# Association of N- terminal Pro Brain Natriuretic Peptide with Echocardiographic Measures of Diastolic Dysfunction in Cirrhosis

**Abstract**

**Background:** Liver cirrhosis is associated with cardiac dysfunction in 40%–60% of the patients. Serum NT-ProBNP is a potential additional marker of cirrhotic cardiomyopathy. **Materials and Methods:** It was a cross-sectional analytical study done in a tertiary care center in South India on 100 patients of cirrhosis of liver. Diastolic function was assessed from mitral inflow parameters as well as tissue Doppler imaging of the left ventricle in 95 patients. Serum NT-ProBNP levels was measured once at the time of inclusion into the study. Cirrhotic cardiomyopathy was diagnosed in those with abnormal echocardiographic parameters and its association with NT-Pro BNP levels was analyzed. Data were analyzed using SPSS version 22. **Results:** Diastolic dysfunction was found in 40 (42.1%) participants. Twenty-two (23.2%) had Grade I, 16 (16.8%) had Grade II, and 2 (2.1%) had Grade III diastolic dysfunction. The mean NT-Pro-BNP was elevated (107.38 [±66.76] ng/ml) in patients with diastolic dysfunction. NT-ProBNP was higher in Child–Pugh B and C disease when compared to milder disease. NT-ProBNP was not a good screening tool for cardiomyopathy in cirrhotic patients. Area under the curve was 0.517 with 95% confidence interval and the $P = 0.77$. However, positive correlation was present between the NT-ProBNP value and two echocardiographic parameters of diastolic dysfunction (E/A, E/E'). **Conclusion:** Increased serum NT-ProBNP levels in cirrhosis of liver have a positive correlation with echocardiographic measures of diastolic dysfunction of the heart but it is not a good tool for screening for cirrhotic cardiomyopathy.

**Keywords:** *Cardiomyopathy, echocardiography, liver cirrhosis, N-terminal pro-BNP*

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## Introduction

Cirrhosis of liver is associated with a hyperdynamic circulation. Cirrhotics may have diastolic dysfunction of the left ventricular (LV), which gets manifest under stressful situations.[1] This diastolic dysfunction worsens with the Child–Pugh stage of the disease. It also worsens the postoperative outcome in patients undergoing liver transplant and shunt procedures.[2] Diagnosis is based on echocardiographic assessment of diastolic parameters. Tissue Doppler is the preferred echocardiographic modality. This requires skill and expertise which may not be readily available. ProBNP and its precursor NT-ProBNP are released from the ventricles in response to pressure or volume overload especially in cirrhotics where the renin angiotensin system is activated. NT-ProBNP is more stable and has a longer half-life than BNP. Previous studies have found these biomarkers to be elevated in cirrhosis with

systolic as well as diastolic dysfunction, albeit with lower levels in diastolic heart failure.[3] These biomarkers have variable association with severity of disease and have been reported to correlate with post liver transplant mortality. However, they have not been evaluated as a screening tool especially for the scenarios where echo is not readily available.

## Materials and Methods

This is a cross-sectional analytical study done in patients with cirrhosis of liver attending the Medicine and Medical gastroenterology Outpatient and inpatient department in tertiary care hospital done over a period of 18 months, the study was performed in conformance with the Declaration of Helsinki ethical guidelines, after obtaining institutional ethics committee approval. Informed consent was obtained from the patients willing to participate in the study.

The aim was to estimate the prevalence of LV diastolic dysfunction in the sample population and determine if there was any association between serum NT-ProBNP and echo parameters. Assuming the prevalence of 44% with absolute precision of 10%, the sample size was estimated to be 95. Calculations were done based on 95% confidence levels using Open Epi software, version 3.01 updated 2013/04/06 accessed on 2013/12/13 Assuming 5% attrition, the final sample size was estimated to be 100.

All adult patients more than 18 years of age, who had cirrhosis were included. Cirrhosis was defined as those having liver span <8 cm on abdominal examination, ascites, and splenomegaly. Those with ultrasound evidence of shrunken and nodular liver (size <8 cm), splenomegaly >13 cm and enlarged portal vein (diameter more than 1.3 cm) or evidence of esophageal varices on endoscopy or histopathological evidence of cirrhosis on liver biopsy were included. Alcoholics were asked to abstain for a week before inclusion in the study. Patients with diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, essential hypertension, known heart disease, and severe anemia were excluded. Serum NT-Pro BNP was estimated once at the time of inclusion into the study by ELISA (QAYEE-BIO, Bio gene life sciences, India).

Ninety-five patients underwent transthoracic echocardiography (echo) to look for LV systolic and diastolic dysfunction. Diastolic function was assessed from mitral inflow parameters as well as tissue Doppler imaging (TDI).

In the apical four chamber view, with sample volume of 1–3 mm placed between the mitral leaflet tips, pulse wave Doppler imaging was performed at a sweep speed of 50–100 mm/s and averaged over three consecutive cardiac cycles by a single cardiology resident. Doppler measurements of the mitral inflow velocities included (i) peak early filling velocity (E), (ii) late diastolic filling velocity (A), (iii) E/A ratio, (iv) the time interval between the peak and end of E wave-Deceleration time (DT), And (v) time interval between aortic valve closure and mitral valve opening (Isovolumic relaxation time [IVRT]).

Myocardial TDI was done by placing the sample volume at the septal/lateral insertion of the mitral leaflets to assess the longitudinal myocardial excursion in both systole and diastole. Early diastolic (E') and late diastolic (A') velocities of the mitral annulus were measured. E' velocity provides information on LV relaxation and compliance.

LV diastolic dysfunction was graded as first degree (mild), second degree (moderate), and third degree (severe). First-degree diastolic dysfunction was defined as E/A < 0.8, E/E' <8, DT > 200 msec and IVRT > 100 msec. Second-degree diastolic dysfunction was defined as E/A 0.8–1.5, E/E' 8–13, DT 160–200 ms, IVRT < 90 ms. Third-degree diastolic dysfunction was defined as E/A >2, E/E' >13, DT < 160 ms, IVRT < 80 ms.

Data are presented as mean, standard deviation, and proportions. *T*-test and ANOVA test were used for comparison between means of two groups and more than two groups, respectively. Chi-square test was done to test significance between proportions. Pearson correlation analysis was used to determine the relation between cardiac parameters and N-terminal B type natriuretic peptide levels. $P < 0.05$ was considered to be statistically significant. Data were analyzed using IBM SPSS Statistics for Windows, version.

## Results

The mean age of the patients was 48.67 years (±9.16). About 41% of the patients were in the age group of 50–59 years. 91% were male and 9% were female. 16% belonged to Child–Pugh A, 45% belonged to Child–Pugh B and 39% belonged to Child–Pugh C.74% were alcoholics and had alcoholic-related cirrhosis and remaining 26% were nonalcoholics. Majority of the alcoholics consumed toddy (32%). Nonalcoholic cirrhosis was secondary to hepatitis B (16%), hepatitis C (6%), autoimmune disease (2%), and Budd–Chiari syndrome (1%). The most common clinical presentation was abdominal distention (94%), followed by pedal edema (91%) and passage of high colored urine (91%). Of the 100, 34% had alcoholic hepatitis. 26% patients had QTc >440 ms.

Of the 100 patients, 95 patients under went TDI, remaining 5 died before echocardiography was done. Systolic dysfunction was found in 3 (3.15%). Their LVEF was <55% at rest, diastolic dysfunction was found in 40 (42.1%) of the patients. 22 (23.2%) patients had Grade I diastolic dysfunction, 16 (16.8%) patients had Grade II diastolic dysfunction and 2 (2.1%) patients had Grade III diastolic dysfunction. On assessing the severity of cirrhosis, 5 (33.3%) out of 15 patients in Child–Pugh A, 15 (38.09%) out of 42 in Child–Pugh B, and 20 (52.63%) out of 38 in Child–Pugh C had diastolic dysfunction. The mean value NT-Pro-BNP in patients with diastolic dysfunction was 107.38 (±66.76) ng/ml, was higher than in those without diastolic dysfunction. NT-ProBNP values were higher in those with Child–Pugh B and C disease when compared to milder disease. Clinical characteristics were similar in those with and without diastolic dysfunction [Table 1]. A ROC curve was plotted for NT-ProBNP. It was found that NT-ProBNP value of 123 ng/ml had a sensitivity of 80% and specificity of 13% and a value of 96 ng/ml had a sensitivity of 60% and specificity of 51% in diagnosing diastolic dysfunction. Area under the curve (0.517) with 95% confidence interval and the $P = 0.77$ was not significant [Figure 1]. NT-ProBNP was not found to be a good screening tool. However, positive correlation between the NT-ProBNP value and two echocardiographic parameters of diastolic dysfunction (E/A, E/E') was present [Figures 2 and 3].

| Clinical feature | With diastolic dysfunction (*n*=40) | Without diastolic dysfunction (*n*=55) | *P* |
|---|---|---|---|
| Age (mean±SD) | 48.9±9.39 | 48.44±9.14 | 0.810 |
| Male, sex (%) | 36 (41.9) | 50 (58.1) | 0.881 |
| Alcoholic etiology (%) | 30 (40) | 45 (60) | 0.421 |
| Child–Pugh Class A (%) | 5 (33.3) | 10 (66.7) | 0.234 |
| Child–Pugh Class B (%) | 15 (35.7) | 27 (64.3) | |
| Child–Pugh Class C (%) | 20 (52.6) | 18 (47.4) | |
| History of limb swelling (%) | 36 (90) | 52 (94.5) | 0.402 |
| Decreased urine output (%) | 25 (62.5) | 35 (63.6) | 0.910 |
| Abdominal distension (%) | 40 (100) | 52 (94.5) | 0.133 |
| Passage of high colored urine (%) | 36 (90) | 52 (94.5) | 0.402 |
| Hematemesis (%) | 5 (12.5) | 10 (18.18) | 0.453 |
| Melena (%) | 11 (27.5) | 26 (47.27) | 0.05* |
| Altered sleep rhythm (%) | 26 (65) | 42 (76.36) | 0.225 |
| Constipation (%) | 6 (15) | 9 (16.36) | 0.857 |
| Haemoglobin (g/dl) | 9.9±1.42 | 9.88±1.45 | 0.948 |
| Total leukocyte count(cells/cu.mm) | 7507±3518 | 7688±3713 | 0.810 |
| Total bilirubin (mg/dl) | 4.64±4.29 | 4.64±4.74 | 0.998 |
| Serum albumin (mg/dl) | 2.73±0.46 | 2.83±0.59 | 0.372 |
| Aspartate aminotransferase (IU/L) | 93.73±66.72 | 84.6±49.52 | 0.446 |
| Gammaglutamyl transferase | 61.28±88.8 | 54.87±55.32 | 0.670 |
| International normalised ratio | 1.63±0.37 | 1.77±0.46 | 0.133 |
| Urea | 31.78±20.7 | 27.7±15 | 0.275 |
| Serum creatinine | 1.08±0.58 | 1±0.27 | 0.391 |
| ECG (QT c >440 ms) (%) | 6 (15) | 18 (32.7) | 0.05* |
| NT-ProBNP (ng/ml), mean±SD | 122.4±99.5 | 97.14±26.86 | 0.075 |

**Table 1: Clinical characteristics of study participants with and without diastolic dysfunction**

SD: Standard deviation, ECG: Electrocardiogram, NT-ProBNP: N-terminal-pro hormone BNP. *P* significant
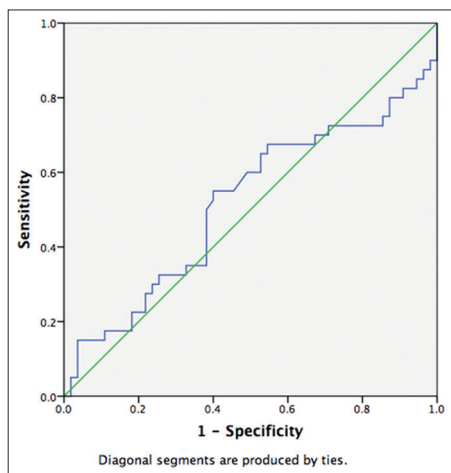


Figure 1: A ROC curve plotted for NT-ProBNP levels in those with and without left ventricular diastolic dysfunction
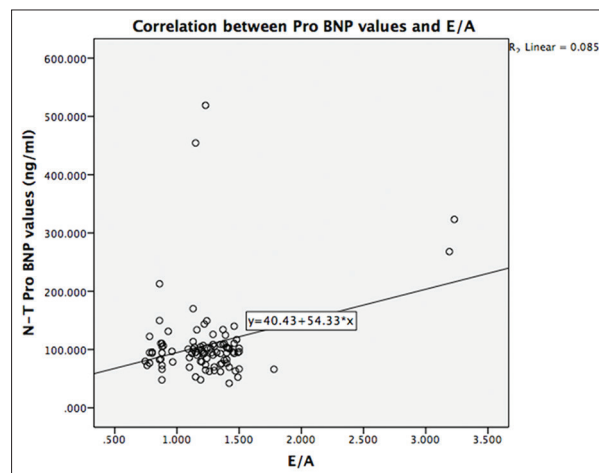


Figure 2: Correlation between NT-ProBNP Values and left ventricular diastolic parameters on echocardiography

## Discussion

Cirrhotic cardiomyopathy is characterized by impaired contractile response to stress and or impaired diastolic relaxation in the absence of any underlying cardiac disorder. It is prevalent in at least 50% of cirrhosis cases and worsens their prognosis. The biomarker, NT-ProBNP has been established as a marker of systolic heart failure and its role in diastolic heart failure is being studied. As the prevalence

of cirrhosis is high in our part of the country, there is need to determine if a biomarker like NT-ProBNP can replace Echo-derived measures of diastolic dysfunction such as E/A ratio, DT for the screening of Cirrhotic cardiomyopathy.

The prevalence of cirrhotic cardiomyopathy was found to be 42.1% in this study. This was similar to an earlier study from South-east Asia, in which prevalence was 44.6%.[4] Previous Indian studies showed higher prevalence
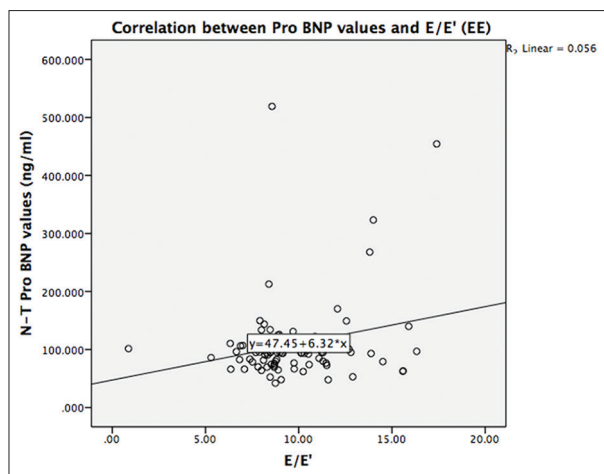
**Figure 3:** Correlation between NT-ProBNP Values and left ventricular diastolic parameters on tissue Doppler echocardiography

of (84%) and (70%), respectively.[5,6]Another study showed a slightly higher prevalence of 51%.[7] This variation in prevalence may be attributable to varying ethnicity of the study participants and their genetic predisposition to alcohol-induced cardiac myocyte injury.

In our study, the number of male patients was more than female patients similar to an earlier study, probably because alcoholism is common among males in this region. The study participants varied widely between ages 30 and 75 years, the maximum number of patients were in the age group of 50–59 years similar to earlier studies.[4-6] However, our study participants were older than those included in another study.[7]

The most common etiology of cirrhosis of liver in this study was alcohol (74%) and this remained the leading cause in previous studies also. Distribution of study participants according to the severity of cirrhosis of liver into Child–Pugh class A (16%), B (45%), C (39%) was similar to earlier studies.[4,5] Diastolic dysfunction was found in 42.1% of the patients which was higher than (20.3%) other Indian studies.[4-6] Ours is a tertiary care referral hospital which received more often advanced stages of cirrhosis, hence the high prevalence. Although more number of patients of CTP category C had diastolic dysfunction, no statistical difference was observed amongst various grades of cirrhosis. However, previous studies show that increasing age, female gender, longer duration of cirrhosis, and increasing severity of cirrhosis were associated with higher prevalence of diastolic dysfunction.[8-10] Those participants were nonalcoholic while our study population was predominantly that of alcoholic cirrhosis.

NT-ProBNP levels were higher in cirrhotics with diastolic dysfunction but there was no statistical significance. It had poor specificity and sensitivity at a cut off of 96 ng/ml, hence cannot be an independent screening tool for diastolic dysfunction in cirrhosis. This was different from earlier studies which found it to be good marker of diastolic

dysfunction.[4,9,11-18] This may be because our sample size is small and some participants were on diuretics.

We also looked at the correlation between NT-ProBNP and echocardiographic parameters of diastolic dysfunction, for use in a larger clinical setting. NT-ProBNP had statistically significant correlation with two echocardiographic diastolic parameters (E/A, E/E'). Previous studies also showed a positive correlation between the NT-ProBNP levels and ECHO parameters.[9,11,13] Future studies should use a larger sample size and a longitudinal design to assess the outcomes in those with elevated NT-Pro BNP levels.

## Conclusion

Increased NT-ProBNP levels in cirrhosis of liver have a positive association with echocardiographic measures of diastolic dysfunction of the LV, but are not a good screening tool for the diagnosis of cirrhotic cardiomyopathy. Raised levels of this biomarker may indicate cirrhotic cardiomyopathy but cannot be used as an independent diagnostic tool.

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### Conflicts of interest

There are no conflicts of interest.

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