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Evaluation Of Cardiac Functions In Patients Of Chronic Liver Disease Using Serum NTpro-Brain Natriuretic Peptide And Tissue Doppler Imaging

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Abstract

Introduction

Cirrhotic cardiomyopathy is characterized by hyper dynamic circulation with diastolic dysfunction at rest. This study focuses on cardiac functions of Chronic liver disease (CLD) patients using Serum NTpro-Brain Natriuretic Peptide (BNP), Echocardiograhy and Tissue Doppler imaging (TDI)

Material Methods

85 diagnosed cases of CLD were assessed using serum NTpro-BNP, conventional echocardiography, and tissue Doppler imaging.

Results

Patients mean age was 42.8 ± 11.36 years with maximum cases belonging to age group interval of 31-40 years (38.8%) and the least in >60 years age interval (5.9%). The study observed male preponderance with 84.70% males and 15.30% females. Alcoholism was appraised as the most common aetiological factor (72.95%). Rest were others (HBsAg & HCV-Negative and Non- Alcoholic) cases (17.65%), mixed (HBsAg or HCV-Positive and Alcoholic) cases (8.23%). All the patients had normal systolic function in all Child-Pugh-Turcotte (CPT) score classes with diastolic dysfunction maximally prevalent in Class C of CPT Scores (28.23%) and Class B of CPT scores (2.35%). Significant correlation was found between NTpro-BNP levels and Mitral valve echocardiography parameters like E, A, E/A (all P< 0.000). Significant correlation was found between NTpro-BNP levels and TDI parameters like E/E' (P<0.01) at LV and E' (P<0.01), E/E' (P<0.01), IVRT (P<0.05), MPI index (P<0.05) at RV as well as S' at septum (P<0.01).

Conclusion

Maximum cases of CLD had underlying diastolic dysfunction. The use of serum NTpro- BNP, Echocardiography and TDI all together work as a better tool for early detection of cardiac dysfunction.

Keywords: Cirrhotic cardiomyopathy, NTpro-BNP, Echocardiograhy, Tissue Doppler imaging, Child-Pugh-Turcotte score

Introduction

A progressive deterioration of liver functions for more than six months is termed as Chronic liver disease (CLD). CLD is a continuous process of destruction, inflammation, and regeneration of liver parenchyma, resulting in fibrosis and cirrhosis of liver [1]. CLD has caused significant morbidity and mortality worldwide. In the United States, according to the National Vital Statistics Report from the Centre for Disease Control and Prevention (CDC), approximately

4.5 million adults had chronic liver disease, out of which 1.8 percent is the adult population. There were 44,358 deaths (13.5 deaths per 100,000 population)

from chronic liver disease and cirrhosis [2] According to the latest WHO data, CLD deaths in India reached 259,749 or 2.95% of total deaths, accounting for one-fifth (18.3%) of all CLD deaths globally [3].

CLD has a hyperdynamic condition characterized by increased cardiac output and decreased peripheral vascular resistance. Several studies by Carvalho et al., and Mihailovici et al.have consistently reported such findings. Successive publications of such studies have elaborated that cardiomyopathy [4,5]. Number of cardiac abnormalities can develop due to hemodynamic profile, resulting in cirrhotic cardiomyopathy. This may finally give rise to electrophysiological abnormalities along with abnormal contractile cardiac response to stress and altered cardiac diastolic relaxation, in the absence of known cardiac disease [6].

The actual prevalence of cirrhotic cardiomyopathy is limited because of the fact that the disease usually remains unnoticed due to near normal cardiac function unless the patients are exposed to stress. It has been estimated that as many as 50 % of patients developed some signs of cardiac dysfunction undergoing liver transplantation [7] and in the post liver transplantation period; about 7–21 % of patients died from heart failure [8]. Several possible mechanisms as chronotropic and inotropic incompetence due to defective cardiac β- adrenergic receptor signalling, sympathetic over-activity and prolonged exposure to noradrenaline [7-9]. Effect of endogenous cannabinoids (most importantly anandamide) and elevated catecholamine levels as a result of sympathetic over activity in CLD cases explain the development of systolic dysfunction in CLD [10].

In contrast with systolic dysfunction, diastolic dysfunction is characteristic of CLD with Cardiomyopathy and seems to be its first manifestation [11]. Reduced early diastolic ventricular filling and increased atrial filling, prolonged isovolumetric relaxation time (IVRT>80 ms) and deceleration time >200 ms, are prominent Echocardiographic features. Patients with advanced liver disease, should undergo stress echocardiography and Tissue Doppler imaging (TDI) as a diagnostic approach because it can detect subtle systolic and diastolic dysfunctions before the ventricular ejection fraction is decreased [12-13]. Although in the recent past, newer techniques have been developed for the assessment of cardiovascular disturbances in CLD, newer modalities like B-type Natriuretic peptides (BNP and pro-BNP) can be used as Prognostic as well as diagnostic purposes. High concentration of BNP directly correlates to cardiac dysfunction and has high reliability in severity of disease and also stated that their role can also be implicated in diseases like cardiac disturbances with CLD [14].

Justification for raised levels of pro-BNP in severe form of CLD is due to the relative decrease in systolic dysfunction and ejection fraction after physical strenuous activity, micro- vascular fibrosis leading to thrombosis in multiple organs and triggering microvascular ischemia especially in heart muscles, which is responsible for high BNP levels [14]. There is less data available on assessing the cardiac functions in CLD. Also, biomarkers have variable association with severity of disease and have not been evaluated as a screening tool especially for such scenarios. So this study was planned to evaluate the cardiac functions of chronic liver disease patients using Serum NTpro-BNP, Echocardiograhy and TDI.

Material And Methods

This single centre, hospital based cross-sectional observational study was conducted in department of Medicine at DR. B.R.A.M.H Raipur located in Central India. 85 patients who had clinically, biochemically and radiologically proven chronic liver disease for a period of 2 years from December 2019 to November 2021 were included in this study. Patients with major cardiovascular disease or chronic Kidney Disease were excluded from the study. After explaining the study procedure, written informed consent obtained from all the subjects selected for the study. Case records were collected from the medical records department after availing necessary ethical approval from the institution and were meticulously looked for various aspects such as age, sex, clinical presentation were identified. All cases underwent echocardiography, and tissue doppler imaging by PHILIPS MODEL-EPIQ 7. Lab investigations like CBC, LFT, RFT, SE, PT-INR and Serum NT-proBNP were identified. The collected data were tabulated and statistically analyzed using SPSS© for windowsTM Vs 17, IBMTM Corp NY and Microsoft excelTM 2007, Microsoft® Inc USA. Pearson

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correlation analysis was performed to check the correlation between two categorical variables and Chi square test was used to analyze the significance of difference between frequency distribution of the data. P value <0.05 was considered as statistically significant.

Results

Patients demographic data showed that age group 31-40 years had the maximum frequency which is 38.8% and the minimum frequency was found in >60 Years age which is 5.9%. Mean age of cases was 42.8 ± 11.36 years. Gender wise our study had majority of males (84.70%) and few female cases (15.30%). Maximum cases suffering from CLD were alcoholic (72.95%) and remaining were distributed amongst other causes like others (HBsAg &HCV-Negative and Non- Alcoholic) were 17.65%, mixed etiology (HBsAg or HCV- Positive & Alcoholic) were 8.23%, and only HBsAg infection (1.17%). In present study, while assessing correlation between NTpro- BNP levels and Mitral valve echocardiography parameters like E, A, E/A, we found a significant correlation between them [E (P< 0.000), A (P< 0.000), E/A (P< 0.000)], but could not establish any significant correlation between the NTpro-BNP values and Tricuspid valve echocardiography parameters (all P>0.05). Furthermore, we could establish significant difference between the compensated and decompensated patients regarding the echocardiographic parameters in RV, LVEDD and E, A, E/A at MV and E at TV. There was significant correlation found between NTpro-BNP levels and TDI parameters like E/E' (P<0.01) at LV and E' (P<0.01), E/E' (P<0.01), IVRT (P<0.05), MPI index (P<0.05) at RV as well as S' at septum (P<0.01). No other parameters were significantly correlated with NTpro-BNP levels. When compared between compensated and decompensated patients, no significant difference regarding TDI parameters was found in our study. Moreover, while evaluating CPT Score and Cardiac dysfunction, we found that systolic dysfunction was not present in any CPT Score class but diastolic dysfunction was maximally present in Class C CPT Score class (28.23%) followed by Class B CPT score (2.35%). No diastolic dysfunction was seen in Class A CPT score.

Discussion

The foremost hemodynamic feature of cirrhosis is the hyperdynamic syndrome, a circulatory state characterized by low arterial pressure, high cardiac output and decreased peripheral vascular resistance. Both hemodynamic and cardiac profiles denote the pathophysiological scenario known as "cirrhotic cardiomyopathy", a clinical condition which plays a role in the course of cirrhosis [1]. By means of echocardiography, some studies carried out a non-invasive assessment of cardiac dimension and systolic and diastolic function in cirrhotic patients at rest and elicited that some morphological and functional parameters may be taken as early markers of cardiac abnormalities in liver cirrhosis [7]. The natriuretic peptides that are released by cardiomyocytes in response to cardiac volume or pressure overload play an important role in the diagnosis of asymptomatic left ventricular dysfunction and also have a prognostic role in heart failure. Furthermore, recent studies have shown that increased levels of NT-proBNP are present in patients with chronic liver disease, and particularly in ascitic cirrhosis even in the absence of LV clinical dysfunction [12,14]. NTpro- BNP has been recently suggested to be an even better indicator of early cardiac dysfunction because of its stability and longer biological half- life [14].

Baseline Characteristics-

In our study, the mean age noted was 42.8 ± 11.36 years. Maximum cases prevailed in age group interval of 31-40 (38.8%). Sex predilection for males (84.70%) with most common aetiology of alcoholism (72.95%) was appraised in our study. Female population contributed to 15.30% cases. Remaining cases were distributed amongst other causes like others (HBsAg &HCV-Negative and Non-Alcoholic) were 17.65%, mixed etiology (HBsAg or HCV-Positive & Alcoholic) were 8.23%, and only HBsAg infection (1.17%).Our study findings were in consensus with study conducted by Mihailocivi et al., and Mushtaq et al [5,15].

Correlation between NTpro-BNP values and echocardiography parameters-

In present study, a significant correlation between NTpro-BNP levels and mitral valve echocardiography parameters like E, A, E/A was established, which was in consensus with findings of Singh et al where they found positive correlation

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between NTpro- BNP level and E/A ratio [16]. We could not find any significant correlation between the NTpro-BNP values and Tricuspid valve echocardiograph parameters. Furthermore, we could establish significant difference between the compensated and decompensated patients regarding the echocardiographic parameters in RV, LVEDD and E, A, E/A at MV and E at TV. Similar findings were found by Fattouh et al., where serum NTpro-BNP level was correlated with E wave velocity of TV inflow and E/A ratio of RV [14]. Another studies by Henriksen et al., and kazankov et al., had demonstrated correlations with different parameters as PW thickness, DT and IVS while Wong et al., correlated with DT [17,18].

Correlation between NTpro-BNP values and TDI parameters

In present study, we established a significant correlation found between NTpro-BNP levels and TDI parameters like E/E' at LV and E', E/E', IVRT, MPI index at RV as well as S' at septum. Whereas, no other parameters were significantly correlated with NTpro-BNP levels. Findings of Fattouh et al., Meric et al., and Merli et al., were also in consensus with our study findings [19,20]. When compared between compensated and decompensated patients, we could not find any significant difference regarding TDI parameters in our study. Combining TDI with Doppler indices by using parameters as E/E' allows refining the criteria required to detect patients with diastolic dysfunction especially for those with hyperdynamic state accompanying liver cirrhosis. We were further supported by findings of Fattouh et al., as TDI showed no significant difference between compensated and decompensated cirrhotic patients similar to our study. The systolic functions of patients in that study were not affected when assessed by FS and EF which were within normal limits. Systolic peak velocity of the LV measured by TDI was not reduced which could be attributed to the hyperdynamic status accompanying cirrhosis. The E/A ratio of both mitral and TVs inflow were significantly lower in cases and the IVRT was significantly longer [14].

Comparison between CPT Score and Cardiac dysfunction-

In our study, we agreed to the study findings of Fattouh et al. In their Study E/A ratio of both mitral and TVs inflow were significantly lower in cases and the IVRT was significantly longer. Also, no diastolic dysfunction was seen in Class A CPT score, which was similar to our study findings [14].

Conclusion

Cases of cirrhotic cardiomyopathy are those that might have cardiac dysfunction in the absence of other cardiovascular aetiology. The use of serum NTpro-BNP, Echocardiography and TDI all together work as a better tool for early detection of cardiac dysfunction. Presently, none of the tools can diagnose cirrhotic cardiomyopathy accurately, Hence, patients of chronic liver disease should be screened early for underlying cardiac dysfunction using serum NTpro-BNP, Echocardiography and TDI.

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TABLES AND FIGURES-

"Table 1 : Baseline characteristics of patients included in the study (n=85)"

Categorical variables	**Percentage**
Sex	
Males	84.70
Females	15.30
Underlying liver pathology	
Alcoholic	72.95
HBsAg &HCV-Negative & Non Alcoholic	17.65

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Mixed (HBsAg/HCV-Positive & Alcoholic)	8.23
HBsAg positive	1.17
Continuous variables- **Mean age (years)**	**Mean ± SD** 42.8 ± 11.36

HCV- Hepatitis C, HBsAg- Hepatitis B surface antigen

"**Table 2 :** Correlation between NTpro-BNP values and echocardiography as well as TDI parameters (n=85)"

Parameter	**r**	**P value**
AO(mm)	.029	.793
LA(mm)	.140	.202
RV(mm)	.015	.891
PA(mm)	-.010	.929
LVPW(mm)	-.067	.542
IVS(mm)	.124	.258
LVEDD(mm)	-.170	.120
LVESD(mm)	-.047	.669
EF (%)	.009	.933
FS (%)	-0.53	.633
MV		
E (m/s)	-.471	.000**
A (m/s)	.373	.000*
E/A	-.616	.000*
DT (m/s)	.197	.071
TV		
E (m/s)	-.089	.420
A (m/s)	-.189	.083
E/A	.190	.082
DT (m/s)	-.058	.598

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LV		
A' (cm/s)	-.137	.212
E' (cm/s)	.119	.278
S' (cm/s)	-.135	.219
E/E'	-.388	.000**
IVRT (m/s)	-.208	.056
IVCT (m/s)	-.183	.093
MPI index	.079	.474
RV		
A' (cm/s)	-.012	.915
E' (cm/s)	-.374	.000**
S' (cm/s)	-.095	.388
E/E'	.309	.004**

IVRT (m/s)	-.257	.018*
IVCT (m/s)	-.137	.211
MPI index	.228	.036*

* P- value considered significant difference at 95% CI (P<0.05) ** P- value considered significant difference at 99% CI (P<0.01) AO- Aorta, LA- Left atrium, RV- Right ventricle, PA- Pulmonary artery, LVPW- Left ventricular posterior wall, IVS- Interventricular septum, LVEDD- Left ventricle end diastolic diameter, LVESD- Left ventricle end systolic diameter, EF- Ejection fraction, FS- Fractional shortening, MV= Mitral valve, E= Early diastolic inflow velocity, A= Velocity during active atrial contraction, E/A= Early to atrial flow velocities, Dt= Deceleration time, LV= Left ventricle, S= Systolic myocardial velocity, E/e= Mitral annular early diastolic velocity, IVCT= Isovolumetric contraction time IVRT= Isovolumetric relaxation time, MPI=

myocardial performance index, RV= Right ventricle, E/e= Mitral annular early diastolic velocity

"Table 3 : Comparison between the compensated and decompensated patients regarding the echocardiography as well as TDI parameters (n=85)"

Parameter	**Compensated (n=5) Mean ± SD**	**Decompensated (n=80) Mean ± SD**	**P value**
AO(mm)	23.9 (2.6)	24.2 (2.5)	0.79
LA(mm)	26 (2.6)	26.6 (2.4)	0.59
RV(mm)	17.1 (3.8)	13.5 (3.6)	0.03*

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PA(mm)	16.9 (1.5)	16.9 (1.5)	0.9
LVPW(mm)	7.5 (0.8)	7.7 (0.8)	0.5
IVS(mm)	7.2 (0.7)	6.9 (0.6)	0.28
LVEDD(mm)	43.4 (4)	49.5 (3.8)	0.000**
LVESD(mm)	28.8 (5.6)	29.2 (5.3)	0.87
EF (%)	62.7 (4.14)	61.7 (4.07)	0.59
FS (%)	39.7 (3.19)	42 (3.31)	0.13
MV			
E (m/s)	1.2(0.1)	1.1 (0.1)	0.03*
A (m/s)	1.1 (0.1)	1 (0.1)	0.03*
E/A	1.1 (0.2)	1.1 (0.1)	0.04*
DT (m/s)	192.7 (5.1)	190 (4.5)	0.19
TV			
E (m/s)	0.8 (0.05)	0.9 (0.05)	0.000**
A (m/s)	0.7 (0.1)	0.7 (0.1)	0.9
E/A	1.2 (0.1)	1.2 (0.1)	0.9
DT (m/s)	186.3 (4.3)	189 (4.3)	0.17
LV			
A' (cm/s)	8.2 (0.4)	8.2 (0.38)	0.9
E' (cm/s)	16.6 (1.3)	16.5 (1.35)	0.9
S' (cm/s)	9.1 (0.5)	9.1 (0.54)	0.9
E/E'	6.7 (0.9)	6.7 (0.87)	0.9
IVRT (m/s)	46.6 (3.2)	46 (3.68)	0.7
IVCT (m/s)	42.8 (4)	42.4 (4.07)	0.8
MPI index	0.3 (0.1)	0.3 (0.05)	0.9
RV			
A' (cm/s)	11.3 (0.5)	11.4 (0.48)	0.6
E' (cm/s)	16.9 (1.1)	16.9 (1.04)	0.9
S' (cm/s)	12.9 (1.5)	12.9 (1.43)	0.9
E/E'	5.2 (0.4)	5.2 (0.41)	0.9
IVRT (m/s)	42 (2.9)	41.6 (3.06)	0.7

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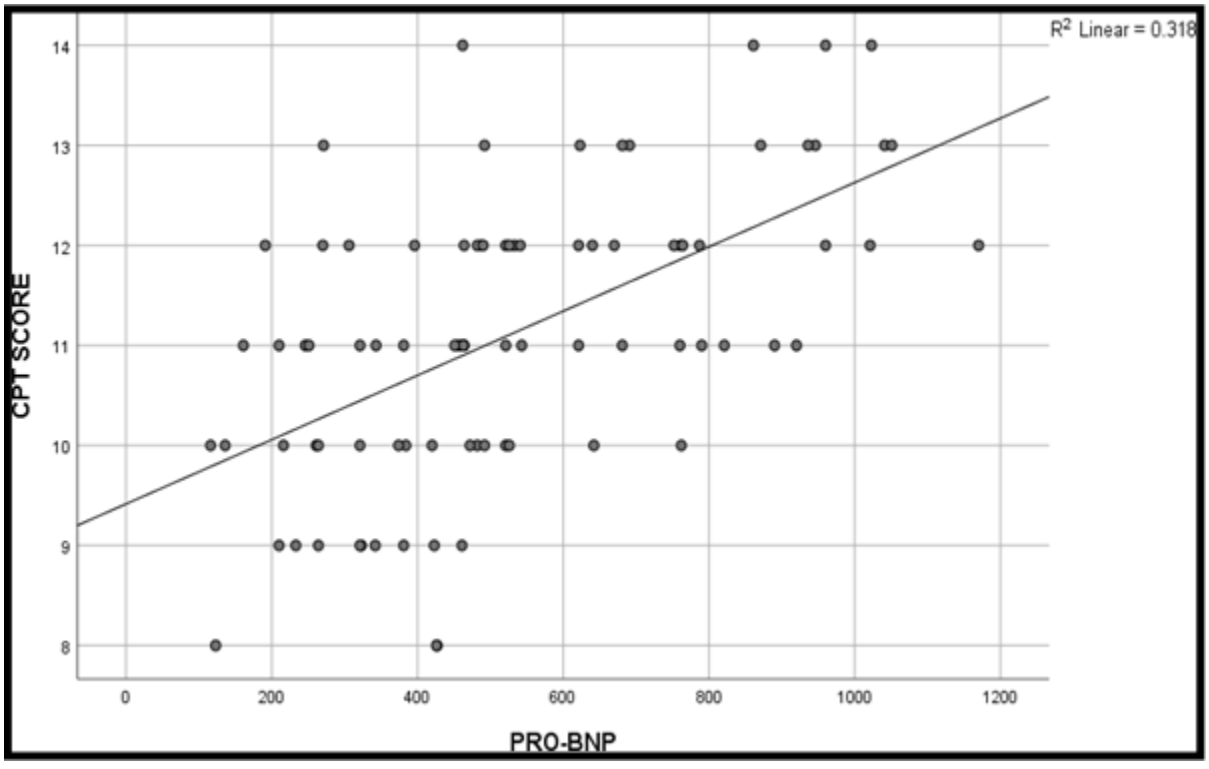
IVCT (m/s)	40.1 (2.4)	39.7 (2.63)	0.7
MPI index	0.3 (0.04)	0.3 (0.04)	0.9
SEPTUM			
A' (cm/s)	7.3 (0.3)	7.3 (0.35)	0.9
E' (cm/s)	12.1 (1.4)	12 (1.39)	0.8
S' (cm/s)	8.2 (0.4)	8.2 (0.43)	0.9

S' (cm/s) 8.2 (0.4) 8.2 (0.43) 0.9

* P- value considered significant difference at 95% CI (P<0.05) ** P- value considered significant difference at 99% CI (P<0.01) AO- Aorta, LA- Left atrium, RV- Right ventricle, PA- Pulmonary

artery, LVPW- Left ventricular posterior wall, IVS- Interventricular septum, LVEDD- Left ventricle end diastolic diameter, LVESD- Left ventricle end systolic diameter, EF- Ejection fraction, FS- Fractional shortening, MV= Mitral valve, E= Early diastolic inflow velocity, A= Velocity during active atrial contraction, E/A= Early to atrial flow velocities, Dt= Deceleration time, LV= Left ventricle, S= Systolic myocardial velocity, E/e= Mitral annular early diastolic velocity, IVCT= Isovolumetric contraction time IVRT= Isovolumetric relaxation time, MPI= myocardial performance index, RV= Right ventricle, E/e= Mitral annular early diastolic velocity

"Figure 1 : Correlation between NTpro-BNP levels and CPT Scores of patients"



P-value = 0.00**, CPT- Child-Pugh-Turcotte score.

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