

**PREDICTION OF GLOMERULAR FILTRATION RATE  
BY  
SCHWARTZ FORMULA IN CHILDREN  
AGED 5 - 12 YEARS ADMITTED  
IN AN URBAN REFERRAL CENTRE**

*Dissertation Submitted for*

**MD DEGREE EXAMINATION  
BRANCH VII - PEDIATRIC MEDICINE**



**INSTITUTE OF CHILD HEALTH  
AND  
HOSPITAL FOR CHILDREN  
MADRAS MEDICAL COLLEGE  
THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY  
CHENNAI.**

**SEPTEMBER 2006**

## CERTIFICATE

Certified that this dissertation entitled "**PREDICTION OF GLOMERULAR FILTRATION RATE BY SCHWARTZ FORMULA IN CHILDREN AGED 5-12 YEARS ADMITTED IN AN URBAN REFERRAL CENTRE**" is a bonafide work done by **Dr.K.SURESH KANNAN, M.D.**, Post Graduate Student of Pediatric Medicine, Institute of Child Health and Hospital for Children, Egmore, Chennai - 600 008, during the academic year 2003 - 2006.

**Prof. Dr. Prabha Senguttuvan**  
**M.D.,DCH., D.M.,**  
Head of Dept of Pediatric Nephrology,  
Institute of Child Health and  
Hospital for Children,  
Madras Medical College,  
Chennai.

**Prof. Dr. C. D. Natarajan M.D.,DCH.,**  
Addl.Prof of Pediatrics,  
Institute of Child Health and  
Hospital for Children,  
Madras Medical College,  
Chennai.

**Prof. Dr. Mangayarkarasi Senguttuvan**  
**M.D.,DCH.,**  
Director and Superintendent,  
Institute of Child Health and  
Hospital for Children  
Madras Medical College, Chennai.

**Prof. Dr. Kalavathi Ponniraivan**  
**B.Sc., M.D.,**  
The Dean,  
Madras Medical College,  
Chennai.

## **DECLARATION**

I declare that this dissertation entitled "**PREDICTION OF GLOMERULAR FILTRATION RATE BY SCHWARTZ FORMULA IN CHILDREN AGED 5-12 YEARS ADMITTED IN AN URBAN REFERRAL CENTRE**" has been conducted by me at the Institute of child health and Hospital for Children, under the guidance and supervision of my unit chief **Prof.Dr.C.D.Natarajan, MD., DCH.**, and the head of department of Nephrology, **Prof.Dr.Prabha Senguttuvan, M.D.,DCH., D.M.,(Nephro)**. It is submitted in part of fulfillment of the award of the degree of M.D (Pediatrics) for the September 2006 examination to be held under the Tamil Nadu Dr.M.G.R Medical University, Chennai. This has not been submitted previously by me for the award of any degree or diploma from any other university.

**(Dr. K. SURESH KANNAN)**

## **SPECIAL ACKNOWLEDGEMENT**

My sincere thanks to **Prof. Dr. Kalavathi Ponniraivan, B.Sc., M.D.**, the Dean, Madras Medical College for allowing me to do this dissertation and utilize the institutional facilities.

## ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to **Prof.Dr.Mangayarkarasi Senguttuvan M.D., D.C.H.**, Professor of Pediatrics, Director and Superintendent of Institute of Child Health and Hospital for Children for permitting me to undertake this study.

I am extremely thankful to **Prof.Dr.C.D.Natarajan, M.D., D.C.H.**, Addl. Professor of Pediatrics and our unit chief for his guidance, invaluable help, encouragement and support throughout the study.

I am extremely thankful to **Prof.Dr.Prabha Senguttuvan, M.D., D.C.H., D.M.**, Head of the Department of Pediatric Nephrology for her guidance, invaluable help, encouragement and support throughout the study.

I would like to thank our unit Assistant Professors, **Dr.P.Sabapathy Raj, M.D., D.C.H., Dr.R.Somasekar, M.D., D.C.H.**, and **Dr.S.Madhivanan, M.D., D.C.H.**, for their valuable guidance and support in doing this study.

I extend my sincere thanks to **Dr. Kothainayagai, M.D., D.C.H.**, Registrar for her valuable suggestion and guidance in doing this work.

I would like to thank **Mrs. Basilea Watson**, statistician, Madras Medical College, for her invaluable help.

I sincerely thank all the children and their parents who have submitted themselves for this study without whom this study would not have been possible.

## CONTENTS

<b>Sl. No.</b>	<b>Title</b>	<b>Page No.</b>
<b>I</b>	<b>INTRODUCTION</b>	<b>1</b>
<b>II</b>	<b>REVIEW OF LITERATURE</b>	<b>14</b>
<b>III</b>	<b>STUDY JUSTIFICATION</b>	<b>24</b>
<b>IV</b>	<b>AIM OF THE STUDY</b>	<b>25</b>
<b>V</b>	<b>MATERIALS AND METHODS</b>	<b>26</b>
<b>VI</b>	<b>OBSERVATIONS</b>	<b>31</b>
<b>VII</b>	<b>DISCUSSION</b>	<b>47</b>
<b>VIII</b>	<b>SUMMARY &amp; CONCLUSION</b>	<b>51</b>
	<b>BIBLIOGRAPHY</b>	
	<b>ANNEXURE</b>	

## I. INTRODUCTION

Glomerular filtration rate (GFR) provides an excellent measure of the filtering capacity of the kidneys. Glomerular filtration rate (GFR) is the best estimate of functional renal mass. It is the most widely used indicator of renal function in patients with renal disease. The severity and the prognosis of any renal disease are usually predicted on this parameter. A low or decreasing GFR is a good index of chronic kidney disease. Since the total kidney GFR is equal to the sum of the filtration rates in each of the functioning nephrons, the total GFR can be used as an index of functioning renal mass. A decrease in GFR precedes kidney failure in all forms of progressive kidney disease. Monitoring changes in GFR can delineate progression of kidney disease. The level of GFR is a strong predictor of the time to onset of kidney failure as well as the risk of complications of chronic kidney disease. Additionally, estimation of GFR in clinical practice allows proper dosing of drugs excreted by glomerular filtration to avoid potential drug toxicity.<sup>24</sup>

### FUNCTIONAL ANATOMY

Each individual renal tubule and its glomerulus is a unit (nephron). There are approximately 1.3 million nephrons in each kidney.<sup>23</sup> The formation of nephron is complete at birth, but final maturation with tubular growth and elongation continues during the first decade of life.<sup>22</sup>



The glomerulus is about 200 micrometers in diameter and is formed by the invagination of a tuft of capillaries into the dilated blind end of nephron (Bowman's capsule). The capillaries are supplied by an afferent arteriole and drained by an efferent arteriole.<sup>23</sup> The glomerular capillaries are lined by endothelial cells having very thin cytoplasm that has fenestrations. The glomerular basement membrane (GBM) is continuous and has endothelial and mesangial cells on one side and epithelial cells on the other. The glomerular basement membrane (GBM) has 3 layers namely lamina densa, lamina rara interna and lamina rara externa. The visceral epithelial cells cover the capillary and project cytoplasmic foot processes, which attach to the lamina rara externa.<sup>22</sup> Filtration slits are present in between the foot processes. The slits are approximately 25 nm wide and each is closed by a thin membrane. Stellate cells called mesangial cells are located between the GBM and endothelium. The mesangial cells are contractile and play a role in the regulation of glomerular filtration. They also secrete various substances, take up immune complexes, and are involved in the production of glomerular disease.<sup>23</sup>

## **GLOMERULAR FILTRATION**

As blood passes through glomerular capillaries, the plasma is filtered through the glomerular capillary walls. The ultra filtrate is cell free, contains all substances in plasma (electrolytes, glucose, phosphate, urea, creatinine, peptides and low molecular weight proteins) except proteins having a molecular weight of 68,000 or more. The filtrate is collected in Bowman's

space and enters the tubules, where its composition is modified by solute and fluid secretion and absorption in accordance with tightly regulated homeostatic mechanisms until it leaves the kidney as urine.<sup>22</sup>

Glomerular filtration is the net result of opposing forces across the capillary wall. The force for ultra filtration (glomerular capillary hydrostatic pressure) stems from the systemic arterial pressure as modified by the tone of the afferent and efferent arterioles. The major force opposing ultra filtration is the glomerular capillary oncotic pressure, which is created by the gradient between the high concentration of plasma proteins within the capillary and the almost protein free ultra filtrate in Bowman's space.<sup>22</sup>

Filtration may be modified by the rate of glomerular plasma flow, the hydrostatic pressure within the Bowman's space and the permeability of the glomerular capillary wall.<sup>22</sup>

Although glomerular filtration begins around the 9<sup>th</sup> week of fetal life, kidney function is not necessary for normal intrauterine homeostasis as placenta serves as the major excretory organ. After birth GFR increases until growth ceases towards the end of 2<sup>nd</sup> decade of life. To facilitate the comparison of Glomerular Filtration Rates of children and adults, GFR is standardized to the surface area (1.73 m<sup>2</sup>) of a 70 kg adult. Even after correction, GFR of a child does not approximate adult values until the third year of life.<sup>22</sup>

## GFR MEASUREMENT

Glomerular filtration rate cannot be measured directly. If a substance in stable concentration in the plasma is physiologically inert, freely filtered at the glomerulus, and neither secreted, reabsorbed, synthesized, nor metabolized by the kidney, the amount of that substance filtered at the glomerulus is equal to the amount excreted in the urine. The fructose polysaccharide inulin has each of the above properties and has long been considered an ideal substance to estimate GFR. The amount of inulin filtered at the glomerulus equals the GFR multiplied by the plasma inulin concentration:  $GFR \times P_{in}$ . The amount of excreted inulin equals the urine inulin concentration ( $U_{in}$ ) multiplied by the urine flow rate ( $V$ , volume excreted per unit time).

Since filtered inulin = excreted inulin:

$$(1) \quad GFR \times P_{in} = U_{in} \times V$$

$$(2) \quad GFR = U_{in} \times V / P_{in}$$

The term  $(U_{in} \times V)/P_{in}$  is defined as the clearance of inulin and is an accurate estimate of GFR. The inulin clearance, in mL/min, refers to that volume of plasma per unit time that is cleared of inulin by renal excretion.<sup>24</sup>

The classic method of inulin clearance requires an intravenous infusion and timed urine collections over a period of several hours making it costly and cumbersome. As a result a number of alternative measures for

estimating GFR have been devised. The urinary clearances of exogenous radioactive markers (125I-iothalamate and 99mTc-DTPA) provide excellent measures of GFR but are not readily available. Plasma clearance of exogenous substances including iohexol and <sup>51</sup>Cr-EDTA has been used as well but require estimates of body size, which decreases their precision. Capillary electrophoresis allows for measurement of non-radio labeled iothalamate in blood and urine with promising results. Serum cystatin C has been used to estimate GFR but data are conflicting as to whether it provides a sufficient improvement to warrant widespread clinical use.<sup>24</sup>

The most widely used measures of GFR in clinical practice are based on the 24-hour creatinine clearance or serum creatinine concentration.<sup>24</sup>

Creatinine is mainly derived from the metabolism of creatine in muscle, and its generation is proportional to the total muscle mass. Creatinine is an anhydride of creatine, a compound present in skeletal muscle as creatine phosphate. It has a molecular weight of 113 d. The serum creatinine levels reflects total body supplies of creatinine and correlate with muscle mass. After initial decrease during the first month of life, it increases steadily with age, both reflecting muscle mass.<sup>25</sup>

The mean creatinine generation is higher in men than in women, in younger than in older individuals, and in blacks than in whites. This leads to differences in serum creatinine concentration according to age, gender, and race, even after adjusting for GFR. Muscle wasting is also associated with reduced creatinine generation resulting in lower serum creatinine

concentration than expected for the level of GFR in malnourished patients with chronic kidney disease. Creatinine generation is also affected by meat intake to a certain extent, because the process of cooking meat converts a variable portion of creatine to creatinine. Therefore, serum creatinine is lower than expected for the level of GFR in patients following a low protein diet. It is a waste product of muscle cell metabolism that is filtered by the glomeruli and secreted by tubules. The renal excretion pattern of endogenous creatinine is similar to that of inulin in humans and several animal species.<sup>24</sup>

The traditional assay for measurement of creatinine is the alkaline picrate method, which detects non-creatinine chromogens in serum (approximately 0.2 mg/dL), as well as creatinine. Urine does not contain non-creatinine chromogens, nor are these compounds retained in chronic kidney disease. Thus, historically, measured creatinine clearance has systematically underestimated true creatinine clearance. By coincidence, the difference between measured and true creatinine clearance is similar in magnitude to the clearance of creatinine, due to tubular secretion. Hence, measured creatinine clearance has historically approximated the level of GFR.<sup>24</sup>

Serum creatinine alone is not an accurate index of the level of GFR. The use of the serum level of creatinine as an index of GFR rests on three important assumptions:

- (1) Creatinine is an ideal filtration marker whose clearance approximates GFR,
- (2) Creatinine excretion rate is constant among individuals and over time and
- (3) Measurement of serum creatinine is accurate and reproducible across clinical laboratories.

Although the serum creatinine concentration can provide a rough index of the level of GFR, none of these assumptions are strictly true, and numerous factors can lead to errors in estimation of the level of GFR from the serum creatinine concentration alone.<sup>24</sup>

## **GFR PREDICTION EQUATIONS**

Equations estimating GFR based on serum creatinine are more accurate and precise than estimates of GFR from measurement of serum creatinine alone. Many studies have documented that creatinine production varies substantially across sex, age, and ethnicity. Equations have the advantage of providing an estimate of GFR which empirically combines all of these average effects while allowing for the marked differences in creatinine production between individuals.<sup>24</sup>

Equations to predict GFR and creatinine clearance from serum creatinine have been tested in a large number of studies. Use of relevant equations in children and adults has been shown to give more valid estimates of GFR than serum creatinine alone.

## **GFR PREDICTION EQUATIONS IN CHILDREN**

Several formulas for estimating GFR in children have been developed. The most widely studied of these are the Schwartz and Counahan-Barratt formulae. Both provide an estimate of GFR based on a constant multiplied by the child's height divided by serum creatinine.<sup>24</sup> Other formulas that were devised for prediction of Glomerular filtration rate in children are Shull equation, Traub equation and Ghazali Barratt equation.

### **SCHWARTZ FORMULA**

The complex relationship between Plasma Creatinine and GFR during growth has prompted investigators to develop empirical formulas for estimating GFR by linking Plasma Creatinine with some parameter of body size or age. Using body length Schwartz et al<sup>21</sup> derived a formula that yields values of GFR that correlate very closely with those obtained from creatinine clearance and inulin clearance.

$$\mathbf{GFR = k L / PCr}$$

where GFR is expressed in ml / min / 1.73 m<sup>2</sup>, L is the Length measured in cm, PCr is plasma creatinine in mg / dl and *k* a constant of proportionality is a function of urinary creatinine excretion per unit of body size.

One method of calculating *k* is by regression analysis. The individual values of L / P Cr are correlated with the clearance of creatinine or inulin. The mean value of *k* can also be calculated from individual values

i.e.,  $k = \text{GFR PCr} / L$ . In general, with large and normally distributed sample populations, the mean value of  $k$  agrees within 0.01 with the values calculated by regression analysis.<sup>21</sup>

Under steady state conditions  $k$  is directly proportional to the muscle component of body weight, which corresponds reasonably well to the daily urinary creatinine excretion rate. During growth and especially after the postnatal and pubertal surges, one would expect to find differences in percentage of muscle mass among various age groups. By statistically comparing the various age and sex groups of infants and children, Schwartz et al<sup>21</sup> have found relatively clear cut groupings that provide simple and easy to remember values of  $k$ .

The values of  $k$  are as follows;

0.33 in LBW infants,

0.45 in full term AGA infants up to one year or more of postnatal life,

0.55 in children starting at age 2 and in adolescent girls, and

0.70 in adolescent boys commencing with pubertal changes in body habitus.

Using the Talbot coefficient of 1 gram of urinary creatinine excretion per 17.9 kg of muscle mass, Schwartz et al<sup>21</sup> have calculated a value of  $k$



equaling 0.55 corresponds to a muscle mass of approximately 39% of the body weight.

Schwartz et al<sup>21</sup> have observed that the value of  $k$  changes very little during normal growth and provides a satisfactory estimate of GFR, even while the accretion of muscle mass causes the plasma creatinine concentration to rise. They have also suggested that  $k$  tends to be lower than the prescribed values when malnutrition or obesity is present. From anatomic data and creatinine excretion measurements, it is known that both obesity and malnutrition are associated with a decrease in the percentage of body weight that is muscle and in the latter case, a decrease in the body protein content.

Other formulas used in children in the estimation of GFR are as follows.

#### **COUNAHAN-BARRATT FORMULA**

$$\text{GFR (ml / min / 1.73 sq.m)} = \frac{0.43 \times \text{Length}}{\text{Sr.Creatinine}}$$

#### **SHULL EQUATION**

$$\text{C}_{\text{Cr}} \text{ (ml / min / 1.73 sq.m)} = \frac{\{(0.035 \times \text{Age}) + 0.236\}}{\text{Sr. Creatinine}} \times 100$$

**TRAUB EQUATION**

$$C_{Cr} (\text{ml} / \text{min} / 1.73 \text{ sq.m}) = \frac{0.48 \times \text{Length}}{\text{Sr.Creatinine}}$$

**GHAZALI-BARRATT EQUATION**

$$C_{Cr}(\text{ml}/\text{min}/1.73\text{sq.m})= \frac{0.12 \times \{15.4 + (0.46 \times \text{Age})\} \times \text{Weight}}{\text{Sr.Creatinine} \times \text{BSA}}$$

**PREDICTION EQUATIONS IN ADULTS**

The most frequently used equation for estimating GFR in adults is the Cockcroft-Gault equation which was developed for estimating creatinine clearance but has been tested widely in its prediction of GFR.<sup>24</sup>

**Cockroft-Gault formula**

A commonly used surrogate marker for actual creatinine clearance is the Cockcroft–Gault formula, which employs creatinine measurements and a patient’s weight to predict the clearance. The formula, as originally published, is:

$$x = \frac{(140 - \text{Age}) \times \text{Weight}}{72 \times \text{Sr.Creatinine}}$$

This formula uses weight (actually mass) measured in kilograms and creatinine measured in mg / dL. The resulting value is multiplied by a constant of 0.85 if the patient is female. This formula is useful because the calculations are relatively simple and can often be performed without the aid of a calculator.

A modification of this formula, useful for the common unit of measure, is:

$$x = \frac{(140 - \text{Age}) \times \text{Weight} \times \text{constant}}{\text{Sr.Creatinine}}$$

This formula uses metric units (weight in kilograms, creatinine in  $\mu\text{mol/L}$ ). The *constant* is 1.23 for men and 1.04 for women. It is named after the scientist who first published the formula (Cockcroft & Gault, 1976). The equation is popular because, it is easy to calculate.<sup>24</sup>

### **MDRD formula**

The most recently advocate formula for calculating the GFR is the one that was developed as a result of the *Modification of Diet in Renal Disease* (MDRD) study

For creatinine in mg/dL

$$x = 186 \times \text{Sr.Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times \text{constant}$$

For creatinine in  $\mu\text{mol/L}$

$$x = 32788 \times \text{Sr.Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times \text{constant}$$

The constant is 1 for a white male, and is multiplied with 0.742 for females and multiplied 1.21 for African Americans. Creatinine levels in  $\mu\text{mol/L}$  can be converted to  $\text{mg/dL}$  by dividing them by 88.4. A more elaborate version of the MDRD equation also includes albumin and blood urea nitrogen levels.<sup>24</sup>

## II. REVIEW OF LITERATURE

Gbadegesin RA et al<sup>1</sup> in their article in West Afr J Med 1995 Oct-Dec, based on their study in a group of 42 children, out of whom 21 had a GFR value  $< 60 \text{ ml/min/} 1.73 \text{ m}^2$  as estimated by creatinine clearance, have observed that in detecting patients with creatinine clearance less than  $60 \text{ ml/min/} 1.73 \text{ m}^2$ , Schwartz formula had a sensitivity of 52%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 68%. They have concluded that in detecting patients with impaired renal function who may need more accurate methods of estimating GFR, Schwartz formula has a low sensitivity and therefore may not be useful as a screening method.

Gbadegesin RA et al<sup>3</sup> have published an article in Ann Trop Paediatr June 1997 based on their study in 34 children with the nephrotic syndrome and 30 apparently healthy children with no evidence of renal disease at the University College Hospital, Ibadan. They have used two methods, Altman-Bland analysis and correlation coefficients, to assess agreement between measured GFR (by endogenous creatinine clearance) and GFR estimated by formula. They observed that the height/plasma creatinine formula of Schwartz et al. is a poor predictor of GFR as measured by endogenous creatinine clearance in Nigerian children and that the Schwartz formula overestimated GFR in over two-thirds of the children. They have suggested that these observations may be due to differences in the constant,  $k$ , used in the formula, which was found to vary widely in their study with a mean

value of 0.45 compared with 0.55 in the formula. They have suggested that the height/creatinine formulae for predicting GFR be tested and validated for accuracy in a given environment before routine use in clinical settings.

Springate JE et al<sup>4</sup> in their article in *Am J Dis Child*, October 1992 based on their study in 87 children between the ages 2 yrs and 20 yrs with plasma clearance of technetium Tc 99m-labeled DTPA as their reference method for determination of GFR have observed that the Cr-GFR formula identified children with impaired renal function (DTPA clearance, less than 80 ml / min / 1.73 m<sup>2</sup>) with a sensitivity of 95% and a specificity of 93%. They also observed that the sensitivity and specificity of elevated serum creatinine level for this purpose were 80% and 96%, respectively. They also observed that of the children with renal insufficiency (DTPA clearance, 40 to 79 ml / min / 1.73 m<sup>2</sup>), 91% were correctly identified by the Cr-GFR formula, but only 65% of these children had elevated serum creatinine levels. They also found that although all children with renal failure (DTPA clearance, less than 40 ml / min / 1.73 m<sup>2</sup>) had abnormally high serum creatinine levels, the specificity of this test was significantly lower than that of the Cr-GFR formula (75% vs. 100%, respectively). They have concluded that the Cr-GFR formula is superior to serum creatinine level for estimating GFR and this formula provides a simple, reasonably accurate screening test for the presence and severity of impaired renal function.

Seikaly MG et al<sup>5</sup> in their article in *Pediatr Nephrol*. December 1996 based on their study in 133 children (aged between 1 and 18 years) with 125

Iodine-iothalamate clearance (C<sub>IO</sub>) as the reference standard for measuring GFR have observed that the overestimation of GFR by Schwartz formula was inversely proportional to the level of renal function and when C<sub>IO</sub> was > 90 ml/min per 1.73 m<sup>2</sup>, Schwartz formula overestimated GFR by only 0.1% +/- 3%, but when C<sub>IO</sub> was < or = 15 ml/min per 1.73 m<sup>2</sup>, Schwartz formula overestimated GFR by 164% +/- 42% and when renal function is normal or mildly reduced (GFR > 50 ml/min per 1.73 m<sup>2</sup>), Schwartz formula overestimated C<sub>IO</sub> by only 10.3 +/- 3.0%, compared with 90.3 +/- 14.5% when renal function was moderately to severely curtailed (GFR < or = 50 ml/min per 1.73 m<sup>2</sup>). They have concluded that Schwartz formula is valid in predicting GFR only in children with normal renal function and mild insufficiency.

Morris MC et al<sup>6</sup> in their article in Arch Dis Child August 1982 based on their study in 163 children with varying levels of renal function have concluded that Ht/Pcr is a clinically useful aid to the estimation of renal function, reducing the need for formal GFR measurements by at least half.

Schwartz GJ et al<sup>7</sup> in their article in Pediatrics August 1976 based on statistical analysis of data in 186 children have arrived at a formula which allows accurate estimation of glomerular filtration rate (GFR) from plasma creatinine and body length.  $GFR (ml/min/1.73 \text{ sq m}) = 0.55 \text{ length (cm)}/PCr (mg/dl)$ . They also observed that its application to clearance data in a separate group of 223 children revealed excellent agreement with GFR estimated by the Creatinine clearance ( $r = .935$ ) or Inulin

clearance ( $r = .905$ ). They had suggested that this formula should be useful for adjusting dosages of drugs excreted by the kidney and detecting significant changes in renal function.

Skinner R et al<sup>8</sup> have published an article in Arch Dis Child May 1994 based on their study on 39 patients who underwent GFR measurement at least six months after potentially nephrotoxic chemotherapy by the plasma clearance of <sup>51</sup>Cr labeled ethylenediaminetetra-acetic acid (<sup>51</sup>Cr-EDTA) and GFR estimation by both Schwartz and Counahan Barratt formulae. They observed that the limits of agreement of the estimated GFR with the measured GFR were unacceptably wide in each case, despite highly significant correlation coefficients. They further observed that the bias was smallest for the modified Counahan-Barratt formula. They have suggested that the use of these formulas to estimate GFR in children was insufficiently accurate for research purposes and has limitations in clinical practice. They have also suggested use of correlation coefficients to evaluate different methods of measuring GFR was inappropriate.

Pierrat A et al<sup>9</sup> have published an article in Kidney Int October 2003 based on their study in 198 children (with two kidneys, single kidney, or renal transplant) and 116 adults (single kidney and transplanted). They measured inulin clearance and creatinine clearance and predicted GFR by Cockcroft-Gault formula and MDRD formula in adults and children and, in children by Schwartz formula only. Data were compared with analysis of variance (ANOVA), regression statistics, and concordance studies. They



observed that in patients over 12 years of age, Cockcroft-Gault was almost similar to GFR corrected for body surface and creatinine clearance exceeded GFR by more than 20%. They also observed that Schwartz was above creatinine clearance excepted for transplanted children. They also observed that in younger children, no prediction approached GFR. They also observed that predictions were well correlated with GFR, but concordance studies showed Schwartz with dispersed results and GFR overestimated (20 mL/min/1.73 m<sup>2</sup>). They also observed that Cockcroft-Gault was close to GFR and results were dispersed, MDRD in children gave a large overestimation and badly dispersed results, in transplanted adults its prediction was good. They have concluded that Cockcroft-Gault prediction could be used for children over 12 years of age and adults and that it should not be considered as creatinine clearance but as GFR corrected for body surface and it was merely a prediction as 95% of the results are between +/- 40 mL/min/1.73 m<sup>2</sup> in children and +/- 30 mL/min/1.73 m<sup>2</sup> in adults. They also concluded that in younger children no formula was satisfying.

Haenggi MH et al<sup>10</sup> have published an article in Arch Pediatr February 1999. Based on clearance data obtained in 200 patients (1 month to 23 years) during the years 1988-1994 they have calculated the factor  $k$  as a function of age. They have studied forty-four additional patients prospectively in conditions of either hydropenia or water diuresis in order to evaluate the possible variation of  $k$  as a function of urine flow rate. They have observed that the correlation between the values of GFR, as estimated by the formula, and the values measured by the standard clearance of inulin

was highly significant and the scatter of individual values was however substantial. They have also observed that when  $k$  was calculated using Creatinine clearance, the formula overestimated inulin clearance at all urine flow rates and when calculated from Ccr,  $k$  varied as a function of urine flow rate. When calculated from inulin clearance, in the same conditions,  $k$  remained constant. They have concluded that the formula  $GFR = k \times Ht / Pcr$  can be used to estimate GFR and the scatter of values precludes the use of the formula to estimate GFR in pathophysiological studies. They have also suggested that the formula should only be used when  $k$  is calculated from Cin, and the plasma creatinine concentration is measured in well defined conditions of hydration.

Filler G et al<sup>2</sup> have published an article in *Pediatr Nephrol* October 2003 from the Department of Pediatrics, Division of Nephrology, Children's Hospital of Eastern Ontario, University of Ottawa, Canada. 536 children (aged 1.0-18 years) with various renal pathologies undergoing nuclear medicine GFR clearance studies (99m) Tc-DTPA single-injection technique) were tested. Cystatin C was measured with a nephelometric assay. The Schwartz GFR was calculated using enzymatically determined serum creatinine in micromoles per liter using the constant 48 for adolescent males and 38 otherwise. Using the Bland and Altman analysis they tested the agreement between the Schwartz formula and gold standard GFR. They observed a considerable bias, with a mean difference of +10.8% and a trend towards overestimation of the GFR by the Schwartz formula with lower GFRs. In contrast, the Bland and Altman analysis applied on the GFR

estimate derived from cystatin C showed the mean difference to be negligible at +0.3% and no trend towards overestimation of the GFR with lower GFRs. In the regression analysis of the estimate and the GFR, the Schwartz estimate showed significant deviation from linearity, whereas the cystatin C estimate did not. They have concluded that the cystatin C-based GFR estimate shows significantly less bias and serves as a better estimate for GFR in children.

Martini S et al<sup>11</sup> have published an article in *Acta Paediatr* September 2003. They studied 99 children (51 male / 48 female), with a median age of 8.3 years (1.0-17.9). They have taken Inulin clearance (Cin) as the gold standard for assessing glomerular filtration rate (GFR). GFR was also estimated by the plasma creatinine concentration (Pcreat), creatinine clearance (Ccreat), the Haycock-Schwartz formula and the plasma concentration of cystatin C (PcysC) They have used a cut-off of Cin of 100 ml/min per 1.73 m<sup>2</sup> to describe children with impaired GFR. Their observations based on Logistic regression, ROC analysis and linear regression all showed that Ccreat was the best parameter to discriminate between impaired and normal GFR, followed by the Haycock-Schwartz formula, PcysC, and finally Pcreat, each one being significantly more predictive than the next. They have concluded that GFR is better assessed by the Haycock-Schwartz formula than by PcysC or Pcreat alone and when urine collection is not possible, simply measuring the child's Pcreat and height is the best, easiest and cheapest way to assess GFR

Stejskal J et al<sup>12</sup> in *Cesk Pediatr* November 1990 have compared different methods used commonly in pediatric practice to assess glomerular filtration (GFR) i.e., creatinine clearance and assessment of GFR by means of Schwartz formula with plasma clearance of polyfructosan S. The patients were divided into three groups by the magnitude of polyfructosan S clearance as greater than 100 ml/min/1.73m<sup>2</sup>, 50-100 ml/min/1.73 m<sup>2</sup> and less than 50 ml/min/1.73 m<sup>2</sup>. The authors correlated the clearance of polyfructosan S with creatinine clearance and assessment of GFR according to Schwartz. The method which proved to be most sensitive for detection of reduced GFR in the area of 50-100 ml/min/1.73m<sup>2</sup> was creatinine clearance with urine collection one hour after a previous water load ( $r = 0.748$ ). In the stage of chronic renal failure with GFR less than 50 ml/min/1.73 m<sup>2</sup> the correlation was close with the three-hour creatinine clearance ( $r = 0.957$ ) and equally close was the correlation with GFR according to Schwartz ( $r = 0.885$ ). They have discussed the probability of detection of impaired GFR by commonly used methods and draw attention to the advantages of examination of plasma clearance by polyfructosan S.

Bokenkamp A et al<sup>13</sup> have published an article in *Pediatrics* May 1998 based on their study in 184 children. Inulin clearance (Cin) was calculated. Serum levels of creatinine and cystatin-C were estimated. They have observed that the reciprocal of cystatin C correlated better with Cin ( $r = 0.88$ ) than the reciprocal of creatinine ( $r = 0.72$ ). They have also observed that stepwise regression analysis identified no covariates for the correlation between cystatin C and Cin, whereas height was a covariate for

creatinine. They also observed that when using an estimate of GFR from serum creatinine and height, correlation with  $C_{in}$  was similar to cystatin C, but female gender and dystrophy were associated with an overestimation of GFR. They have concluded that unlike creatinine, serum cystatin C reflects renal function in children independent of age, gender, height, and body composition.

Fong J et al<sup>15</sup> have published an article in *Clin Pharmacol Ther* August 1995 based on their study in 100 individuals aged between 0.1 to 20.8 years admitted to a pediatric intensive care unit. Urine was collected by indwelling bladder catheters. Serum levels of creatinine were determined. Creatinine clearance was calculated according to the standard formula. GFR was estimated according to a published method, in which GFR is based on serum creatinine levels, patient length, and a constant that varies with the age and sex of the child. For each patient, the percentage difference between methods was calculated as the difference between the methods divided by the average obtained by the two methods and expressed as a percentage. Bias was calculated as the absolute value of the percentage difference. They have observed that GFR measured and estimated significantly correlated. Estimated values were greater than measured values in 84 patients. They have concluded that a method to estimate GFR in children that is based on age and sex, but not critical illness, does not correspond with measured 24-hour Creatinine clearance. They have also concluded that use of this method to adjust dosage of drugs eliminated by the kidney might result in significant over dosage in most critically ill children.

Counahan R et al<sup>16</sup> have published an article in Arch Dis Child November 1976. Based on the relation between the true plasma creatinine concentration (Pc) and the glomerular filtration rate corrected for body surface area (GFR/SA) was investigated in 108 individuals, they have arrived at the following formula  $GFR/SA \text{ (ml/min per } 1.73\text{m}^2\text{SA)} = 0.43 \times Ht \text{ (cm)}/PCr \text{ (mg/100 ml)}$ . They have tested the formula in a second group of 83 children, and its accuracy and precision was compared to the 24-hour creatinine clearance. They found that the values estimated were superior to the creatinine clearance overall, and was as good, even if all results involving suspect 24-hour-urine collections were eliminated from analysis.

Leger F et al<sup>17</sup> in *Pediatr Nephrol*. November 2002 based on their analysis on 97 patients have formatted an equation i.e.,

$$GFR(\text{ml/min}) = [56.7 \times \text{Bodyweight}(\text{kg}) + 0.142 \times \text{Length}^2(\text{cm})] / PCr(\mu\text{M}).$$

They have suggested that this equation would be useful for estimating GFR in children when isotopic determination of the <sup>51</sup>Cr-EDTA clearance cannot be performed.

### **III. STUDY JUSTIFICATION**

The estimation of Glomerular filtration rate (GFR) by creatinine clearance is a bit cumbersome, as we have to collect urine for 24 hours and the serum sample being obtained at the middle of collection period.

Further, in the creatinine clearance method where 24 hour urine collection is required it is difficult to collect urine in small infants, non toilet trained children and children with wide range of voiding difficulties.

The prediction of Glomerular filtration rate (GFR) by Schwartz formula requires only a sample of serum creatinine at a given point of time and the height of the patient.

Further, there has been no Indian statistics regarding the validity of Schwartz formula, which is being applied in many centers across the world in the prediction of Glomerular filtration rate (GFR).

#### **IV. AIM OF THE STUDY**

To study the validity / accuracy of Schwartz formula in predicting Glomerular filtration rate (GFR), comparing it with creatinine clearance.



## **V. MATERIALS AND METHODS**

### **Place of study**

Institute of child health & Hospital for children, Chennai.

### **Period of study**

July 2004 to February 2006

### **Study Design**

Evaluation of a diagnostic modality.

### **Study population**

Children aged 5 – 12 years.

**Inclusion criteria**

1. Children without any evidence of renal disease with normal hydration.
2. Nephrotic syndrome patients
3. Acute Glomerulonephritis patients
4. All CRF patients admitted in nephrology ward as predicted by creatinine clearance

**Exclusion criteria**

Children with obstructive uropathy, neurogenic bladder and voiding dysfunction.

**Sample size**

The patients are grouped based on their GFR values as estimated by creatinine clearance as follows<sup>22</sup>.

< 25 ml / min / 1.73m<sup>2</sup>

25 – 50 ml / min / 1.73m<sup>2</sup>

50 – 75 ml / min / 1.73m<sup>2</sup>

> 75 ml / min / 1.73m<sup>2</sup>

For an  $\alpha$  error of 0.05 and a power of study of 0.8 with a 95 % confidence interval a sample size of 35 patients in each group is calculated.

**Maneuver**

1. All children who satisfied the inclusion criteria and whose parents gave consent for study were recruited.
2. The height and weight of the children were taken at the beginning of 24 hours urine collection period.
3. The patient's body surface area was estimated by Mosteller's formula.

$$\text{Body surface area (m}^2\text{)} = \{\text{Height (cm) X Weight (kg) / 3600}\}^{1/2}$$

4. Body mass index {Kg / m<sup>2</sup>} was calculated.
5. 24 hours urine collection was made.
6. Serum creatinine estimation was done at the end of 12<sup>th</sup> hour during the 24 hours collection period.
7. Urine concentration of creatinine was estimated.
8. Creatinine clearance was estimated using the formula  $UV / P$ . The value obtained was corrected to 1.73 m<sup>2</sup> body surface area.
9. Simultaneously GFR was predicted by Schwartz formula.

Values obtained by Creatinine clearance and Schwartz formula were compared.

## **STATISTICAL ANALYSIS**

The sensitivity, specificity, positive predictive value, negative predictive value, and the overall accuracy of the Schwartz formula will be calculated. Correlation coefficient will be arrived at. Bland and Altman plot for method comparison<sup>27, 28</sup> will be done and results analyzed.

### **Sensitivity**

This is the probability that an individual shown to be below a particular cutoff by creatinine clearance will have the value below the same cutoff by Schwartz formula, and hence, the true positive rate of the test.

### **Specificity**

This is the probability that an individual shown to be above a particular cutoff by creatinine clearance will have the value above the same cutoff by Schwartz formula, and hence, the true negative rate of the test.

### **Positive Predictive Value**

This is the probability that an individual shown to be below a particular cutoff by Schwartz formula will have the value below the same cutoff by creatinine clearance.

### **Negative Predictive Value**

This is the probability that an individual shown to be above a particular cutoff by Schwartz formula will have the value above the same cutoff by creatinine clearance.

### **Bland & Altman method of comparison<sup>27, 28</sup>**

The Bland & Altman plot is a statistical method to compare two measurement techniques. In this graphical method the differences between the two techniques are plotted against the averages of the two techniques.

## VI. OBSERVATIONS

A total of 146 children were recruited for study. They were classified into four groups based on their glomerular filtration rate values as estimated by creatinine clearance.

Out of the total 146, 37 children were chronic renal failure (CRF) patients, 60 children were suffering from nephrotic syndrome, 20 children had acute glomerulo nephritis out of which three had acute renal failure and 29 children were suffering from other illnesses ranging from viral fever to congenital heart disease with normal hydration without any evidence of renal involvement.

Out of the 37 children with CRF, 5 children had chronic glomerulo nephritis, 5 children had juvenile nephronophthisis, 2 children had dysplastic kidneys, 2 children had Hemolytic Uremic Syndrome (HUS) which progressed to CRF, 2 children had Rapidly Progressive Glomerulo Nephritis (RPGN), one had Membrano Proliferative Glomerulo Nephritis (MPGN), one patient had Fanconi's syndrome, two had Systemic Lupus Erythematosus (SLE), one child had tubulo interstitial nephritis, 5 children had chronic renal failure without any etiological diagnosis ( obstructive uropathy and VUR excluded) and the remaining 11 had nephrotic syndrome (NS) as the presenting feature and progressing to chronic renal failure over period of time. The NS patients included those having frequent relapses, steroid resistance, steroid dependent and cyclophosphamide resistance.

**Table.1.**

**Correlation of GFR values obtained by Schwartz formula with that of Creatinine clearance. (n = 146)**

<b>Schwartz formula</b>	<b>Creatinine clearance</b>			
	<b>&lt;25 ml/min/1.73m<sup>2</sup></b>	<b>25-49.99 ml/min/1.73m<sup>2</sup></b>	<b>50-74.99 ml/min/1.73m<sup>2</sup></b>	<b>&gt;=75 ml/min/1.73m<sup>2</sup></b>
<b>&lt;25 ml/min/1.73m<sup>2</sup></b>	23(57.5 %)	1		
<b>25-49.99 ml/min/1.73m<sup>2</sup></b>	9	10(28.6 %)		
<b>50-74.99 ml/min/1.73m<sup>2</sup></b>	4	13	13(36.1%)	2
<b>&gt;=75 ml/min/1.73m<sup>2</sup></b>	4	11	23	33(94.3%)
<b>Total</b>	40	35	36	35

40 children have a glomerular filtration rate value less than 25 ml/min/1.73m<sup>2</sup>, 35 children have a glomerular filtration rate value between 25-49.99 ml/min/1.73m<sup>2</sup>, 36 children have a glomerular filtration rate value between 50-74.99 ml/min/1.73m<sup>2</sup> and 35 children have a glomerular filtration rate value of 75 ml/min/1.73m<sup>2</sup> and above.

Out of the 40 children having a glomerular filtration rate value less than 25 ml / min / 1.73 m<sup>2</sup> as estimated by creatinine clearance 23(57.5%) children had the values in same range when predicted by Schwartz formula

and 17 had their glomerular filtration rate values predicted 25 ml/ min / 1.73 m<sup>2</sup> and above.

Out of the 35 children having a glomerular filtration rate value between 25 and 49.99 ml/ min / 1.73 m<sup>2</sup> as estimated by creatinine clearance, 10 (28.5%) children had the values in same range when predicted by Schwartz formula. One pt had a predicted glomerular filtration rate value below 25 ml/ min / 1.73 m<sup>2</sup> and 24 had their glomerular filtration rate values predicted 50 ml/ min / 1.73 m<sup>2</sup> and above.

Out of the 36 children having a glomerular filtration rate value between 50 and 74.99 ml/ min / 1.73 m<sup>2</sup> as estimated by creatinine clearance, 13 (36.1%) children had the values in same range when predicted by Schwartz formula and 23 had their glomerular filtration rate values predicted 75 ml/ min / 1.73 m<sup>2</sup> and above.

Out of the 35 children having a glomerular filtration rate value above 75 ml/ min / 1.73 m<sup>2</sup> as estimated by creatinine clearance, 33 (94.3%) children had the values in same range when predicted by Schwartz formula and two patients had a predicted glomerular filtration rate value below 75 ml/ min / 1.73 m<sup>2</sup> .



**Table.2.**

**Correlation of GFR values ( $<75$  ml/min/ $1.73\text{m}^2$ ) obtained by Schwartz formula with that of Creatinine clearance. (n = 146)**

<b>Schwartz formula</b>	<b>Creatinine clearance</b>	
	<b><math>&lt;75</math> ml/min/<math>1.73\text{m}^2</math></b>	<b><math>\geq 75</math> ml/min/<math>1.73\text{m}^2</math></b>
<b><math>&lt;75</math> ml/min/<math>1.73\text{m}^2</math></b>	73	2
<b><math>\geq 75</math> ml/min/<math>1.73\text{m}^2</math></b>	38	33

In detecting patients with creatinine clearance  $<75$  ml/min/ $1.73\text{m}^2$ , the Schwartz formula has a sensitivity of 65.8%, a specificity of 94.3%, a positive predictive value of 97.3% and a negative predictive value of 46.5%. The overall predictive accuracy of Schwartz formula is 72.6%.

**Table.3.**

**Correlation of GFR values (<25 ml/min/1.73m<sup>2</sup>) obtained by Schwartz formula with that of Creatinine clearance. (n = 146)**

<b>Schwartz formula</b>	<b>Creatinine clearance</b>	
	<b>&lt;25 ml/min/1.73m<sup>2</sup></b>	<b>&gt;=25 ml/min/1.73m<sup>2</sup></b>
<b>&lt;25 ml/min/1.73m<sup>2</sup></b>	23	1
<b>&gt;=25 ml/min/1.73m<sup>2</sup></b>	17	105

In detecting patients with creatinine clearance <25 ml/min/1.73m<sup>2</sup>, the Schwartz formula has a sensitivity of 57.5%, a specificity of 99.1%, a positive predictive value of 95.8% and a negative predictive value of 86.1%.

**Table.4.**

**Correlation of GFR values (25-49.99 ml/min/1.73m<sup>2</sup>) obtained by Schwartz formula with that of Creatinine clearance. (n = 105)**

<b>Schwartz formula</b>	<b>Creatinine clearance</b>	
	<b>25-49.99 ml/min/1.73m<sup>2</sup></b>	<b>&gt;=50 ml/min/1.73m<sup>2</sup></b>
<b>25-49.99 ml/min/1.73m<sup>2</sup></b>	10	0
<b>&gt;=50 ml/min/1.73m<sup>2</sup></b>	24	71

In detecting patients with creatinine clearance between 25 and 49.99 ml/min/1.73m<sup>2</sup>, the Schwartz formula has a sensitivity of 29.4%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 74.7%.

**Table.5.**

**Correlation of GFR values (50-74.99 ml/min/1.73m<sup>2</sup>) obtained by Schwartz formula with that of Creatinine clearance. (n = 71)**

<b>Schwartz formula</b>	<b>Creatinine clearance</b>	
	<b>50-74.99 ml/min/1.73m<sup>2</sup></b>	<b>&gt;=75 ml/min/1.73m<sup>2</sup></b>
<b>50-74.99 ml/min/1.73m<sup>2</sup></b>	13	2
<b>&gt;=75 ml/min/1.73m<sup>2</sup></b>	23	33

In detecting patients with creatinine clearance between 50 and 74.99 ml/min/1.73m<sup>2</sup>, the Schwartz formula has a sensitivity of 36.1%, a specificity of 94.3%, a positive predictive value of 86.7% and a negative predictive value of 58.9%.

**Table.6.**

**Correlation of GFR values obtained by Schwartz formula with that of Creatinine clearance in children with a BMI < 15.<sup>26</sup> (n = 83)**

<b>Schwartz formula</b>	<b>Creatinine clearance</b>			
	<b>&lt;25 ml/min/1.73m<sup>2</sup></b>	<b>25-49.99 ml/min/1.73m<sup>2</sup></b>	<b>50-74.99 ml/min/1.73m<sup>2</sup></b>	<b>&gt;=75 ml/min/1.73m<sup>2</sup></b>
<b>&lt;25 ml/min/1.73m<sup>2</sup></b>	14(66.7%)	1		
<b>25-49.99 ml/min/1.73m<sup>2</sup></b>	5	8(57.1%)		
<b>50-74.99 ml/min/1.73m<sup>2</sup></b>	2	4	8(34.8%)	1
<b>&gt;=75 ml/min/1.73m<sup>2</sup></b>		1	15	24(96%)
<b>Total</b>	21	14	23	25

Out of the 21 children with BMI less than 15kg/m<sup>2</sup>, having a glomerular filtration rate value less than 25 ml/ min / 1.73 m<sup>2</sup> as estimated by creatinine clearance, 14(66.7%) children had the values in same range when predicted by Schwartz formula and 7 had their glomerular filtration rate values predicted 25 ml/ min / 1.73 m<sup>2</sup> and above.

Out of the 14 children with BMI less than 15kg/m<sup>2</sup>, having a glomerular filtration rate value between 25and 49.99 ml/ min / 1.73 m<sup>2</sup> as

estimated by creatinine clearance, 8 (57.1%) children had the values in same range when predicted by Schwartz formula. One pt had a predicted glomerular filtration rate value below 25 ml/ min / 1.73 m<sup>2</sup> and 5 had their glomerular filtration rate values predicted 50 ml/ min / 1.73 m<sup>2</sup> and above.

Out of the 23 children with BMI less than 15kg/m<sup>2</sup>, having a glomerular filtration rate value between 50 and 74.99 ml/ min / 1.73 m<sup>2</sup> as estimated by creatinine clearance, 8 (34.8%) children had the values in same range when predicted by Schwartz formula and 15 had their glomerular filtration rate values predicted 75 ml/ min / 1.73 m<sup>2</sup> and above.

Out of the 25 children with BMI less than 15kg/m<sup>2</sup>, having a glomerular filtration rate value above 75 ml/ min / 1.73 m<sup>2</sup> as estimated by creatinine clearance, 24(96%) children had the values in same range when predicted by Schwartz formula and one patient had a predicted glomerular filtration rate value below 75 ml/ min / 1.73 m<sup>2</sup> .

**Table.7.**

**Correlation of GFR values ( $<75$  ml/min/ $1.73\text{m}^2$ ) obtained by Schwartz formula with that of Creatinine clearance in children with a BMI  $< 15$ . (n = 83)**

<b>Schwartz formula</b>	<b>Creatinine clearance</b>	
	<b><math>&lt;75</math> ml/min/<math>1.73\text{m}^2</math></b>	<b><math>\geq 75</math> ml/min/<math>1.73\text{m}^2</math></b>
<b><math>&lt;75</math> ml/min/<math>1.73\text{m}^2</math></b>	42	1
<b><math>\geq 75</math> ml/min/<math>1.73\text{m}^2</math></b>	16	24

In detecting patients having a BMI  $< 15$  kg/m<sup>2</sup> with creatinine clearance  $<75$  ml/min/ $1.73\text{m}^2$ , the Schwartz formula has a sensitivity of 72.4%, a specificity of 96%, a positive predictive value of 97.7% and a negative predictive value of 60%.

**Table.8.**

**Correlation of GFR values obtained by Schwartz formula with that of Creatinine clearance in children with a BMI of 15 and above.<sup>26</sup> (n =63)**

<b>Schwartz formula</b>	<b>Creatinine clearance</b>			
	<b>&lt;25 ml/min/1.73m<sup>2</sup></b>	<b>25-49.99 ml/min/1.73m<sup>2</sup></b>	<b>50-74.99 ml/min/1.73m<sup>2</sup></b>	<b>&gt;=75 ml/min/1.73m<sup>2</sup></b>
<b>&lt;25 ml/min/1.73m<sup>2</sup></b>	9(47.4%)			
<b>25-49.99 ml/min/1.73m<sup>2</sup></b>	4	2(9.5%)		
<b>50-74.99 ml/min/1.73m<sup>2</sup></b>	2	9	5(38.5%)	1
<b>&gt;=75 ml/min/1.73m<sup>2</sup></b>	4	10	8	9(90%)
<b>Total</b>	19	21	13	10

Out of 63 children with a body mass index (BMI) of 15 kg/m<sup>2</sup> and above, 19 children have a glomerular filtration rate value less than 25 ml/min/1.73m<sup>2</sup>, 21 children have a glomerular filtration rate value between 25 and 49.99 ml/min/1.73m<sup>2</sup>, 13 children have a glomerular filtration rate value between 50-74.99 ml/min/1.73m<sup>2</sup> and 10 children have a glomerular filtration rate value 75 ml/min/1.73m<sup>2</sup> and above, as estimated by creatinine clearance.



Out of the 19 children with BMI of  $15 \text{ kg/m}^2$  and above, having a glomerular filtration rate value less than  $25 \text{ ml/ min / } 1.73 \text{ m}^2$  as estimated by creatinine clearance, 9 (47.4%) children had the values in same range when predicted by Schwartz formula and 10 had their glomerular filtration rate values predicted  $25 \text{ ml/ min / } 1.73 \text{ m}^2$  and above.

Out of the 21 children with BMI of  $15 \text{ kg/m}^2$  and above, having a glomerular filtration rate value between 25 and  $49.99 \text{ ml/ min / } 1.73 \text{ m}^2$  as estimated by creatinine clearance, 2 (9.5%) children had the values in same range when predicted by Schwartz formula and 19 children had their glomerular filtration rate values predicted  $50 \text{ ml/ min / } 1.73 \text{ m}^2$  and above.

Out of the 13 children with BMI of  $15 \text{ kg/m}^2$  and above, having a glomerular filtration rate value between 50 and  $74.99 \text{ ml/ min / } 1.73 \text{ m}^2$  as estimated by creatinine clearance, 5 (38.5%) children had the values in same range when predicted by Schwartz formula and 8 had their glomerular filtration rate values predicted  $75 \text{ ml/ min / } 1.73 \text{ m}^2$  and above.

Out of the 10 children with BMI of  $15 \text{ kg/m}^2$  and above, having a glomerular filtration rate value above  $75 \text{ ml/ min / } 1.73 \text{ m}^2$  as estimated by creatinine clearance, 9 (90%) children had the values in same range when predicted by Schwartz formula and one patient had a predicted glomerular filtration rate value below  $75 \text{ ml/min/}1.73 \text{ m}^2$ .

**Table.9.**

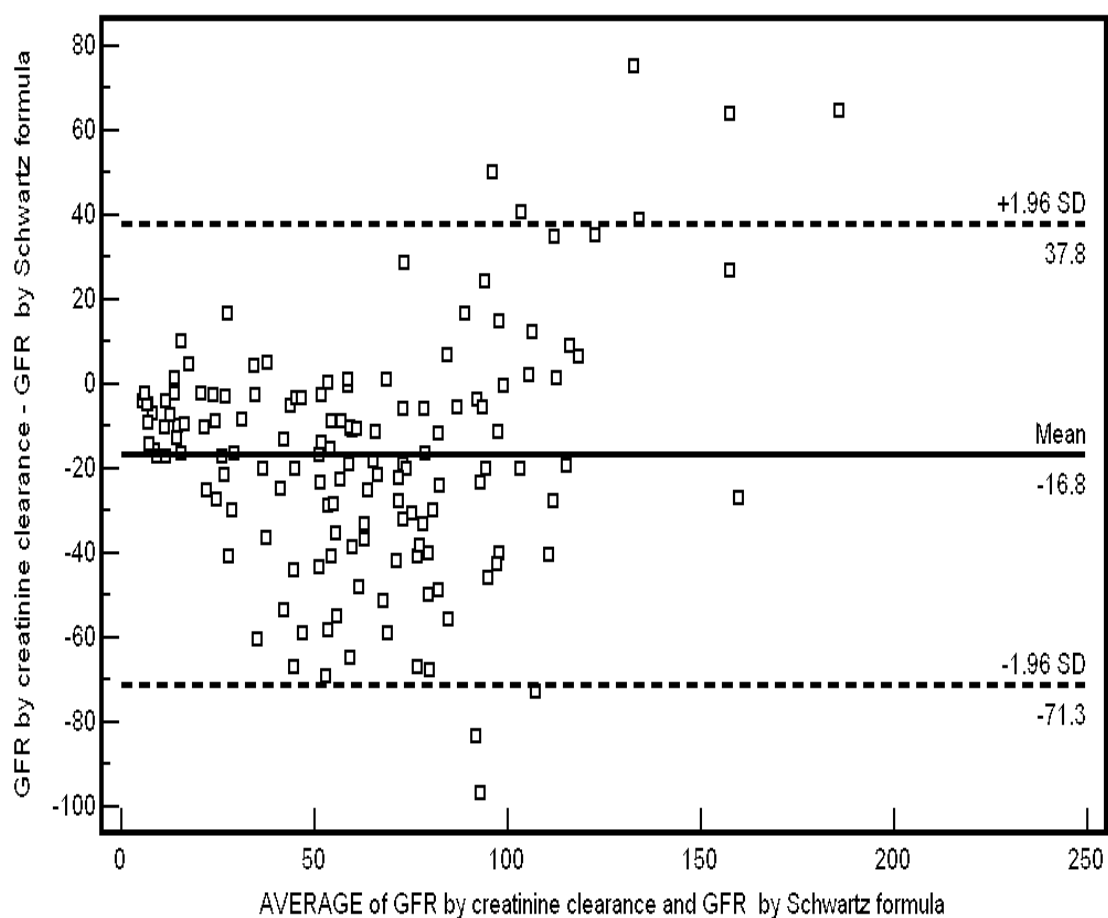
**Correlation of GFR values ( $<75$  ml/min/ $1.73\text{m}^2$ ) obtained by Schwartz formula with that of Creatinine clearance in children with a BMI of 15 and above. (n = 63)**

<b>Schwartz formula</b>	<b>Creatinine clearance</b>	
	<b><math>&lt;75</math> ml/min/<math>1.73\text{m}^2</math></b>	<b><math>\geq 75</math> ml/min/<math>1.73\text{m}^2</math></b>
<b><math>&lt;75</math> ml/min/<math>1.73\text{m}^2</math></b>	<b>31</b>	<b>1</b>
<b><math>\geq 75</math> ml/min/<math>1.73\text{m}^2</math></b>	<b>22</b>	<b>9</b>

In detecting patients having a BMI of  $15 \text{ kg/m}^2$  and above, with creatinine clearance  $<75$  ml/min/ $1.73\text{m}^2$ , the Schwartz formula has a sensitivity of 58.5%, a specificity of 90%, a positive predictive value of 96.9% and a negative predictive value of 29%.

**Bland and Altman Plot for Method Comparison.**<sup>27, 28</sup>

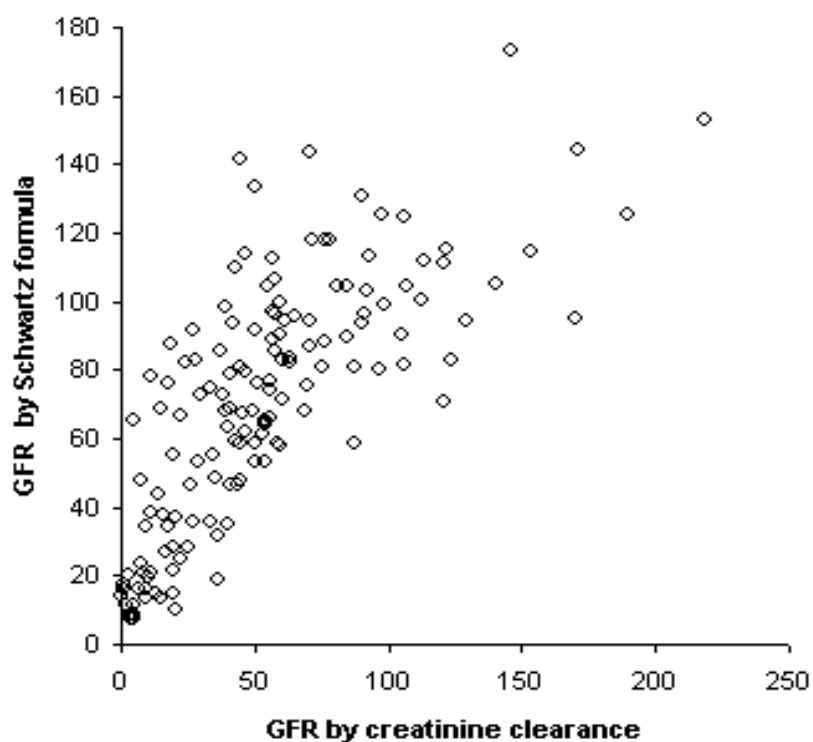
This is a statistical method of comparing two tests. The average of the values obtained by creatinine clearance and Schwartz formula are graphically plotted against the difference between the values obtained by the two methods.



**Fig.1: Bland and Altman plot for method comparison, plotting the difference between creatinine clearance and Schwartz formula against the average of creatinine clearance and Schwartz formula.**

The average difference is -16.8, with a standard deviation of 27.8. The limits of agreement are (-71.3, 37.8). This means that the values obtained by Schwartz formula may be 71 ml/min/1.73 m<sup>2</sup> above or 38 ml/min/1.73 m<sup>2</sup> below creatinine clearance. The 95% confidence interval for the lower limit of agreement is -79.1 to -63.5 and the 95% confidence interval for the upper limit of agreement is 29.9 to 45.6.

## Pearson Correlation



**Fig.2. Pearson Correlation**

**Table .10.**

### Correlation results.

n	146
r statistic	0.75
95% CI	0.67 to 0.81
2-tailed p	<0.0001

There is a significant correlation ( $r=0.75$ ) between Schwartz formula and creatinine clearance with a 95% confidence interval of 0.67 to 0.81 ( $p < 0.0001$ ).

## VII. DISCUSSION

In the present study totally 146 children were included. 35 children had a GFR value above 75 ml / min / 1.73 m<sup>2</sup> and 111 children had values less than 75 ml / min / 1.73 m<sup>2</sup> as estimated by creatinine clearance.

**Table.11.**

**Comparison of results of the present study with other studies.**

<b>Results</b>	<b>Present study N = 146</b>	<b>Gbadegesin RA et al<sup>1</sup> N =42</b>
Sensitivity	65.8%	52%
Specificity	94.3%	100%
Positive predictive value	97.3%	100%
Negative predictive value	46.5%	68%

In the present study, in detecting patients with GFR <75 ml/min/1.73m<sup>2</sup>, the Schwartz formula has a sensitivity of 65.8%, a specificity of 94.3%, a positive predictive value of 97.3% and a negative predictive value of 46.5%. Gbadegesin RA et al<sup>1</sup> in their study in a group of 42 children, out of whom 21 had a GFR value < 60 ml/min/ 1.73 m<sup>2</sup> as estimated by creatinine clearance, have observed that in detecting patients

with creatinine clearance less than 60 ml/min/1.73 m<sup>2</sup>, Schwartz formula had a sensitivity of 52%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 68%. The results of the present study are comparable to theirs, although they have taken 60 ml/min/1.73 m<sup>2</sup> as their cut off for defining decreased renal function.

In the present study, comparing the Schwartz formula and endogenous creatinine clearance there is a significant correlation coefficient ( $r = 0.75$ ). The limits of agreement are (-71.3, 37.8). Skinner R et al<sup>8</sup> in their study on 39 patients who underwent GFR measurement at least six months after potentially nephrotoxic chemotherapy by the plasma clearance of <sup>51</sup>Cr labeled ethylenediamine tetra-acetic acid (<sup>51</sup>Cr-EDTA) and GFR estimation by both Schwartz and Counahan Barratt formulae had observed that the limits of agreement of the estimated GFR with the measured GFR were unacceptably wide in each case, despite highly significant correlation coefficients.

Filler G et al<sup>2</sup> in their study in 536 Children (aged 1.0-18 years) with various renal pathologies undergoing nuclear medicine GFR clearance studies ((<sup>99m</sup>Tc-DTPA single-injection technique) tested the agreement between the Schwartz formula and gold standard GFR using the Bland and Altman analysis. They observed a considerable bias, with a mean difference of +10.8% and a trend towards overestimation of the GFR by the Schwartz formula with lower GFRs. In the present study in 146 children on testing the agreement between values obtained by Schwartz formula and the GFR

values estimated by creatinine clearance, there is also considerable bias with a mean difference of -16.8 and a trend towards overestimation of GFR by Schwartz formula. The overestimation may be due to the differences in the constant  $k$  between various populations. This needs further evaluation, to standardize the values of  $k$  for our children, before using the formula in our clinical setup, in predicting the glomerular filtration rate.

The patients were grouped into two based on their Body Mass Index (BMI) to assess whether nutritional status has any effect on the prediction of glomerular filtration rate by Schwartz formula that uses a constant  $k$  which tends to differ, when malnutrition or obesity is present.<sup>21</sup> 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 Schwartz formula. A BMI value of less than 15 is considered moderate malnutrition and less than 13 as severe malnutrition in growing children.<sup>26</sup> In detecting patients having a BMI  $< 15 \text{ kg/m}^2$  with creatinine clearance  $< 75 \text{ ml/min/1.73m}^2$ , the Schwartz formula has a sensitivity of 72.4%, a specificity of 96%, a positive predictive value of 97.7% and a negative predictive value of 60%. In detecting patients having a BMI of  $15 \text{ kg/m}^2$  and above, with creatinine clearance  $< 75 \text{ ml/min/1.73m}^2$ , the Schwartz formula has a sensitivity of 58.5%, a specificity of 90%, a positive predictive value of 96.9% and a negative predictive value of 29%.



**Table. 12.**  
**Comparison of results of Schwartz formula in children having**  
**BMI < 15 and BMI >=15**

<b>RESULTS</b>	<b>Overall N=146</b>	<b>BMI &lt; 15 N=83</b>	<b>BMI &gt;= 15 N=63</b>
Sensitivity	65.8%	72.4%	58.5%
Specificity	94.3%	96%	90%
Positive predictive value	97.3%	97.7%	96.9%
Negative predictive value	46.5%	60%	29%

There is no significant effect of malnutrition in the prediction of GFR by Schwartz formula, in the present study.

## VIII. SUMMARY AND CONCLUSION

- The Schwartz formula predicts GFR better in children with normal renal function.
- In predicting GFR in children with impaired renal function, the Schwartz formula has
  - a sensitivity of 65.8%.
  - a specificity of 94.3%.
  - a positive predictive value of 97.3%.
  - a negative predictive value 46.5%.
- There is a significant correlation ( $r = 0.75$ ) between Schwartz formula and creatinine clearance.

To conclude, the Schwartz formula has a sensitivity of 65.8% in detecting children with impaired renal function, and therefore may not be useful as a screening method, and these children may need more accurate methods of estimating GFR.

## BIBLIOGRAPHY

1. Gbadegesin RA, Asinobi AO, Osinusi K, Adeyemo AA: Is the height/plasma creatinine formula of Schwartz useful as a screening test in detecting Nigeria children with low GFR? *West Afr J Med*. 1995 Oct-Dec;14(4):242-5.
2. Filler G, Lepage N: Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? *Pediatr Nephrol*. 2003 Oct;18(10):981-5. Epub 2003 Aug 13.
3. Gbadegesin RA, Adeyemo AA, Asinobi AO, Osinusi K: Inaccuracy of the Schwartz formula in estimating glomerular filtration rate in Nigerian children. *Ann Trop Paediatr*. 1997 Jun;17(2):179-85.
4. Springate JE, Christensen SL, Feld LG: Serum creatinine level and renal function in children. *Am J Dis Child*. 1992 Oct;146(10):1232-5.
5. Seikaly MG, Browne R, Bajaj G, Arant BS Jr: Limitations to body length/serum creatinine ratio as an estimate of glomerular filtration in children. *Pediatr Nephrol*. 1996 Dec;10(6):709-11.
6. Morris MC, Allanby CW, Toseland P, Haycock GB, Chantler C: Evaluation of a height/plasma creatinine formula in the measurement of glomerular filtration rate.
7. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics*. 1976 Aug;58(2):259-63.
8. Skinner R, Cole M, Pearson AD, Keir MJ, Price L, Wyllie RA, Coulthard MG, Craft AW: Inaccuracy of glomerular filtration rate estimation from height/plasma creatinine ratio. *Arch Dis Child*. 1994 May;70(5):387-90.

9. Pierrat A, Gravier E, Saunders C, Caira MV, Ait-Djafer Z, Legras B, Mallie JP: Predicting GFR in children and adults: a comparison of the Cockcroft-Gault, Schwartz, and modification of diet in renal disease formulas. *Kidney Int.* 2003 Oct;64(4):1425-36.
10. Haenggi MH, Pelet J, Guignard JP: Estimation of glomerular filtration rate by the formula  $GFR = K \times T/Pc$ . *Arch Pediatr.* 1999 Feb;6(2):165-72.
11. Martini S, Prevot A, Mosig D, Werner D, van Melle G, Guignard JP: Glomerular filtration rate: measure creatinine and height rather than cystatin C! *Acta Paediatr.* 2003 Sep;92(9):1052-7.
12. Stejskal J, Novakova J, Reitschlagrova V: Validity of routinely used methods of testing glomerular filtration in pediatric practice. *Cesk Pediatr.* 1990 Nov;45(11):662-6.
13. Bokenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J: Cystatin C—a new marker of glomerular filtration rate in children independent of age and height. *Pediatrics.* 1998 May;101(5):875-81.
14. Filler G, Lepage N: Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? *Pediatr Nephrol.* 2003 Oct;18(10):981-5. Epub 2003 Aug 13.
15. Fong J, Johnston S, Valentino T, Notterman D: Length/serum creatinine ratio does not predict measured creatinine clearance in critically ill children. *Clin Pharmacol Ther.* 1995 Aug;58(2):192-7.
16. Counahan R, Chantler C, Ghazali S, Kirkwood B, Rose F, Barratt TM: Estimation of glomerular filtration rate from plasma creatinine concentration in children. *Arch Dis Child.* 1976 Nov;51(11):875-8.

- 17.Leger F, Bouissou F, Coulais Y, Tafani M, Chatelut E: Estimation of glomerular filtration rate in children. *Pediatr Nephrol.* 2002 Nov;17(11):903-7. Epub 2002 Sep 11.
- 18.Price CP,Finney H: Developments in assessment of glomerular filtration rate. *Clin Chim Acta* 2000;297:55-66.
- 19.Arant BS Jr: Postnatal development of renal function during the first year of life. *Pediatr Nephrol* 1987;1: 308.
- 20.Schwartz GJ, Haycock GB, Spitzer A: plasma creatinine and urea concentration in children: Normal values for age and sex. *J Pediatr* 1976; 88:828-37.
- 21.Schwartz GJ, Brion LP, Spitzer A: The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children and adolescents. *Pediatr Clin North Am* 1987; 34:443-64.
- 22.Nelson textbook of pediatrics 17<sup>th</sup> edition.
- 23.Review of medical physiology William F Ganong 20<sup>th</sup> edition.
- 24.K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, Classification and Stratification. [http: \\ www.kidney.org](http://www.kidney.org)
- 25.Holliday's Pediatric Nephrology 5<sup>th</sup> edition.
- 26.Nutrition and Child development KE Elizabeth 3<sup>rd</sup> edition.
- 27.Bland JM, Altman DG (1986) Statistical method for assessing agreementbetween two methods of clinical measurement. *The Lancet*, i, 307-310.
- 28.Bland JM, Altman DG (1999) Measuring agreement in method comparison studies. *Statistical Methods in Medical Research*, 8, 135-160.

**ANNEXURE****PROFORMA**

Name: Sl.No:

Age: I.P.No:

Sex:

Height:

Weight:

Body Surface Area:

Body Mass Index:

Clinical diagnosis:

Serum Creatinine:

24 Hours Urine Volume:

Urine Creatinine:

GFR by creatinine clearance:

GFR by Schwartz formula: