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Relation of Serum Creatinine with Renal Resistive Index in Nephrotic Syndrome

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ABSTRACT: Nephrotic syndrome is a very common childhood disease, commonly affecting children between 2-6 years of age. As serum creatinine level reflects the glomerular filtration rate. In clinical practice, creatinine clearance is often used as a marker of glomerular filtration rate.
Aims: To see whether renal resistive index increases in children with nephrotic syndrome with high serum creatinine level.
Settings and Design: Hospital based analytical study
Methods and Material: Serum creatinine values were evaluated in relation to the severity of nephrotic syndrome. 63 children were taken into study (>1 year and <12 years), and were divided into 2 groups (≤6years and >6 years). The serum creatinine values of each group were compared with the renal resistive index of nephrotic syndrome. RRI was determined from USG renal Doppler by applying the following formula:
PEAK SYSTOLIC VELOCITY- END DIASTOLIC VELOCITY/ PEAK SYSTOLIC VELOCITY
Results: Out of 34 children (≤6years) 12 children showed normal serum creatinine, 22 cases showed serum creatinine (>0.5mg/dl), where the RI was 0.66±0.16, 0.65±0.13, 0.66±0.10 in the right kidney and 0.61±0.08, 0.63±0.20, 0.68±0.11 in the left kidney in different poles with p-value 0.95 and 0.22 respectively. Similarly, out of 29 cases (>6years) 7 cases showed serum creatinine (>0.8mg/dl), where the RI was 0.65±0.18, 0.70±0.11, 0.74±0.29 in right kidney and 0.66±0.10, 0.72±0.17, 0.84±0.10 in left kidney with p-value 0.728 and 0.0481 in right and left kidneys respectively.
Conclusions: Our findings suggest that with increasing severity of renal disease as evidenced by abnormal serum creatinine level, there is increase in RRI on higher range.
Key-words:renal resistive index, nephrotic syndrome, USG renal Doppler, Serum creatinine.

I. INTRODUCTION:

Nephrotic syndrome is a major cause of chronic renal disease among the pediatric age group. It affects 1-3 per 100,000 children <16 years of age. Without treatment it is associated with high risk of death, most commonly from infections. Fortunately 80% of children with nephrotic syndrome responds to steroid therapy.[1]Despite treating nephrotic syndrome with prednisone for over 50 years, the exact mechanism of disease remains unclear. Nephrotic syndrome can be classified based on the etiology, congenital NS (presentation before 3 months of age), idiopathic or primary NS (INS) and secondary nephrotic syndrome. Idiopathic nephrotic syndrome being the most common type. Based on the response to steroid therapy, it is classified into: Steroid-sensitive nephrotic syndrome (SSNS), Steroid-resistant nephrotic syndrome (SRNS), Steroid-dependent nephrotic syndrome (SDNS), and Frequent and infrequent relapsing nephrotic syndrome (FRNS)[2.] However, recent data suggest that over 30 % of SSNS children relapse in adulthood[3,4.] The most common histological diagnosis in SRNS is focal segmental glomerulosclerosis. More than 60 % of children with SRNS who fail to achieve remission with pharmacological intervention will progress to end-stage renal disease.[5]

Recently, several studies showed that Doppler ultrasonographic parameters, particularly the resistive index (RI) calculated as [(peak-systolic velocity − end-diastolic velocity)/peak-systolic velocity], correlated with tubulointerstitial and vascular lesions. Ikee et al. showed that RI correlated well with renal arteriolosclerosis[6]. Interstitial fibrosis, accompanied by the loss of tubules and capillaries, is a common finding in essentially all progressive renal diseases. Tubulointerstitial lesions proved to be the best histologic correlate of renal function and long-term prognosis[4].RI increases in various kidney diseases[7-15]. Several studies have shown the associations of RI with renal function and patient prognosis[16,17,18,19.] Patients with nephrotic syndrome are at risk to develop renal failure. Therefore, accurate assessment of renal function is important in these children. Serum creatinine level was used as an approximation of the degree of renal dysfunction. It lies in normal range in children with uncomplicated nephrotic syndrome, such as minimal change nephropathy. Values higher than the normal indicate reduced renal function. As renal resistive index is a non invasive marker of renal function, and high RRI indicate poor renal prognosis, therefore in this study we aim to compare RRI with serum creatinine in

children with nephrotic syndrome, which will give an indirect information on prognostication of the children with nephrotic syndrome.

II. SUBJECTS AND METHODS:

A total of 63 children upto 12 yrs of age with nephrotic syndrome attending the dept of pediatrics from may 2019 to june 2020 weretaken. Informed written consent was taken from parents/ guardians who took part in the study. Detailed history, clinical examination and relevant laboratory and radiological investigations, including Doppler ultrasonography of renal artery was done. The received data along with the data regarding age, gender, locality, socioeconomic status, clinical features was recorded in a predesigned proforma. Renal function test was done for all the patients after admission.

The Doppler USG was performed by USG machine (Toshiba aplio 500) using 2.5- to 5-MHz curved array transducers for adequate depth of penetration to visualize the abdominal aorta and its major branches: celiac, mesenteric, and renal arteries. Adjustment of the color Doppler parameters, including color gain, PRF (color velocity scale), and wall filter, was performed in areas of laminar flow, in either the aorta or a normal segment of a renal artery. Proper color Doppler adjustment was done to "screen" the vessel quickly for stenosis, because elevated velocities in stenotic regions then produce a color aliasing artifact that is readily apparent. Our sonographer preferred the decubitus or oblique positions to visualize the renal arteries. Pulsed Doppler sampling was performed with angles of 60 degrees or less. The PRF was adjusted so that the waveforms are large and easy to read but without causing aliasing. Left and right decubitus patient positions were preferred for the kidney examination (left decubitus for the right kidney and vice versa). Echogenicity and thickness of the renal parenchyma was noted and measure the kidney length. Also the kidneys were assessed for atrophy, scarring, hydronephrosis, calculi, or masses. A longitudinal survey of the abdominal aorta was performed from the celiac artery to the iliac bifurcation and evaluate the amount of atherosclerotic plaque. This was done with both gray-scale and colour flow Doppler. Flow abnormalities at the origin of the celiac and superior mesenteric arteries were looked for that indicate significant stenosis. The size and location of abdominal aortic aneurysms were noted. Finally, angle-corrected PSV measurements were obtained from the abdominal aorta at the level of the renal arteries. These aortic velocity measurements were used to determine the renal artery–aorta velocity ratio.

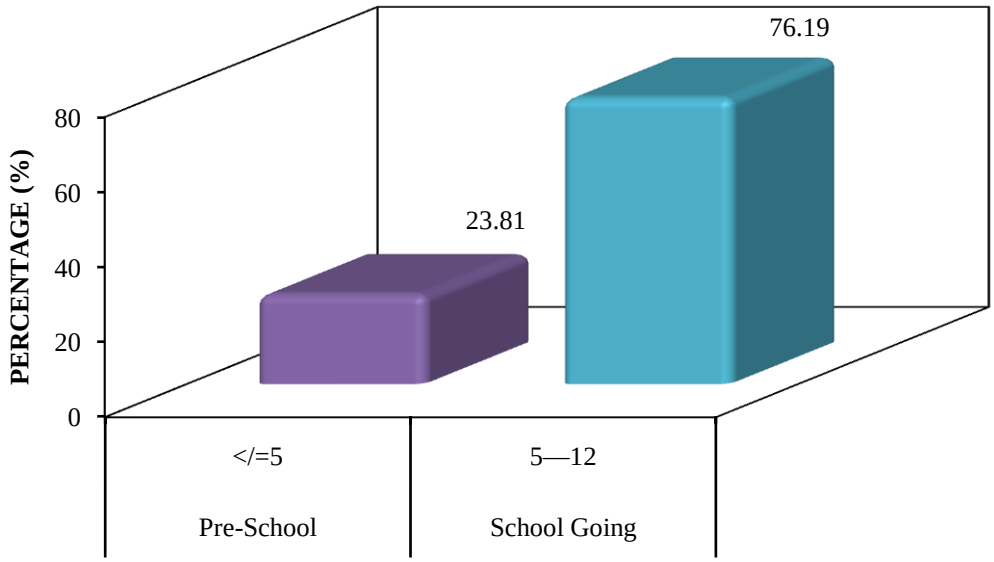
When possible, we located the origin of the renal arteries on transverse images of the aorta using an anterior transducer approach. Each renal artery was examined with colour flow imaging from its origin to the hilum of the kidney, including the main hilar branches. We looked for areas of high-velocity flow, indicated by colour shifts or aliasing, as well as turbulence related flow disturbances, as these may be related to stenosis. We routinely had obtained PSV measurements from the origin, proximal, mid, and distal segments of each renal artery. Finally, waveforms were also obtained from the segmental arteries in the upper, mid, and lower poles of each kidney. Thus, at least seven waveforms were captured from each side. It was important to obtain clean, crisp waveforms with well-defined borders for analysis. This was accomplished by adjusting the spectral display so that the waveforms were large and easily measured. This allowed the examiner to readily determine the PSV, acceleration time or index, and the resistivity index (RI).

The serum creatinine were derived by analyzing the subjects' serum, and they were compared to the locally standardized laboratory values. Normal serum creatinine range in children ≤6 years is 0.2-0.5 mg/dl and in children >6 years is 0.4-0.8 mg/dl.[149]The statistical analysis of data was performed using the computer programme, Statistical Package for Social Sciences (SPSS for windows, version 21.01, Chicago, SPSS Inc.) and microsoft excel 2010. Results on continous measurement are presented as mean±standarddeviation are compared using Analysis of Variance (ANOVA). Where the p-value was found significant ($p < 0.05$) among 3 groups, post hoc analysis was done to find out the significance between 2 individual groups. Discrete data are expressed as number (%) and are analysed using Chi-square and Fischer's exact test (where the cell counts were <5 or 0). Pearson's and correlation coefficient ® was used to measure the associations among continous variables. For all analysis, the statistical significance was fixed at 5% level. (p value <0.05).

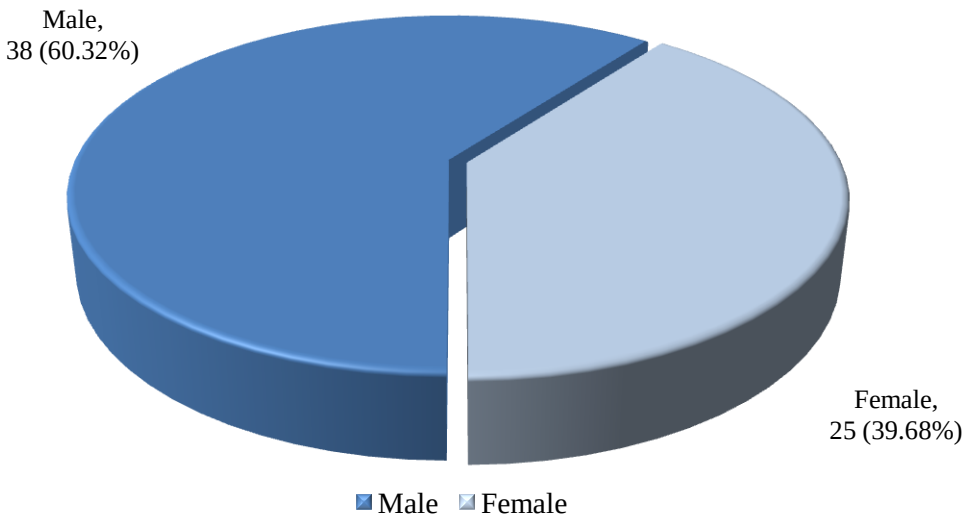
III. RESULTS:

Total of 63 children with nephrotic syndrome were taken in our study. The mean age of the children included in the study was 6.39±2.62 years (fig1) with male:female ratio of 1.52:1 (fig2). The mean age of diagnosis was 4.68%±2.26 years. On assessing the nutritional status (fig3), 95.24% (60) had normal nutritional status, 1.59% (1) had moderate malnutrition and 3.17% (2) had severe malnutrition.

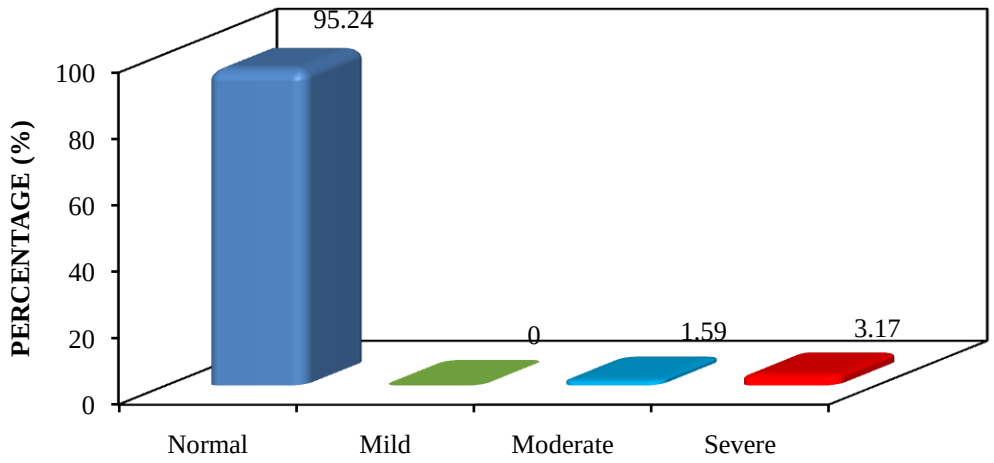
FIG–1
AGE WISE DISTRIBUTION



FIG–.2
GENDER WISE DISTRIBUTION

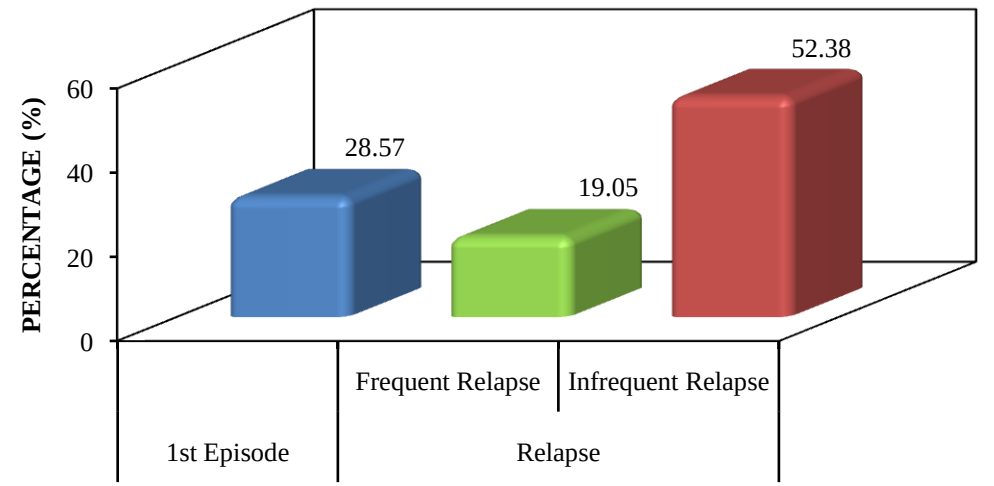


FIG–3
GRADE OF MALNUTRITION



Cases were divided into 1st episode, frequent relapse and infrequent relapse to categorise based on the disease severity (fig4). 28.57% (18) presented at 1st episode. 71.43% (45) cases presented with relapse. Of the total cases, 19.05% (12) cases had frequent relapse and 52.38% (33) cases had infrequent relapse. But due to limitation of facilities available (renal biopsy), severity of nephrotic syndrome cases could not be categorized into FSGS, MPGN, Membranous nephropathy, etc.

FIG–4
CATEGORY WISE DISTRIBUTION



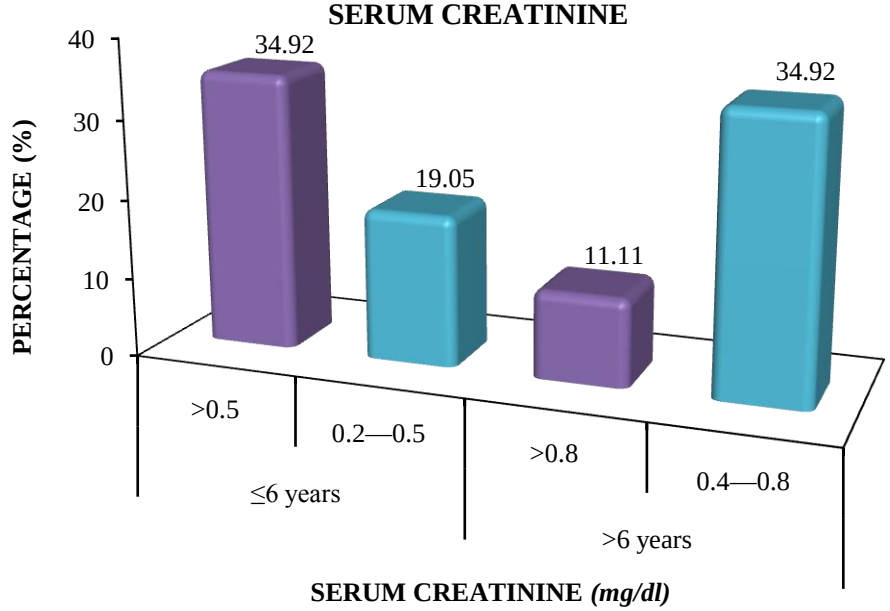
TABLE– 1
SERUM CREATININE

SERUM CREATININE *(mg/dl)*	NUMBER *(n)*	PERCENTAGE *(%)*
≤6 years:		
◆ >0.5	22	34.92

◆ 0.2—0.5 (normal)	12	19.05
>6 years:		
◆ >0.8	7	11.11
◆ 0.4—0.8 (normal)	22	34.92
TOTAL	63	100
Mean ±S.D.	0.56±0.23 *mg/dl*	

Table 1 (fig:5) shows the mean distribution of serum creatinine in the cases. 34 children were ≤6 years. Out of these 34 cases, 22 cases (34.92*%)* showed serum creatinine value >0.5 mg/dl and the rest 12 cases (19.05*%*) showed the value between 0.2 to 0.5 mg/dl. 29 cases were in the age group of >6 years. Of which 7 cases (11.11*%*) presented with serum creatinine value >0.8 mg/dl and the rest 22 cases (34.92*%)* showed this value to be between 0.4-0.8 mg/dl. Mean value of serum creatinine among cases was found to be 0.56±0.23 *mg/dl.*

FIG– 5
SERUM CREATININE



TABLE– 2
RELATION OF SERUM CREATININE WITH MEAN RI VALUES IN DIFFERENT POLES OF BOTH KIDNEYS IN ≤ 6 YEARS OF AGE

SERUM CREATININE *(mg/dl)*	RIGHT KIDNEY			*p value*	LEFT KIDNEY			*p value*
	n	*Mean*	*±S.D.*		*n*	*Mean*	*±S.D.*	
>0.5*mg/dl*:								
◆ Upper Pole	22	0.66	0.16		22	0.61	0.08	
◆ Middle Pole	22	0.65	0.13	0.9572	22	0.63	0.20	0.2234
◆ Lower Pole	22	0.66	0.10		22	0.68	0.11	
0.2–0.5*mg/dl*:								
◆ Upper Pole	12	0.69	0.09		12	0.63	0.06	
◆ Middle Pole	12	0.58	0.19	0.1494	12	0.71	0.11	0.0642
◆ Lower Pole	12	0.63	0.10		12	0.71	0.10	

FIG– 6
RELATION OF S. CREATININE WITH MEAN RI VALUES IN DIFFERENT POLES OF BOTH KIDNEYS IN ≤ 6 YEARS

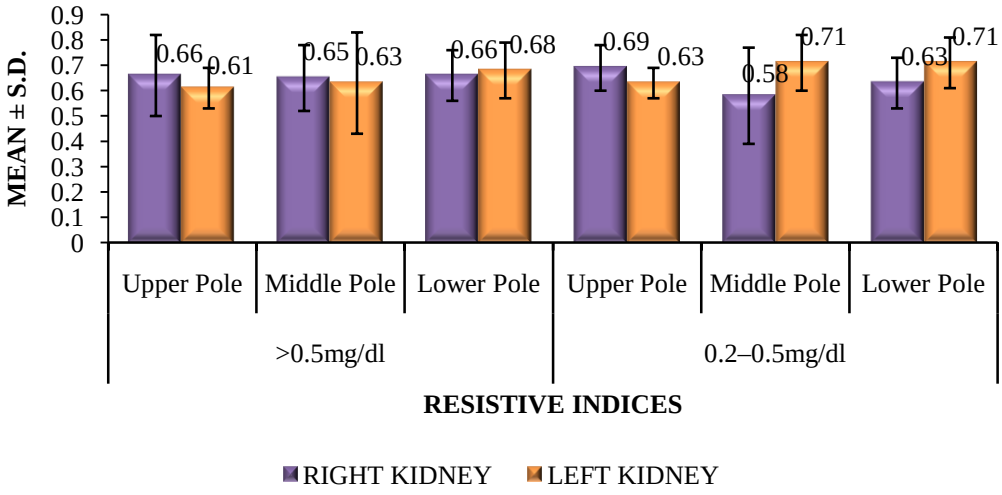


Table 2 (fig 6) the relation of serum creatinine with mean RI values was compared in cases ≤ 6 years of age. Out of 34 cases ≤ 6 years, 12 cases showing serum creatinine value within normal range had RI values ranging between 0.58±0.19 to 0.69±0.09 in the right kidney in the three poles. Whereas RRI was between 0.63±0.06 to 0.71±0.11 in the left kidney. In both of these cases the relation was statistically insignificant p-value of 0.1494 and 0.0642 respectively. 22 cases showed the serum creatinine value above normal range, where the RRI ranged between 0.65±0.13 to 0.66±0.16 in the right kidney and 0.61±0.08 to 0.68±0.11 in the left kidney in the three poles. Here also the relation was statistically insignificant with p-value of 0.9572 and 0.2234 for right and left kidney respectively.

TABLE–3
RELATION OF SERUM CREATININE WITH MEAN RI VALUES IN DIFFERENT POLES OF BOTH KIDNEYS IN > 6 YEARS OF AGE

SERUM CREATININE *(mg/dl)*	RIGHT KIDNEY			*p value*	LEFT KIDNEY			*p value*
	n	*Mean*	*±S.D.*		*n*	*Mean*	*±S.D.*	
>0.8*mg/dl*:								
◆ Upper Pole	7	0.65	0.18		7	0.66	0.10	
◆ Middle Pole	7	0.70	0.11	0.7218	7	0.72	0.17	0.0481*
◆ Lower Pole	7	0.74	0.29		7	0.84	0.10	
0.4–0.8*mg/dl*:								
◆ Upper Pole	22	0.67	0.14		22	0.65	0.17	
◆ Middle Pole	22	0.64	0.15	0.7218	22	0.68	0.13	0.4241
◆ Lower Pole	22	0.65	0.07		22	0.71	0.15	
Left Kidney >0.8 *mg/dl*: Post-hoc Test... UP vs MP: Diff=0.0600, 95%CI=-0.1142 to 0.2342, p=0.6599 UP vs LP: Diff=0.1800, 95%CI=0.0058 to 0.3542, p=0.0422 MP vs LP: Diff=0.1200, 95%CI=-0.0542 to 0.2942, p=0.2117								

FIG– 7
RELATION OF S. CREATININE WITH MEAN RI VALUES IN DIFFERENT POLES OF BOTH KIDNEYS IN > 6 YEARS

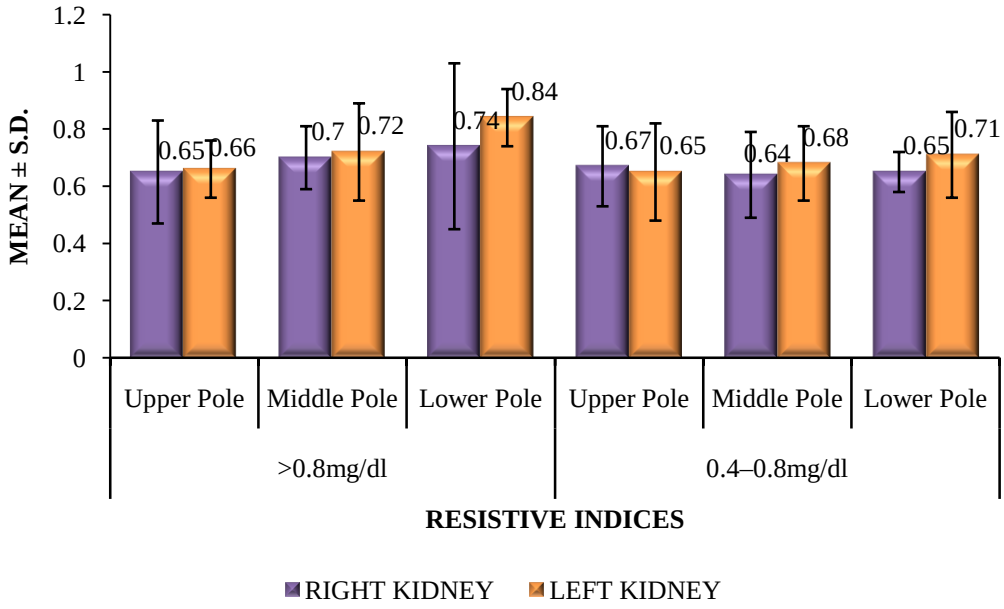


Table 3 (fig 7) shows the relation of serum creatinine with mean RRI in both kidneys in cases >6 years of age. Out of 29 cases in this age group, 22 cases showed serum creatinine value within normal range with RI value 0.67±0.14, 0.64±0.15 and 0.65±0.07 in the right kidney in upper, middle and lower poles respectively. Whereas this value was 0.65±0.17, 0.68±0.13 and 0.71±0.15 in upper, middle and lower poles respectively in the left kidney. In both of these cases the relation was statistically insignificant with p-value of 0.7218 and 0.4241 in right and left kidneys respectively. 7 cases showed the serum creatinine value above normal range (>0.8mg/dl), where the RI was 0.65±0.18, 0.70±0.11 and 0.74±0.29 in upper, middle and lower poles respectively in the right kidney and 0.66±0.10, 0.72±0.17, and 0.84±0.10 in upper, middle, lower poles respectively in left kidney. The relation was statistically insignificant for right kidney with p-value of 0.728. However, the relation was statistically significant in left kidney with p-value 0.0481.

IV. DISCUSSION:

The mean age of children in our study was 6.39±2.62 years, which is higher than the average found in A. Safaeiet al[20] and Bakkali et al[21]. The mean age of diagnosis of nephrotic syndrome among the cases ranged between 2yrs and 6 yrs (mean= 4.68%±2.26 yrs.) with male:female ratio of 1.52:1 showing male preponderance as seen in other studies (Solani et al[22], Gulati et al[23]). On assessing the nutritional status 95.24% (60) had normal nutritional status, 1.59% (1) had moderate malnutrition and 3.17% (2) had severe malnutrition. In the study, Solarin A. et al[24] showed the mean weight of the studied subjects was25.13±10.45kg with mean BMI 17.1±2.6kg/m^2 and in study by KniażewskaM et al[25] showed the mean BMI of 20.05±3.0.

We evaluated the relationship between increasing serum creatinine and variation of RRI in each kidneys [Table 2 and table 3] (represented by fig 6 and fig 7). For purpose of this study, serum creatinine level was used as an approximation of the degree of renal dysfunction. We divided the cases into two groups (≤ 6 and >6 years) with two different sets of normal values of serum creatinine as per the standard protocol. The mean serum creatinine in the age group of ≤6 years was found to be 0.56 ±*0.24*mg/dlwhile in children >6 years mean serum creatinine level was 0.63±*0.23*mg/dl. Study by Sapartini G. et al[26] the mean value of serum creatinine was found to be 0.7±0.4 mg/dl, which is higher than the mean value of the present study. Gulati S. et al[27] found the mean serum creatinine level to be 0.90±0.21 mg/dl, which is higher than the present study. In the study conducted in Nigeria by Omolola M. A. et al[28]mean serum creatinine was 0.6±0.5mg/dl, which is almost similar to the present study.Saleh S. et al[29] mean serum creatinine level was 0.713 ± 0.15 mg/dl.

Out of 34 children (≤6 years) 12 cases showed the serum creatinine value within normal range and 22 cases showed the serum creatinine value above normal range. The RI value was between 0.58±0.19 to 0.69±0.09 and 0.65±0.13 to 0.66±0.16 in the right kidney in different poles. Whereas this value was between 0.63±0.06 to 0.71±0.11 and 0.61±0.08 to 0.68±0.11 in the left kidney. In all these cases the relation was statistically

insignificant with p value ranging from 0.0642-0.9572 respectively.

Out of 29 cases (> 6 years) 22 cases showed the serum creatinine value within normal range and RI value ranged from 0.64±0.15-0.67±0.14 in the right kidney and 0.65±0.17-0.71±0.15 in the left kidney. In both of these cases the relation was statistically insignificant with p value of 0.7218 and 0.4241 in right and left kidneys respectively. 7 cases showed serum creatinine value >0.8mg/dl, where the RI was between 0.65±0.18 to 0.74±0.29 in the right kidney and 0.66±0.10 to 0.84±0.10 in left kidney. The relation was statistically insignificant for right kidney with p-value of 0.728. However, the relation was found to be statistically significant with p-value 0.0481 for the left kidney. There seems to be a trend toward more abnormal waveforms with higher creatinine levels particularly in left kidney.

Our present study was in accordance with the study by J.F.Plattet al[30] where they also found out a weak correlation between serum creatinine level and RI value, reflected by a linear correlation coefficient of 0.34. In patients with normal renal RI, the mean creatinine level was 1.7± 1.7, whereas in those with abnormal RI values (greater than or equal to 0.70), the mean creatinine level was 3.7± 3.6. But the study conducted in Nigeria byOmolola M. A. et al[28] did not show any such correlation between the two parameters.

Hence, It is found from our study that in cases (>6years) with higher serum creatinine (>0.8mg/dl), RRI was on the higher side of the normal range. From which we can draw the inference that RRI increases in cases with impaired renal function.

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