ORIGINAL RESEARCH PAPER

Volume-8 | Issue-4 | April-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A STUDY ON NT-PRO BNP AND TROP I AS A MARKER OF CARDIAC DYSFUNCTION IN CIRRHOTIC PATIENTS OF JHARKHAND

General Medicine

Rohit Keshav Junior Resident, Department of Internal Medicine, Room no. 33, Hostel No. 06, RIMS, Bariatu, Ranchi

Bindey Kumar Professor, Department of Internal Medicine, Rajendra Institute Of Medical Sciences, Ranchi

Aman Sinha* Junior Resident, Department of Internal Medicine, Rajendra Institute Of Medical Sciences, Ranchi *Corresponding Author

Abhishek Bhardwaj Junior Resident, Department of Internal Medicine, Rajendra Institute Of Medical Sciences, Ranchi

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%). There was statistically significant rise in NTProBNP and Troponin I levels as degree of liver dysfunction worsens. There was no significant correlation seen in NTProBNP and Troponin I in patients of cirrhosis of liver of different etiologies. NT-pro BNP and Trop I are 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 and can recommend measurement of the biomarkers for the same when suspected, in patients with chronic liver disease patients.

KEYWORDS

Cirrhosis, Cardiac dysfunction, NT-pro BNP, Trop I.

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 cirrhotics 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 B-type or brain natriuretic peptide (BNP) is a natriuretic hormone which was initially identified in the brain but is primarily released from the cardiac ventricles in response to increased ventricular filling pressures. The cleavage of its pro-hormone, pro-BNP, results in the production of biologically inert 76-amino acid peptide N-terminal-pro-BNP (NT-pro-BNP) and the biologically active 32-amino acid peptide BNP, both of which can be measured by clinical assays. Pro-B-type natriuretic peptide (proBNP1-108), the 108-amino acid prohormone is secreted from the cardiomyocytes secondary to cardiac wall distension and stretching, and neurohumoral activation in response to ventricular volume and pressure overload.

Patients with cirrhosis have elevated levels of N-terminal pro-B-type natriuretic peptide (NT-ProBNP), without signs of reduced hepatic degradation of this hormone, and elevated plasma levels of BNP in these patients correlated best with diastolic dysfunction. The role of

NT-ProBNP in the formation of esophageal varices and the relationship between proBNP plasma concentration and presence of varices has also not been established.[10]

Also it is known that elevated serum troponin concentrations reflect cardiac injury. Cardiac troponin I can be selectively measured by clinical assays and has been shown to be highly specific for myocardial injury, especially myocardial ischemia. Elevated troponin I concentrations are frequently observed in ischemic cardiac diseases. Although cirrhosis appears to be associated with few coronary diseases and myocardial infarctions in many autopsy studies, there is no information on the coronary microcirculation in these patients. Moreover histological investigations in cirrhotic patients have shown myocardial hypertrophy and changes including cardiomyocyte edema, fibrosis, exudation, and nuclear vacuolation. These histological injuries could induce and explain the mild cardiac troponin I increases. Thus, the measurement of cardiac troponin I could help identify patients with myocyte injuries who may have functional disorders and prevent adaptation under certain clinical conditions that result in acute hemodynamic disturbance such as during liver transplantation or intrahepatic portosystemic shunts.[11]

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 [12], 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.[13]

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 biochemical markers such as NT-pro BNP and Trop I.

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 done and Serum biomarkers like NT-pro BNP and Trop I were also measured.

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%).

The Biochemical parameters were compared among patients of cirrhosis of liver according to Child class and statistically significant correlation was observed. There was statistically significant rise in NTProBNP and Troponin I levels as degree of liver dysfunction worsens.

TABLE 6: COMPARISON OF BIOCHEMICAL PARAMETERS ACCORDING TO CHILD CLASS

Parameters	Child A n=35	Child B n=73	p -value	Child B N=73	Child C n=42	p -value	Significance
NTProBNP	319.50± 106.90	681.73± 192.20	<0.001	681.73± 192.20	1334.55± 370.10	<0.001	Significant
Troponin I	0.09±0.01	0.135± 0.01	<0.001	0.135± 0.01	0.173± 0.01	<0.001	Significant

The Biochemical parameters were compared in patients of cirrhosis of Child Class A with healthy controls. Troponin I levels were higher in patients of Child Class A as compared to controls but this difference was not statistically significant. However Serum NTProBNP levels were statistically significantly higher in patients of Child Class A as compared to controls.

The Biochemical parameters were compared between patients of cirrhosis of Child Class B and healthy controls and it was found that Serum NTProBNP, Troponin I levels were statistically significantly higher in Child Class B patients as compared to controls. Thus as disease process advances there occurs decline in cardiac function.

The Biochemical parameters were compared between patients of cirrhosis of Child Class C and healthy controls and it was found that Serum NTProBNP and Troponin I levels were statistically significantly higher in Child Class C patients as compared to controls. Thus as disease process advances there occurs decline in cardiac and renal function.

When biochemical parameters were compared in patients of cirrhosis of liver of Child Class C before and after paracentesis it was found that Serum NTProBNP and Troponin I levels statistically significantly declined in Child Class C patients after paracentesis (significant).

Table 7: Comparison Of Biochemical Parameters In Patients Of Cirrhosis Of Liver With Different Etiologies

Category	NTProBNP	Troponin I
Alcohol(N=67)	822.16±463.4	0.14±3.19
Hepatitis(N=60)	825.32±474.77	0.14±3.39
Others (N=17)	645.60±364.40	0.13±2.32
Significance	NS	NS
p-value	>0.05	>0.05

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

DISCUSSION

The present study was done to study cardiac dysfunction as assessed by cardiac biomarkers 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 [14].

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.[15]; 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.

Subtle cardiac abnormalities have been described in patients with cirrhosis of liver. Natriuretic peptide hormones have been reported to be sensitive markers of early cardiac disease. Therefore, in the present study it evaluated for the status of the natriuretic peptides as markers of cardiac dysfunction in cirrhosis and its association with severity. This study aimed at answering the following questions:

1. Do plasma levels of natriuretic peptides provide any information about abnormal cardiac dysfunction in cirrhosis?
2. Is there an association between the plasma levels of natriuretic peptides and severity cardiac dysfunction?
3. Can plasma natriuretic peptides be used to identify early cirrhotic cardiomyopathy?

In the present study, NT pro BNP was statistically significantly raised in patients of cirrhosis of liver as compared to controls. This is in accordance to the study conducted by JH Henriksen et al,[10] who reported increased plasma concentrations of NT pro BNP in patients with cirrhosis. Similar studies conducted by La Villa G et al.,[16] and Nakano R et al.,[17] who showed raised plasma levels of brain natriuretic peptides in patients with cirrhosis.

The BNP gene is predominantly expressed in myocytes of failing left ventricles, with BNP increasingly secreted into the circulation. Thus increased plasma concentrations of BNP are associated with impaired function of the left ventricle regardless of the underlying cause. The larger N terminal pro-hormone fragments of pro BNP are more stable and have been suggested to have a longer biological half life.

In the present study, the mean NT pro BNP was significantly raised in patients of liver cirrhosis as compared to controls and directly correlated to severity of cirrhosis of liver as measured by Child Pugh Score There was statistically significant difference in levels of NTProBNP between controls and patients graded as Child A, Child B and Child C. This is concordant to study conducted by JH Henriksen et al.[10], who researched a significant correlation of levels of NTProBNP with Child score indicating a relation with severity of liver disease. This is in keeping with earlier observations that cardiac dysfunction is more frequent and pronounced in patients with severe than mild liver disease. These findings were confirmed by multiple regression analysis. Similar studies conducted by Yildiz R et al.[18] who found similar results which is in concordance with the present study.

In the present study, patients with cirrhosis of liver with cardiac dysfunction as demonstrated by echocardiography were compared with healthy controls who did not have cardiac dysfunction. There was statistically significant difference in NTProBNP levels between the two groups suggesting increased plasma concentrations of NTProBNP is due to cardiac dysfunction. The value of NTProBNP positively correlates with interventricular septal thickness (IVST), posterior wall thickness (PWT), and deceleration time (DT) in milliseconds, Left atrial diameter (LAD) and negatively correlates with E/A ratio. This is concordant with the study conducted by Florence Wong et al.[13] Levels of brain natriuretic peptide were correlated significantly with septal thickness, left ventricular diameter at the end of the diastole and deceleration time.

Advanced cirrhosis is associated with advanced cardiac dysfunction and NTProBNP levels have predictive value for concomitant cardiac dysfunction and cirrhosis progression.

In the present study, NTProBNP levels were compared with Echocardiographic regression in patients with liver cirrhosis; showed statistical significant correlation with left ventricular end systolic and diastolic dimensions. The left atrium size was increased in the patients with elevated pro BNP values. This is in concordance with our study conducted by JH Henriksen et al[10].

Further paracentesis caused significant improvement in cardiac functions. This is in concordance with the study conducted by Pozzi et al.[9]

There was no statistical significant difference in levels of NTProBNP among patients of cirrhosis of liver with different etiologies. However it increased with disease severity whatever may be the etiology.

Thus it can be concluded that abnormal plasma levels of NTProBNP provide information about abnormal cardiac function in patients with cirrhosis, and that elevated levels of BNP correlates best with diastolic dysfunction and relative wall thickness in these patients. Because cardiac dysfunction is largely asymptomatic in cirrhosis, clinical assessment is not always reliable, and since investigations such as radionuclide angiography are time consuming and costly as screening procedures, NTProBNP levels may be used as a simple, feasible and reliable indicator of cardiac abnormalities in these patients. A high level of NTProBNP in the absence of any medications, especially diuretics should suggest the need for further cardiac investigations, while a normal or low NTProBNP level has excellent negative predictive value.

In the present study, it was also studied for the plasma concentration of cardiac Troponin I, a specific marker of myocardial injury, in patients with liver cirrhosis without previous cardiac disease, enrolled in the

present study, and found that patients with liver cirrhosis had statistically significant raised plasma concentrations of Troponin I as compared to controls. This is in concordance with the study conducted by Pateron et al,[11] where cardiac Troponin I concentrations were elevated in 32% of patients of liver cirrhosis. Their results show a high prevalence of slightly elevated serum cardiac Troponin I in patients with liver cirrhosis, especially in those with alcoholic cirrhosis. Pateron et al, concluded that elevated Troponin I is associated with subclinical left ventricular myocardial damage. These findings may be linked to a lack of left ventricular adaptation in certain patients with cirrhosis of liver and cirrhotic cardiomyopathy. Pateron et al, also concluded that this increase in Troponin I levels occur in the absence of increases in creatinine kinase. This suggests that the troponin I levels are increased in the absence of myocardial cell plasma membrane injury and represent a stress rather than injury related response. This also suggests that any additional cardiac stress in cirrhotics with elevated troponin I levels could lead to myocardial failure. Moreover histological investigations in certain patients with cirrhosis have shown myocardial hypertrophy and changes including cardiomyocyte edema, fibrosis, exudation, and nuclear vacuolation as shown by Ocel et al[19] These histological injuries could induce and explain mild cardiac Troponin I increases.

In the present study, the value of Troponin I positively correlated with severity of cirrhosis of liver as measured by child Pugh Score. There was statistically significant difference between Control and Child A, Child B and Child C. The value of Troponin I was statistically significantly increased in patients with liver cirrhosis having cardiac dysfunction as per echocardiography suggesting that Troponin I correlate with cardiac dysfunction. In our study there was also a direct correlation between value of Troponin I with interventricular septal thickness and posterior wall thickness which is marker of ventricular hypertrophy and with deceleration time which is characteristically seen in cirrhotic cardiomyopathy; and a negative correlation with E/A ratio, which are markers of diastolic dysfunction.

In the present study similar results regards Troponin I were observed as of NTProBNP. There was statistical significant rise in levels of Troponin I as liver dysfunction worsens from Child Class A to Child Class C. But there was no significant change in levels of Troponin I seen after paracentesis.

Also there was no significant difference in levels of cardiac Troponin I among patients of cirrhosis of liver with different etiologies. This is in concordance with the study conducted by Alexander Jacob et al.[20]

Thus, measurement of cardiac troponin I could help to identify patients with myocyte injuries who may have function disorders and prevent adaptation under certain clinical conditions that result in acute hemodynamic disturbance such as during liver transplantation.

CONCLUSION

This study was undertaken to observe cardiac dysfunction as assessed by cardiac biomarkers in patients of cirrhosis of liver with and without ascites, and to correlate it with disease severity.

NT-pro BNP and Trop I are 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.

CONFLICT: No conflict of interest
FUNDING: No funding

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