*ejpmr, 2019,6(3), 455-459*

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

# ROLE OF RENAL DOPPLER STUDY IN ACUTE GRAFT REJECTION IN POST RENAL TRANSPLANT PATIENTS

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**Article Received on 19/01/2019** **Article Revised on 09/02/2019** **Article Accepted on 02/03/2019**

## ABSTRACT

Acute graft rejection is one of the common complications in the early renal transplant period. Early diagnosis and treatment plays an important role in the graft success and survival. **Aim:** To study the role of renal Doppler in predicting acute graft rejection in renal transplant patient and to compare with histopathological examination of the renal biopsy. **Methodology:** 80 post renal transplant patients in the first three months of transplantation were included in the study. Doppler imaging of the transplant kidney was done using color and spectral Doppler. Cut-off values were obtained from receiver operator curve for Resistive Index and Pulsatility Index values. **Results:** Using the cut-off of 0.69 for RI and 1.42 for PI, the sensitivity of the test is 85% and 75% respectively but with reduced specificity. **Conclusion:** Doppler imaging is not a helpful tool for differentiating acute graft rejection from other parenchymal complications, but it is a sensitive non invasive modality in predicting graft rejection among transplant patients.

**KEYWORDS:** Doppler, Resistive index, Pulsatility Index, renal transplant, graft rejection.

## INTRODUCTION

Several imaging modalities have been studied in reliably diagnosing acute graft rejection. In the early post transplant patients, the most easily available and portable mode of imaging is Doppler ultrasound with no radiation risk or risk associated with toxic pharmaceutical agents. Prior studies have shown that doppler ultrasound parameters resistive index (RI) and pulsatility index (PI) have good sensitivity in diagnosis acute graft refection[1]; however, differentiation from other parenchymal causes for graft dysfunction is difficult in view of overlapping findings. This study aims to test the accuracy of Doppler parameters resistive index and pulsatility index in predicting the acute graft rejection in the early post transplant period.

## AIM

To study the role of renal Doppler in predicting acute graft rejection in renal transplant patient and to compare with histopathological examination of the renal biopsy.

## OBJECTIVES

### Primary objective

To calculate sensitivity, specificity, and other statistical parameters in the diagnosis of acute graft rejection using Doppler parameters compared with histopathological examination.

To identify logical cut-off values for resistive index and pulsatility index in predicting acute rejection.

### Secondary Objective

To identify a logical cut-off value for resistive index and pulsatility index in predicting overall parenchymal complication in a transplant patients.

## METHODOLOGY

### Study design

Observational study of all renal transplant recipients of Medical College, Thiruvanthapuram during the period (18 months from May 2015 to October 2016) for evaluation of post transplant status of their kidney in the first three months from the day of transplantation.

### Inclusion criteria

All patients who have undergone renal transplantation in Medical College, Trivandrum.

**Exclusion Criteria**

Patients who have developed transplant renal artery stenosis or thrombosis.
Accelerated acute rejection.
Persisting post-transplant surgical complications like lymphocoele or urinoma.
Patients not willing to participate in the study.

## METHODOLOGY

The subjects who satisfy the inclusion criteria were subjected for Doppler ultrasound (US) imaging of the transplant kidney performed with Mindray DC-N6 machine. The studies were performed on serial intervals on post op days 1, 3, 7, 14, 30 and 90, at the time of renal compromise and the day of renal biopsy. Pulsed Doppler examination was performed and the wave forms form at least three interlobar arteries are obtained in each study. From the waveform, the peak systolic and the end diastolic velocities are calculated which are then used to determine the resistive and pulsatility index. The mean value of resistive index and pulsatility index taken from 3 wave forms of interlobar arteries of a single study were used for analysis. Diagnosis was obtained by biopsy or by clinical results. Patients were then divided into two groups according to the biopsy and/or by clinical results. Group 1 were patients with acute rejection and Group 2 were patients without acute rejection. Among the patients without rejection, the Resistive index (RI) and Pulsatility index (PI) values of day 7 are used for analysis. For the patients who are diagnosed as having complications, the RI and PI values on the day of renal biopsy are used for analysis.

Resistive index is calculated by the formula[2,3]

RI = (PSV-EDV)/PSV, where, PSV is the peak systolic velocity and EDV is the end diastolic velocity.

Pulsatility index is calculated by the formula[3]

PI = (PSV-EDV)/MV, where MV is the mean velocity.

**Sample Size**

In a study published in AJR by Genkins et al[4] 'Duplex Doppler sonography of renal transplants: lack of sensitivity and specificity in establishing pathologic diagnosis' resistive index of greater than or equal to 0.9 was used to indicate acute rejection, sonography had a sensitivity of only 9% and a specificity of 91% for this diagnosis. Substituting in the formula,

Total number of positive cases = $(Z\alpha)P_1 Q_1 / d^2$

Where $(Z\alpha)^2 = (1.96)^2 = 3.84$

$P_1$ = Sensitivity

$Q_1 = 1 - P$ (100-P if P is taken as a percentage)

d = precision

Total number of positive cases = 3.84 x 9 x 91 / 10 x 10 = 31.449

A pilot study was conducted in the department of nephrology during the period of one year (November 2013 to November 2014): 17 out of 42 patients were found to have acute rejection diagnosed by the renal biopsy as a gold standard test. Thus with the prevalence of acute rejection rate as 40.47%, the sample size calculated is 31.449/40.47% = 77.7, i.e., 78 post transplant patients.

For specificity,

Total number of negative cases = $(Z\alpha)P_2 Q_2 / d^2$

Where $(Z\alpha)^2 = (1.96)^2 = 3.84$

$P_2$ = Specificity

$Q_2 = 1 - P$ (100-P if P is taken as a percentage)

d = precision here it is taken as 10

Total number of negative cases = 3.84 x 91 x 9 / 10 x 10 = 31.449

Sample size is calculated as 31.449/(100 – 40.47%) = 52.828 . i.e., 53

Thus minimum number of sample size to measure both sensitivity and specificity is atleast 78 post transplant patients.

**Data analysis**

Data analysis was done with the help of Excel 2013 and IBM SPSS statistics 22 software.

## OBSERVATIONS AND RESULTS

80 patients were imaged in total. The mean age in our study was 37. Fifty-eight patients were male (72.5%) and 22 patients were female (28.5%). 20 patients (25%) had acute rejection and 60 patients (75%) did not have complications or had other parenchymal complications other than acute graft rejection. The distribution of the parenchymal complications in the transplant patients is shown in table.

**Table 1: Distribution of parenchymal complication in post-transplant patients.**

| No | Parenchymal complications | No of patients | Percentage |
|---|---|---|---|
| 1 | Acute rejection | 20 | 44.4% |
| 2 | Acute tubular necrosis | 21 | 46.7% |
| 3 | Tacrolimus toxicity | 2 | 4.4% |
| 4 | Pyelonephritis | 2 | 4.4% |

The receiver operator curve (ROC) of resistive index and pulsatility index in acute rejection are shown in figure 1 and 2 respectively

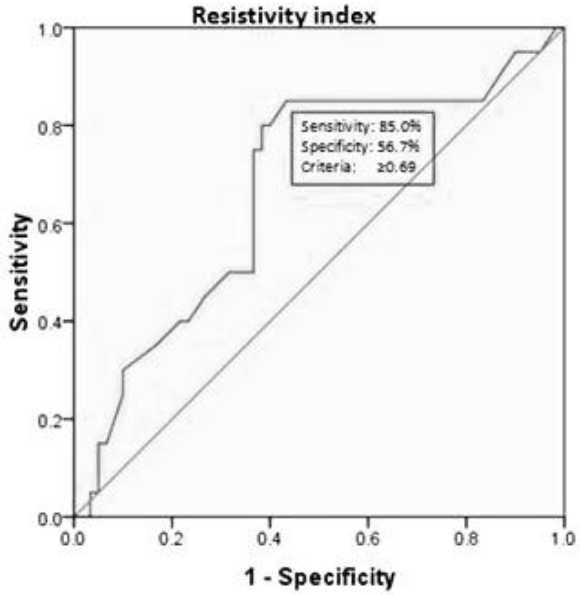


**Figure 1: ROC of resistive index in transplant patient for acute rejection.**

From the graph, a cut off value of 0.69 was derived. This cut off has a sensitivity of 85% and specificity of 56.7%.

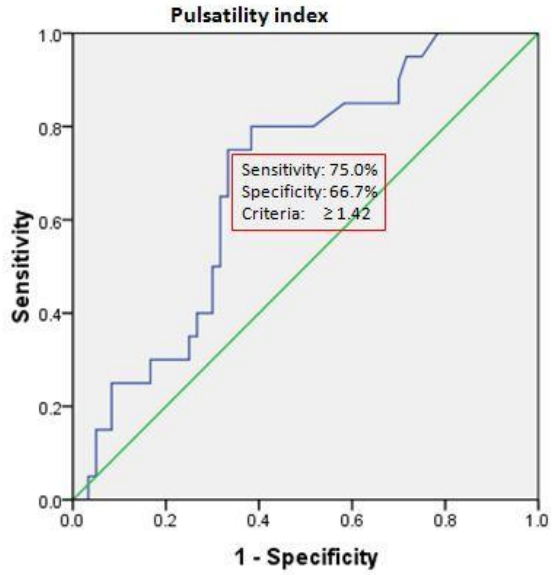


**Figure 2: ROC of pulsatility index in renal transplant patients for acute rejection.**

From the graph, a cut off value of 1.42 was derived. This cut off has a sensitivity of 75.00% and specificity of 66.7%.

The comparison of ROC curves of resistive index and pulsatility index in acute rejection is shown in figure 3. Comparing the resistivity index and the pulsatility index, the area under the ROC curve (AUROC) was found to be 67% and 68.5% respectively. The pulsatility index compare to the resistivity index has 1% increase in AUROC.

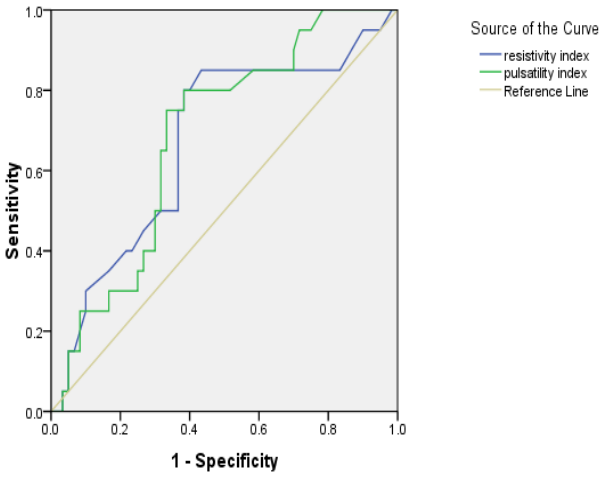


**Figure 3: Comparison of ROC curves of resistive index and pulsatility index in acute rejection.**

The ROC of resistive index and pulsatility index for parenchymal complication are shown in figure 4 and 5 respectively

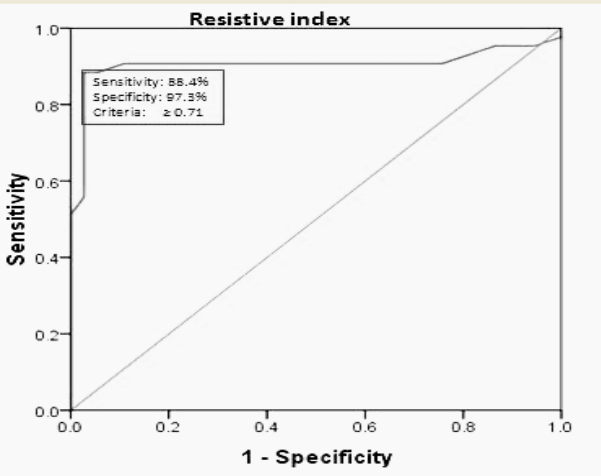


**Figure 4: ROC of resistive index in patients with any parenchymal complications**

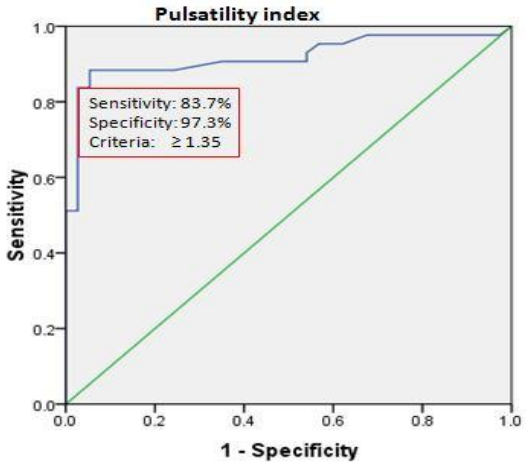


**Figure 5: ROC of pulsatility index in patients with any parenchymal complication.**

From the graph, a cut off value of 1.35 was derived. This cut off has a sensitivity of 83.7% and specificity of 97.3%.

## DISCUSSION

In this study, resistivity index and pulsatility index were used to predict acute graft rejection in transplant patients in the first 3 months. The final diagnosis was confirmed by renal biopsy. The optimal cut-off for resistivity index in detecting acute rejection was 0.69, with sensitivity of 85% and specificity of 56.7%. The optimal cut-off for pulsatility index in detecting acute rejection was 1.42, with poor sensitivity and specificity of 75% and 66.7% respectively. Hence the pulsatility index is not as reliable as resistivity index.

Rifkin et al, derived a cut-off of 0.7 for resistivity index with a sensitivity of 94% and specificity of 49%, cut-off of 0.8 with a sensitivity of 69% and specificity of 85% and a cut-off of 0.9 with a sensitivity of 13% and specificity of 100%.[5] Similarly, Sharma et al derived a cut-off of 0.7 for resistivity index with a sensitivity of 90.2% and specificity of 59.4% and 0.8 with a sensitivity of 43.6% and specificity of 94.1%.[6]

When applying this cut-off to the sample in this study, the sensitivity and specificity was found to be 80% and 60% respectively for 0.7, 50% and 66.7% respectively for 0.8 and 20% and 91.7% respectively for 0.9.

Sharma et al, in his study "Utility of serial Doppler ultrasound scans for the diagnosis of acute rejection in renal allografts" published in 2004, also derived a cut-off of 1.4 for pulsatility index with a sensitivity of 77.6% and specificity of 34.5%, cut off of 1.8 with a sensitivity of 43.6% and specificity of 94.1%. [6]

When applying the same value, the sensitivity and specificity of pulsatility index was found to be 75% and 65% respectively at a cut-off of 1.4 and 40% and 73.3% respectively at a cut-off of 1.8.

The present study, when compared to the previous studies show similar cutoff values for resistive index and pulsatility index, with better sensitivity, but specificity is poor as in the previous study. Compare to the above studies, even at higher cut-off of 0.8 and 0.9 there is slightly reduced specificity in our study. This reduced specificity even at high RI of >0.9 is because of marked high resistance flow with RI >0.9 and PI >2.0 is seen 3 cases of acute tubular necrosis.

Additionally, in detecting overall parenchymal complications including rejection, acute tubular necrosis, tacrolimus toxicity and pyelonephritis, the optimal cut-off of 0.71 for resistive index with sensitivity of 88.4% and specificity of 97.3% and a cut-off of 1.35 for pulsatility index with sensitivity of 83.7% and specificity of 97.3%.

Preliminary studies and this study show that resistive index may not help in accurately differentiating acute rejection from other complication, but it does helps in accurately differentiating the overall parenchymal complication which includes acute rejection and ATN in >90% cases in our study.[1] As ATN can resolve on its own with conservative management, treatment for acute rejection can be initiated based on resistive index for better graft survival while waiting for the renal biopsy report. The study can be further expanded to evaluate the serial change in RI and PI in differentiating acute rejection from other complications.

## LIMITATION OF THE STUDY

Ultrasound is operator dependence, as the transplant kidney is more superficial in iliac fossa, so much of pressure during scan can lead to falsely increased resistance.

Even though the transplant kidney is so superficial in retroperitoneal space, so much obesity and so much gaseous bowel distention can reduce the amount of ultrasound waves that reaches the renal arteries which may leads to false values.

## CONCLUSIONS

Renal Doppler study using resistive index can be reliably used in diagnosing post renal transplant complication. However, for differentiating acute rejection from other parenchymal complication, resistive index lacks specificity but shows increased sensitivity of 85% with a cut off value ≥0.69 as per this study. Hence, Doppler sonography plays very important role in early diagnosis so that immediate treatment can be started in those patients. This helps in avoiding the delay in starting the treatment until the confirmatory renal biopsy report, so that increase in the success and graft survival can be achieved.

Among the RI values, RI ≥0.69 is found to be best parameter based on this study, but an increase in RI value to >0.9 can further narrow the diagnosis towards acute rejection than other parenchymal complications.

In our study the cut-off of pulsatility index is very less compare to the previous literature, hence not taken as reliable indicator as RI in this study.

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