# Prediction of Tubulo Interstitial Injuries by Doppler Ultrasound in Patients with Glomerular Disease: Value of Resistive Index and Atrophic Index

**Dr. G. Balaraju[*], Dr. K.S. Amaravathi[**], DR. S. Ashok kumar[***] .Dr. Gopikrishna Kenchi[****], Dr. S. Ravinder[*], Dr. B. Sudarsi[**]**

[*] M.D., Associate Professor of Medicine, Osmania General Hospital, Hyderabad, Telangana State, India.
[**] M.D., Assistant Professor of Medicine, Osmania General Hospital, Hyderabad, Telangana State, India.
[***] M.D., Professor of Medicine, Osmania General Hospital, Hyderabad, Telangana State, India.
[****] Postgraduate Student, Osmania General Hospital, Hyderabad, Telangana State, India.

***Abstract*- Background :** Doppler ultrasound is increasingly used in Nephrology for diagnosis of renovascular hypertension and evaluation of allograft dysfunction. However, its utility in glomerular disease remains controversial.

**Objectives :** Using Doppler Ultrasound, we prospectively tested the role of resistive index (RI) and atrophic index(AI) in predicting tubulointerstitial lesions in patients with glomerular disease as demonstrated by renal biopsy.

**Methods :** 56 patients with primary or secondary glomerular diseases were examined by Doppler ultrasonography immediately before renal biopsy. The resistive and atrophic indices (RI & AI) were calculated and compared with histological changes in biopsy specimen.

**Results :** Receiver Operator Characteristics analysis showed RI of 0.60 as an optimal value for discriminating tubulointerstitial changes with sensitivity of 84.9% and specificity of 91%. An AI of 0.65 was shown to be optimal for discriminating tubulointerstitial injury with sensitivity of 74.9% and specificity of 87%. There was a significant correlation between atrophic and resistive indices.

**Conclusion :** Measurement of RI by Doppler ultrasound can be considered as a supplementary diagnostic tool in glomerular diseases to predict the severity of tubulointerstitial injury.

## I. Introduction

Applications of Doppler Ultrasound in Nephrology are increasing day by day. 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.1Studies published in the last two decades indicated that Doppler can be used reliably in several types of intrinsic renal diseases,2 obstructive uropathy,3 acute renal failure4 and renovascular hypertension.5 The diagnostic utility of Doppler in glomerular disease is under debate. Some studies show encouraging results,6,7 whereas others are disappointing.8 Different renal parenchymal diseases may present with distinct features on Doppler despite similar conventional ultrasound appearance. Renal vasculitis and tubulo-interstitial nephropathies are more frequently identified than glomerulonephritis since glomerular component accounts for only eight percent of renal parenchyma, whereas the highest percentage is occupied by the vascular and tubulointerstitial compartment.6Among 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.9 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.10 Atrophic index (AI) was a new parameter proposed by Sugiyura *et al*10 for quantifying the atrophic changes in renal parenchyma . [2]

The RI is a ratio of peak systolic and end diastolic velocity, derived from the Doppler spectrum of any vessel . Initially this index was introduced by Pourcelot [50] for the grading of stenoses of the carotid artery. There is some evidence that several factors influence intrarenal RI: (i) the extent of stenosis; (ii) the distensibility/stiffness of the vascular system; (iii) non-renal factors and (iv) the location of intrarenal Doppler measurement.

Applications of Doppler Ultrasound in Nephrology are increasing day by day. 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.[1] Studies published in the last two decades indicated that Doppler can be used reliably in several types of intrinsic renal diseases,[2] obstructive uropathy,[3] acute renal failure[4] and renovascular hypertension.[5] The diagnostic utility of Doppler in glomerular disease is under debate. Some studies show encouraging results,[6,7] whereas others are disappointing.[8] Different renal parenchymal diseases may present with distinct features on Doppler despite similar conventional ultrasound appearance. Renal vasculitis and tubulo-interstitial nephropathies are more frequently identified than glomerulonephritis since glomerular component accounts for only eight percent of renal parenchyma, whereas the highest percentage is occupied by the vascular and tubulointerstitial

compartment.[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.[9] 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.[10] Atrophic index (AI) was a new parameter proposed by Sugiyura *et al*[10] for quantifying the atrophic changes in renal parenchyma .

## II. AIM AND OBJECTIVES OF THE STUDY

This study is aimed at validating the usefulness of renal Doppler indices - resistive index and atrophic index in predicting the tubulointerstitial injury in glomerular disease and plan for early intervention.

## III. MERTHODOLOGY: PATIENTS AND METHODS

**Inclusion Criteria :** Patients with

1) Proteinuria >1 g/day
2) Proteinuria >0.5g/day with hematuria
3) Hematuria with RBC casts,
4) Rapidly worsening renal function

**Exclusion Criteria**

- Kidney size <8.5cm
- Kidney size 8.5 – 9 cm with increased echo texture of grade III
- Multiple cysts
- Acute pyelonephritis/perinephric abscess
- Solitary kidney
- Isolated tubulointerstitial component in renal biopsy

**Materials and methods :**

Prospective observational study

Study period : January 2013 to August 2014.

Set - up: Osmania General Hospital, Hyderabad

**Study Design :**

The study population consisted of 56 patients of Glomerular diseases attending the upgraded department of medicine in Osmania General Hospital , Hyderabad . Renal doppler was done to study population who subsequently underwent renal biopsy. The patients convening to the inclusion criteria were enrolled in to the study after being explained about the proceedings of the study and after they signed the consent form. The patients presenting with hematuria were evaluated with Renal colour doppler ( Resistive index and Atrophy index ). A detailed history was taken about the presence of risk factors and duration risk factors. Glomerular diseases was differentiated into following types : 1)MCD 2)MN 3)Mesangial Proliferative Glomerulo Nephritis 4)Ig A Nephritis 5)FSGS 6)DPGN 7)MPGN 8)Class IV Lupus Nephritis 9)Class III Lupus Nephritis 10)Class II Lupus Nephritis 11)Crescentic Nephritis

Renal Biopsy reports were collected. The Sensitivity and specificity of Resisitive index and Atrophy index calculated.

**Statistical Analysis :**

All data obtained were recorded and presented as Mean with 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, whenever appropriate by using SPSS 16 software,, was used to find out whether the distribution of frequencies was equal among the groups .A P - value < 0.05 was considered statistically significant. The Sensitivity and Specificity of individual indices were calculated.

## IV. OBSERVATION AND RESULTS

Out of 56 patients , only 50 patients with glomerular disease diagnosed by renal biopsy were included in the study. Out of 50 patients ,19(38%) patients were < 30 years , 27(54%) patients were between 30 - 40 years and 4(8%) patients were > 40 years and a M:F ratio of 1:1.27.

The baseline characteristics of the patients are given in Table 1 .

**Table 1: Baseline characteristics of the patients**

| | | | Range | Mean |
|---|---|---|---|---|
| 1 | **Age ( yrs )** | | 6 to 44 | 30.80 |
| 2 | **Gender** | **Males** | 22(44% ) | |
| | | **Females** | 28(56%) | |
| 3 | **24 hr urine protein (gm/L)** | | 1.64 - 3.62 | 2.63 |
| 4 | **Serum Creatinine ( umol/L )** | | 124.96 - 272.80 | 198.88 |
| 5 | **GFR ( ml/sec)** | | 0.42 - 1.24 | 0.83 |
| 6 | **Serum Albumin ( gm/L )** | | 24 - 38 | 31 |
| 7 | **Serum Cholesterol( mmol/L)** | | 4.14 - 6.86 | 5.50 |
| 8 | **Hypertension at presentation** | | 20 (40 % ) | |
| 9 | **Nephrotic syndrome** | | 15 (33%) | |
| 10 | **Renal Failure at onset** | | 15 ( 33% ) | |
| 11 | **Resistive Index** | | 0.56 - 0.72 | 0.64 |
| 12 | **Atrophic Index** | | 0.60 - 0.70 | |

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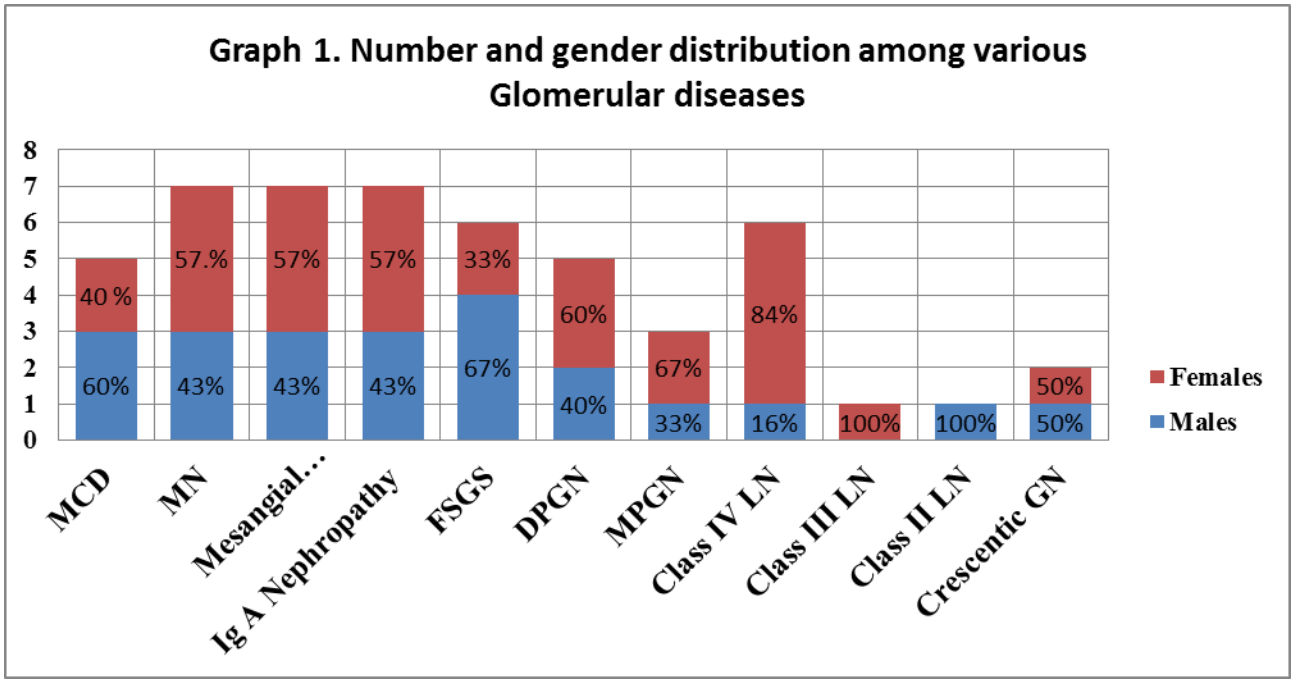
The histopathology results of the study subjects are summarised in Graph 1.




RI and AI in different glomerular diseases is depicted in Table 2.

**Table 2. RI and AI in different glomerular diseases**

| S.No | Glomerular disease | RI | | AI | | Total |
|---|---|---|---|---|---|---|
| | | **≥0.6** | **<0.6** | **≥0.65** | **<0.65** | |
| **1** | MCD | 4(80%) | 1(20%) | 4(80%) | 1(20%) | 5 |
| **2** | MN | 6(86%) | 1(14%) | 6(86%) | 1(14%) | 7 |
| **3** | Mesangial proliferative GN | 6(86%) | 1(14%) | 6(86%) | 1(14%) | 7 |
| **4** | IgA Nephropathy | 6(86%) | 1(14%) | 6(86%) | 1(14%) | 7 |
| **5** | FSGS | 5(83%) | 1(17%) | 5(83%) | 1(17%) | 6 |
| **6** | DPGN | 4(80%) | 1(20%) | 4(80%) | 1(20%) | 5 |
| **7** | MPGN | 3(100%) | - | 3(100%) | - | 3 |
| **8** | Class IV LN | 5(83%) | 1(17%) | 5(83%) | 1(17%) | 6 |
| **9** | Class III LN | 1(100%) | - | 1(100%) | - | 1 |
| **10** | Class II LN | 1(100%) | - | - | 1(100%) | 1 |
| **11** | Crescentic GN | 1(50%) | 1(50%) | 1(50%) | 1(50%) | 2 |
| **Total** | | **42(84%)** | **8(16%)** | **41(82%)** | **9(18%)** | **50** |

The Sensitivity and Specificity of RI ≥ 0.60 and AI ≥ 0.65 was 84.90% , 91% ,74.90% 87 % respectively.

**Table 3. Sensitivity And Specificity Of RI And AI**

| | Sensitivity( % ) | Specificity( % ) |
|---|---|---|
| RI ≥ 0.60 | 84.90 | 91 |
| AI ≥ 0.65 | 74.90 | 87 |

Association between various factors and Tubulo interstitial Injury is shown in Table 4.

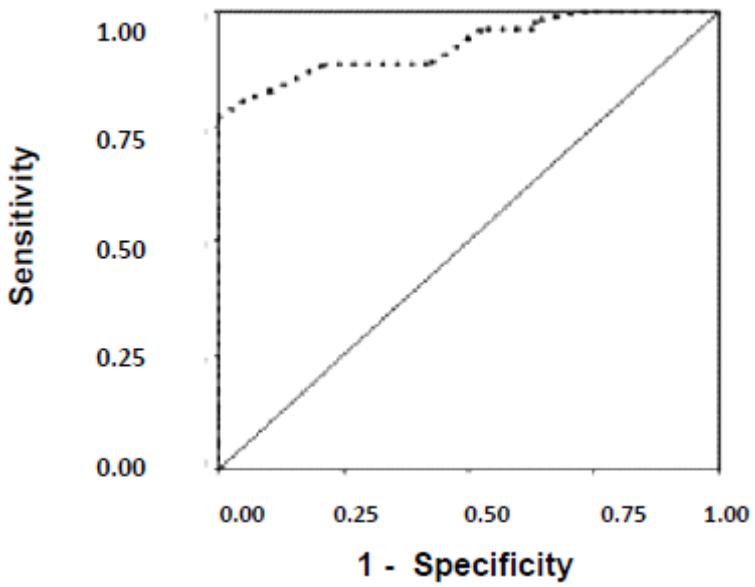
**Table 4. Association between various factors and Tubulo interstitial Injury**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | **0** | | **≥1** | | | |
| | | **Mean** | **SD** | **Mean** | **SD** | | |
| **Age** | **yrs** | 23.05 | 9.98 | 34.96 | 14.12 | 3.37 | 0.01 |
| **24 hr Urine Prot gm /day** | | 0.97 | 2.61 | 1.01 | 0.41 | 0.61 | |
| **GFR ml / sec** | | 64.36 | 18.92 | 45.03 | 25.62 | 2.99 | 0.01 |
| **Cholesterol mg / dl** | | 238.53 | 66.57 | 204.7 | 44.27 | 2.47 | 0.02 |
| **Gender** | **Male** | 5 | | 17 | | 0.49 | 0.48 |
| | **Female** | 6 | | 22 | | | |
| **RI** | **< 0.60** | 5 | | 3 | | 33.2 | 0.01 |
| | **≥ 0.60** | 1 | | 41 | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **AI** | **< 0.65** | 4 | | 5 | | 14.5 | 0.01 |
| | **≥ 0.65** | 2 | | 40 | | | |
| **Smoking** | **Yes** | 0 | | 10 | | | 0.01 |
| | **No** | 19 | | 21 | | | |
| **Hypertension** | **Yes** | 3 | | 16 | | 4.21 | 0.04 |
| | **No** | 11 | | 20 | | | |

The entire range of RI in the study ( 0.52 - 0.73 ) was evaluated for predictive ability by ROC analysis. The resultant ROC curve is given in the figure.

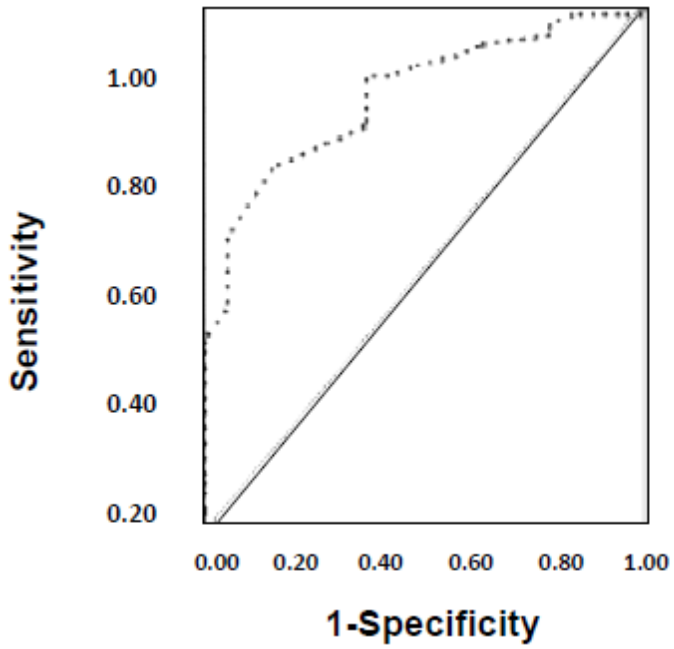
**Graph 2 ROC Curve of Predictive value of RI**




The ROC curve indicated that RI value of 0.60 as the optimal value for discriminating Tubulointerstitial injury with sensitivity of 84.90 % and specificity of 91 % .

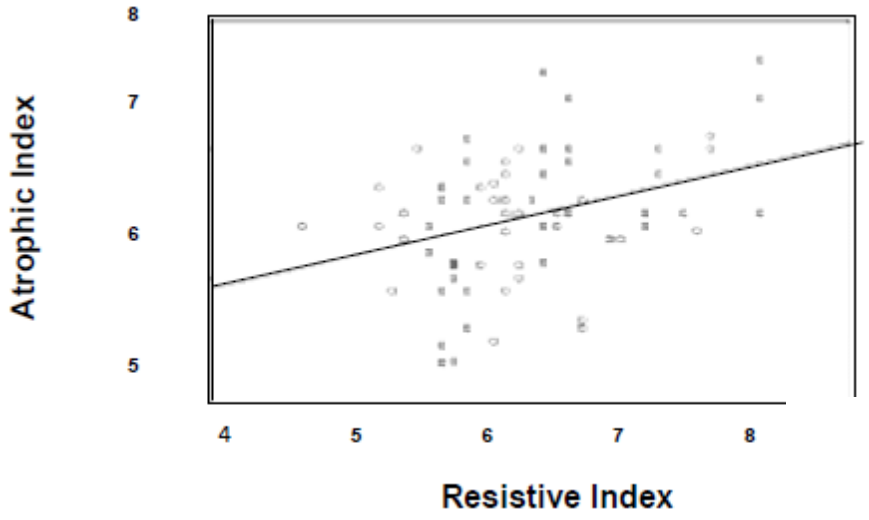
AI was a new parameter proposed to evaluate the degree of atrophic changes in renal parenchyma. As with RI the full range of AI (0.53-0.76) was evaluated for the predictive ability in discriminating tubulointerstitial injury by ROC.

**Graph 3 ROC Curve of Predictive value of AI**




The ROC indicated that AI of 0.65 had 74.9 % sensitivity and 87 %specificity .

**Graph 4 Correlation of the RI and AI**




The correlation between RI and AI was statistically significant ( p value < 0.01 ) . Both are dependant variables in detecting Tubulointerstitial injury .

## V. DISCUSSION

The usefulness of Doppler ultrasound in medical renal disease seems to be underestimated.. Renal parenchymal resistance as measured by RI represent the global resistance offered to blood flow by different parenchymal structures vascular, interstitial or glomerular compartments either separately or all together. This is especially true of vasculointerstitial compartment because when the damage is confined to glomeruli the RI does not seems to increase. Studies by Platt JF, Rubin JM, etal[2] and MR Prabahar et al[11] reported that RI correlated with tubulointerstitial changes. The mechanism of raised RI in tubulointerstitial disease is probably the interstitial fibrosis surrounding the vessels increasing the vascular impedance.[12]

This prospective study 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 in contrast to Sugiura T et al**[10],** study. This study has also shown significant correlation between RI and AI which may be the reason for the above finding. RI correlated well with tubulointerstitial injury than with the glomerular injury whereas AI correlated both with glomerular as

well as tubulointerstitial injury. This could account for lack of good correlation (r= 0.358) between them although it is statistically significant.

In the present study , sensitivity and specificity of RI of value ≥ 0.60 was 84.90% and 91% respectively and of AI ≥ 0.65 was 74.90 % and 87 % respectively.

The present study used RI O.60 as a cut off point instead of 0.7. Several studies have shown that a mean RI of people without pre-existing renal disease was 0.60± 0.01.[2,9] Exceptions to this are children <4 yrs, adults >60 yrs. The mean RI of our healthy population (109 subjects) was 0.58± 0.03. Our ROC curve found 0.6 as the best discriminatory value. The present study shows that RI of 0.6 should be accepted as a cut off value in glomerular disease in Indian population.

The relationship between age and RI could have influenced the results but there was no statistically significant difference between patients with high, high normal or low RI . More over as stated earlier, a different value may be more appropriate in individual diseases.[9] For example in obstruction, to differentiate obstructive from unobstructed pelvicalyceal system RI of 0.7 was found to be the most appropriate with sensitivity of 92% and specificity of 88%.[3] On the other hand in Reno vascular hypertension, a value of >0.8 or more strongly predicted lack of improvement after revascularisation.[13]

We have also tested the value of AI 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. By ROC analysis the optimal discriminatory value was 0.65 which was again lower than in comparison with similar study.[10] The significance of AI in glomerular diseases requires further research.

The present study had few potential limitations. The Doppler and pathologic analyses were carried out by a single observer. It is well known fact that both are observer dependent parameters, hence significant intra observer variability does exist. This should be borne in mind while interpreting the results of this study. We administered antihypertensive drugs 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 converting enzyme inhibitors reduce RI only in diabetic subjects not in patients without diabetes.[14] The present study had no diabetic patients.

## VI. CONCLUSION

We conclude that resistive and atrophic indices can be used to predict the presence of tubulointerstitial lesion in glomerular disease with high sensitivity and specificity. RI fared better than AI to predict the presence of tubulointerstitial disease.There was a significant correlation between atrophic and resistive indices. Elevated RI and AI independently predict the tubulointerstitial injury. Hence measurement of resistive index can be considered as a supplementary diagnostic tool in glomerular diseases to asses severity of tubulointerstitial injury.

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## AUTHORS

**First Author** – Dr. G. Balaraju, M.D., Associate Professor of Medicine, Osmania General Hospital, Hyderabad, Telangana State, India.
**Second Author** – Dr. K.S. Amaravathi, M.D., Assistant Professor of Medicine, Osmania General Hospital, Hyderabad, Telangana State, India.
**Third Author** – DR. S. Ashok kumar, M.D., Professor of Medicine, Osmania General Hospital, Hyderabad, Telangana State, India.
**Fourth Author** – Dr. Gopikrishna Kenchi, Postgraduate Student, Osmania General Hospital, Hyderabad, Telangana State, India.
**Fifth Author** – Dr. S. Ravinder, M.D., Associate Professor of Medicine, Osmania General Hospital, Hyderabad, Telangana State, India.
**Sixth Author** – Dr. B. Sudarsi, M.D., Assistant Professor of Medicine, Osmania General Hospital, Hyderabad, Telangana State, India.