Section: General Medicine

Original Research Article

RENAL RESISTIVE INDEX AS EARLY DIAGNOSTIC INDICATOR OF HEPATORENAL SYNDROME IN DECOMPENSATED LIVER DISEASE

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Abstract

Background: Hepatorenal syndrome (HRS) is a common complication of late-stage cirrhosis due to renal vascular system vasoconstriction, resulting in decreased GFR. The study aimed to determine the usefulness of RRI in the early diagnosis of HRS in decompensated liver cirrhosis patients with ascites and liver cirrhosis patients without ascites. **Materials and Methods:** This cross-sectional observational study was conducted on 50 consecutive patients with DCLD with ascites and 50 cirrhotic patients without ascites admitted in GRH, Madurai, for nine months, from January 2021 to September 2021. Laboratory investigations included liver function tests, renal function tests, complete blood count, serum and urine electrolytes, urine creatinine, urine examination, viral markers, serum protein, PT, INR, and APTT. Ultrasonography of the abdomen and the Intrarenal artery Doppler for the resistive index (RI) calculation. **Result:** There is a significant difference between groups in the Bilirubin category, INR category, Presence of ascites, Presence of HE, RRI category, and HRS category. There is a significant difference in mean total bilirubin, INR, PT above the cut-off, Albumin, Sr. Creatinine on days 1, 4, and 7, Sodium, MELD score, Child-Pugh score, and RRI between groups. A strong positive correlation was found between RI and HRS development. RI also showed a strong negative correlation with serum sodium and albumin levels, with a weak correlation with bilirubin levels and no correlation with patient age. **Conclusion:** The study demonstrates that RI can identify non-azotemic patients with Decompensated Liver Disease at high risk for renal failure and HRS, predicting HRS early and prioritising liver transplantation.

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.[1,2] The HRS is a common complication of late-stage cirrhosis due to vasoconstriction of the renal vascular system, leading to a decreased glomerular filtration rate (GFR). Characterised 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.[3] According to a major five-year study, the chance of HRS development in cirrhotics with ascites was 40%. 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. In 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.[3,4] Early in HRS, renal hemodynamic changes begin, i.e., even before changes in serum creatinine are detectable.[3] 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.[5,6]

The study aimed to determine the usefulness of RRI in the early diagnosis of HRS in decompensated liver cirrhosis patients with ascites and liver cirrhosis patients without ascites.

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MATERIALS AND METHODS

This cross-sectional observational study was conducted on 50 consecutive patients with DCLD with ascites and 50 cirrhotic patients without ascites admitted in GRH, Madurai, for nine months from January 2021 to September 2021. Ethical Committee approval and informed consent were obtained before the study started.

Inclusion Criteria

Age ≥18 years and patients with ascites secondary to chronic liver disease were included.

Exclusion Criteria

Acute infections, cardiovascular instability, diabetes mellitus, hypertension, malignant disease, patients with nephropathies, with pathomorphological findings in ultrasound like decreased kidney size, reduction of renal parenchymal width, and significant renal parenchymal hyperechogenicity, hypotension (systolic BP <90mm Hg), and patients on beta-blocker were excluded.

Laboratory investigations included liver function tests, renal function tests, complete blood count, serum and urine electrolytes, urine creatinine, urine examination, viral markers, serum protein, PT, INR, and APTT. Ultrasonography of the abdomen and the Intrarenal artery Doppler for the resistive index (RI) calculation. RI was calculated using the formula: RI = (peak systolic flow − peak diastolic flow)/peak systolic flow, and RI ≥0.77 was taken as a diagnostic of HRS.

Statistical Analysis: The data were entered in an MS Excel sheet and analysed using SPSS version 16. Continuous data with normal distribution was expressed as mean with standard deviation. Categorical data were expressed as frequency and percentage. Fisher's exact test was used to compare the frequency between the groups. An unpaired 't' test was used to compare the mean values between the two groups. Pearson's correlation test measured the direction and degree of association between RRI and other parameters. P<0.05 was considered statistically significant.

RESULTS

In In total 100 study population, 50 patients had DCLD and 50 had CLD. Most (50%) of the study population were 40-49 years old. The mean age is 41.3 years, with a standard deviation of 6.6 years. The minimum age is 19 years, and the maximum is 56 years. About 89% were males, and 11% were females. Alcohol (77%) was the most common aetiology, followed by viral (HBV & HCV) aetiology (13%). Other etiologies in the order of NASH are Cryptogenic, Wilson disease, and autoimmune hepatitis.

The mean bilirubin is 1.21 mg/dL with a 0.56 mg/dL standard deviation. The minimum is 0.7 mg/dL, and the maximum is 4.1 mg/dL. The mean INR is 1.18, with a standard deviation of 0.47. The minimum INR noted was 0.8, and the maximum INR noted was 3.3.

Around 50% of the patients had ascites. Hepatic encephalopathy was present in 12% of the DCLD patients. RI was <0.77 in all CLD patients, while only in 24% of the DCLD patients. While RI was ≥0.77 in 76% of the DCLD patients, 81.6% had developed HRS. However, only 1.6% of DCLD patients with RI <0.77 developed HRS. Those DCLD patients developing AKI due to aetiology other than HRS were excluded from the study. There is no significant difference in age and gender between groups [Table 1].

Table 1: Comparison of various parameters for liver status in patients with chronic liver disease

		CLD (N=50)	DCLD (N=50)	P value
Age category	<30 years	0	4 (8%)	0.242 (NS)
	30 – 39 years	17 (34%)	16 (32%)	
	40 – 49 years	26 (52%)	24 (48%)	
	50 – 59 years	7 (14%)	6 (12%)	
Gender	Female	3 (6%)	8 (16%)	0.201 (NS)
	Male	47 (94%)	42 (84%)	
Bilirubin category	<2mg/dL	50 (100%)	44 (88%)	0.041*
	2 – 3mg/dL	0	3 (6%)	
	>3mg/dL	0	3 (6%)	
INR category	<1.7	50 (100%)	36 (72%)	<0.0001*
	1.7 – 2.3	0	11 (22%)	
	>2.3	0	3 (6%)	
Presence of ascites		0	50 (100%)	<0.0001*
Presence of HE		0	6 (12%)	0.027*
RRI category	<0.77	50 (100%)	12 (24%)	<0.0001*
	≥0.77	0	38 (76%)	
HRS category	Absent	50 (100%)	18 (36%)	<0.0001*
	Present	0	32 (64%)	

Table 2: Comparison of mean values of various parameters for liver status in patients with chronic liver disease

Liver status	Mean ± SD		P value
	CLD	DCLD	
Age in years	41.2 ± 5.5	40.7 ± 7.6	0.386 (NS)
Total bilirubin (mg/dL)	1.01 ± 0.19	1.4 ± 0.7	0.001*
INR	0.92 ± 0.05	1.43 ± 0.57	<0.0001*

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PT above cut-off	0.88 ± 2.4	3.3 ± 2.7	<0.0001*
Albumin (g/dL)	4.3 ± 0.39	2.81 ± 0.64	<0.0001*
Sr. Creatinine on day 1	0.96 ± 0.22	1.35 ± 0.67	<0.0001*
Sr. Creatinine on day 4	0.98 ± 0.16	1.79 ± 0.82	<0.0001*
Sr. Creatinine on day 7	0.96 ± 0.15	2.27 ± 1.07	<0.0001*
Sodium (mEq/L)	139 ± 3	130.5 ± 8	<0.0001*
MELD score	7.5 ± 1.43	18.5 ± 8.6	<0.0001*
Child-Pugh score	5 ± 0.01	8.7 ± 1.86	<0.0001*
RRI	0.57 ± 0.06	0.75 ± 0.11	<0.0001*

Table 3: Comparison of various parameters for RRI category in patients with chronic liver disease

		RRI category		P value
		<0.77 (N=62)	**≥0.77 (N=38)**	
Age category	<30 years	1 (1.6%)	3 (7.9%)	0.379 (NS)
	30 – 39 years	22 (35.5%)	11 (28.9%)	
	40 – 49 years	32 (51.6%)	18 (47.4%)	
	50 – 59 years	7 (11.3%)	6 (15.8%)	
Gender	Female	4 (6.5%)	7 (18.4%)	0.063 (NS)
	Male	58 (93.5%)	31 (81.6%)	
Bilirubin category	<2mg/dL	62 (100%)	32 (84.2%)	0.005*
	2 – 3mg/dL	0	3 (7.9%)	
	>3mg/dL	0	3 (7.9%)	
INR category	<1.7	62 (100%)	24 (63.2%)	<0.0001*
	1.7 – 2.3	0	11 (28.9%)	
	>2.3	0	3 (7.9%)	
Presence of ascites		12 (19.4%)	38 (100%)	<0.0001*
Presence of HE		1 (1.6%)	5 (13.2%)	0.018*
Child-Pugh category	A	61 (98.4%)	0	<0.0001*
	B	1 (1.6%)	26 (68.4%)	
	C	0	12 (31.6%)	
Hepatorenal syndrome	Absent	61 (98.4%)	7 (18.4%)	<0.0001*
	Present	1 (1.6%)	31 (81.6%)	

Table 4: Comparison of mean values of various parameters for RRI category in patients with chronic liver disease

	Mean ± SD		P value
	RRI category		
	<0.77 (N=62)	**≥0.77 (N=38)**	
Age in years	41.2 ± 6.1	41.4 ± 7.5	0.821 (NS)
Total bilirubin	1.02 ± 0.19	1.51 ± 0.8	0.001*
INR	0.93 ± 0.05	1.58 ± 0.57	<0.0001*
PT above cut-off	0.82 ± 2.17	4.2 ± 2.5	<0.0001*
Albumin (g/dL)	4.2 ± 0.49	2.5 ± 0.4	<0.0001*
Sr. Creatinine on day 1	0.92 ± 0.22	1.54 ± 0.67	<0.0001*
Sr. Creatinine on day 4	0.96 ± 0.17	2.08 ± 0.72	<0.0001*
Sr. Creatinine on day 7	0.97 ± 0.16	2.68 ± 0.87	<0.0001*
Sodium (mEq/L)	139 ± 3.1	127 ± 6.9	<0.0001*
MELD score	7.46 ± 1.68	22 ± 6.5	<0.0001*
Child-Pugh score	5.25 ± 0.59	9.5 ± 1.4	<0.0001*

Table 5: Correlation of Renal resistive index with various parameters

Correlation of Renal resistive index with	Pearson's r	P value	Inference
Age in years	0.005	0.958 (NS)	No relationship
INR	0.622	<0.0001*	Significant positive correlation of moderate strength
Total Bilirubin (mg/dL)	0.366	<0.0001*	Significant positive correlation of weak strength
Albumin (g/dL)	0.762	<0.0001*	Significant negative correlation of strong strength
Sodium (mEq/L)	0.718	<0.0001*	Significant negative correlation of strong strength
Serum creatinine Day 1 (mg/dL)	0.485	<0.0001*	Significant positive correlation of moderate strength
Serum creatinine Day 4 (mg/dL)	0.691	<0.0001*	Significant positive correlation of strong strength
Serum creatinine Day 7 (mg/dL)	0.769	<0.0001*	Significant positive correlation of strong strength
MELD score	0.787	<0.0001*	Significant positive correlation of strong strength
Child-Pugh score	0.812	<0.0001*	Significant positive correlation of very strong strength

There is a significant difference between groups in the Bilirubin category, INR category, Presence of ascites, Presence of HE, RRI category, and HRS category [Table 1].

There is a significant difference in mean total bilirubin, INR, PT above cut-off, Albumin, Sr. Creatinine on days 1, 4 and 7, Sodium, MELD score, Child-Pugh score, and RRI between groups [Table 2].

There was no significant difference in age and gender between the RRI categories. There is a significant difference between groups between the Bilirubin category, INR category, Presence of ascites, Presence of HE, Child-Pugh category, and Hepatorenal syndrome [Table 3].

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Among those patients with RI <0.77, mean serum creatinine values were 0.92, 0.96, and 0.97 mg/dl on Days 1, 4, and 7, respectively. While those with RI ≥0.77, mean serum creatinine values were 1.54, 2.08, and 2.68 mg/dl, respectively.

There is a significant difference in mean total bilirubin, INR, PT above cut-off, Albumin, Sr. Creatinine on days 1, 4 and 7, Sodium, MELD score, and Child-Pugh score between the RRI categories [Table 4].

About 34.2% (13/38) of patients were diagnosed with HRS on Day 1 in the RI ≥0.77 group. On follow-up over the next seven days, 47.4% of patients developed HRS. On the correlation of RI≥0.77 with the HRS development using Pearson's correlation test, there was a significant, very strong positive correlation with a correlation coefficient of 0.769 with a P value <0.0001.

While comparing RI with MELD score, the mean MELD in patients with RI <0.77 (62 patients) was 7.46 and in patients with RI ≥0.77 (38 patients) was 22. The correlation coefficient was 0.787, indicating a strong positive correlation with a P value of <0.0001.

While comparing RI with the Child-Pugh score, the mean Child-Pugh score in patients with RI<0.77 (62 patients) was 5.25, and in patients with RI ≥0.77 (38 patients), it was 9.5. The correlation coefficient was 0.812, indicating a strong positive correlation with a P value of <0.0001.

RI also showed a strong negative correlation with serum sodium and albumin levels with correlation coefficients of -0.718 and -0.762, respectively, with a P value of <0.0001. RI showed a weak correlation with bilirubin levels and no correlation with the age of the patients [Table 5].

DISCUSSION

RRI is a hemodynamic parameter that has received significant consideration in recent years as a potential tool for the early diagnosis of HRS in patients with decompensated liver cirrhosis. HRS is a severe complication of cirrhosis, which is characterised by acute renal dysfunction. The early diagnosis of HRS is crucial for proper management and intervention. Our study found numerous key insights that contribute to the growing body of knowledge on the role of RRI in diagnosing HRS in decompensated liver cirrhosis patients with ascites and liver cirrhosis patients without ascites.[4,7]

In total 100 study population, 50 patients had DCLD and 50 had CLD. Most (50%) of the study population were 40-49 years old. About 89% of the study population were males, and 11% were females. Alcohol (77%) was the most common aetiology, followed by viral (HBV & HCV) aetiology (13%). Other etiologies in the order of NASH Cryptogenic, Wilson disease, and autoimmune hepatitis. Around 50% of the patients had ascites. Hepatic encephalopathy was present in 12% of the DCLD patients. RI was <0.77 in all CLD patients, while only in 24% of the DCLD patients. While RI was ≥0.77 in 76% of the DCLD patients, 81.6% had developed HRS. However, only 1.6% of DCLD patients with RI <0.77 developed HRS. Those DCLD patients developing AKI due to aetiology other than HRS were excluded from the study.

Among those patients with RI <0.77, mean serum creatinine values were 0.92, 0.96, and 0.97 mg/dl on Days 1, 4, and 7, respectively. While those with RI ≥0.77, mean serum creatinine values were 1.54, 2.08, and 2.68 mg/dl, respectively. About 34.2% (13/38) of patients were diagnosed with HRS on Day 1 in the RI ≥0.77 group. On follow-up over the next seven days, 47.4% of patients developed HRS. On the correlation of RI ≥0.77 with the HRS development using Pearson's correlation test, there was a significant, very strong positive correlation with a correlation coefficient of 0.769 with a P value <0.0001.

While comparing RI with the MELD score, the mean MELD in patients with RI <0.77 (62 patients) was 7.46, and in patients with RI ≥0.77 (38 patients), it was 22. The correlation coefficient was 0.787, indicating a strong positive correlation with a P value of <0.0001. So, there is a connection between renal RI and the advancement of liver illness. This correlation reflects the pathogenic mechanisms strongly linked to the progression of liver disease.

The association between RRI and the severity of liver cirrhosis and its predictive value with the MELD score was also shown by Sameh et al,[8] in research, including 120 patients with HCV liver cirrhosis. According to El-Shazly et al., child-Pugh C patients had a significantly higher RRI than child-Pugh B or A patients.[9] In our study, while comparing RI with the Child-Pugh score, the mean Child-Pugh score in patients with RI<0.77 (62 patients) was 5.25 and in patients with RI ≥0.77 (38 patients) was 9.5. The correlation coefficient was 0.812, indicating a strong positive correlation with a P value of <0.0001.

In cirrhotic patients, RI was considerably greater than in healthy controls (0.62 vs. 0.52, p<0.01), according to Goyal et al.[10] Patients with ascites had a higher value (0.70 vs. 0.62, p < 0.01) than those without it. For subsequent HRS development, his cut-off value was RI >0.70 (p = 0.006), a significant independent predictor. RI also showed a strong negative correlation with serum sodium and albumin levels with correlation coefficients of -0.718 and -0.762, respectively, with a P value of <0.0001. RI showed a weak correlation with bilirubin levels and no correlation with the age of the patients. A study by Romano et al. suggested that increased intrarenal RI indicated a faster loss in renal function and higher long-term mortality in non-proteinuric patients with CKD of unknown cause; nevertheless, as a stand-alone marker, it performed poorly in discrimination.[11]

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This evidence is quite encouraging regarding early diagnosis, early treatment, and prediction of HRS. Renal RI could seem like an easy-to-use, effective, and non-invasive technique at the patient's bedside. Even when dealing with people who are sick, the method is quite feasible. However, because the renal duplex is particularly difficult to assess in irritable ascitic patients, it must be performed by a skilled, well-trained sonographer.

However, it is imperative to recognise the limitations of our study. The sample size was relatively small, and the study was performed at a single centre, which may limit the broader applicability of our findings. Further multi-centre studies with bigger cohorts are desirable to authenticate and expand upon our findings. Additionally, while RRI shows promise, it should be combined with additional clinical and laboratory parameters to assess renal function and HRS risk thoroughly.

CONCLUSION

This study demonstrated that renal intravascular resistance index (RI) is a better predictor of hepatorenal syndrome (HRS) in decompensated liver disease (DCLD) patients than serum creatinine levels. RI is also a more sensitive marker of renal vasoconstriction, which is the underlying pathophysiology of HRS. Therefore, RI can be used to identify DCLD patients at high risk for HRS, even before they develop azotemia. This can help to avoid nephrotoxic medications and contrast agents and prioritise patients for liver transplantation. RI is an easily available, non-invasive, and cheaper tool than other prognostic markers of HRS, such as the MELD and CHILD-PUGH scores. Therefore, it should be included as a routine part of ultrasonographic evaluation in DCLD patients.

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