Section: Pediatrics

Research

VALIDATION OF USE OF SCHWARTZ FORMULA AGAINST CREATININE CLEARANCE IN THE ASSESSMENT OF GFR IN CHILDREN

M. Raja[1], M.K Senthil Kumar[2], K. Suresh Kannan[3], S.Kalandaryasar[4]

[1]Assistant Professor, Department of Pediatrics, KAPV Government Medical College, Trichy, Tamilnadu, India
[2]Senior Assistant Professor, Department of Pediatrics, KAPV Govt Medical College, Trichy, Tamilnadu, India
[3]Associate Professor, Department of Pediatrics, Government Medical College Hospital, Namakkal, Tamilnadu, India
[4]Senior Resident, Department of Pediatrics, Government Tiruvarur Medical College, Tamilnadu, India

Received : *20/11/2022*
Received in revised form : *26/12/2022*
Accepted : *09/01/2023*

Keywords:
GFR, kidney function, BMI, Sensitivity, Specificity, Bland and Altman plot.

Corresponding Author:
Dr. K. Suresh Kannan,
Email:sureshkannank@yahoo.com
ORCID: 0000-0002-6778-6576

DOI: 10.47009/jamp.2023.5.1.105

Source of Support: Nil,
Conflict of Interest: Nonedeclared

Int J Acad Med Pharm
2023; 5 (1); 510-515

Abstract

Background: GFR is the most important index in monitoring renal functions. Thus, the present study aimed to evaluate the validity or accuracy of the Schwartz formula in predicting GFR by comparing it with creatinine clearance. **Materials and Methods:** In this study, 160 children were involved. They were subdivided according to their GFR by creatinine clearance and BMI. All their GFR measured using both creatinine clearance and bedside Schwartz formula were analyzed and compared. **Result:** In predicting GFR in children with impaired renal function by creatinine clearance <75 ml/min/1.73 m^2, the Schwartz formula has a Sensitivity of 92.04%, specificity of 62.5%, Positive predictive value of 75%, Negative predictive value of 86.53%, Overall predictive accuracy of 78.75. There is a significant correlation (r = 0.8) between the Schwartz formula and creatinine clearance. Children with a BMI of 15 and above have a Sensitivity of 94.44%, specificity of 63.83%, Positive predictive value of 75%, Negative predictive value of 90.90%, and overall predictive accuracy of 80.19%. This was much better than children with BMI <15. Schwartz's formula had good overall predictive accuracy in well-nourished children compared to undernourished children. **Conclusion:** The Bedside Schwartz formula can predict a rough estimate of GFR in well-nourished children. To precisely calculate GFR, other formulas involving other substances like cystatin can be tried.

INTRODUCTION

Glomerular filtration is one of the important functions of the kidney. The kidney's filtration rate, also called the glomerular filtration rate (GFR), shows how the kidneys function. It helps in the regulation of blood composition and volume. The GFR best measures kidney function. As the blood passes through glomerular capillaries, the plasma is filtered through glomerular capillary walls. Small plasma molecules (e.g., electrolytes, glucose, phosphate, urea, creatinine, peptides) filter freely, whereas larger molecules (e.g., albumin and globulins) are retained in the circulation. The filtrate collected in Bowman's space, called glomerular filtrate, enters the tubules. In tubules, their composition is modified by tightly regulated absorption and secretion of solute and fluid by the multiple tubular segments of the nephron and the ductal system.[1-5]

GFR is the most important index in monitoring renal functions. Early renal failures don't show symptoms; monitoring GFR will help detect renal failures in the early stages. In addition, measuring GFR helps assess renal function and adjust drug doses according to renal clearance.[4-8] Thus, the study aimed to evaluate the validity or accuracy of the Schwartz formula in predicting GFR by comparing it with creatinine clearance. Also, we have studied the influence of BMI in predicting eGFR using the Schwartz formula.

MATERIALS AND METHODS

The present study was conducted at the Department of Pediatrics, KAPV Govt. Medical College and MGM GH, Trichy, from October 2020 to October 2021. We have included children aged 5-12 years with inclusion and exclusion criteria as follows:

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Inclusion Criteria

- Children without any evidence of renal disease with normal hydration.
- Nephrotic syndrome patients.
- Acute Glomerulonephritis patients.
- All CRF patients admitted in the ward as predicted by creatinine clearance.

Exclusion Criteria

- Children with obstructive uropathy, neurogenic bladder, and voiding dysfunction.
- SAM Children.

The required sample size was 35 in each group. However, we decided to keep the sample size at 160. Thus, 160 children who met the inclusion criteria were included in the study after getting informed consent from their parents.

The height and weight of the children were taken at the beginning of 24 hours urine collection period. Mosteller's formula estimated the children's body surface area as Body surface area (m^2) = [Height (cm) X Weight (kg) / 3600]^{½} and BMI was calculated.

Further, serum creatinine estimation was done at the end of the 12th hour during the 24 hours urine collection period. First, the urine concentration of creatinine was estimated. Then, creatinine clearance was estimated using the formula UV/P (U-urinary creatinine concentration; P- plasma creatinine concentration; V- volume of urine) The value obtained was corrected to 1.73 m^2 body surface area. Simultaneously GFR was predicted by the Bedside Schwartz formula **{eGFR(ml/min/1.73m^2 = k(0.413) x Height(cm)/serum creatinine(mg/dl)}**. Values obtained by Creatinine clearance and the Schwartz formula were compared and analyzed using statistical methods.

Statistical Analysis

Sensitivity, specificity, positive predictive value, negative predictive value, Bland and Altman plot, and Pearson correlation coefficient were used in this study to calculate the overall accuracy of the Schwartz formula.

RESULTS

All the study participants were classified according to sex, BSA, BMI, eGFR SCHWARTZ formula, and GFR creatinine clearance into subgroups. Of 160 children, 83 (51.9%) were female, and 77 (48.1%) were male. Depending upon the eGFR by Schwartz formula, 11 (6.9%) children have eGFR less than 25 ml/min/1.73m^2, 23 (14.4%) children belong to 25 to 49.99ml/min/1.73m^2, 74 (46.3%) children belong to 50 to 74.99 ml/min/1.73m^2. Out of 160 children, 108 (67.5%) children had eGFR values less than 75ml/min/1.73m^2, according to the Schwartz formula. The remaining 52 had eGFR more than or equal to 75 ml/min/1.73m^2.

Depending upon the GFR by creatinine clearance, 3 (1.9%) children have eGFR less than 25 ml/min/1.73m^2, 24 (15%) children belong to 25 to 49.99ml/min/1,73 m^2, 61 (38.1%) children belong to 50 to 74.99 ml/min/1.73 m^2. Out of 160 children, 88 (55%) had GFR values less than 75ml/min/1.73 m^2 according to creatinine clearance. The remaining 72 had GFR more than or equal to 75 ml/min/1.73 m^2 [Table 1].

Table 1: Classification

		Frequency	Percentage
Sex	Fch	83	51.9
	Mch	77	48.1
BSA (m^2)	0.5 to 0.75	58	36.3
	0.75 to 1.0	64	40
	>1.0	38	23.8
BMI kg/ m^2	<15	59	36.9
	>15	101	63.1
eGFR by SCHWARTZ FORMULA ml/min/1.73 m^2	<25	11	6.9
	25-49.99	23	14.4
	50-74.99	74	46.3
	>=75	52	32.5
eGFR by SCHWARTZ FORMULA ml/min/1.73m^2	<75	108	67.5
	>=75	52	32.5
GFR by CREATININE CLEARANCE ml/min/1.73 m^2	<25	3	1.9
	25-49.99	24	15.0
	50-74.99	61	38.1
	>=75	72	45.0
GFR by CREATININE CLEARANCE ml/min/1.73 m^2	<75	88	55.0
	>=75	72	45.0

In [Table 2], we have described the mean and standard deviation of various clinical variables.

Table 2: Descriptive Statistics

Variables	Mean	Std. Deviation
AGE	8.06	2.07
WEIGHT kg	22.81	6.49

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HEIGHT cm	118.30	12.45
BSA (m2)	0.86	0.16
BMI kg/m2	16.03	2.05
Serum creatinine mg/dl	0.88	0.48
24 hours urine creatinine mg/dl	46.04	35.16
Urine volume (ml)	1129.06	525.11
eGFR SCHWARTZ formula ml/min/1.73 m^2	65.91	23.07
GFR creatinine clearance ml/min/1.73 m^2	71.33	22.64

Table 3: Correlation of GFR values obtained by Schwartz formula with that of Creatinine clearance. (n = 160)

Schwartz Formula	Creatinine clearance (Ml/min/1.73 m^2)				
	<25	25-49.99	50-74.99	>=75	Total
<25	3(100%)	4	3	1	11
25-49.99	0	16(66.6%)	6	1	23
50-74.99	0	4	45(73.7%)	25	74
>=75	0	0	7	45(62.5%)	52
Total	3	24	61	72	160

Table 4: Correlation of GFR values (<75 ml/min/1.73m^2) obtained by Schwartz formula with that of Creatinine clearance in children with a BMI <15. (n = 59)

Schwartz formula	Creatinine clearance (ml/min/1.73 m^2)	
	<75	>=75
<75 ml/min/1.73 m^2	30	10
>=75 ml/min/1.73 m^2	4	15

Table 5: Correlation of GFR values obtained by Schwartz formula with that of Creatinine clearance in children with a BMI of 15 and above (n =101)

Schwartz formula	Creatinine clearance (ml/min/1.73 m^2)			
	<25	25-49.99	50-74.99	>=75
<25ml/min/1.73 m^2	3(100%)	3	3	1
25-49.99ml/min/1.73 m^2	0	10(76.92%)	5	1
50-74.99ml/min/1.73 m^2	0	0	27(71.05%)	15
>=75ml/min/1.73 m^2	0	0	3	30(63.82%)
Total	3	13	38	47

Table 6: Correlation of GFR values (<75 ml/min/1.73m^2) obtained by Schwartz formula with that of Creatinine clearance in children with a BMI of 15 and above. (n = 101)

Schwartz formula	Creatinine clearance (ml/min/1.73 m^2)	
	<75	>=75
<75	51	17
>=75	3	30

According to creatinine clearance, 3, 24, 61, and 72 children have a GFR value less than 25 ml/min/1.73 m^2, between 25-49.99 ml/min/1.73 m^2, between 50-74.99 ml/min/1.73 m^2, and 75 ml/min/1.73 m^2 and above, respectively. All the 3 children (GFR value less than 25 ml/min/1.73 m^2) and 3 (100%) had values in the same range when predicted by the Schwartz formula. But according to the Schwartz formula, 11 children had their GFR predicted to have below 25 ml/min/ 1.73 m^2. Out of the 24 children having a GFR value between 25 and 49.99 ml/ min / 1.73 m^2, 16 (66.6%) children had values in the same range when predicted by the Schwartz formula. Four children had a predicted GFR value below 25 ml/ min / 1.73 m^2, and 4 had their GFR values predicted 50 ml/ min / 1.73 m^2 and above.

Out of the 61 children having a GFR value between 50 and 74.99 ml/ min / 1.73 m^2, 45 (73.7%) children had values in the same range when predicted by the Schwartz formula, and 7 had their GFR values predicted 75 ml/ min / 1.73 m^2 and above, 9 children had their values predicted below 50 ml/min/1.73 m^2. Out of the 72 children having a GFR value above 75 ml/ min / 1.73 m^2, 45 (62.5%) children had values in the same range when predicted by the Schwartz formula, and the remaining 27 children had a predicted GFR value below 75 ml/min/1.73 m^2. [Table 3]

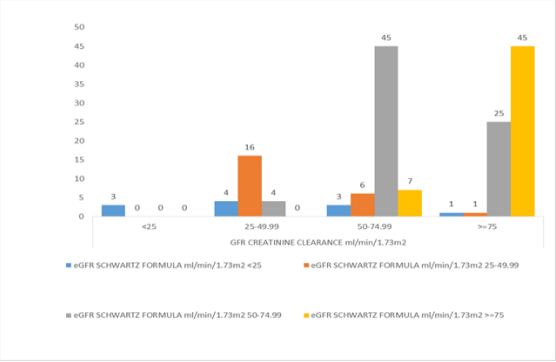

Figure 1: Comparison of GFR values obtained by Schwartz formula with that of Creatinine clearance

In detecting patients with creatinine clearance <75 ml/min/1.73m^2, the Schwartz formula has a sensitivity of 92.04%, a specificity of 62.5%, a positive predictive value of 75%, and a negative predictive value of 86.53%. The overall predictive accuracy of the Schwartz formula is 78.75%.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

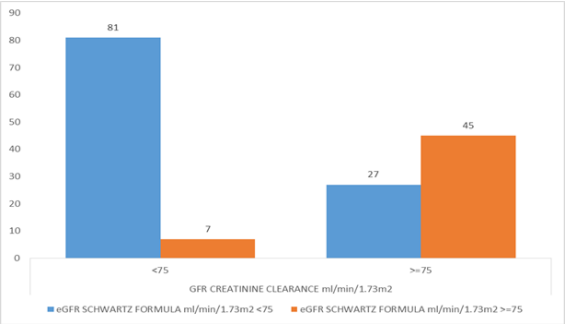

Figure 2: Comparison of GFR values (<75 ml/min/1.73 m^2) obtained by Schwartz formula with that of Creatinine clearance

In detecting patients with creatinine clearance <25 ml/min/1.73m^2, the Schwartz formula has a sensitivity of 100%%, a specificity of 94.9%, a positive predictive value of 27.27%, and a negative predictive value of 100%. The overall predictive accuracy is 95%.

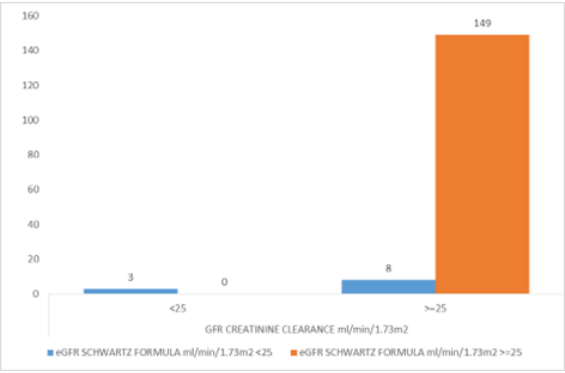

Figure 3: Comparison of GFR values (<25 ml/min/1.73 m^2) obtained by Schwartz formula with that of Creatinine clearance

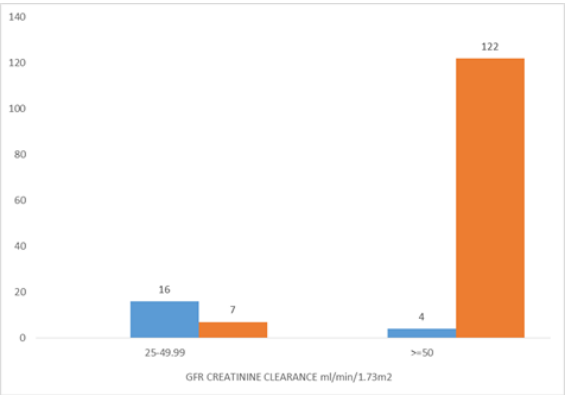

Figure 4: Comparison of GFR values (25-49.99 ml/min/1.73m^2) obtained by Schwartz formula with that of Creatinine clearance

In detecting patients with creatinine clearance between 25 and 49.99 ml/min/1.73 m^2, the Schwartz formula has a sensitivity of 92.61%, a specificity of 94.57%, a positive predictive value of 69.56% and a negative predictive value of 96.82% and the overall predictive accuracy is 92.61%.

In detecting patients with creatinine clearance between 50 and 74.99 ml/min/1.73 m^2, the Schwartz formula has a sensitivity of 73.77%, a specificity of 64.28%, a positive predictive value of 64.28% and a negative predictive value of 86.53%, and overall predictive accuracy is 73.77%.

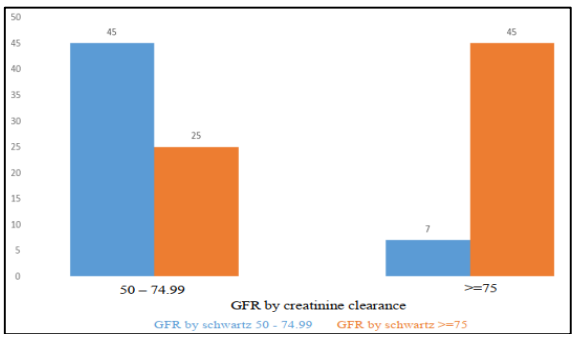

Figure 5: Comparison of GFR values (50-74.99 ml/min/1.73m^2) obtained by Schwartz formula with that of Creatinine clearance

Out of 59 children with BMI less than 15kg/ m^2, no one had GFR less than 25 ml/min/1.73 m^2, by both Schwartz formula and creatinine clearance. Out of the 11 children with BMI, less than 15kg/ m^2 (GFR: 25-49.99 ml/min/1.73 m^2), 6 (54.54%) children had values in the same range when predicted by the Schwartz formula. One child had a predicted GFR value below 25 ml/ min / 1.73 m^2, and 4 had their GFR values predicted 50 ml/ min / 1.73 m^2 and above.

Out of the 23 children with BMI less than 15kg/ m^2, having a GFR value between 50 and 74.99 ml/min/1.73 m^2 as estimated by creatinine clearance, 18 (78.2%) children had values in the same range when predicted by Schwartz formula and 4 had their GFR values predicted 75 ml/ min / 1.73 m^2 and above, and 1 child predicted to have below 50 ml/min/1.73 m^2. Out of the 25 children with BMI less than 15kg m^2 (GFR: above 75 ml/ min / 1.73 m^2), 15(60%) children had values in the same range when predicted by the Schwartz formula, and 10 patients had a predicted GFR value below 75 ml/ min / 1.73 m^2.

In detecting patients having a BMI < 15 kg/ m^2 with creatinine clearance <75 ml/min/1.73m^2, the Schwartz formula has a sensitivity of 88.23%, a specificity of 60%, a positive predictive value of 75% and a negative predictive value of 78.94%, overall predictive accuracy is 76.27%. [Table 4]

Out of 101 children with a BMI of 15 kg/ m^2 and above, 3, 13, 38, and 47 children have a GFR value less than 25 ml/min/1.73 m^2, between 25 and 49.99 ml/min/1.73 m^2, between 50-74.99 ml/min/1.73 m^2 and 75 ml/min/1.73 m^2 and above, as estimated by creatinine clearance. In addition, all the 3 children with a BMI of 15 kg/ m^2 and above, with a GFR value less than 25 ml/ min / 1.73 m^2, had values in the same range when predicted by the Schwartz formula.

Out of the 13 children with a BMI of 15 kg/ m^2 and above, having a GFR value between 25 and 49.99 ml/ min / 1.73 m^2, 10 (76.92%) children had the

ISSN (O): 2687-5365; ISSN (P): 2753-6556

values in the same range when predicted by the Schwartz formula and 3 children had their GFR values predicted to have below 25 ml/ min / 1.73 m^2. Out of the 38 children with a BMI of 15 kg/ m^2 and above, having a GFR value between 50 and 74.99 ml/ min / 1.73 m^2, 27(71.05%) children had the values in the same range when predicted by the Schwartz formula, and 3 had their GFR values predicted 75 ml/ min / 1.73 m^2 and above, 8 of them had their value predicted to be less than 50 ml/min/1.73 m^2. Out of the 47 children with a BMI of 15 kg/ m^2 and above, having a GFR value above 75 ml/ min / 1.73 m^2, 30(63.82%) children had values in the same range when predicted by the Schwartz formula, and 17 patients had their predicted GFR value below 75 ml/min/1.73 m^2. [Table 5]

In detecting patients having a BMI of 15 kg/ m^2 and above, with creatinine clearance <75 ml/min/1.73 m^2, the Schwartz formula has a sensitivity of 94.44%, a specificity of 63.83%, a positive predictive value of 75%, and a negative predictive value of 90.90%, overall predictive accuracy is 80.19%.

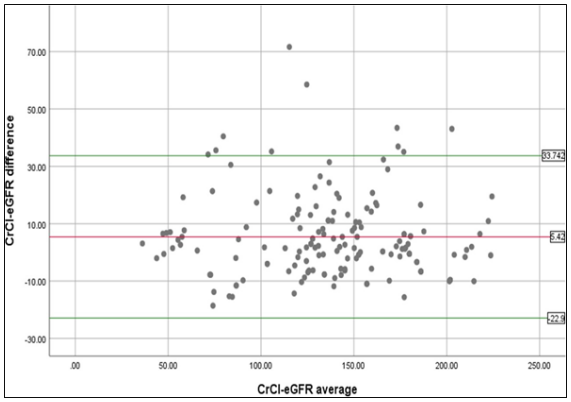

Figure 6: Bland and Altman plot

In detecting patients having a BMI < 15 kg/ m^2 with creatinine clearance <75 ml/min/1.73 m^2, the Schwartz formula has a sensitivity of 88.23%, a specificity of 60%, a positive predictive value of 75% and a negative predictive value of 78.94%, overall predictive accuracy is 76.27%. In detecting patients having a BMI of 15 kg/ m^2 and above, with creatinine clearance <75 ml/min/1.73m^2, the Schwartz formula has a sensitivity of 94.44%, a specificity of 63.83%, a positive predictive value of 75%, and a negative predictive value of 90.90%, overall predictive accuracy is 80.19%. [Table 6]

Bland and Altman Plot for Method Comparison: This statistical method compares two tests. The average values obtained by creatinine clearance and the Schwartz formula are graphically plotted against the difference between the values obtained by the two methods. [figure 6]

The average difference is 5.42 (mean), with a standard deviation of 14.45. Therefore, the limits of agreement are (33.74 -22.5). This means that the values obtained by the Schwartz formula may be 34 m1/min/1.73 m^2 above or 22.5 ml/min/1.73 m^2 below creatinine clearance. The 95% confidence interval for the lower limit of agreement is -20.26 to -24.7 and for the upper limit of agreement is 31.5 to 36, respectively.

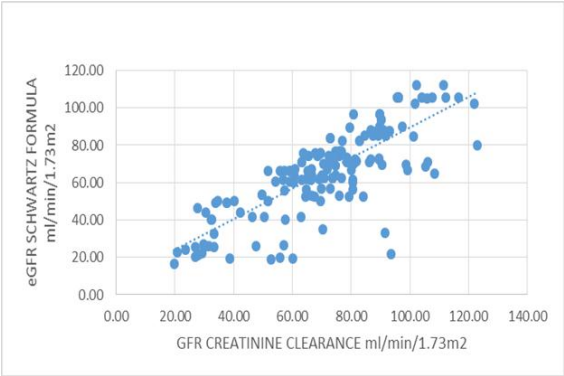

Figure 7: Pearson Correlation

There is a significant positive correlation (r=0.8) between the Schwartz formula and creatinine clearance (p< 0.0001).

DISCUSSION

Measuring GFR in pediatric patients is a much important and difficult process to assess the renal function of children. GFR measured using substance clearance, either endogenous or exogenous substances is considered the golden standard for measuring GFR. However, it needs to collect 24-hour urine samples, which are cumbersome and prone to errors. In children, the use of creatinine clearance to measure GFR is difficult as it requires toilet training and complete voiding and collection of a whole volume of urine. In addition, patients with renal dysfunction tend to clear more creatinine, resulting in falsely high creatinine clearance values. For these reasons, height and creatinine-based formulas for estimating GFR were created. The Schwartz formula is the most commonly used.[1-3,5-7]

The validity of the Schwartz formula to estimate GFR accurately in children has been studied broadly. Studies have revealed that eGFR calculated by the Schwartz formula tends to overestimate the CrCl measured by renal clearance of substances. The original Schwartz formula was developed in patients with chronic kidney disease, using inulin clearance as the reference method and creatinine measured by a modified Jaffe reaction, which seems to overestimate true creatinine value due to interference. Later many changes were made in the measurement of creatinine. Among them is the IDMS reference value, which changes the constant k value to 0.413.[3,8-13]

We used the bedside Schwartz formula and validated its accuracy using creatinine clearance. Creatinine was measured using compensated Jaffe method with a k constant of 0.413. Our observation in this study showed a statistically significant

ISSN (O): 2687-5365; ISSN (P): 2753-6556

correlation coefficient. But according to the Bland Altman plot, the limits of agreement are (33.74, -22.5), which shows a wide difference between the values of measured and eGFR by Schwartz formula compared with creatinine clearance, which is a bigger concern.

In the present study, a BMI value of 15 is taken as the cut-off for analyzing the influence of malnutrition in the prediction of GFR by the Schwartz formula. A BMI value of less than 15 is considered moderate malnutrition, and less than 13 is severe malnutrition in growing children. Children with a BMI of 15 or above have good overall accuracy in detecting eGFR compared to children with low BMI. This shows that BMI is important in estimating GFR using the Schwartz formula, which needs to be evaluated.

Limitations of the current study were that the study was done in a single centre without the use of the gold standard GFR measurement (e.g., iohexol, inulin clearance) as a comparison and the relatively low number of children with renal dysfunction. The value of k should be different based on the estimation method of creatinine.

CONCLUSION

The Bedside Schwartz formula with a constant k value of 0.413 and creatinine measured using compensated Jaffe method with the value reported about IDMS standard can be used to estimate GFR in children, as it had a good sensitivity of 92.04%. But it cannot be used to rule out renal malfunction or accurate measurement of GFR, as it has poor sensitivity. In underweight children, the Schwartz formula seems to overestimate GFR. Thus, the k constant in the Schwartz formula needs to be derived for underweight children, and body surface area also seems to play an important role in estimating GFR. Further studies must validate and derive the k value for underweight children.

Acknowledgement

The authors gratefully acknowledge the guidance and support of Prof. Dr. B. Mythili and Prof. Dr. Sirajuddin Nazeer, KAPV Govt Medical College, Trichy in the conduct of the study. Authors would like to thank the entire faculty in the Department of Pediatrics, KAPVGMC & MGMGH, Trichy for their support in the conduct of this study

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ISSN (O): 2687-5365; ISSN (P): 2753-6556