ORIGINAL ARTICLE

CORRELATION OF GLOMERULAR FILTRATION RATE (GFR) ESTIMATION FORMULAE WITH MEASURED GFR IN PEDIATRIC ONCOLOGY PATIENTS

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Background: In patients with malignancy accurate assessment of renal function is important for administration of chemotherapeutic medicines. Measurement of GFR by inulin, EDTA clearance, iohexol and 24 hrs urinary creatinine clearance (Crcl) is cumbersome so creatinine based GFR formulas have been developed for assessment of kidney function and there are variety of GFR formulas available for clinical use. Objective was to determine the correlation of estimated GFR by creatinine-based estimation formulae with measured GFR by 24-hours creatinine clearance. **Methods:** A cross sectional study was conducted in which all patients who underwent measured GFR (mGFR) assessment at Oncology Unit of NICH between 1st January to 31st December 2019 were enrolled in the study. Estimated Glomerular filtration rate (eGFR) of all these patients was calculated by three formulae Original Schwartz (OS), Updated Schwartz (US) and simple height independent equation (SHID). Correlation was made with mGFR by Crcl taken as gold standard using Pearson's correlation and Linear regression analysis. Bland Altman analysis was also done to see the agreement between eGFR with mGFR. **Results:** Total sixty (60) patients were enrolled with mean age of 8.2±3.6 years. All three eGFR formulae exhibited a statistically significant positive correlation with mGFR (*p*-value <0.01). Linear regression analysis also showed a statistically significant relation between mGFR and eGFRs however, the developed regression models for all three formulae showed a low R2 values. Bland-altman analysis revealed that useful level of agreement does not exist between mGFR and eGFR by OS however, SHID and US were found to be in agreement with mGFR by Crcl. **Conclusion:** SHID and US equations give a good estimate of GFR and may be used in children with malignancies to estimate GFR.

Keywords: GFR; Estimation formulae; Cancer Children

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INTRODUCTION

In oncology patients, one of the major causes of morbidity and mortality is acute kidney injury (AKI). Renal dysfunction may be caused by direct and indirect effects of malignancy and its treatment.[1] Acute kidney injury is the most common side effect of chemotherapeutic agents in oncology patients secondary to glomerular or tubular dysfunction.[2,3] Mechanism of kidney injury by chemotherapeutic agents includes multiple factors like intrinsic kidney damage, pre-renal hypo perfusion, renal tubular necrosis and damage to microvasculature of kidney, renal capillary endothelial injury and renal tubulointerstitial disease.[2–5] Oncology patients are also treated with nephrotoxic antibiotics/antifungal agents like amphotericin B, aminoglycoside, and vancomycin for associated fungal and bacterial infections which may further enhance risk of AKI.[6]

Assessment of baseline kidney function are important before and during chemotherapy for drug doses adjustment and for avoiding complications of nephrotoxic drugs.[2,7] Glomerular filtration rate (GFR) is best marker for assessment of renal function and its decrease correlate with loss of function of nephrons and degree of kidney failure.[8,9] For measurement of GFR commonly used methods are inulin clearance, EDTA clearance and iohexol and 24hour creatinine clearance (Ccrl).[10]

Glomerular filtration rate assessment by inulin, EDTA clearance and iohexol is cumbersome and is not routinely done in clinical settings. 24hours Crcl requires 24hours urine collection which is also not feasible especially in young children for routine use of GFR measurement.[8]

Glomerular filtration rate estimation (eGFR) formulae have been developed for assessment of kidney function and there are variety of GFR formulas available for clinical use. eGFR formulas based on serum creatinine have been used since long and are most commonly employed for GFR monitoring at bed side among which most commonly used is Schwartz formula.[7,8,11] In 2012, KDIGO (kidney disease: Improving Global Outcomes) also recommended use of

Updated Schwartz formula for estimation of GFR in children.[12]

Though there are new reports of more efficacy by using cystatin C (CysC) based equations, but in oncology patients, it has limitation as corticosteroid therapy affects CysC levels in dose dependant manner and in children using steroids, eGFR may be underestimated.[13] Some adult studies have shown that CysC based equations may not reflect true change in GFR who are using nephrotoxic chemotherapy.[14,15]

The GFR validation by different formulae, mostly has been conducted in children cohort with subnormal GFR, which may not hold true for normal GFR ranges in oncology patients.[8]The measurement of GFR by inulin, EDTA clearance, iohexol and 24 hours urinary Crcl is cumbersome so we aimed this study to do the comparison of recently available creatinine based GFR formulae in paediatric cancer patients with creatinine clearance in order to provide data for suitable eGFR equation in oncological patients.

MATERIAL AND METHODS

This cross-sectional study was conducted in Oncology department of National Institute of Child Health (NICH) Karachi. Children with any malignancy who were registered in Oncology department OF NICH between 1st January 2019 to 31st December 2019 and whose 24hour urinary Crcl was measured, were included. Basic demographics including patients' weight in kilograms, height in centimetres and body surface area /m^2 were recorded in a semi-structured proforma. Clinical information regarding diagnosis and laboratory results of baseline tests including mGFR by 24hour urinary Crcl and serum creatinine of the same day were also recorded to calculate eGFR by three creatinine-based equations including Original Schwartz (OS) equation, Updated Schwartz (US) equation and Simple Height Independent (SHID) equation.

All data was entered and analyzed in SPSS version 23. Frequencies and percentages have been reported for categorical variables. Mean±S.D, were calculated for quantitative variables. Estimated Glomerular filtration rate (eGFR) was calculated using following three formulae.

1. **Original Schwartz (OS):** eGFR= k x height (cm)/s.cr (mg). where k=0.45 for full term infants, 0.33 for preterm infants, 0.55 for children above 12 months,
2. **Updated Schwartz** (**US**): eGFR = k x height (cm)/s.cr (mg) where k= 0.413
3. **Simple height independent (SHID) equation:** eGFR = 107.3/s.cr/Q where Q = 0.0270 x age in years + 0.2329.[10]

Shapiro-Wilk normality test was performed to check the normality of data for measured GFR (mGFR) by Crcl and estimated GFR (eGFR) by OS equation, SHID equation and US equation. Correlation of mGFR and eGFR by each of the three equations was determined using Pearson's correlation. Linear regression analysis was also done to identify y-intercept for GFR estimation by each formula. Bland Altman analysis was done to determine the agreement between mGFR by Crcl test (gold standard) and eGFR values by various formulae. Only p-values less than 0.05 were considered significant for all analyses.

Ethical Consideration: The study was approved by the Institutional ethical review board (IERB) of National Institute of Child Health Karachi (IERB).

RESULTS

Overall, sixty (60) patients were enrolled from oncology department of which males were 45 (75%) and females were 15 (25%) with mean age of 8.2±3.6 years (6months to 13years), with diagnosis of T-Cell ALL 31.7%, lymphoma 28%, Ewing sarcoma 13%, osteosarcoma 5%, germ cell tumour 5%, nasopharyngeal carcinoma 3.3%, PNET 3.3%, neuroblastoma 3.3% and 1 case from each LCHC, soft tissue sarcoma, CNS tumor, synovial sarcoma respectively.

Mean mGFR of these patients by Crcl was 93.85 ml/min/1.73m2, mean eGFR by OS, SHID and US were 131.74, 97.64, 99.43 ml/min/1.73m2 respectively. Table 1 shows the means of eGFR by each formula along with Standard deviation and minimum and maximum values. Table-2 Shows the correlation statistics between mGFR and eGFR by various formulae which suggests that all three eGFR formulae exhibit a statistically significant positive correlation with mGFR by Crcl method (*p*-value <0.01). The Pearson r values for correlation between gold standard creatinine clearance test and all studied equations were between 0.5–0.6 which suggest a statistically significant moderate positive correlation between mGFR and eGFR by all of the three studied equations.

For OS 6.67% cases were within 10% and 31.67% were within 30% of measured GFR. In case of SHID equation 30% were within 10% and 58.3% were within 30% of measured GFR. In case of US 36.7% were within 10% 61.7% were within 30% of measured GFR (Table-3).

Linear regression analysis also showed a statistically significant relation between mGFR and eGFRs by different formulae suggesting that a change in mGFR can be reliably predicted by eGFR formulae. However, the developed regression models for all three formulae have a low R2 values (Table-4)

Bland-altman analysis revealed that mean difference values of mGFR and eGFR by OS method differed significantly from zero (*p*-values <0.001) suggesting that useful level of agreement does not exists between GFR measured by gold standard creatinine clearance test and eGFR by OS method. However, mean difference values of mGFR and eGFR by SHID method and US method did not differ significantly from zero (p-values 0.427 and 0.231 respectively). Hence the Bland Altman plot was constructed for these two formulae which suggested that both formulae are in agreement with Crcl test (Figure-1 and 2). Table-5. Represents the distribution of GFR after splitting GFR into three groups, i.e., >90, 60-90 and <60 ml/min/m^{2}and the frequency of GFR values correctly estimated by eGFR formulae in each group. The data suggests that while OS correctly measures most of the cases in >90 ml/min/m^2 group but frequency of correct estimations in 60–90 and <60 group is very low.

Table-1: GFR values calculated by different methods

	GFR ml/min/1.73m2 Min.	GFR ml/min/1.73m2 Max.	GFR ml/min/1.73m2 Mean±S.D
Creatinine clearance test	14.0	230.6	93.853±42.823
Original Schwartz Equation	46.4	275.0	131.742±39.680
Simple Height independent Equation	33.9	208.9	97.636±33.380
Updated Schwartz Equation	34.8	206.5	99.429±30.823

Table-2: Correlation between various GFR equations and gold standard Creatinine clearance test.

	Pearson r Value	*p*-value
Original Schwartz Equation	0.549	<0.001
Simple Height Independent Equation	0.556	<0.001
Updated Schwartz Equation	0.572	<0.001

Table-3: Percentage of eGFR by three equations falling between 10% and 30%of mGFR.

Formulae	Within 10% of measured GFR n (%)	Within 30% of measured GFR n (%)
Original Schwartz	4 (6.67%)	19 (31.67%)
Simple Height independent	18 (30.0%)	35 (58.30%)
Updated Schwartz	22 (36.7%)	37 (61.67%)

Table-4: Linear regression analysis of mGFR by Cr. Clearance test and eGFR by various formulae C

	B ± S.E	Slope	R^2	*p*-value
Original Schwartz Equation	84.026±10.478	0.508	0.301	<0.001
Simple Height independent Equation	58.206±8.503	0.420	0.309	<0.001
Updated Schwartz Equation	60.820±7.988	0.411	0.327	<0.001

Table-5. Frequency of GFR correctly estimated by each of the three formulae in different categories with reference to gold standard creatinine clearance test

Creatinine Clearance	Original Schwartz	Height Independent Schwartz	Updated Schwartz
>90 (n=26)	25 (96.2%)	20 (76.9%)	19 (73.1%)
60-90 (n=24)	1 (4.2%)	11 (45.8%)	12(50.0%)
<60 (n=10)	1 (10.0%)	2 (20%)	1 (10.0%)

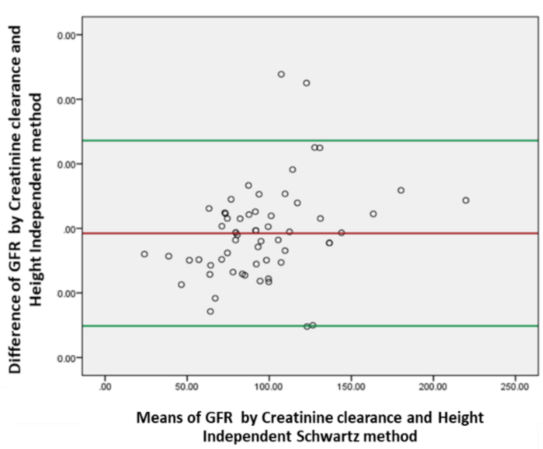

Figure-1: Bland Altman plot for agreement between Creatinine clearance method and Height Independent method.

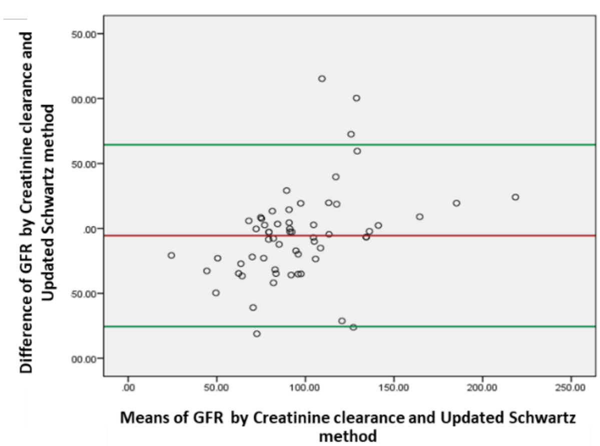

Figure-2: Bland Altman plot for agreement between Creatinine clearance method and Updated Schwartz method.

DISCUSSION

Present study indicated that mean GFR calculated by all three formulae were higher as compared to the gold standard Crcl method. All three equations overestimated the GFR as compared to Crcl but the difference was more in case of OS as compared to SHID and US. OS overestimated GFR in children which is in concordance with a study by Witzel *et al* Who also found OS to overestimate GFR in children as compared to gold standard.[16] Similar findings are reported by Chancharoenthana *et al* that OS overestimate GFR.[17] Another study evaluating the anticoagulant dosing on the basis of GFR also reported that eGFR by Schwartz fails to recognize lower clearances in 28% of patients.[18]

Though mean GFR as estimated by these formulae was higher but still it exhibited a statistically significant positive correlation which suggests that an increase in GFR by CrCl also leads to an increase in eGFR values. Similar results have been reported by a study conducted in Iran; however, they found a higher positive correlation, i.e., 0.79 as compared to present study.[1] Our studied formulae showed a person R2 value up to 0.572 which shows a fair correlation between the Crcl and these formulae. This suggests that these formulae can detect a variance of up to 57.2% in GFR as determined by CrCl test.

Our results showed that among the studied estimation formulae GFR values deviated more than 10% from mGFR values more commonly in case of OS followed by SHID and US which suggests that mGFR values by US are more likely to be close to mGFR values among the three studied formulae. Similar results were observed for a 30% deviation from GFR by CrCl, i.e., GFR values by US were most likely to fall within 30% of mGFR.

Linear regression model also found no statistically significant difference as compared to CrCl test indicating that these formulae can significantly predict any change in the mGFR values but low R2 values suggest that these regressions models can only predict 30.1%, 30.9% and 32.7% variability by OS, SHID and US equations respectively. Safaei et al from Iran also reported similar results.[19]

Agreement test by Bland Altman analysis showed that GFR values as estimated by OS did not agree with the mGFR however, eGFR values SHID formula and US formula were found to be in agreement with the mGFR values. This shows that these two formulae better represent the mGFR values. The study from Iran had also shown US to agree with the mGFR by CrCl.[19]

Correlation between mGFR and eGFR values after splitting the GFR ranges into three clinically important categories in order to evaluate which formula works best in which GFR range, OS was found to be more accurate in identifying the patients with a normal GFR, i.e., >90 ml/min/m2 but it failed to correctly detect patients in lower GFR ranges. US and SHID were more likely to correctly identify patients falling within each of the three groups based on GFR values (Table-5). So, US and SHID can be used in all GFR ranges, while OS can be used in higher GFR ranges. Hence, US and SHID can be a better choice for GFR estimation.

One of the limitations of present study is that we have taken Creatinine clearance as gold standard rather than inulin clearance. This is due to the reason that insulin clearance is a cumbersome and rigorous procedure that involves continuous intravenous infusion and repeated blood and urine samples. For this reason, insulin is not routinely performed in our setup and Crcl is preferred in our paediatric oncology patients.

CONCLUSION

GFR estimation formulae including OS, SHID and US in paediatric oncology patients exhibit a statistically significant positive correlation with gold standard Crcl. A statistically significant agreement was also observed between Crcl and SHID and US method but eGFR values by OS did not agree significantly with mGFR. Hence it may be concluded that SHID and US equations give a better estimate of GFR and may be used in children with malignancies to estimate GFR.

AUTHORS' CONTRIBUTION

SS: Primary investigator, conceptualization, literature search, data collection, data interpretation, manuscript writing. MA: Conceptualization, literature search, data collection, data interpretation, manuscript writing. SUBMITTED: Data interpretation, data analysis, manuscript writing. SK: Conceptualization, data collection, proof reading. WH: Data collection, data interpretation, proof reading. BN: Data collection, data interpretation, proof reading

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