ORIGINAL RESEARCH PAPER

Gastroenterology

INTRA RENAL RESISTANCE INDEX FOR THE ASSESSMENT OF EARLY RENAL FUNCTION IMPAIRMENT IN PATIENTS WITH LIVER CIRRHOSIS

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BACKGROUND

To know the intra-renal resistive index profile in patients with liver cirrhosis. To compare the intra renal resistive index among cirrhosis with and without ascites patients. To know the correlation between intra-renal resistive index with MELD score and Child-Turcotte-Pugh, score. Cirrhotic patients admitted to the Medical Gastroenterology unit at Osmania Hospital, in Hyderabad, from January 2017 to December 2018. Intra Renal resistance index was higher in the presence of cirrhosis, much higher if ascites associated with varices, and hepatic encephalopathy. Making renal resistance index as severity dependent prognostic factor.

INTRODUCTION

Cirrhosis of liver is the tenth leading cause of death in India and a major cause of disease burden among the population[1].

The disease course is further altered by the development of numerable complications like varices, hepatic encephalopathy, coagulopathy, hepatopulmonary syndrome, cirrhotic cardiomyopathy, hepatorenal syndrome that carries a grave prognosis[2].

Among the various complications of advanced cirrhosis, development of hepatorenal syndrome has a devastating course and outcome in cirrhotic patients HRS is usually an extended spectrum of prerenal azotaemia and therefore is potentially reversible. But after the evolution of the disease, the median survival is only 2 weeks without liver transplantation or management with vasoconstrictors. But the disease can be predicted in advance by the estimation of renal resistive index (RI) that increases before a considerable period of time by Doppler ultrasound and so measures can be implemented to prevent the disease progression by avoiding the excess use of diuretics and nephrotoxic agents, avoiding large volume paracentesis[3].

RI is routinely used to diagnose transplant rejection or renal artery stenosis, But here in the current study, we calculated the intrarenal RI in patients with liver cirrhosis and compared its prognostic impact with those of the MELD and the Child-Pugh scores[4]

AIM & OBJECTIVES

Aim of this study is to Measure the intra-renal resistive index profile in different stages of liver cirrhosis (with and without ascites), and to establish relationship between different survival/prognosis scores (CTP, MELD) with intrarenal resistive index.

To know the intra-renal resistive index profile in patients with liver cirrhosis. To compare the intra renal resistive index among cirrhosis with and without ascites patients. To know the correlation between intra-renal resistive index with MELD score and Child-Turcotte-Pugh (CTP) score.

METHODOLOGY

Our study involved cirrhotic patients admitted to the Medical Gastroenterology unit, at Osmania Hospital, in Hyderabad, from January 2017 to December 2018.

Inclusion Criteria

Adult patients over 18 years diagnosed to have cirrhosis of liver were selected

Exclusion Criteria

a. Hepatorenal syndrome,
b. Active gastrointestinal bleeding,
c. Acute infections with potentially or overt cardiovascular instability.
d. Suspected or overt malignant diseases
e. Patients with nephropathies and with morphological findings in ultrasound like decreased kidney size, reduction of parenchymal width and significant parenchymal hyperechogenicity

RESULTS

Child Turcotte Pugh's Classification

Parameter	1 point	2 point	3 point
Sr.bilirubin	<2	2-3	>3
Sr.albumin	>3.5	3.5-2.8	>2.8
INR	<1.7	1.7-2.3	>2.3
Ascitis	None	Mild-Moderate	Severe
Hepatic encephalopathy	None	Minimal	Advanced

MELD uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival52. It is calculated according to the following formula: MELD = 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43.

The Model for End Stage Liver Disease (MELD) score in patients with and ascites in liver cirrhosis. In patients with MELD scores of about 10 is associated with an 8% and with a MELD score approaching 18, nearly 40% of patients develop HRS within 1 year, as a control group, RI was also measured in 60 control subjects without any liver or kidney disease.

Distribution Of Lab Findings (serum) Among Cases And Control Groups

LAB FINDINGS (serum)	CASES		CONTROLS	
	MEAN	SD	MEAN	SD
PLATELET)	106033.33	38568.436	290500.00	56099.941
CREATININE (mg/dl)	.935	.1448	.815	.1287
SODIUM(mmol/L)	134.72	5.221	141.67	2.447
SGPT(U/L)	45.97	27.424	24.00	6.945
SGOT(U/L)	48.70	21.377	27.72	6.415
ALBUMIN(g/dL)	2.905	.5873	2.9052	1.77847
TOTAL BILIRUBIN ((mg/dL)	2.725	1.3555	.918	.1873
INR	1.540	.3984	1.167	.1203

Serum laboratory findings in both cases and control groups (healthy).

MEAN SERUM PLATELET LEVEL was below the normal range (106033/μl, thrmbocytopenia), in cirrhotic cases, where as in healthy controls it was normal in range.

MEAN SERUM CREATININE LEVEL was normal in range in both cases (0.935 mg/dl) and controls (0.815mg/dl) but slightly higher in cirrhotic cases when compared to healthy controls.

MEAN SERUM SODIUM LEVEL was normal in range in both cases (134mmol/L)and controls (141mmol/L)but slightly lower in cirrhotic cases when compared to healthy controls.

MEAN SERUM SGPT and SGOT LEVEL was slightly higher than the normal range in cirrhotic cases, and in healthy controls both were normal in range.

MEAN SERUM ALBUMIN LEVEL was slightly lesser than the normal range in both cases (2.9g/dl) and controls (2.9g/dl).

MEAN TOTAL BILIRUBIN LEVEL was higher than the normal range in cirrhotic cases (2.7mg/dl), and in controls(.9mg/dl).

MEAN INR level was higher than the normal range in cirrhotic cases (1.5), and in controls (1.1) it was normal.

Etiology Of Cirrhosis In Both Groups Of Cases

ETIOLOGY OF CIRRHOSIS	GROUP-1		GROUP-2		Total	
	Count 'N'	Percentage %	Count 'N'	Percentage %	Count 'N'	Percentage %
ALCOHOLIC	23	38.3%	15	25.0%	38	63.3%
HBV	5	8.3%	5	8.3%	10	16.7%
HCV	4	6.7%	2	3.3%	6	10.0%
AUTOIMMUNE	2	3.3%	1	1.7%	3	5.0%
CRYPTOGENIC	1	1.7%	1	1.7%	2	3.3%
WILSON DISEASE	0	.0%	1	1.7%	1	1.7%

Various etiological factors of cirrhosis in both groups of cases, in which with 38 cases alcoholism was the most common cause(63.3%),followed by HBV infection (16.7%), HCV infection (10%), autoimmune (5%), cryptogenic (3.3%).There was only case of Wilson disease presented without ascites (group-2).

Distribution Of Hepatic Encephalopathy Finding Among Cases In Group IVs Group II

HEPATIC ENCEPHALOPATHY	PRESENT		ABSENT	
	Count	n %	Count	n %
GROUP 1	9	15.0%	26	43.4%
GROUP 2	2	3.3%	23	38.3%

The above Table shows, only 18.3% subjects are with hepatic encephalopathy among all cirrhotic cases. Among hepatic encephalopathy cases (n=11), most of them belong to ascitic group (n=9). But this difference between the groups not statistically significant.

Distribution Of Cases According To (child- Turcotte-pugh) Ctp Class (group-1 Versus Group-2)

CTP class	GROUP 1		GROUP-2		Total	
	N	n%	N	n%	N	n%
A	0	0.00%	16	26.70%	16	26.70%
B	15	25.00%	9	15.00%	24	40.00%
C	20	33.30%	0	0.00%	20	33.30%

CHILD-TURCOTTE-PUGH class-A are only seen in non ascitic group (n=16, 26.7%). CHILD-TURCOTTE-PUGH class -B are more (n=24, 40%) among all cirrhotic cases, more frequently among ascitic subjects (25%). CHILD-TURCOTTE-PUGH class-C are only seen ascitic group (n=20, 33.3%) This difference between the groups is highly statistically significant.

DISTRIBUTION OF INTRA RENAL RESISTANCE INDEX AMONG CASES AND CONTROL GROUPS

INTRA RENAL RESISTANCE	RIGHT KIDNEY	LEFT KIDNEY	MEAN OF RIGHT and LEFT KIDNEYS
INDEX	Mean+Standard Deviation	Mean+Standard Deviation	Mean+Standard Deviation
CASES GROUP	0.70+0.44	0.70+0.45	0.70+0.44
GROUP 1	0.73+0.03	0.73+0.03	0.73+0.03
GROUP 2	0.67+0.03	0.67+0.04	0.67+0.04
CONTROL GROUP	0.58+0.03	0.58+0.03	0.58+0.027

MEAN INTRA RENAL RESISTANCE INDEX of CONTROL group lesser than 0.7(0.58+0.027), where as in CASES, ascitic cases (group-1) tend to fall around 0.73+0.03 (>.70), and non ascitic cases (group-2) fall around 0.67+0.04 (<.70).The difference between cases and controls, and between ascitic and non ascitic were found to be highly statistically significant.

DISTRIBUTION OF INTRA RENAL RESISTANCE INDEX AMONG CASES (GROUP-1 VERSUS GROUP-2)

RI	Group 1	Group 2	Total
<0.70[normal]	8(13.3%)	19(31.7%)	27(45%)
>0.70 [abnormal]	27(45%)	6(10%)	33(55%)

The above Table shows, among cirrhotic cases, ascitic patients [group 1] were having more frequency (n=27, 45%) of abnormal RI, where as in non ascitic patients [group 2], more number (n=19, 31.7%) of normal RI cases are there. The difference within the cases between group-1 and group-2.

Relationship Between Intra Renal Resistance Index And Hepatic Encephalopathy Among All Cases (group-1 Versus Group-2)

Hepatic encephalopathy	PRESENT	ABSENT
	MEAN+SD	MEAN+SD
GROUP 1 MEAN RI	0.76+.01	0.72+.03
GROUP 2 MEAN RI	0.70+.01	0.67+.04

The above Table shows, In group-1, statistically significant difference exists between mean of group-1 R.I and group -2 R.I, IN H.E cases, and non H.E cases except in group-2 H.E and non H.E cases (0.3097]

DISCUSSION

Out of 120 study subjects 60 were diagnosed cases of liver cirrhosis, and 60 control subjects (Group-3). Cirrhotic cases are sub divided into ascitic (Group-1, n=35) and non ascitic groups (Group-2, n=25).

Cases and controls are comparable in terms of age, as they

were having nearly similar mean age (44-45 years). And there was no significant statistical difference between them.

Comparetion Of Mean Age In Cirrhotic Cases With Ascitis And Without Ascitis Groups In Various Studies

MEAN AGE(in years)	ASCITIC	NON ASCITIC
D.POPOV et al [5]	56.85 ± 12.26	51.45 ± 12.75
M. GOTZBERGER et al [6]	56.9 ± 14.1	56.5 ± 11.8
DAVID SACERDOTI et al [7]	55+10	53+10
PRESENT STUDY	47+11	39+9

All the above studies, are having are higher mean age group than present study, but in comparison between ascitic and non-ascitic, ascetic[group1] showed higher mean age group which has a similarity with the present study.

Within the cases, ascitic group (Group-1, 47+11) mean age is nearly 10 years more than Non ascitic group (Group-2, 39+9). This may be because of natural history of cirrhosis of liver disease.

The natural history of cirrhotic liver disease progresses from a compensated to a decompensate phase. Ascites is the main complication of cirrhosis55, and the mean time period to its development is approximately 10 years.

Ascites is a landmark in the progression into the decompensate phase of cirrhosis and is associated with a poor prognosis and quality of life; mortality is estimated to be 50% in 2 years.

In cirrhotic patients serum laboratory findings are deranged in most of the variables (except serum Creatinine and serum sodium) when compared to normal healthy controls, and it was statistically significant.

An ascitic cases [group 1] shows more deranged findings when compared with non ascitic cases [group 2]. An ascitic cases [group 1] higher Creatinine, liver enzymes, Total Bilirubin, INR and lower platelets, albumin.

CLINICAL FINDINGS
Majority of the cirrhotic patients had varices (78.3%), all cirrhotic cases with ascites [group 1] and nearly half of the non ascitic [group 2] cases were suffering from varices. This indicates presence of ascites has risk having varices (association).

A similar study done by **D.Popov et al,** had similar findings regarding varices, in their study 73.13% had varices.

Only 11 cases are with hepatic encephalopathy among all cirrhotic cases, Even though the difference is not statistically significant most of them are ascitic variant only (n=9).

A Study of **M Gotzberger et al,** Where out of 46 cases, only 10 cases were having Hepatic Encephalopathy, and 9 out of these 10 cases were suffering with ascites, which is coinciding with the present study population.

Gotzberger M. Singer J. et al, study had nearly half of the study population had different stages of hepatic encephalopathy (54.5%), which is contradicting the present study results.

MELD SCORE
Present Study showed, Mean MELD score of 14.38+4.48, higher mean of MELD score (16.65+3.79) in ascetic [group1], than non-ascitic [group 2] [11.2+3.31]cases.

Manuela Götzberger et al, study on two groups of cirrhotic cases showed nearly similar mean MELD between 12,16 respectively.

Another study by **D.Popov et al** also had nearly similar Mean MELD score (15 +7.17) with present study, and also showed higher mean of MELD (15.3+3.67) in ascitic group, Non ascitic group had lesser score (10.90+3.29) which is coinciding with the present study.

INTRA RENAL RESISTANCE INDEX
In present study, Cirrhotic Cases have higher Renal index than Healthy Controls [group 3], it is supported by many studies (Goyal s et al, Fouad YM et al, Vinodh V et al) that indicates higher Renal index factor associated with cirrhotics[8,9,10]

CORRELATION
A strong positive correlation between Prognostic scores (CTP/MELD) and Mean Intra Renal Resistance Index in all cirrhotic cases, correlation strength increased in ascitic group. Correlation was present even with independent value/measurement of each kidney's (left or right) renal index with these scores.

Both the CPT and MELD scores were significantly related to the RI. 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.**

Manuela Gotzberger et al, study concluded that "The RI may help identify high risk patients that require special therapeutic care by receiver operating characteristic analysis, the RI and the MELD score achieved similar sensitivity and specificity [area under the curve. Cirrhotic patients with elevated RIs have impaired short and long term survival" this further supports the present study.

Nivethitha et al[11], had done a Linear regression analysis between RI and MELD that showed significant correlation. This study supports present study.

CONCLUSION
- Our study shows that the value of RI which is based on sonographic measurements of intrarenal resistance is a non-invasive, economical test that gives useful information and it is used as a prognostic indicator and hence used in the management of cirrhotic patients.
- Intra Renal resistance index was higher in the presence of cirrhosis, much higher if ascites associated with varices, and hepatic encephalopathy. Making Renal resistance index as severity dependent prognostic factor.
- Elevated RIs even disclose the progress of liver disease before there are gross changes occurring in lab results. Therefore, RI may help in identifying a group of high-risk patients with poor prognosis who require special therapeutic care.
- CTP & MELD SCORES were linearly strong positively correlated with Intra Renal resistance index. Making Renal resistance index as a reliable prognostic factor as other existing (CTP & MELD) scores.
- Ultrasound screening of all cirrhotic patients especially with ascites and PHT to estimate the value of RI by Doppler ultrasound is essentially important as the degree of intrarenal vasoconstriction can be predicted early before overt HRS develops and so preventive measures should be undertaken.

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