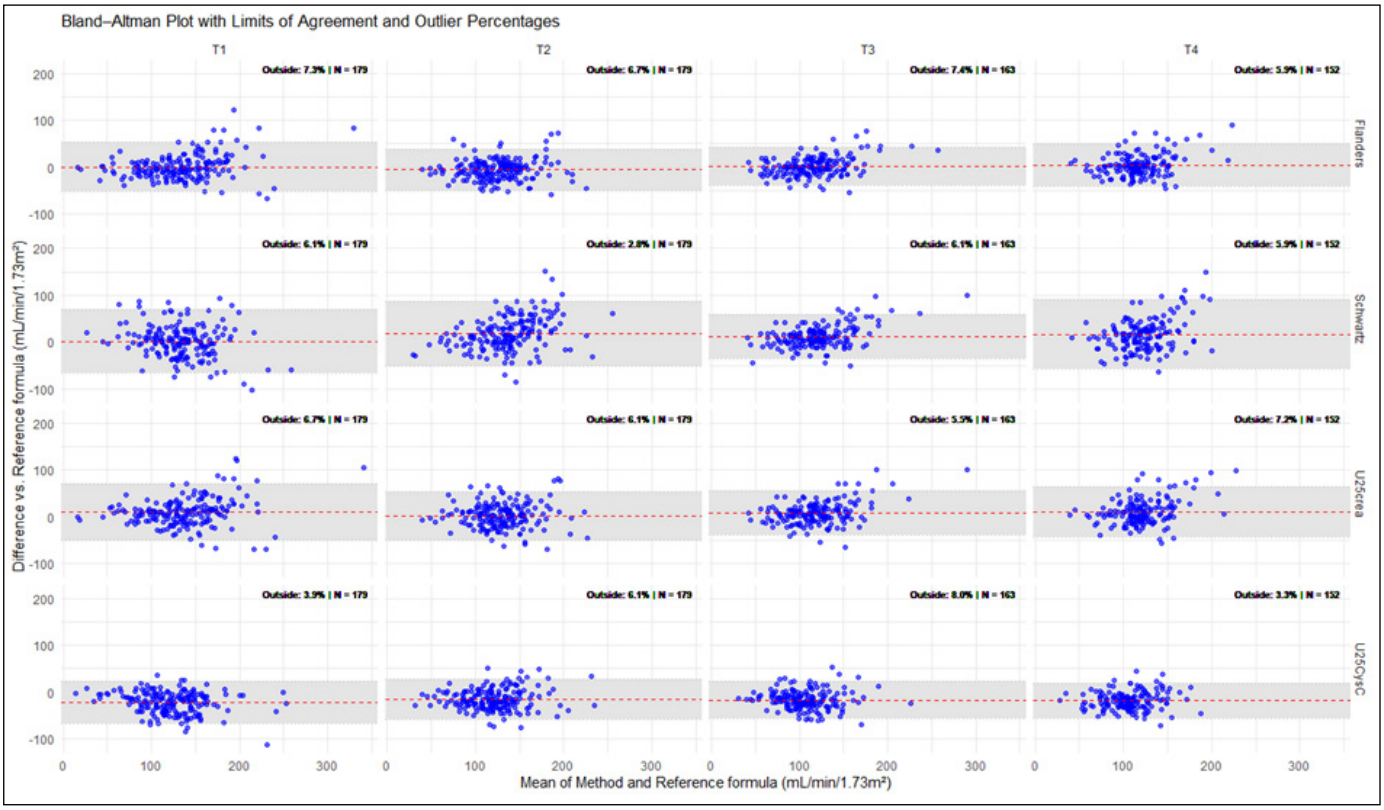

Figure 1. *The Bland-Altman plots at baseline, and at year 1, 2 and 3 of follow-up.*

T1-T4 – timepoints. T1 – baseline; T2, 3, 4 – follow-up at 1, 2, 3 years

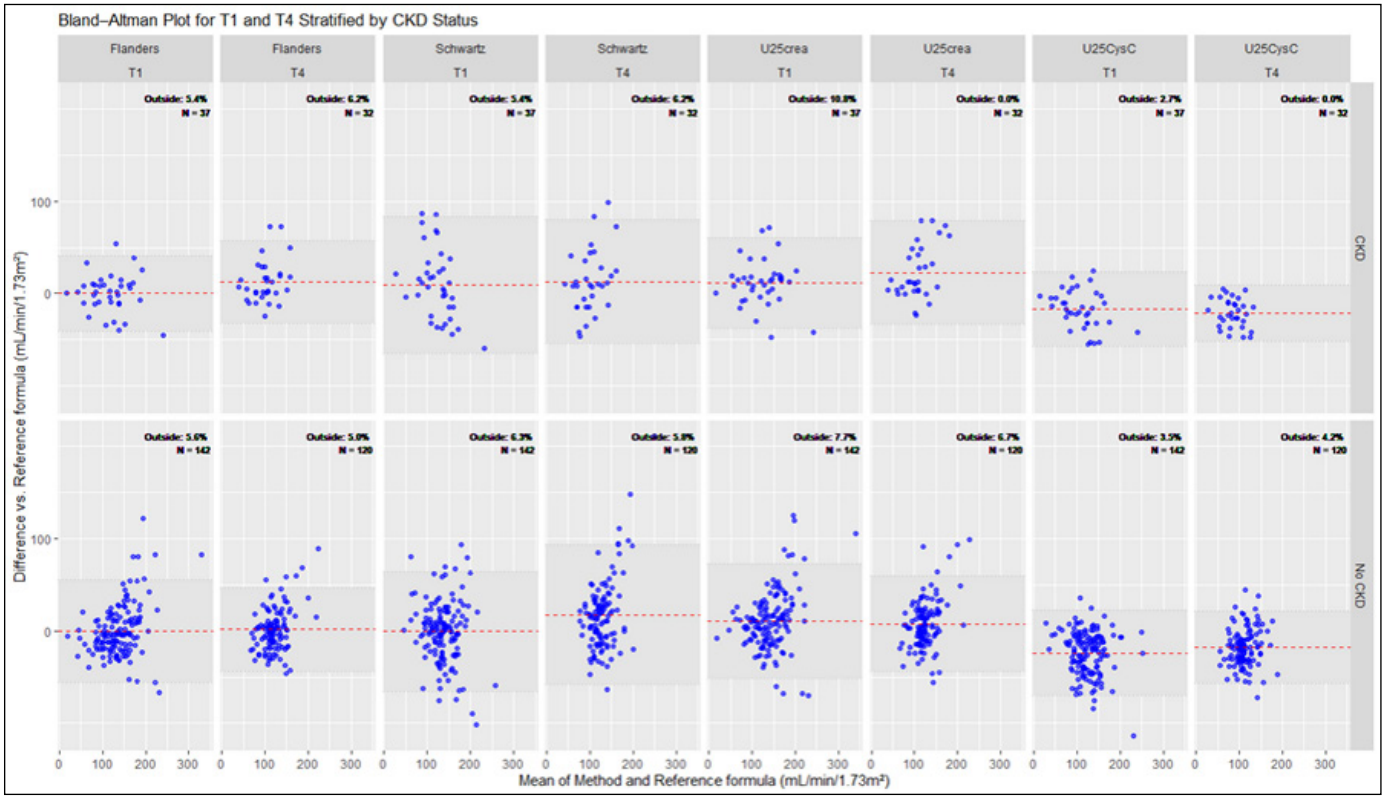

Figure 2. *The Bland-Altman plots stratified by CKD status at baseline and year 3 of follow-up.*
T1-T4 – timepoints. T1 – baseline; T4 – follow-up at 3 years

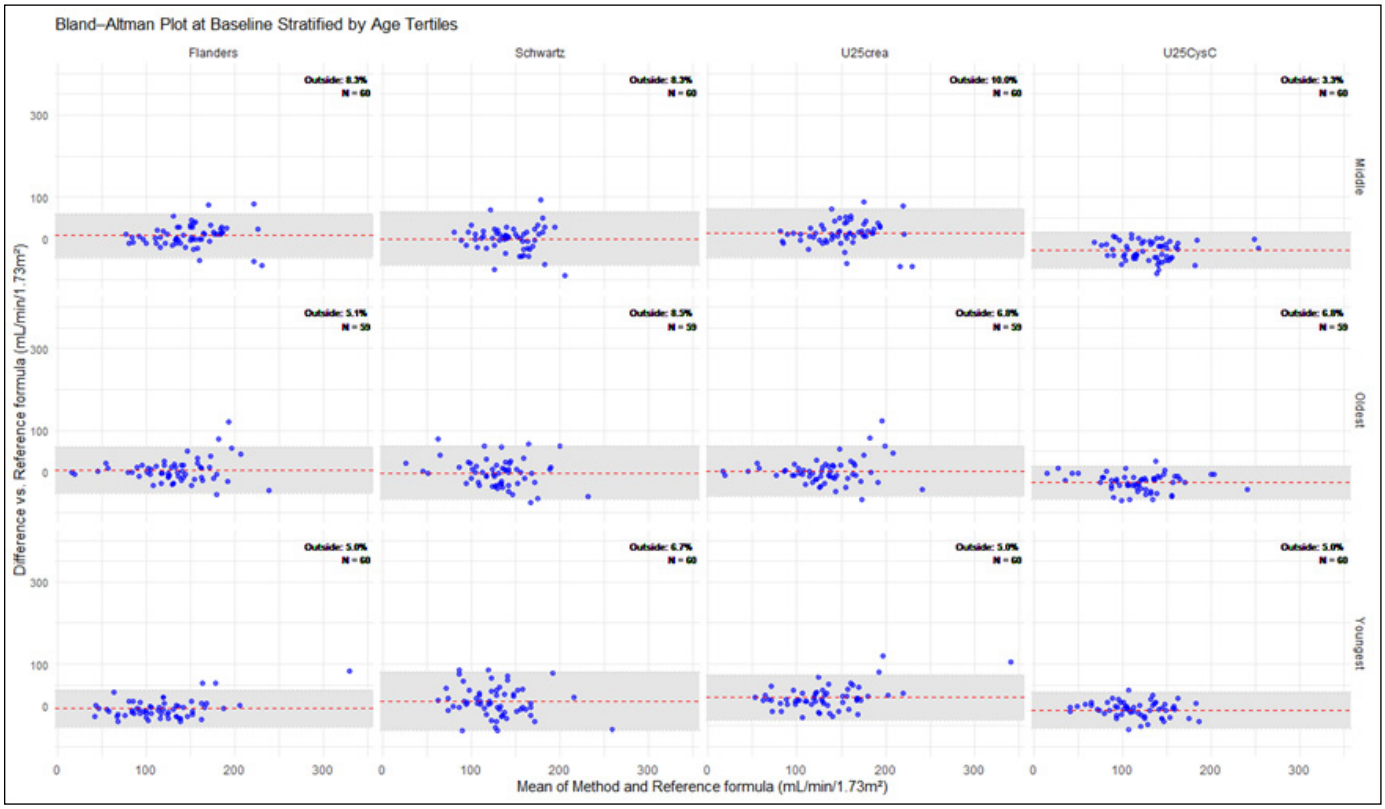

Figure 3. *The Bland-Altman plots stratified by tertiles of age distribution at baseline.*

was largely independent of the CKD status and age. Based on the numerical results the U25CYSC formula could offer best consistency, however underestimating eGFR to a large degree. FLANDERS was closest to the reference formula. Despite the fact that in the Bland-Altman analysis higher percentage extended outside the 95% interval it probably offers best performance when contrasted with the reference formula based on the assessment of 3 different parameters associated with renal function (Schwartz).

In the past several studies in pediatric population compared the various modalities used to estimate renal function. Llanos-Paez et al. investigated different formulae in paediatric oncology patients compared to a chromium 51-labeled ethylene di-

Table 3. *Composite ranking of eGFR equations*

Method	ME	RMSE	Accuracy_30	Accuracy_10	Pct_Outside_LoA	TotalScore
FLANDERS	0.21	26.90	91.06	42.46	7.26	5.0
U25CREA	10.92	32.28	83.24	37.99	6.70	12.5
Schwartz	1.40	34.33	81.01	37.99	6.15	13.5
U25CYSC	–22.53	32.36	78.77	31.28	3.91	19.0

Schwartz Combined (2012) – eGFR based on creatinine, cystatin C, and BUN (Schwartz 2012); Schwartz – eGFR based on creatinine only (Schwartz 2009); FLANDERS – Fladers Metadata; U25CREA – CKiD U25 Creatinine; U25CYSC – CKiD U25 – Cystatin C

Table 4. Composite ranking by age tertiles

Group	Method	ME	RMSE	Accuracy_30	Accuracy_10	Pct_Outside_LoA	Total Score
Tertile 1 (0–5 years)	U25CYSC	–11.73	25.55	91.67	45.00	5.00	8
	FLANDERS	–8.55	24.32	88.33	35.00	5.00	10
	U25CREA	18.98	34.00	76.67	25.00	5.00	16
	Schwartz	9.05	37.02	71.67	35.00	6.67	16
Tertile 2 (5.1–11.5 years)	FLANDERS	6.30	27.37	93.33	48.33	8.33	7
	Schwartz	–2.23	33.01	88.33	41.67	8.33	12
	U25CREA	12.56	31.95	85.00	45.00	10.00	14
	U25CYSC	–30.10	37.46	70.00	28.33	3.33	17
Tertile 3 (11.6–20.8 years)	FLANDERS	2.92	28.83	91.53	44.07	5.08	7
	U25CREA	1.07	30.77	88.14	44.07	6.78	10
	Schwartz	–2.69	32.78	83.05	37.29	8.47	15
	U25CYSC	–25.81	32.94	74.58	20.34	6.78	18

Schwartz Combined (2012) – eGFR based on creatinine, cystatin C, and BUN (Schwartz 2012); Schwartz – eGFR based on creatinine only (Schwartz 2009); FLANDERS – Fladers Metadata; U25CREA – CKiD U25 Creatinine; U25CYSC – CKiD U25 – Cystatin C

Table 5. *Composite ranking by CKD status*

Group	Method	ME	RMSE	Accuracy_30	Accuracy_10	Pct_Outside_LoA	Total Score
CKD = 0	FLANDERS	0.28	28.28	90.85	40.14	5.63	7
	Schwartz	-0.74	33.15	82.39	40.14	6.34	11
	U25CREA	10.78	33.45	83.80	38.73	7.75	15
	U25CYSC	–23.83	33.65	76.06	34.51	3.52	17
CKD = 1	FLANDERS	–0.05	20.74	91.89	51.35	5.41	6
	U25CYSC	–17.51	26.83	89.19	18.92	2.70	13
	U25CREA	11.47	27.28	81.08	35.14	10.81	15
	Schwartz	9.59	38.52	75.68	29.73	5.41	16

Schwartz Combined (2012) – eGFR based on creatinine, cystatin C, and BUN (Schwartz 2012); Schwartz – eGFR based on creatinine only (Schwartz 2009); FLANDERS – Fladers Metadata; U25CREA – CKiD U25 Creatinine; U25CYSC – CKiD U25 – Cystatin C

amine tetraacetic acid excretion test and found that the FLANDERS metadata equation and univariate Schwartz showed best results in their study, however none of the equations appeared to be highly accurate [25].

Laskin et al. in the group of paediatric patients before HSCT described most current, estimating equations – concluding that cystatin C-based equations performed better than creatinine-based formulae, because of possible overestimation due to low muscle mass, for example in children with malnutrition. The sensitivity in detection of abnormal GFR was however still not satisfactory in detecting abnormal filtration rate [16].

Finally, Zachwieja et al. followed a group of 40 patients (both autologous and allogenic HSCT recipients) and checked the variability of glomerular filtration rate (eGFR) during one year follow-up. Their results underline low accuracy of Bedside-Schwartz-Formula compared to cystatin C-based equations [26, 23].

However, none of those studies addressed the assessment of renal function in paediatric patients undergoing the HSCT in terms of CKD. Also, those studies did not compare the performance of the particular formulae in the setting of repeated assessment over a prolonged period of time.

Numerous studies recommend calculating eGFR based on clearance of exogenous substances such as Inulin, ^{125}-Iothalamate, Iohexol, ^{51}Cr-EDTA or ^{99m}Tc- DTPA [9, 11] as they underline lack of interference with the individuals' own production and metabolism of the cleared substance. However, those markers remain difficult to implement in large-scale clinical practice as they frequently require specialized assays to determine results, multiple-time blood sampling is often needed. Their use might oppose cost effectiveness, practicality and last but not least the young patients' comfort. Moreover, any foreign matter administered to human body – particularly via intravenous injection, carries a potential risk of immunization and allergic reaction, which, should it occur carries a significant risk in terms of constitution of hematopoietic stem cells in a recipient and potential complication of graft-versus-host-disease [27, 28].

We demonstrate that the U25CYSC was associated with systematic bias and large individual error despite displaying best precision. However, the deviations we found in precision were not extreme, and thus the formulae with lowest error might be preferred. Clearly, more studies are needed convincingly to tip the scales towards the use of particular formula.

The question of the clinical significance of differences in eGFR values obtained based on various formulae remains open. When applying given formula, one must be mindful of its potential limitations and potential inherent biases.

Our study needs to be taken in the contexts of its limitations. First, we included patients with a broad range of age. However, to tackle this problem we did an analysis stratified by thirds of the age distribution. This analysis did not materially change our conclusions. Second, we performed a post-hoc analysis using all available retrospective data. We did not perform sample size analysis (instead we took data for all patients from a large tertiary care centre for whom at least the baseline values for all variables under study were not missing). Finally, we compared the eGFR methods with eGFR based on a reference formula in its turn. However, the formula by Schwartz Combined 2012 utilizes three different parameters of renal function. This renders it more accurate but also more expensive and thus rarely used in daily laboratory and clinical practice in Poland. On the other hand, the use of simpler solutions seems to offer good agreement [29, 30] with the values of the reference formula we chose for comparisons.

In conclusion, there is a tendency for some of the formulae to perform better than others. In light of small differences in precision, the lowest bias and best clinical accuracy should guide the choice of a formula to estimate GFR. More studies, and novel assessment methods and formulae, might however be needed before we could clearly advocate the use of one of those formulae and not the others.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

This research received no external funding.

ETHICS APPROVAL STATEMENT

The study was approved by the Jagiellonian University Committee for Ethics in Research (No. approval: 118.0043.1.16.2025).

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