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# The Relationship Between Renal Arterial Resistive Index (RRI) and Renal Outcomes in Patients with Resistant Hypertension

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Original Paper

**Introduction.** There is a mutual relationship between hypertension and renal failure, so that hypertension can be considered as a common finding in patients with end-stage renal disorders. Patients with persistent hypertension despite multiple medications are at high risk for adverse cardiovascular and kidney events. Some studies suggest that there is a correlation between RI and renal function in kidney diseases. Therefore, we conducted a study to investigate the relationship between renal arterial resistive index (RRI) and renal outcomes in patients with resistant hypertension.
**Methods.** This 2-years cross-sectional study was performed on patients with resistant hypertension. All patients undergo GFR, serum Cr and urine Alb tests. Then Doppler ultrasound was performed by a radiologist to measure RRI and was evaluated for the relationship between RRI and renal function.
**Results.** Among 133 patients with resistant hypertension, 57.5% were male and the rest were female. Average age of participants and average RI were 48.26 ± 16.90 and 0.63 ± 0.80, respectively. There was no significant relationship between RI and gender ($P > .05$). Relationship between RI index with age, GFR, serum creatinine level, and albuminuria was significant in all cases ($P < .05$). Patients were divided into two groups with RI ≥ 0.7 and RI less than 0.7. Results showed a significant increase in serum creatinine and urinary albumin excretion in group with RI ≥ 0.7 ($P < .05$), while age, protein exertion level, and GFR in the two groups were not statistically significant ($P > .05$), despite the difference in the mean. Results of analysis of difference in the mean RI in 3 groups (macro-, micro-, normo- albuminuria) showed no significant difference between them ($P > .05$).
**Conclusion.** These data demonstrate the clinical importance of renal Doppler that may be an effective way to evaluate the prognosis of renal involvement in resistant hypertension.

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## INTRODUCTION

Hypertension is one of the most common risk factors for chronic kidney disease worldwide, and in developing countries including Iran is one of the most common chronic diseases.[1,2] Blood Pressure (BP) is a common finding in end-stage renal patients, and despite various therapeutic interventions including pharmaceutical medications

and lifestyle modifications, half of the patients still lack normal and stable hypertension due to underlying pathophysiology that has led to resistance to current drugs. Renal Resistance Index (RRI) is an indicator of high blood pressure in coronary arteries. Determining RRI is noninvasive, relatively cheap and fast and requires little training (< 1 month). In addition, RRI is highly renewable.[3,4]

Renal Artery Doppler Ultrasound provides noninvasive assessment of hemodynamic and anatomic as well as renal dysfunction.[5] Doppler ultrasound not only detects macroscopic arteriovenous malformations, but also identifies changes in blood flow at the micro- vascular level.[6] The RI Resistive Index in doppler renal ultrasound is a good indicator of renal vascular resistance due to atherosclerosis.[7,8] Doppler waveform analysis of renal ultrasound through arterial circulation allows RRI measurements and thus provides reliable non-destructive evaluation of intravenous hemodynamics. Intra-renal vascular resistance is not the major determinant of RRI, but rather a complex integral of various factors such as vascular coagulation, vascular resistance of large vessels, and pulse pressure.[9]

Recent evidence suggests that an increased RRI index not only indicates changes in intra-renal perfusion, but also contributes to systemic hemodynamics and subclinical atherosclerosis.[10] Some studies revealed that there is a correlation between RI and renal function in patients with renal disease. RI is also associated with patient age, serum creatinine (S-Cr), blood pressure, blood volume, severe aortic stenosis, and diabetes (DM) in some other studies.[11,12] It was found in the Vegilio study that RI index in patients with prolonged HTN had stronger correlation with disease severity and duration of disease compared to the group with controlled but high blood pressure.[13] Another study suggested that RRI can predict renal vascular changes and renal functional and structural abnormalities in patients with diabetes and HTN even before microalbuminuria.[14,15]

Resistant hypertension is defined as uncontrolled blood pressure (BP) on ≥ 3 anti-hypertensive drugs, one of which should be a diuretic, prescribed at maximally tolerated doses and appropriate dosing frequency and adherence to the prescribed drug regimen. Resistant hypertension is common, counts for 10 to 20% of the general hypertensives.

Patients with persistent hypertension despite multiple medications are at high risk for adverse cardiovascular and kidney events. According to the high prevalence of hypertension in the community as well as resistant hypertension and the presence of RRI as a potential prognostic indicator of the overall involvement in vascular problems and the possibility of doing this study in this center, we decided to evaluate this relationship.

## MATERIALS AND METHODS

This cross-sectional descriptive-analytic study was performed on 130 patients with resistant hypertension according to the diagnosis of a nephrologist in Sayyad Shirazi hospital's clinic, Gorgan, Iran. Inclusion criteria were GFR > 60 cc/min and controlled Hypertension.

Exclusion criteria were: lack of consent to participate in the study, acute non-renal disease, liver and heart failure, associated glomerular and tubulo-intestinal diseases, associated renal vascular diseases, pregnancy, diabetes mellitus.

After obtaining informed consent from patients and registering project with code of Ethics IR.Goums.Rec.1398.102, doppler ultrasound examination of renal arteries was performed on all of the using the same ultrasound device (device model: Philips iu22) and by the same operator. The results were recorded. Also demographic and laboratory records of patients including GFR (MDRD method), Cr, albuminuria was collected through blood tests and 24-hour urine tests in the patient's file. Patients were divided into two groups with RI < 0.7 and RI ≥ 0.7. Finally, the data were assessed and compared between the two groups. The data were entered into SPSS software version 21. Mean, frequency, and percentage were used to describe the data. Regression method, the Pearson correlation coefficient and ANOVA test were used to identify the relationship between variables. The significance level of the study was set at .05.

## RESULTS

This study was performed on 133 patients with resistant hypertension that included and referred from clinic, 76 patients (57.1%) were male and 57 patients (42.9%) were female. The average age of participants was 48.26 ± 16.90. In this study, the average RI of patients was 0.63 ± 0.80. The mean GFR and albuminuria in patients with resistant

hypertension is listed the following table (Table 1).

According to Kolmogorov-Smirnov test, this index was not normally distributed ($P < .001$). Mann-Whitney test was used to examine the relationship between RI and gender and there was no significant correlation between two variables ($P > .05$). According to non-normal distribution of data, Spearman correlation coefficient was used to examine the relationship between RI index with age, GFR, serum creatinine level, and data showed a significant correlation in all of the cases. In other words, RI was directly correlated with age, creatinine, and albuminuria; whereas by increasing the RI the GFR decreases ($P < .05$, Table 2).

After dividing the patients into two groups with RI ≥ 0.7 and RI < 0.7, 97 patients (73.5%) showed RI < 0.7 while 36 patients (26.5%) showed RI index ≥ 0.7. There was a significant difference in serum creatinine and urinary albumin levels in two groups with significantly higher levels in group with RI ≥ 0.7. However, no significant relationship was found between the two groups in the age, GFR, and proteinuria despite the difference in mean values between the two groups (Table 3). Among 133 patients, 57 patients (42.1%) had microalbuminuria and 38 patients (28.6%) had macroalbuminuria and the rest had normal urinary albumin excretion. Based on urinary albumin, patients were divided into 3 groups with normal urinary albumin, microalbuminuria and macroalbuminuria. The results of the mean difference of RI in the three groups with ANOVA showed no significant difference between them ($P > .05$). The average RI of patients with microalbuminuria and macroalbuminuria was 0.62 ± 0.51 and 0.64 ± 0.53, respectively; which was not significant according to Chi-square test ($P > .05$).

**Table 1.** Mean ± SD of Age, RI, Serum Cr, Urin Alb, GFR, and Total Urine Protein of Patientsv

| Parameter | Mean ± SD |
|---|---|
| Age | 48.26 ± 16.90 |
| RI | 0.63 ± 0.80 |
| Serum Cr, g/dL | 1.23 ± 0.75 |
| GFR, mL/ min/1.73 $m^2$ | 88.94 ± 12.3 |
| Albuminuria, mg/g Cr | 863.43 ± 381.02 |

**Table 2.** Correlation and Relationship of RI with Age, Serum Cr, GFR, and Total Urine Protein in Patients

| Parameter | Correlation Coefficient | *P* |
|---|---|---|
| Age | +0.189 | > .05 |
| Serum Cr | +0.506 | < .001 |
| GFR | -0.498 | < .001 |
| Proteinuria | +0.324 | < .001 |
| Albuminuria | +0.162 | < .001 |

**Table 3.** Relationship Between Mean Cr, GFR, Proteinuria, Albuminuria, and Age in 2 Groups of Patients Based on RI Segmentation

| Parameter | RI < 0.7 | RI ≥ 0.7 | *P* |
|---|---|---|---|
| Serum Cr | 1.14 ± 0.35 | 1.3 ± 0.86 | < .001 |
| GFR | 87.67 ± 18.19 | 76.57 ± 12.75 | > .05 |
| Proteinuria | 500.73 ± 64.61 | 700.58 ± 99.37 | > .05 |
| Age | 46.90 ± 17.34 | 51.31 ± 15.35 | > .05 |
| Albuminuria | 620.15 ± 245.15 | 1114.48 ± 423.91 | < .05 |

## DISCUSSION

Hypertension is one of the precautionary risk factors for global mortality and has a mutual cause and effect relationship with renal disorders.[16] Kidney ultrasound is an important tool in the diagnosis of kidney diseases. This type of imaging provides the physician with a wide range of morphological information about the kidney, including the size, shape, thickness of the renal cortex, presence of renal scars, obstruction, stones, cysts, tumors, fluid accumulation, and infection inside or outside the kidney. In addition, abnormalities of kidney blood perfusion caused by disorders in the main renal arteries and its branches can be assessed and evaluated by Doppler ultrasound.[17] From a clinical perspective, kidney doppler ultrasound can provide a better evaluation in patients with hypertension and detect the common causes of secondary HTN induced by the kidney, such as specific forms of parenchymal and renovascular HTN disease, severe renal injury or long-term HTN by the renal resistive index (RI) parameter.[18] Although ultrasound findings do not provide diagnosis of specific etiology in renal parenchymal diseases, some symptoms can lead to further prediction of HTN-related causes.[19] The RI index in Doppler ultrasound reflects intravascular resistance. The mechanism of elevated RI index along with decreasing renal glomerular function in patients with resistant hypertension is still unknown. The RI index of the interlobar arteries appears to be a reliable indicator of pathologic renal vascular changes.[20,21]

Therefore, in the present study, we investigated the relationship between renal artery resistive

index (RI) and GFR and albuminuria in patients with resistant hypertension. This study consists of 133 patients with resistant hypertension evaluated with renal doppler ultrasound. The average age of the patients was 48.26 ± 16.90 and majority of them were male 57.1%. About one-third of patients range in the age of 63 to 74 years. Which is in accordance with high prevalence of HTN in older and male population. Sevencan *et al.* examined 268 patients with hypertension by Doppler ultrasound and divided them into two groups of < 0.7 and ≥ 0.7 according to RI. The average age of the patients was 63.57 ± 10.3. The percentage of male patients in both groups was 32.4% and 31.8%, respectively.[22] In another study by Prejbisz, male patients with resistant hypertension had the highest frequency (59.6%) with an overall mean age of 47.7 ± 10.4.[10] Differences in frequency of age and sex of patients may be due to differences in the statistical population of the studies.

In the present study, the average renal artery resistive index was 0.63 ± 0. 80. Relationship between RI index and age was significant, as RI index increased with age. However, the average age of the two groups with RI ≥ 0.7 and RI < 0.7 did not show any statistically significant difference. Derchi *et al.* studied 291 patients with HTN and asserted that the RI index would increase as the age increases,[23] which is consistent with the results of the present study.

In this study, mean renal artery resistance index was 0.63 ± 0.80. Relationship between RI index and age was significant and RI index increased with age. However, the average age of the two groups with RI ≥ 0.7 and < 0.7 did not show any statistically significant difference. Derchi *et al.* also studied 291 HTN patients and reported that as age increased, the RI index would increase,[23] which is consistent with the present study.

In this study albuminuria was statistically significant in all cases using Spearman correlation coefficient. Patients with RI > 0.7 also had significantly higher albumin excretion in comparison with the other group. In a study in 2007, two groups of patients were selected based on a RI levels ≥ 0.7 and < 0.7. After a 6-month follow-up, data revealed that 50% of patients with higher RI suffer from a significant decrease in renal function.[24] In another study, the RI index was significantly associated with renal function, long-term cytological changes in renal tubules, systemic vascular disease, and albuminuria; with the higher RI index of patients with macrobuminuria (> 300 mg/dL) than microalbuminuria or normoalbuminuria.[25] In contrast, in other studies by Masulli *et al.*[26] and Narooeinejad *et al.*[27] There was no significant relationship between RI and albuminuria in patients, which was not consistent with the present study. The cause of the differences may be attributed to the false positive and false negative results in the RI index. This may be due to differences in the age and sex of the individuals, which is why the new references define RI index according to the age and sex. False positive results may also be reported in obese or hypoechogenic patients or in cases where the operator does not have sufficient skills and experience. Renal artery stenosis due to the fibromuscular dysplasia affecting distal branches of the kidney is one of the potential causes of false negative result.[28,29]

In the present study, there is a significant relationship between RI and serum Cr in patients with resistant hypertension, which increased with elevated creatinine levels. This study revealed that patients with resistant HTN with RI ≥ 0.7 experienced higher Cr excretion compared to the group with RI < 0.7, which was statistically significant ($P < .001$). Studies of Milovanceva and Soldo showed that there was a correlation between RI index and serum creatinine, which is consistent with the results of our study.[20] In the study of Ohta *et al.*, the RI index was 0.7 ± 0.09 and the mean creatinine clearance was 07.1 ± 38.9 and there was a significant relationship between these two, so that patients with RI index > 0.7, showed higher serum Cr levels.[30] Based on the results of these studies, it can be estimated that RI shows a high level of correlation with serum Cr level and can be used as a predictor in patients with advanced hypertensive nephropathy.

In the present study, there was a significant relationship between GFR and RI index in patients with resistant hypertension, while there was no significant difference in GFR by dividing patients into two groups. Kawai *et al.* reported that patients with hypertension and low GFR had a higher RI index.[8] Other studies have also reported that systemic atherosclerosis induced macroangiopathy affects renal hypertension and leads to a drop in GFR.[31,32]

## CONCLUSION

In this study we find that among patients with resistant hypertension, increased renal interlobar arterial resistance index (RI) is associated with higher albuminuria and lower glomerular filteration rate. After dividing these patients into two groups based on the amount of RI this relationship was only significant in terms of serum Cr and albuminuria. These results highlight the clinical importance of renal doppler ultrasound in the evaluation of patients with resistant hypertension. This non-invasive, relatively cheap, and convenient imaging technique is not only effective in identifying secondary causes of HTN but also helpful for assessing prognosis of early kidney involvement. Doppler ultrasound evaluation in addition to diagnosing secondary causes of hypertension can be useful in determining prognosis of renal involvement with predicting albuminuria and clearance loss, However; if the study was prospectively corroborated, this link would be stronger.

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## AUTHORS CONTRIBUTION

All the authors contributed equally to this manuscript.

## CONFLICT OF INTEREST

This study had no conflict of interest for the authors.

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