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General Medicine

A STUDY ON CARDIAC DYSFUNCTION USING ECHOCARDIOGRAPHY IN CIRRHOTIC PATIENTS OF JHARKHAND

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ABSTRACT Cirrhosis is defined anatomically as a diffuse process with fibrosis and nodule formation and represents a terminal stage of a number of chronic liver diseases. Cirrhotic patients demonstrated both structural and functional cardiac abnormalities, resulting in both systolic and diastolic dysfunction, which appeared to correlate with the severity of the liver disease. In this study we plan to evaluate the clinical aspects of cirrhosis and its effect on cardiac structure and function as assessed by means of an echocardiogram. This hospital based observational study was carried on 150 cirrhotic patients admitted in Rajendra Institute of Medical Sciences, Ranchi, Jharkhand. The mean age of the study group was 42.30±8.42 SD with 127 (85%) males and 23 (15%) females. Maximum number of patients were alcoholic (44.66%) and Hepatitis B positive (34.66%) followed by unknown etiology/others (11.33%). Maximum number of patients 73(48.66%) in the study group belonged to child B as graded by Child Pugh Score followed by Child Pugh C (28%). When Echocardiographic variables were assessed in patients of cirrhosis of liver with different classes of cirrhosis, there was statistically significant difference in both systolic and diastolic variables as degree of liver dysfunction worsens. There was no significant correlation seen in various echocardiographic parameters in patients of cirrhosis of liver of different etiologies. Therefore, it is recommended that physicians should be aware for the possibility of myocardial diastolic dysfunction in patients with chronic liver disease patients.

KEYWORDS : Cirrhosis, Cardiac dysfunction, Echocardiogram.

INTRODUCTION:

Cirrhosis is defined anatomically as a diffuse process with fibrosis and nodule formation and represents a terminal stage of a number of chronic liver diseases. There is currently no single accepted definition of cirrhosis that is acceptable to all clinicians and pathologists. At the Fifth Pan American Congress of Gastroenterology, it was concluded that the essential features of cirrhosis were considered to be concurrent parenchymal necrosis, regeneration and diffuse fibrosis resulting in disorganisation of lobular architecture.[1]

Cirrhosis is the end-stage consequence of fibrosis of hepatic parenchyma, resulting in nodule formation that may lead to an altered hepatic function and blood flow. Both fibrosis and cirrhosis are consequences of a sustained wound-healing response to chronic liver injury from a range of causes, including viral, autoimmune, drug induced, cholestatic and metabolic diseases. [2]

The clinical manifestations of cirrhosis vary widely from no symptoms at all to frank liver failure, and are determined by both the nature and severity of underlying liver disease. Besides the well known complications of portal hypertension and its consequences like variceal bleed, splenomegaly, hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, hepatocellular carcinoma and hepatorenal syndrome, cirrhosis is also associated with a host of cardiopulmonary sequelae such as hepatopulmonary syndrome, plexogenic pulmonary hypertension, pericardial effusion and cirrhotic cardiomyopathy.[3] Liver Cirrhosis is associated with a wide range of cardiovascular abnormalities which include a hyper dynamic circulation characterized by an increase in cardiac output with a corresponding decrease in peripheral vascular resistance. Despite the increased cardiac output in cirrhotics, an impaired ventricular contractility in response to both physiological and pharmacological stimuli has been described. Other cardiac abnormalities include hypertrophy or enlargement of different cardiac chambers and electrophysiological changes such as QT prolongation. This constellation of cardiac abnormalities is termed as ***cirrhotic cardiomyopathy***.[4]

The **Diagnostic criteria for Cirrhotic Cardiomyopathy include:** [5,6,7,8]

Systolic Dysfunction:
- Blunted increase in cardiac output on exercise, volume challenge and pharmacologic stimuli
- Resting EF<55%

Diastolic Dysfunction:
- E/A ratio <1.0
- Prolonged deceleration time(>200 ms)
- Prolonged Isovolumetric relaxation time(>80 ms)

Supportive Criteria
- Electrophysiological abnormalities.
- Electromechanical uncoupling/dysfunction.
- Prolonged QTc interval (>0.44 sec) (significantly related to the underlying liver disease. The QTc interval is thought to revert to normal following improvement in liver function and liver transplantation.
- Enlarged left atrium/increased myocardial mass
- Increased NTProBNP and Troponin I.

Cirrhotic patients demonstrated both structural and functional cardiac abnormalities, resulting in systolic and diastolic dysfunction, which appeared to correlate with the severity of the liver disease. Several potential molecular causes for impaired myocardial function in cirrhotic patients have been identified. These include changes in the cardiomyocyte plasma membranes, β-adrenoceptor density and function, altered K^+ channels, altered L-type Ca^{2+} channels, and altered Na^+/Ca^{2+} exchanger. [9]

The integration of M-mode, two-dimensional, and Doppler, ECG findings with pulse recordings provides an exceptionally powerful tool for the noninvasive physiologic assessment of left ventricular (LV) performance. Overall LV performance reflects the interplay of preload, after load, heart rate and contractility.

Measures of left ventricular systolic performance

Ejection Phase Indices: These are measures of overall LV performance that use data collected during ventricular ejection. The

commonly used ejection phase indices include LV volume or work output, systolic time intervals, ejection fraction (EF), percent fractional shortening, and mean velocity of LV fiber shortening (Vcf).
For the assessment of left ventricular function, M-mode and two-dimensional echocardiography assume synergistic rather than merely additive roles. While M-mode echocardiography allows continuous tracings appropriate for quantitation of LV performance in the region visualized within the ultrasound beam, only two dimensional echocardiography allows acquisition of simultaneous morphologic, anatomic, and functional data.

Doppler echocardiography provides LV blood flow velocity, acceleration rate and volume output data without the need for LV geometric assumptions.

Measures of left ventricular diastolic performance
Diastole is divided into four phases: isovolumetric relaxation, rapid filling, slow filling (diastasis) and atrial contraction. Diastolic filling can be defined as the period from the onset of mitral valve opening to mitral valve closure. The two major determinants of diastolic filling are ventricular relaxation (characterized by the rate and duration of the decrease of left ventricular pressure after systole) and compliance (defined by volume changes over the change in pressure during diastolic filling).[10]

As with the many studies that have looked upon the mortality of the patients with liver cirrhosis, the speed of progression of the disease and the various situations in which the condition of the patient deteriorates, many have been inconclusive about the reason for death in patients of liver cirrhosis as the disease progresses. While evidence has been produced that left ventricular systolic function is usually normal at rest in these cirrhotic patients [11], scanty information is available on whether this applies to diastolic function and cardiac structure as well. This is of pathophysiological relevance because in other diseases diastolic function has proved to be an early marker of cardiac structural abnormality that in advanced cirrhosis may be favoured by the influence that stimulation of the rennin-angiotensin-aldosterone and the sympathetic nervous systems exerts on tissue growth.[12]

These things have been studied in varied details and also there is paucity of work in this field especially with reference to Jharkhand. Hence, in this study we plan to evaluate the clinical aspects of cirrhosis, its effect on cardiac structure and function as assessed by means of an echocardiogram.

MATERIALS AND METHODS
This study was conducted on patients satisfying the inclusion and exclusion criteria in Department of Medicine, Rajendra Institute of Medical Sciences, Ranchi from the period December, 2017 to November, 2018.

Inclusion criteria:-
- The patients in Medicine Ward of RIMS, Ranchi and diagnosed as cirrhosis of liver as evidenced clinically and by USG abdomen and/or portal hypertension (portal vein diameter> 13 mm and/or presence of esophageal varices) with/without liver biopsy were the subjects of present study.
- Patient age greater than 18 years.
- Those who gave written consent.

Exclusion criteria:
- Age < 18 years
- Pregnant Females
- Patients with recent bleeding, severe anaemia and other conditions which could alter cardiovascular status.
- Patients with primary cardiac disease, cardiomegaly, congestive cardiac failure atrial fibrillation and other arrhythmias.
- Patients with hypertension, diabetes mellitus, renal, pulmonary diseases
- Patients with malignancy, recent GI bleed and history of abdominal paracentesis (within 7 days)
- Any substance abuse or conditions, which in the opinion of investigator that could alter the cardiovascular status or would make it difficult for the potential participant to participate in the intervention.

Patients fulfilling the above criteria were enrolled into the study and data was collected and recorded as per a prepared Performa for each patient. All the participants were subjected to detailed history taking, thorough clinical assessment, routine investigations like Complete Blood Count with Differential count, LFT, PT with INR, RFT, Serum sodium and potassium, viral markers, Urine routine and microscopy, Ascitic fluid examination, Ultrasound abdomen, Chest X-ray. Tests to assess cardiac dysfunction like ECG and Echocardiography were also done.

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver. 2.11.1 were used for the analysis of e data and Microsoft word and Excel have been used to generate graphs, tables etc. Results of demographic characteristics and biochemical and echocardiographic measurements were expressed as mean ± standard deviation. The measurements of the controls and each of the cirrhotic groups were compared. One way analysis of variance (ANOVA) with Tukey's post hoc pair-wise multiple comparison procedures was used to analyse group data. Bivariate data were compared by Student's paired/unpaired t tests as appropriate.

RESULTS
A total of 150 patients of cirrhosis of liver admitted in Medicine ward were included in study group and 150 healthy individuals were selected as control group.

TABLE 1:
DEMOGRAPHIC PROFILE

	Control	Case
Number (n)	150	150
Mean age	41.12	42.30
Standard deviation (SD)	6.70	8.42

The mean age of the study group was 42.30±8.42 SD. In case of control the mean age was 41.12±6.70.

TABLE 2:
DISTRIBUTION ACCORDING TO SEX

	Group		%	
Study	Case (n=150)	Control (n=150)	Case	Control
Male	127	129	84.66	86.0
Female	23	21	15.33	14.0

Of the 150 patients in study group 127 (85%) were males and 23 (15%) were females with similar sex distribution in control group.

TABLE 4:
DISTRIBUTION OF PATIENTS ACCORDING TO ETIOLOGY

	Etiology	Number (n=150)	%
1	Alcohol	67	44.66
2	Hepatitis B	52	34.66
3	Hepatitis C	8	5.33
4	Wilson's disease	6	4.0
5	Unknown Etiology/Others	17	11.33

Maximum number of patients were alcoholic (44.66%) and Hepatitis B positive (34.66%) followed by unknown etiology/others (11.33%) followed by Hepatitis C (5.33%) and Wilson's disease (4.0%).

TABLE 5:
DISTRIBUTION OF PATIENTS ACCORDING TO CHILD PUGH SCORE

Group	Number (n=150)	%
A	35	23.33
B	73	48.66
C	42	28.0

Maximum number of patients 73(48.66%) in the study group belonged to child B as graded by Child Pugh Score followed by Child Pugh C (28%) followed by Child Pugh A (23.33%).

When Echocardiographic variables were assessed in patients of cirrhosis of liver with different classes of cirrhosis, there was statistically significant difference in both systolic and diastolic

variables as degree of liver dysfunction worsens. There was statistically significant increase in PWT, IVST, LAD and Deceleration Time (DT in milliseconds) as Child Score worsens. Also statistically significant negative correlation was seen in LVEF, LVEDD, LVESD, E/A Ratio with worsening of Child score and thereby cardiac dysfunction.

When Echocardiographic variables were compared between patients of cirrhosis of liver of Child Class A and healthy controls, there was statistically significant difference in diastolic variables between cases and controls; however there was no statistical significant difference in systolic parameters between cases and controls.

TABLE 7: COMPARISON OF ECHOCARDIOGRAPHIC PARAMETERS ACCORDING TO CHILD CLASS

Para-meters	Child Class A (n=35)	Child Class B (n=73)	p -value	Child Class B (n=73)	Child Class C (n=42)	p -value	Significance
LVEF	60.56±1.03	56.47±1.97	<0.001	56.47±1.97	53.30±3.10	<0.001	Significant
LVEDD	46.68±1.13	44.21±1.64	<0.001	44.21±1.64	41.20±1.36	<0.001	Significant
LVESD	44.10±0.75	41.52±1.87	<0.001	41.52±1.87	37.30±1.34	<0.001	Significant
PWT	0.91±0.02	0.95±0.02	<0.001	0.95±0.02	1.00±003	<0.001	Significant
IVST	0.85±0.02	0.90±0.03	<0.001	0.89±0.03	0.94±0.04	<0.001	Significant
LAD	3.44±0.09	3.70±0.10	<0.001	3.70±0.10	3.99±0.10	<0.001	Significant
E/A	0.97±0.02	0.91±0.02	<0.001	0.91±0.02	0.87±0.03	<0.001	Significant
DT (milli sec.)	220.56±3.72	230.70±2.15	<0.001	230.70±2.15	247.65±8.08	<0.001	Significant

There was statistically significant increase in PWT, IVST, LAD and Deceleration Time (DT in milliseconds) and decrease in E/A Ratio, thereby implying that significant diastolic cardiac dysfunction exists as cirrhosis develops irrespective of severity and grades of cirrhosis however systolic dysfunction may not be evident in early stages of disease.

When Echocardiographic variables were compared between patients of cirrhosis of liver of Child Class B and healthy controls, there was statistically significant cardiac (systolic and diastolic) dysfunction between controls and cases. There was statistically significant difference in PWT, IVST, LAD and Deceleration Time (DT in milliseconds) and statistical significant decrease in LVEF, LVEDD, LVESD and E/A Ratio between cases and controls. This change was statistically significant when compared with patients of cirrhosis of liver with Child Class A implying significant cardiac dysfunction as disease becomes more advanced.

When Echocardiographic variables were compared between patients of cirrhosis of liver of Child Class C and healthy controls, there was statistically significant cardiac dysfunction between controls and cases. There was statistically significant difference in PWT, IVST, LAD and Deceleration Time (DT in milliseconds) and statistical significant decrease in LVEF, LVEDD, LVESD, E/A Ratio between cases and controls. This implies that significant cardiac dysfunction occurs as disease becomes more advanced.

In patients of cirrhosis of liver of Child Class C when echocardiographic parameters were assessed before and after paracentesis there is statistically significant improvement in diastolic functions as assessed by increase in E/A ratio and decrease in DT. However, statistically no significant improvement is seen in systolic functions.

There was no significant correlation seen in various echocardiographic parameters in patients of cirrhosis of liver of different etiologies.

TABLE 17:
COMPARISON OF ECHOCARDIOGRAPHIC PARAMETERS IN PATIENTS OF CIRRHOSIS OF LIVER WITH DIFFERENT ETIOLOGIES

Category	EF	EDD	ESD	PWT	IVST	LAD	E/A	DT
Alcohol (n=67)	53.66±3.29	46.26±3.50	35.90±3.71	0.96±4.26	0.90±0.80	3.74±0.23	0.87±4.96	235.60±13.07
Hepatitis (n=60)	54.64±3.48	46.52±3.33	36.64±3.20	0.96±4.25	0.91±0.70	3.35±0.22	0.88±4.01	234.24±11.30
Others (n=17)	54.13±2.66	48.46±2.47	38.13±2.19	0.96±3.20	0.88±0.49	3.66±0.17	0.90±3.82	226.80±7.42
Signi.	NS	NS	NS	NS	NS	NS	NS	NS
p-value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

DISCUSSION

The present study was done to study cardiac dysfunction in patients of cirrhosis of liver and its correlation with severity.

A total number of 150 cases were enrolled in the study group after application of inclusion and exclusion criteria and equal number of age and sex matched control were taken for reference value of hematological and echocardiographic parameters.

Maximum number of patients 66 (44.0%) in the study group were in the age group of 40-60 years. Mean age of the study group was 42.3±8.42 year while mean age of the controls was 41.12±6.20 years. Of the 150 patients in the study group, 127 patients (84.66%) were males and 23 patients (15.33%) were females with similar sex distribution in controls. These findings are consistent with those reported by Gupta D et al [13].

Alcoholism was the most common underlying cause of liver cirrhosis in the present study population which was present in 67(44.66%) of patients. It was consistent with study done by Deibert et al.[14]; It was followed by hepatitis 'B' and unknown etiology/others with 52 (34.66%) and 17 (11.33%) respectively.

In the present study, 115 (76.66%) patients belonged to Class B (48.66%) and class C (28.0%) as per Child Pugh Score suggesting that most of the patients approached the hospital in a relatively advanced stage of liver disease.

It was further studied for cardiac dysfunction with echocardiography in patients of liver cirrhosis and found that cardiac dysfunction was present in patients in the present study. It was consistent with findings of Soon Koo Baik et al[4], who stated that diastolic dysfunction is present amongst patients with cirrhosis who have advanced liver disease. The prevalence of various types of cardiac dysfunction in cirrhotics directly correlates with severity of liver cirrhosis as per Child Pugh score.

In the present study, the severity of cardiac dysfunction did not differ significantly with etiologies. This is in concordance with the study conducted by Alexander Jacob[15] in Indian population and did not found any significant difference in cardiac dysfunction according to etiology of liver cirrhosis.

In the present study, when controls with cirrhotics were compared, there was statistically significant rise in interventricular septal thickness, left ventricle posterior wall thickness, left atrial size, deceleration time, and decrease in E/A ratio, which are parameters of diastolic dysfunction however there was no significant systolic dysfunction in cases with Child Class A. This is in concordance with study conducted by Pozzi et al.[9]

In the present study, there was evidence of diastolic dysfunction in all the groups of cirrhotics, as indicated by statistically significant prolongation of deceleration time and significant reduction in E/A ratio as compared to the controls. Both the E/A ratio and deceleration time reflect impedance to ventricular filling.

In 1996, Finucci and colleagues[16] found that compared to controls,

cirrhotics had increased left atrial volume, deceleration time (DT) and decreased ratio of peak E to peak A filling velocities. Our study is concordant with above findings.

In 1997, Pozzi M et al.[9] studied 27 cirrhotic patients and found that in patients with liver cirrhosis, E/A ratio was reduced as compared with controls while left ventricle wall thickness was increased, irrespective of the cause of liver disease. In all cirrhotics both right and left atrial were significantly greater. Thus they concluded that, advanced cirrhosis is associated with left ventricle diastolic dysfunction and wall thickness also increases. This is also concordant with the present study. In 2001, Wong and colleagues[12] studied the cardiac response to exercise in patients with cirrhosis. It was observed that baseline diastolic dysfunction was present in patients with cirrhosis as reflected by a prolonged inter ventricular relaxation time, left atrial enlargement, and left ventricular wall thickening despite increased mean ejection fraction.

In the present study, there was direct correlation between the cardiac dysfunction and Child Pugh class of liver disease. This is shown by direct correlation of Child Pugh score with deceleration time (DT), E/A ratio, which are parameters of diastolic dysfunction. This is in concordance with a study conducted in 2004 by Alexander Jacob et al.[15] in an Indian population who demonstrated that there is prolongation of declaration time in cirrhotics suggesting impedance to left ventricular filling, indicative of diastolic dysfunction in non-alcoholic subjects, and is in direct correlation with Child Pugh score as observed in our study group.

The study conducted by Hammid A et al,[17] revealed a highly significant decrease in E-velocity and E/A ratio and a high significant increase in A-velocity in group of cirrhosis when compared to the control group. This diastolic dysfunction deteriorated more with the progression of liver disease (Child B and C subgroups when compared to child A subgroup) which is in concordance to our study.

Left ventricular ejection fraction (LVEF), left ventricular end systolic dimension, left ventricular end diastolic dimension are parameters of systolic dysfunction used in our study and are found to be statistically significantly deranged in cirrhotics as compared to controls and correlated statistically with severity of liver cirrhosis as per Child Pugh.

In a study conducted by Hammid A et al. they found a significant decrease in LV diameters, increase LA diameter and wall thickness in group of liver cirrhosis when compared to the control group, with statistically significant decrease of LVEF, LVESD and LVEDD in the Child B group when compared to the control group. These finding are in concordance to the present study.

In the present study, cardiac dysfunction assessed by 2D echo in patients with cirrhosis of liver was compared with those who did not have cardiac dysfunction (Healthy controls). It was found that there was statistically significant difference in interventricular septal thickness (IVST), posterior wall thickness (PWT), E/A ratio and Deceleration time (DT) in milliseconds, which once again reinforce the presence of diastolic dysfunction in cirrhotics as compared to controls.

CONCLUSION

This study was undertaken to observe cardiac dysfunction in patients of cirrhosis of liver with and without ascites, and to correlate it with disease severity. Echocardiography is important to detect early cardiac dysfunction and extent of cirrhotic cardiomyopathy generally correlates to the degree of liver insufficiency.

Therefore, it is recommended that physicians should be aware for the possibility of myocardial diastolic dysfunction in patients with chronic liver disease patients. Simple manoeuvres that can exacerbate the diastolic dysfunction, as a high sodium diet, fluid overload, exercise and stress, hepatototoxic drugs should be avoided in patients with low E/A ratio. Furthermore, cirrhotic patients should be subjected to careful cardiac assessment prior to any surgery and other interventional therapies that could potentially stress and precipitate cardiac dysfunction.

Further studies with a large sample size and serial assessment of cardiac function are required to corroborate these findings and their relation with the progression and severity of cirrhosis.

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