



# The renal resistive index is a non-invasive indicator of hepatorenal syndrome in cirrhotics

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## Keywords

Cirrhosis, hepatorenal syndrome, renal artery Doppler, renal resistive index

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## Abstract

**Introduction:** Hepatorenal syndrome (HRS) is defined as unexplained kidney failure in a patient with liver disease. The poor prognosis is due to both liver and renal failure, the latter being due to intrarenal vasoconstriction. The intrarenal arterial Doppler is a non-invasive tool used to study the extent of this vasoconstriction.

**Aim:** To determine if the intrarenal Doppler helps in indicating HRS in established cases of liver cirrhosis.

**Materials and Methods:** A total of 30 cirrhotics aged above 18 years with no prior or co-existing renal disorders were subjected to liver function tests, renal function test, complete blood count, urine examination, viral markers, ultrasonography abdomen, and the intrarenal artery Doppler for the resistive index (RI) calculation. RI was calculated using the formula:  $RI = (\text{peak systolic flow} - \text{peak diastolic flow}) / \text{peak systolic flow}$  and  $RI \geq 0.77$  was taken as diagnostic of HRS.

**Results:** Out of the 18 patients whose  $RI < 0.77$ , 17 had normal creatinine. 12 patients who had raised RI, 6 had raised creatinine (2.68), while the other 6 had normal creatinine (0.88) implying that renal RI (RRI) is an early indicator of HRS even before creatinine could rise to fulfill the criteria for HRS.

**Conclusion:** RRI is a useful tool for indicating HRS in cirrhosis of the liver.

## Introduction

Hepatorenal syndrome (HRS) is defined as unexplained kidney failure in a patient with liver disease who does not have clinical, laboratory, or anatomic evidence of other known causes of kidney failure.<sup>[1]</sup>

The HRS is a common complication of late-stage cirrhosis, due to site vasoconstriction of the renal vascular system, leading to a decreased glomerular filtration rate (GFR). Characterized by major interferences in circulatory function and the combined effect of renal and liver failure, HRS signals a poor prognosis.

HRS is considered to be a frequent complication of late-stage cirrhosis. The chance of development of HRS in cirrhotics with ascites was 40% according to a major 5 years study.<sup>[2]</sup>

The pathophysiological tell-tale feature of HRS is vasoconstriction of the renal circulation. Enhanced production of renal vasodilator factors, mainly prostaglandins keep renal perfusion in the normal range initially in decompensated cirrhosis. Later stages of the disorder, the renal perfusion drops owing to severe arterial underfilling causing maximum activation of vasoconstrictor systems, reduced renal vasodilator factors, or both.

Early in the course of HRS, renal hemodynamic changes begin, i.e., even before changes in serum creatinine are detectable.

Duplex Doppler ultrasonography is a widely used non-invasive method to assess vascular patency and blood flow in many sites. The resistive index (RI) can be used to assess vascular resistance through a simple analysis of the Doppler waveform. The RI is calculated as per the formula given below:

$$RI = \frac{\text{Peak systolic velocity} - \text{End diastolic velocity}}{\text{Peak systolic velocity}}$$

The normal value of RI is 0.60-0.70 and is measured at the arcuate arteries (corticomedullary junction) or interlobar arteries (adjacent to medullary pyramids).<sup>[3]</sup>

## Materials and Methods

About 30 patients aged  $\geq 18$  years, with ascites secondary to chronic liver disease, were admitted to a rural tertiary hospital and evaluated clinically. Laboratory evaluation included liver function tests, renal function tests, complete blood count, urine

examination, viral markers, ultrasonography (USG) abdomen, and the renal artery Doppler for renal RI (RRI).

Patients with acute infections, cardiovascular instability, diabetes mellitus, malignant diseases, patients with nephropathies and with pathomorphological findings in ultrasound like decreased kidney size, reduction of renal parenchymal width, and significant renal parenchymal hyperechogenicity were excluded.

The diagnosis of liver cirrhosis was based on typical clinical and sonographical findings (irregular homogeneity of the liver, liver surface nodularity, reduced size of the liver).

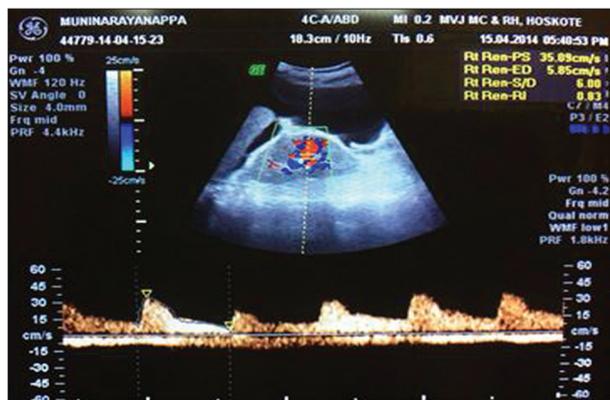
The study was approved by the Institution's Research and Ethical Committee Board and informed consent for the trial was obtained from each person.

Duplex Doppler evaluation of the renal arteries was done using a 3.5 MHz convex transducer (GE Voluson 730 Pro). To reduce masking by intestinal gas the patients were asked to fast at least 4 h before the examination. Doppler signals were taken from interlobar arteries and arcuate arteries in both kidneys. Color Doppler ultrasound was used to help to identify the arteries. Three similar, sequential time-velocity waveforms of Doppler signals were obtained at each point of measurement during suspended respiration. The RI was calculated by the ultrasound/Doppler machine using the formulae as given earlier. Patients were excluded if it was not possible to measure the RI in two different places in each kidney due to massive ascites or masking by gas. Interobserver variability was kept to the minimum by having the same ultrasonologist perform the Doppler studies [Figure 1].

An RRI of  $\geq 0.77$  was taken as diagnostic of HRS.

### Statistical analysis

All data were expressed as means  $\pm$  standard deviations. Statistical analysis was done using SPSS-16. Differences between groups were analyzed by Student's *t*-test;  $P \leq 0.05$  was viewed significant.



**Figure 1:** Doppler picture of renal artery that shows a tracing of the Doppler waves with the top yellow triangle as peak systolic flow and the bottom triangle as the peak diastolic flow and the renal resistive index measured as 0.83 as shown in the upper right corner

## Results

A total of 30 patients, between the age 30 and 75 years (average 49.56 years), as per the inclusion criteria, were studied.

There were 24 (80%) males and 6 (20%) females. 2 patients had no history of alcohol consumption and were hepatitis B surface antigen positive, while the rest were alcohol dependent, consuming alcohol for 6-60 years.

Table 1 shows the clinical, biochemical, and prognostic parameters which were taken into consideration when comparing subjects with  $RI \geq 0.77$  and  $RI < 0.77$ .

### Age and sex distribution

Out of the 30 cirrhotics, 11 males and 1 female had  $RI \geq 0.77$ , while 13 males and 5 females had  $RI < 0.77$ . Age of the patients ranged from 30 to 75 years with a mean of 50.66 in those with  $RI \geq 0.77$  and 48.83 in those with  $RI < 0.77$ . The *P* values were not significant as shown in Table 1.

**Table 1:** Comparison of clinical, biochemical and prognostic parameters in patients with  $RI \geq 0.77$  and  $RI < 0.77$

Parameters	$RI \geq 0.77$	$RI < 0.77$	<i>P</i> value
	Mean $\pm$ SD (12)	Mean $\pm$ SD (18)	
Age	50.66 $\pm$ 13.96	48.83 $\pm$ 11.78	0.51
HE (%)	HE (+) 5 (41.67) HE (-) 7 (58.33)	HE (+) 2 (11.11) HE (-) 16 (88.89)	0.038
Jaundice (%)	Jaundice (+) 11 (91.67)	Jaundice (+) 6 (33.33)	0.001
Ascites (%)	Massive 10 (83.33) Moderate 2 (16.67)	Massive 6 (33.33) Moderate 12 (66.67)	0.02
Duration of alcohol	18.75 $\pm$ 8.8	16.22 $\pm$ 13.12	0.18
Portal vein	12.47 $\pm$ 1.33	12.45 $\pm$ 1.96	0.14
Urea	52.25 $\pm$ 37.31	27.27 $\pm$ 13.81	0.0003
Creatinine	1.78 $\pm$ 1.15	1.04 $\pm$ 0.34	<0.0001
eGFR Cockcroft-Gault	55.66 $\pm$ 39.54	68.11 $\pm$ 28.88	0.23
eGFR MDRD	53.59 $\pm$ 37.99	70.44 $\pm$ 32.31	0.53
Albumin	2.66 $\pm$ 0.34	2.73 $\pm$ 0.5	0.19
Total bilirubin	4.82 $\pm$ 3.37	2.48 $\pm$ 2.14	0.02
Direct bilirubin	1.74 $\pm$ 1.18	0.98 $\pm$ 0.66	0.03
Indirect bilirubin	3.02 $\pm$ 2.32	1.41 $\pm$ 1.38	0.05
SGOT	89 $\pm$ 30.46	64 $\pm$ 20.55	0.01
SGPT	36.1 $\pm$ 27.48	40.41 $\pm$ 18.42	0.5
ALP	117.17 $\pm$ 50.96	164.22 $\pm$ 69.94	0.28
INR	1.6 $\pm$ 0.42	1.63 $\pm$ 0.5	0.6
MELD score	22.33 $\pm$ 7.73	15.72 $\pm$ 4.29	0.029
CPT	10.8 $\pm$ 1.64	9.3 $\pm$ 1.97	0.03

SD: Standard deviation, RI: Resistive index, HE: Hepatic encephalopathy, eGFR: Epidermal glomerular filtration rate, MDRD: Modification of diet in renal disease, SGOT: Serum glutamate oxaloacetate transaminase, SGPT: Serum glutamic-pyruvic transaminase, ALP: Alkaline phosphatase, INR: International normalized ratio, CPT: Child-Pugh Turcotte score

## Clinical parameters

### Hepatic encephalopathy

About 7 patients presented with hepatic encephalopathy of which 5 (71.42%) had RI  $\geq 0.77$ , and 2 had RI  $< 0.77$ . Out of the 5 who had hepatic encephalopathy, 4 of them had abnormal creatinine values while the other 2 in whom the RI  $< 0.77$  the creatinine was normal. Equally important is the fact that out of the 18 whose RI was  $< 0.77$  16 (88.89%) did not have encephalopathy. The implication is that HE and HRS do not necessarily go hand in hand. The differences between subjects with RI  $\geq 0.77$  and RI  $< 0.77$  were significant ( $P = 0.038$ ).

### Jaundice

About 17 patients had jaundice, of which 11 (64.7%) had RI  $\geq 0.77$ . The difference between those with RI  $\geq 0.77$  and RI  $< 0.77$  was significant,  $P = 0.001$  [Table 1].

### Ascites

Out of 30 patients with ascites, 16 had massive ascites and 14 had moderate ascites as detected in abdominal ultrasonography. Among 16 patients with massive ascites, 10 (62.5%) had RI  $\geq 0.77$  and the difference from those patients with RI  $< 0.77$  was significant,  $P = 0.02$  [Table 1].

## Biochemical parameters

### Renal functions

Out of the 12 patients who had raised RI, 6 had raised creatinine (2.68), while the other 6 had normal creatinine (0.88). However, out of the 18 patients whose RI  $< 0.77$ , 17 had normal creatinine as shown in Figure 2. The mean creatinine was 1.78 in patients with  $> 0.77$  RI and 1.04 in patients with RI  $< 0.77$ , the difference being significant, with a  $P < 0.0001$ .

### Epidermal GFR (eGFR)

The eGFR as estimated by Cockcroft-Gault formula and modification of diet in renal disease showed that 6 of the 12 patients who had RI  $\geq 0.77$  and high creatinine values had gross reduction in eGFR and the remaining 6 whose creatinine were within normal limits had normal range of eGFR, whereas in those with RI  $< 0.77$ , only 1 had high creatinine as well as reduced eGFR. The differences between patients with RI  $\geq 0.77$  and those with  $< 0.77$  were not found to be significant as shown in Table 1.

### Liver functions

Total bilirubin was elevated with a mean of 4.82 mg/dl in those patients whose RI was  $\geq 0.77$  compared to 2.48 mg/dl, in those with RI  $< 0.77$ , the  $P$  value being significant,  $P = 0.03$ .

The differences in serum glutamate oxaloacetate transaminase (SGOT) were equally significant,  $P = 0.01$  [Table 1].

The international normalized ratio (INR) in 10 of 12 patients whose RI was  $\geq 0.77$  had an average of 1.6, while 15 of the 18 patients whose RI  $< 0.77$  had INR with an average of 1.63,  $P = 0.6$ , thereby indicating no significant correlation between RI and INR.

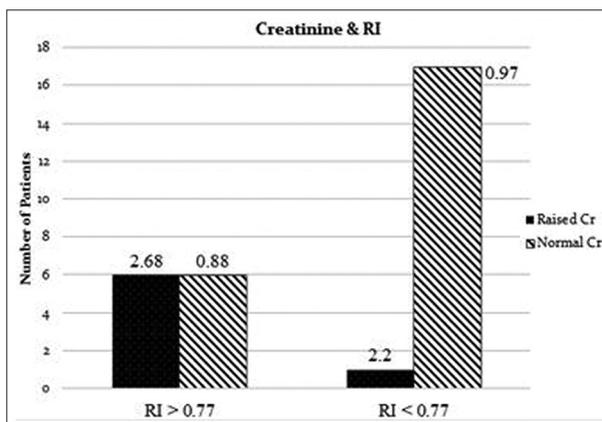


Figure 2: Correlation between creatinine and resistive index

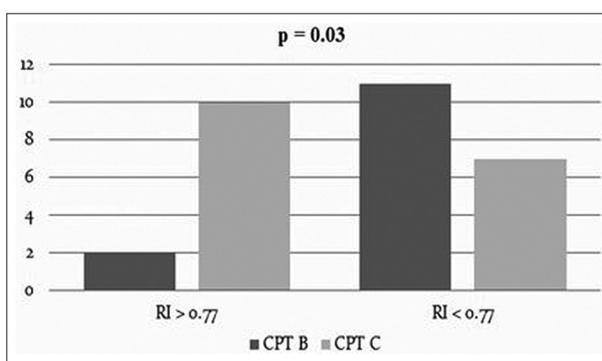


Figure 3: Number of patients with Child-Pugh-Turcotte score and resistive index

## Prognostic scoring and follow-up

### Child-Pugh-Turcotte (CPT) score

About 10 out of 17 patients with Child-Pugh Score of C had RI  $\geq 0.77$  compared to 2 of the 13 patients with Child-Pugh Score B as shown in Figure 3.

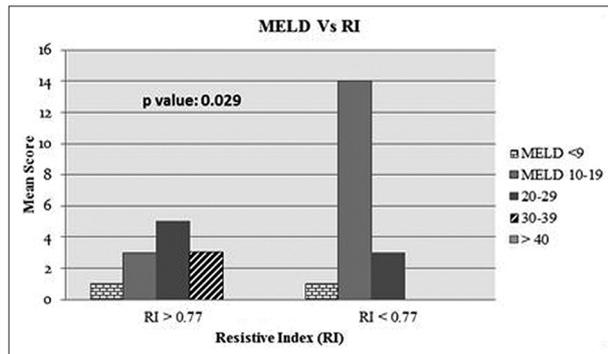
### Model for end-stage liver disease (MELD) score

As shown in Figure 4, the MELD score was significantly different ( $P = 0.029$ ) between patients with RI  $\geq 0.77$  and  $< 0.77$ . There were 8 patients with RI  $\geq 0.77$  who had the MELD score greater than 20 compared to 3 in whom the RI was  $< 0.77$ . 8/12 had a MELD score  $> 20$  when RI  $> 0.77$ , whereas when RI  $< 0.77$ , 15/18 had MELD score  $< 20$ , giving a negative predictive value of 83%.

## Follow-up

There were 15 patients who were followed up, of which 8 had raised RI and 7 had normal RI at the initial visit. Out of 8 patients with raised RI, 4 died (out of hospital), 2 continued to have raised RI, and 2 patients reverted to a normal RI following treatment with albumin, noradrenaline, and large volume paracentesis.

The follow-up of the 7 patients with normal RI revealed that 6 continued to have normal RI while 1 progressed to a raised RI.



**Figure 4:** Correlation of model for end-stage liver disease scores and resistive index

## Discussion

To diagnose HRS the patient should have low GFR indicated by creatinine level  $>1.5$  mg/dL or 24 h creatinine clearance lower than 40 ml/min, or no sustained improvement in renal function (drop in serum creatinine to  $<1.5$  mg/dL or rise in creatinine clearance  $>40$  ml/min) despite diuretic withdrawal and expansion of plasma volume with 1.5 L of plasma expanders. In addition, there should be the absence of shock, current bacterial infection, fluid loss, nephrotoxic medications, proteinuria  $<500$  mg/day, and no USG evidence of intrinsic parenchymal disease or obstructive uropathy.

Patients with liver cirrhosis regularly acquire renal failure due to intrarenal vasoconstriction. Manifest HRS is associated with a very poor outcome with no definite therapeutic strategies. The Doppler ultrasound measurement of the RI is used to quantify intra-renal vascular resistance in cirrhotic patients before HRS develops and could, therefore, be used as a strategy for treatment.

In our study, patients with  $RI \geq 0.77$  had mean creatinine of  $1.78 \pm 1.15$  indicating the presence of renal dysfunction, while those with an  $RI < 0.77$  had a mean creatinine of  $1.04 \pm 0.34$ ,  $P < 0.0001$ . Out of the 12 patients, in our study with  $RRI \geq 0.77$ , 6 had normal creatinine. This implies that the RRI is an early indicator of HRS even before creatinine could rise to fulfill the criteria for HRS.

During follow-up, 8 out of 15 patients who had  $RRI \geq 0.77$  initially, 2 reverted to a normal RI following treatment with albumin, noradrenaline, and large volume paracentesis which can possibly explain by the fact that those patient's creatinine had not risen up at that time to match the criteria for HRS.

In 2002, Bardi *et al.*<sup>[4]</sup> found out that RI in patients with HRS was significantly higher ( $\geq 0.70$ ) compared to the normal subjects in his study.

Platt *et al.*<sup>[5]</sup> measured intrarenal resistance, in 180, cirrhotic patients without kidney dysfunction. The mean initial RI in patients who subsequently developed the HRS was  $0.77 \pm 0.05$ . Kastelan *et al.*<sup>[6]</sup> investigated RI in 46 cirrhotics divided into three groups, those with cirrhosis and normal renal function, cirrhosis with renal dysfunction without HRS, and cirrhosis with HRS. They found that RI ( $\geq 0.70$ ) was significantly increased in the cirrhotic patients with HRS compared to the other two

groups. Götzberger *et al.*<sup>[7]</sup> in their study found the average RI levels in patients with liver cirrhosis and creatinine of  $1.0 \pm 0.4$  was 0.77.

The total bilirubin in our study was higher in patients with  $RI \geq 0.77$  ( $4.82 \pm 3.37$ ) when compared to patients with  $RI < 0.77$  ( $2.48 \pm 4.14$ ) in a statistically significant manner ( $P = 0.02$ ), which is a similar finding ( $P < 0.05$ ) in a study done by Platt *et al.*<sup>[5]</sup>

In our study, it was seen that patients with  $RI \geq 0.77$  had massive ascites when compared to patients with  $RI < 0.77$  and statistically significant ( $P = 0.02$ ). This finding confirms that elevated RI is seen in patients who have worsened in their disease. Similar findings were observed in a study done by Götzberger *et al.*<sup>[7]</sup> ( $0.74$  vs.  $0.67$ ,  $P < 0.01$ ), Celebi *et al.*,<sup>[8]</sup> and Rivolta *et al.*<sup>[9]</sup>

A study conducted by Goyal *et al.*<sup>[10]</sup> revealed that patients with cirrhosis and ascites showed significantly increased RI ( $0.72 \pm 0.02$ ) when compared to cirrhosis without ascites ( $0.62 \pm 0.06$ ). Elevated  $RI > 0.70$  was present in 16% (8/50) patients in the group with cirrhosis alone and in 60% (30/50) patients in the group who had cirrhosis and ascites.

Patients with HRS ( $RI \geq 0.77$ ) had jaundice ( $P = 0.001$ ), encephalopathy ( $P = 0.038$ ), massive ascites ( $P = 0.02$ ), raised urea ( $P = 0.0003$ ), creatinine ( $P < 0.0001$ ), bilirubin ( $P = 0.01$ ), SGOT ( $P = 0.016$ ), and serum glutamic-pyruvic transaminase ( $P < 0.0001$ ) when compared to those without HRS ( $RI < 0.77$ ) in a statistically significant manner. There is no doubt therefore of the usefulness of the RI in predicting HRS in cases of established cirrhosis and which can translate into the early initiation of treatment for impending HRS.

Both the CPT and MELD scores were significantly related to the RI (0.03 and  $<0.029$ , respectively). This relationship implies that the RI could also be used to predict which patient is likely to worsen and can, therefore, be used as a prognostic indicator. A similar correlation was found in the study done Popov *et al.*<sup>[11]</sup>

HRS is the outcome of vasoconstrictor systems<sup>[1,2]</sup> (i.e., the renin-angiotensin system, the sympathetic nervous system, and arginine vasopressin) on the renal vasculature, in an attempt to ameliorate the intense underfilling of the arterial circulation. Thus, there is a drop in renal perfusion and GFR with intact tubular function. The RRI provides us with an easy non-invasive tool to detect this deterioration in renal function as well as being a prognostic indicator.

## Limitations of the study

Since there is no definitive cut-off for RI in HRS, the cut-off value of RI (0.77), in our study, for differentiating HRS from the absence of HRS in cirrhotics, was far beyond the normal (0.60-0.70). Repeat renal Doppler was not done in patients with raised RI but normal creatinine. This may have indicated patients who were progressing into HRS.

## Conclusion

This study shows that renal Doppler RI is a useful non-invasive tool for indicating the presence of hepatorenal syndrome as well

as acting as a prognostic indicator in patients with cirrhosis of the liver. Further studies to look into the aspect of raised RRI with normal creatinine would help in the treatment of HRS.

### Acknowledgments

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