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PREDICTION OF TUBULOINTERSTITIAL INJURY BY DOPPLER ULTRASOUND IN GLOMERULAR DISEASES:VALUE OF RESISTIVE AND ATROPHIC INDICES

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Abstract

Introduction: Application of Doppler Ultrasound in Nephrology is increasing day by day. A series of articles published during the last two decades indicated the potential of Doppler ultrasound for improving the sonographic assessment of renal dysfunction. Among the Doppler derived indices, resistive index is the most studied parameter for quantifying the alterations in renal blood flow that may occur with glomerular diseases. The diagnostic utility of Doppler in glomerular disease is under debate. Some studies show encouraging results whereas others are disappointing.[3] Although Doppler can't substitute renal biopsy, studies have shown that it canbe useful in prognostication and to quantitate the severity.

Materials and methods: A Prospective observational study was conducted from January 2015 to December 2016. All patients who are admitted in the Department of Nephrology, King George Hospital with biopsy proven Glomerular diseases were included in study after taking informed consent. Patients with Proteinuria >1 g/day, Proteinuria >0.5g/day with hematuria, hematuria with RBC casts, rapidly worsening renal function were included in the study. Renal Doppler was done to the study population who subsequently underwent renal biopsy. Of 82 patients enrolled 75 patients were included in the study. Rest of seven patients were excluded due to isolated tubulointerstitial component and hypertensive nephrosclerosis on renal biopsy. All patients were enquired regarding the symptoms, detailed history was taken from the patients and complete physical examination of patients was carried out.

Results: A total of 75 patients were included in the study [Table 1]. In the present study age of the patients ranged between 16-60 years (mean 33.4±1.29). Serum creatinine ranged from 0.6-5.2 mg/dl (mean 1.81±1.26). Glomerular filtration rate ranged from 7.21-138.74 ml/min (mean 63.96±36.14). Urinary protein excretion ranged from 1.2-9.8 g/day (mean 4.15±2.04). Serum albumin ranged from 1.8-4.2 mg/dl (mean 2.95±0.44). 49(65.33%) patients in the present study were found to have nephrotic range proteinuria. 36(48%) patients presented with renal failure at the time of presentation. MPGN and FSGS were the chief pathological diagnoses [Fig 1].

Conclusion: Nevertheless, the present study suggests that Doppler ultrasonography might be considered as an important diagnostic and prognostic significance in glomerular diseases. Doppler resistive index can be used to predict the presence of tubulo interstitial lesion in glomerular diseases with high sensitivity and specificity. There is good correlation between resistive index and severity of tubulo interstitial injury. Reno vascular resistive index can be considered as a supplementary diagnostic tool in glomerular diseases to asses severity of tubulo interstitial injury. Resistive index and atrophic indices can be useful as a prognostic marker to identify the patients at risk ofprogression.

Key Words: Doppler Ultrasound, Urinary protein, Glomerular diseases, Serum creatinine.

INTRODUCTION

Application of Doppler Ultrasound in Nephrology is increasing day by day. A series of articles published during the last two decades indicated the potential of Doppler ultrasound for improving the sonographic assessment of renal dysfunction. Among the Doppler derived indices, resistive index is the most studied parameter for quantifying the alterations in renal blood flow that may occur with glomerular diseases.[1] The diagnostic utility of Doppler in glomerular disease is under debate. Some studies show encouraging results[2,3] whereas others are disappointing.[3] Although Doppler can't substitute renal biopsy, studies have shown that it canbe useful in prognostication and to quantitate the severity.[4] Tubulointerstitial lesions proven tobe the best histologic correlate of long term renal survival in various glomerular diseases.[5,6]

Among the Doppler derived indices, Resistive index (RI) is the most studied parameter for quantifying the alterations in renal blood flow that may occur with glomerular disease. The RI seems to be related to the site of the disease in renal parenchyma .In patients with simultaneous glomerular and interstitial disease the RI was found to be higher than in patients with isolated glomerular disease. The measurement of resistive index which reflects renal vascular resistance has been found to be useful in detecting tubulointerstitial disease severity. Atrophic index (AI) was a new parameter proposed by Sugiyura et al for quantifying the atrophic changes in renal parenchyma.[7]

Gray scale sonography is often routinely performed to evaluate a patient with suspected or known renal disease. Although this provides anatomic information, it lacks the ability to provide significant physiologic data. Duplex Doppler ultrasound has the potential to provide physiologic information concerning the renal arterial blood flow and resistance. Studies published in the last two decades indicated that Doppler can be used reliably in several types of intrinsic renal diseases, obstructive uropathy, acute renal failure and renovascular hypertension.[8] The diagnostic utility of Doppler in glomerular disease is under debate. Some studies show encouraging results whereas others are disappointing. Different renal parenchymal diseases may present with distinct features on Doppler despite similar conventional ultrasound appearance.[9]

However this requires renal biopsy which is an invasive procedure. This study was done to find out the utility of Doppler Ultrasound in glomerular diseases. Specifically the role of resistive and atrophic indices and their role as prognostic markers were evaluated.

MATERIALS AND METHODS

Study Participants: All patients who are admitted in the Department of Nephrology, King George Hospital with biopsy proven Glomerular diseases were included in study after taking

informed consent.

Study Design: Prospective observational study.

Study Period: January 2015 to December 2016.

Inclusion Criteria: Patients with Proteinuria >1 g/day, Proteinuria >0.5g/day withhematuria, hematuria with RBC casts, rapidly worsening renal function.

Exclusion Criteria:
- Kidney size <8.5cm
- Associated hepatic disease
- Multiple renal cysts
- Acute pyelonephritis/perinephric abscess
- Solitary kidney
- Isolated tubulointerstitial injury in renal biopsy
- Pregnant women.

The study population consists of 82 patients presented with features of Glomerular diseases attending the department of Nephrology in King George Hospital, Visakhapatnam. The patients convening to the inclusion criteria were enrolled into the study after procuring informed consent. Renal Doppler was done to the study population who subsequently underwent renal biopsy. Of 82 patients enrolled 75 patients were included in the study. Rest of seven patients were excluded due to isolated tubulointerstitial component and hypertensive nephrosclerosis on renal biopsy. All patients were enquired regarding the symptoms, detailed history was taken from the patients and complete physical examination of patients was carried out.

Statistical Analysis: Doppler ultrasound was used to measure resistive index and atrophic index Statistical analysis was carried out using the SPSS software. (SPSS version 16.0, SPSS inc). All data obtained were recorded and presented as Mean ± standard deviation. Student t-test was used to find out whether the difference in means between groups was statistically significant. Chi-square test or Fisher's exact test were used, whenever appropriate by using SPSS 16 software, to find out whether the distribution of frequencies was equal among the groups. Correlation between variables were tested by means of Spearman correlation rank test.

A p-value<0.05 was considered statistically significant. Tubulo interstitial score of 0 represents no injury and 1-4 were considered as its presence. The Sensitivity and Specificity of individual indices were calculated from a series of 2×2 tables, in which tubulointerstitial injury or no injury represented in one axis and RI or S/L represented the other. After the sensitivity and specificity of each cut off 35 point was available as ROC (receiver operator characteristics) curve was plotted with ordinate indicating sensitivity, abscissa representing 1-specificity. The resultant ROC curve described the diagnostic efficacy of the test. The Sensitivity and specificity of both

resistive index and atrophic indices were calculated. With the SPSS 16 software the effects of the age, sex, renal failure at diagnosis, hypertension, proteinuria, body mass index, resistive and atrophic indices on tubulo interstitial injury were calculated. Progression of the disease in the present study was defined as >50% raise in serum creatinine from baseline.

RESULTS

A total of 75 patients were included in the study [Table 1]. In the present study age of the patients ranged between 16-60 years (mean33.4±1.29).Serum creatinine ranged from 0.6-5.2 mg/dl (mean 1.81±1.26). Glomerular filtration rate ranged from 7.21–138.74ml/min (mean 63.96±36.14). Urinary protein excretion ranged from 1.2–9.8 g/day (mean 4.15±2.04). Serum albumin ranged from 1.8-4.2 mg/dl (mean2.95±0.44). 49(65.33%) patients in the present study were found to have nephrotic range proteinuria. 36(48%) patients presented with renal failure at the time of presentation. MPGN and FSGS were the chief pathological diagnoses [Fig 1]

Table 1: Base Line Characteristics of the Study Population

S.No	Base Line Characteristics	Mean ±SD
1	Age	33.4±1.29
2	Sex	40(53.3%)males
3	24 hr urine protein	4.15±2.04
4	Creatinine	1.81±1.26
5	GFR	63.96±36.14
6	Albumin	2.95±0.44
7	Cholesterol	227.2±71.01
8	Microhematuria	44(58.67%)
9	Hypertension	48(64%)
10	Nephrotic syndrome	49(65.33%)
11	Renal failure at onset	36(48%)

Figure 1: Biopsy Results of Study Population

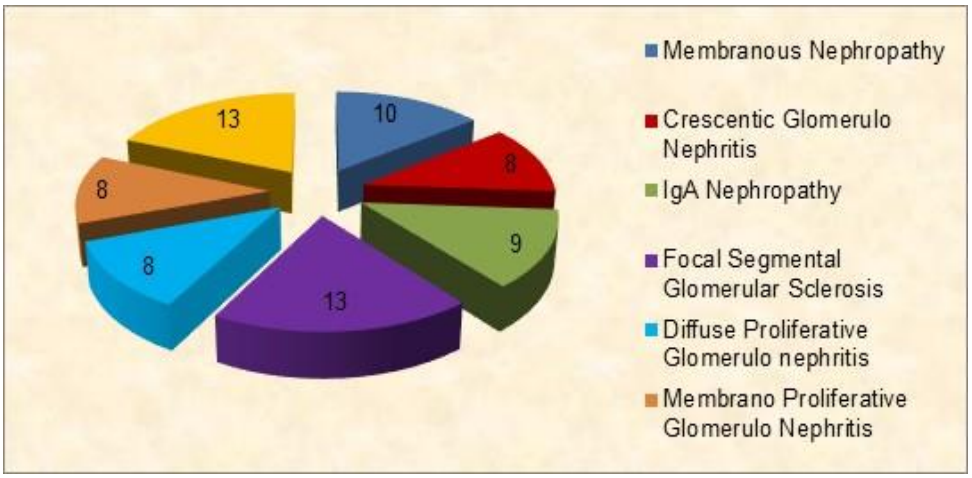
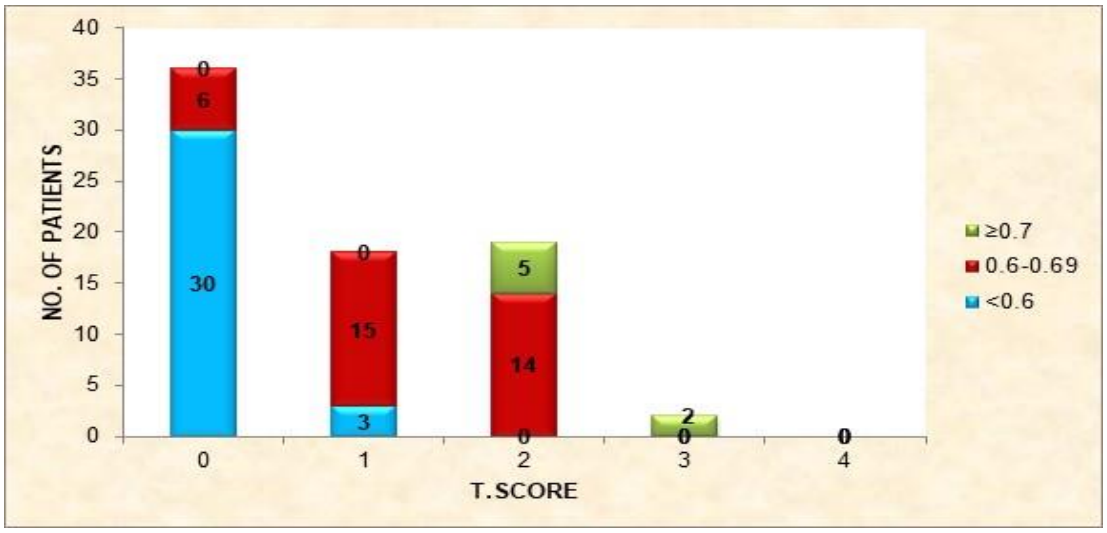


Figure 2: Resistive Index With Relation to Tubulointerstitial Injury Score

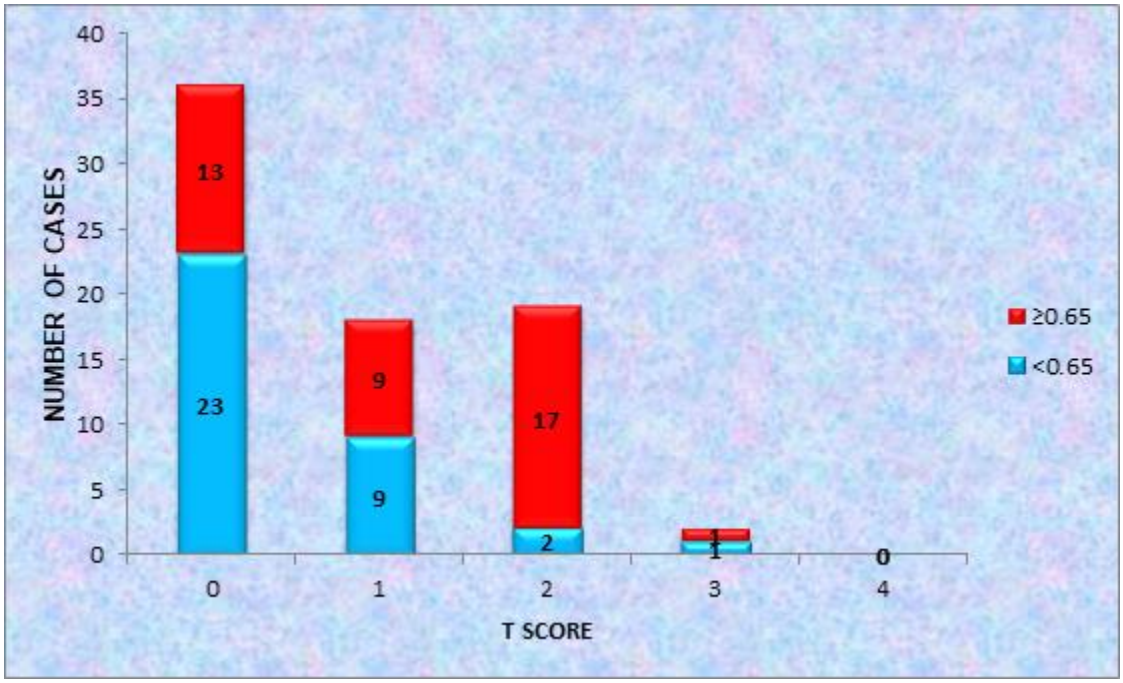


Maximum number of patients (30) with RI<0.6 are in the T-score 0 group. 15 patients with RI 0.6-0.69 are in the T-score 1 group, 14 patients in T-score 2 groupand 5 patients with RI ≥0.7 are in the T-score 2 group.[Fig 2]

Table 2: Sensitivity and Specificity of Resistive Index

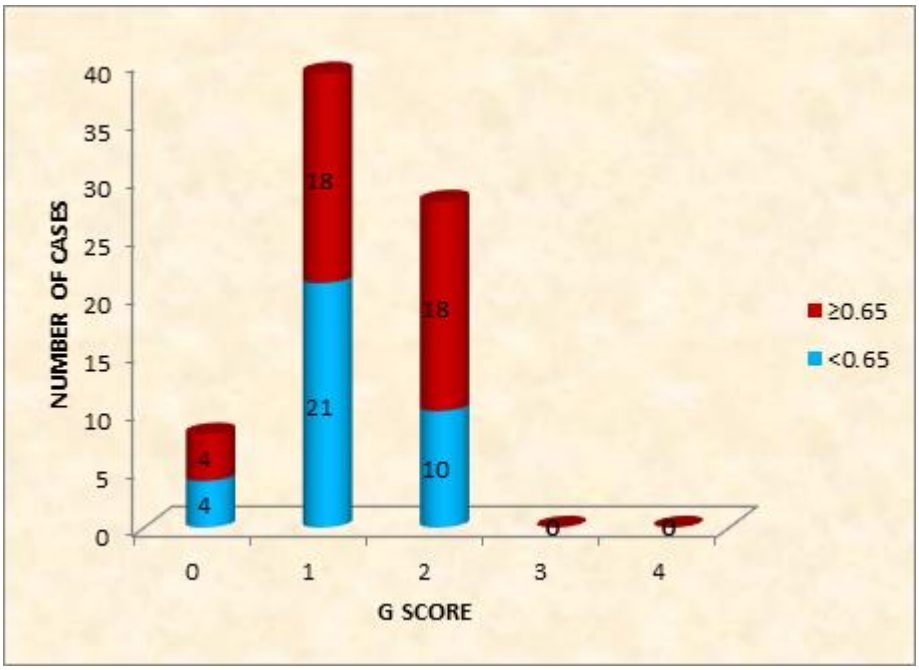
	PRESENT STUDY	
	SENSITIVITY(%)	**SPECIFICITY (%)**
RESISTIVEINDEX (RI) ≥0.60	92.3	82.4

Figure 3: Atrophic Index With Relation To Tubulointerstitial InjuryScore



In the present study, Maximum number of patients (23) with AI<0.65 are inthe T-score group.17 patients are present in the ≥0.65 group.

Figure 4: Atrophic index with relation to glomerulosclerosisscore

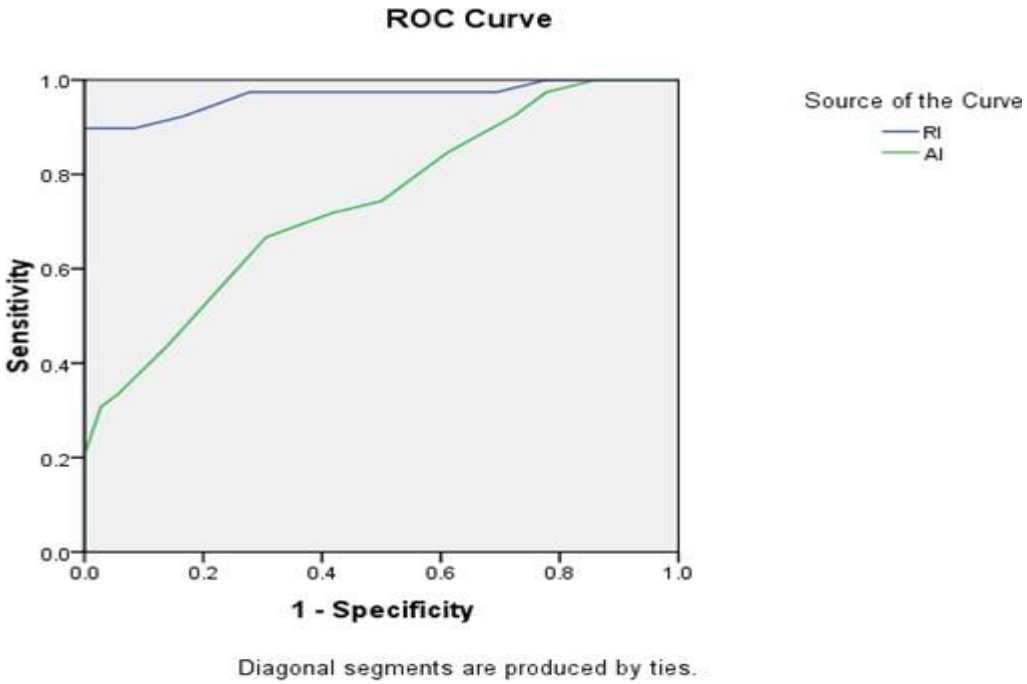


In the present study, Maximum number of the patients are present in the G-score group 1.

Table 3: Sensitivity and Specificity of Atrophic Index

	PRESENT STUDY	
	SENSITIVITY (%)	**SPECIFICITY (%)**
ATROPHIC INDEX(RI) ≥0.65	71.05	64.9

Figure 5: ROC Curves of RI and AI with Tubulointerstitial Injury



Area under curve is 0.967 at the level of 0.60 RI has sensitivity if 92.3% andspecificity of 82.4%. Area under curve is 0.738.at the level of 0.65 AI has sensitivity if 71.05% and specificity of 64.9%.

DISCUSSION

In the present study, the various utilities of the resistive index measured by Doppler ultrasonography, in glomerular diseases were evaluated. This study demonstrated that extent of tubulointerstitial injury can be predicted by measurement of resistive and atrophic indices. In this study preferential focus was on tubulointerstitial lesions rather than glomerular lesions. Renal parenchymal resistance measurable by resistive index represent global resistance offered to blood flow by different parenchymal structures vascular, interstitial or glomerular compartments either separately or altogether. This is especially true of vasculo interstitial compartment because when the damage is confined to glomeruli the RI does not seems to increase. Previous studies reported that presence of interstitial damage could elevate RI significantly.[1,4,6]

Present results support these reports. The value of atrophic index tested which can be easily measured at bed side. This index was introduced to reduce the error while measuring the renal length alone to identify the atrophic changes of the kidneys as renal length can be normal with thin parenchyma in some cases. In a recent report, RI predicted renal outcome in chronic nephropathies[10,11]. The tubulointerstitial lesion has been found to be the best histologic correlate of declining in renal function and long-term prognosis.[12] Taken together with the present study results that RI reflects tubulointerstitial changes and RI can be utilised to predict renal outcome. The study has also shown good correlation between resistive index and tubulo interstitial injury,

hence resistive index has a role in estimating progression of glomerular diseases. Kang et al[13] showed that degree of glomerular and peritubular capillary loss in patients with progressive renal disease correlated with severity of glomerular sclerosis and interstitial fibrosis. Therefore, it is very likely that RI, reflecting renovascular resistance, is a possible marker for renal damage. Although the mechanisms by which Tubulo interstitial damage can cause an increase in RI remain unknown, alterations in postglomerular vessels by interstitial fibrosis can cause increased resistance to renal cortical blood flow, with a subsequent reduction of glomerular perfusion, independent of the severity of glomerulosclerosis.

Malfunctioning atrophic tubules in the areas of interstitial fibrosis can also affect glomerular function. Regarding the histopathologic significance of an increase in RI, there are two possibilities. One possibility is that the vessels themselves are injured. The other possibility is that interstitial fibrosis surrounding the vessels increases vascular impedance, thereby increasing resistive index. Prospective study done by Prabahar et al[14] demonstrated that extent of the tubulointerstitial injury can be predicted by measurement of RI and AI. Combination of these two have not been proven to be useful than either index alone. Resistive index correlated well with tubulointerstitial injury than with that of glomerular injury, whereas atrophic index correlated both with glomerular as well as tubulointerstitial injury. This study has also shown 54 significant correlation between RI and AI which may be the reason for the above finding. In contrast to the above study Sugiura et al[15] retrospectively studied the role of Doppler ultrasound in glomerular diseases. They found that a combination of the resistive index and the atrophic index could predict presence of the tubulointerstitial lesion in glomerular diseases with high specificity and sensitivity. Of the clinical indices studied, elevated RI, proteinuria, hypertension, and low eGFR were independent risk factors for CKD progression. In contrast atrophic index has no significance in evaluating renal prognosis in CKD. This was consistent with a 4-year follow-up study by Sugiura and Wada et al.[16] Poorer prognosis of patients with RI≥0.7 than those with lower RI was also consistent with other studies showing the potential significance of RI as a prognostic indicator[17,18]. In the normal RI group, despite having heavier proteinuria at renal biopsy, patients who underwent steroid therapy showed a similarly high rate of survival as those who did not undergo steroid therapy, the patients in the high-normal RI group showed excellent response to steroids. However, steroid therapy did not significantly improve renal outcome in the patients in the high RI group. RI is considered to be useful not only as a prognostic indicator but also as a noninvasive determinant of indication for steroids.[19] The resistive index 0.6 was used as a cutoff point instead of 0.7. Several studies have shown that a mean RI of people without preexisting renal disease was 0.60±0.0186.

Exceptions to this are children <4 years, 55 adults >60 years. The mean resistive index of our healthy population 32 subjects was 0.57±0.3, which is similar to the resistive index observed in Platt et al[14] 0.58 ±0.05 (109 kidneys). More over as stated earlier a different value may be more appropriate in individual diseases. For example, in obstruction to differentiate obstructive system from unobstructed, resistive index of 0.7 was found to be most appropriate with sensitivity of

92% and specificity of 88%. On the other hand in reno vascular hypertension a value of 0.8 or more strongly predicted lack of improvement after revascularization.

Antihypertensive drugs were administered until a day before the Doppler study for patient safety. There was a possibility that drugs might decrease RI because of inadequate washout period. It is well known that converting enzyme inhibitors decrease RI whereas calcium channel blockers do not reduce RI. But this finding is disputed by recent observations that angiotensin converting enzyme inhibitors reduce RI only in diabetic subjects not in patients without diabetes

The ROC curve indicated that RI value of 0.6 was the best discriminatory value with 92.3% sensitivity and 82.4 specificity in the present study. Whereas study done by Prabahar et al[7] The ROC curve indicated that RI value of 0.60 was the optimal value for discriminating tubulointerstitial injury with sensitivity of 82.7% and specificity of 92% and study done by Sugiura et al[8] receiver operator characteristic analysis showed a resistive index of 0.65 to be the optimal for discriminating tubulointerstitial changes with specificity of 100% and sensitivity of 57.1%. But study done by Sugiura et al[8] was retrospective study done in japanese population. In this study they introduced the term atrophic index. In combination, the 2 indices showed improved sensitivity. when the patients were divided into groups where both resistive and atrophic indices were normal (respectively 0.65 and 0.70) or where either or both were high, 66 sensitivity rose to 85.7%, while specificity remained 94.4%.In our study there was a positive correlation between RI and AI where r value was 0.261. Where as in the study of Sugiura et al correlation between RI and AI was 0.30 and in Prabahar et al r value was 0.358. Figure 7. Correlation Between RI And AI. A definite relationship has been noted between severity of interstitial changes and the echogenicity of the cortex at ultrasonography. A significant positive correlation has been found between cortical echogenicity and focal tubular atrophy in the study done by Hricak et al[9].These observations were consistent with the anatomy of the cortex, most of which was composed of tubules and interstitial tissue. However, Platt et al. reported that the accepted ultrasonographic criterion for abnormal renal echogenicity (kidney echogenicity liver) was neither sensitive (62%) nor specific (58%) for renal disease. If stricter criteria for abnormality (kidney echogenicity > liver) were adopted, specificity rose (96%) but sensitivity remained only 20%. When the 67 stricter criteria of Platt et al. were applied to the present cases, those with high echogenicity showed considerable tubulointerstitial injury. All of these cases, however, had either an RI over 0.60 or an AI over 0.65. Recently, Manley and O'Neill et al reported a method for quantifying renal cortical echogenicity. Prints of images were digitized by a scanner, and pixel density was measured by an image analysis software.

While this is an interesting method that might detect interstitial changes, it is complicated and cannot be carried out easily at the bedside. In the present study atrophic index(S/L) method has advantages in this regard. We examined the receiver operator characteristics (ROC) method to determine whether the resistive index (RI) could discriminate tubulointerstitial lesion. In ROC analysis, specificity and sensitivity are calculated and displayed graphically for every score. A

test that separates individuals with a disease from those without should show a curve that rises rapidly at the critical score (indicating concurrent high sensitivity and specificity) and maintains a plateau for all subsequent value (indicating high sensitivity and decreasing specificity) .In the prediction of tubulointerstitial injury graph it was clearly shows RI has more area under curve compared to AI which were 0.967 and 0.738 respectively with RI shows 96.2% sensitivity comparatively higher than AI 71.05%.

The present study has few potential limitations. The Doppler and pathologic analysis were carried out by a single observer, as both are observer dependent, hence significant intra observer variability does exists. This should be borne in mind while interpreting results of this study. Ikee et al[9] investigated regarding reproducibility of measurements, interobserver and intraobserver variances in their study were 4.0% and 5.1%, respectively. The median follow up in this study was eight months which is short period to assess disease progression. Hence more data needed before pronouncing resistive index as a prognostic marker. Serum creatinine was used as a marker to measure glomerular filtration rate, the limitations of which were known.

CONCLUSION

Nevertheless, the present study suggests that Doppler ultrasonography might be considered asan important diagnostic and prognostic significance in glomerular diseases. Doppler resistive index can be used to predict the presence of tubulo interstitial lesion in glomerular diseases with high sensitivity and specificity. There is good correlation between resistive index and severity of tubulo interstitial injury. Reno vascular resistive index can be considered as a supplementary diagnostic tool in glomerular diseases to asses severity of tubulo interstitial injury. Resistive index and atrophic indices can be useful as a prognostic marker to identify the patients at risk of progression.

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