SERUM PRO-BRAIN NATRIURETIC PEPTIDE (PRO-BNP) IN PATIENTS WITH CIRRHOSIS: RELATION TO CARDIAC DYSFUNCTION AND SEVERITY OF DISEASE

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ABSTRACT

BACKGROUND AND AIMS

Subclinical cardiac dysfunction is present in many patients with cirrhosis and is an important cause of morbidity and mortality post-transplant. We tried to study the prevalence of cardiac dysfunction in cirrhotics and assess the relationship between pro-BNP as a marker of cardiac dysfunction and the severity of cirrhosis. We also evaluated the clinical aspects of cirrhosis and their relation to cardiac dysfunction.

METHODS

Eighty five patients with cirrhosis due to any etiology were evaluated using ECG, 2D echocardiography, pro-BNP and severity of liver disease according to CTP class. Pro-BNP was assessed using electrochemiluminescence immunoassay. Data was analysed with SPSS for Win version 16 software.

RESULTS

Majority of the patients (60%) were in the age group 30-50 yrs. Most common etiology was alcohol (48.23%). Significant correlation noted between Child class and cardiac dysfunction ($A < B < C$, $p = 0.000$), pro-BNP and Child class ($p = 0.001$), pro-BNP and QTc interval ($p = 0.001$). A low pro-BNP cut off level (100ng/ml) led to increased sensitivity, but decreased specificity for detection of cardiac dysfunction.

CONCLUSION

Cardiac dysfunction is common in cirrhotics and the frequency increases with the severity of cirrhosis. Markers like pro-BNP can predict underlying cardiac dysfunction with reliable sensitivity and specificity. Presence of cardiac dysfunction is a surrogate marker of advanced liver disease.

KEYWORDS

Pro-BNP, CTP Class, Cardiac Dysfunction.

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INTRODUCTION

Liver cirrhosis is associated with a wide range of cardiovascular abnormalities including hyperdynamic circulation, cirrhotic cardiomyopathy, and pulmonary vascular abnormalities. Patients with end-stage liver disease manifest a hyperdynamic circulation characterized by warm skin, spider angioma, palmar erythema, and bounding pulse. These cardiovascular changes were described over 50 years ago by Kowalski and Abelman in a group of alcoholic cirrhotic patients.¹

Major stresses on the cardiovascular system such as liver transplantation, infections and insertion of Transjugular Intrahepatic Portosystemic Shunts (TIPS) can unmask the presence of cirrhotic cardiomyopathy and thereby convert latent to overt heart failure. Diastolic dysfunction is present in the vast majority of patients with cirrhotic cardiomyopathy, and that simple echocardiographic indices such as the E/A ratio may detect diastolic dysfunction even at rest. This may therefore represent the best available screening test to diagnose cardiac dysfunction.

Impaired ventricular contractility in response to stimuli is also described in cirrhotic patients.^{2,3} Initially, this was thought to be a manifestation of latent alcoholic cardiomyopathy, but later studies in non-alcoholic patients and in experimental animal models revealed the same pattern of blunted cardiac contractile responsiveness.^{4,5} Thus, these cardiovascular changes are now termed "cirrhotic cardiomyopathy."^{6,7} Due to the associated systemic vasodilatation, overt heart failure is generally not a feature of cirrhotic cardiomyopathy.

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The Transjugular Intrahepatic Portosystemic Shunt (TIPS) produces an acute increase in preload by shifting traffic from the portal vein circulation to the systemic circulation, leading to worsening of the hyperdynamic state. These consequences are responsible for an increased probability of death in patients with CCM immediately after TIPS.⁸

Another trigger for decompensation of CCM is LT. It is the third leading cause of death after rejection and infection,⁹ 47% of patients have radiographic acute pulmonary edema immediately after LT,¹⁰ and 3% developed new dilated cardiomyopathy in the first 6 months.¹¹

Several studies have shown that if pro-BNP and BNP were elevated, these were related to the severity of cirrhosis, myocardial dysfunction, myocardial hypertrophy, and QT prolongation.^{12,13} The most common way to study the LV systolic function is using two-dimensional echocardiography.

For the analysis of diastolic function, the mitral E/A ratio has been analyzed in most reported studies of CCM, concluding that a ratio ≤ 1 is associated with increased mortality risk. A mitral E/A ratio ≤ 1 is present in 50–70% of patients with ESLD, being more evident with the disease progression (MELD ≥ 20) and lowest in patients with ascites.^{14,15}

Predicting patients that are at a higher risk of developing cardiopulmonary complications after TIPS insertion remains difficult. A recent study found that an E/A ratio of ≤ 1 was predictive of slow ascites clearance (Hazard ratio=7.3, 95% confidence interval=1.3-40.7, $P=0.021$) and death after TIPS (Hazard ratio=4.7, 95% confidence interval=1.1-20.2, $P=0.035$).¹⁶

These findings are in agreement with a previous study showing a higher mortality rate in patients with an E/A ratio of <1 .¹⁷ Post-operative mortality from heart failure and cardiomyopathy has been reported shortly after liver transplantation.¹⁸

NATRIURETIC PEPTIDES

BNP is mainly expressed in heart. Its concentration is highly increased in patients with congestive heart failure. Pro-BNP is a preferred marker in the diagnosis of heart failure, clinical relevance of which is frequently and extensively reviewed. In the normal heart, main site of BNP gene expression is atria. Ventricular gene expression is drastically increased in diseases that affect ventricles. FDA has cleared a pro-BNPng/ml cut-off of 100ng/ml for optimal diagnostic accuracy. Normal subjects older than 75 years have concentrations above 100ng/ml.¹⁹

MATERIALS AND METHODS

1. Design : observational study.
2. Study protocol approved by institutional Ethics committee.
3. Consent obtained from each patient.
4. Patients included in study from Oct 2011 to Oct 2013.

Inclusion Criteria

1. Patients with cirrhosis <60 yr. age irrespective of etiology were evaluated for presence of cardiac dysfunction.
2. Patients with proven cirrhosis diagnosed by:
 - a. Altered LFT for >6 months with esophageal varices or USG showing shrunken nodular liver with features of portal hypertension or
 - b. Biopsy if available showing cirrhosis.

Exclusion Criteria

1. Patients with primary cardiac or pulmonary disease.
2. Patients with hypertension and severe anemia (Hb <8 gm%).
3. Patients on Diuretics and B-blockers.

4. Patients on cardiac medications.
5. Patients with DM and thyroid disorders.
6. Patients with active infections (UTI, RTI, Sepsis).
7. Mean arterial pressure <60 mmHg.

All the patients admitted to Department of Gastroenterology at Osmania Medical College with cirrhosis of liver and its complications were screened for the study. Those who qualified for the study underwent a baseline 2D-Echo, ECG and blood collected for serum pro-BNP estimation before any kind of treatment was administered to avoid any confounding effect. Serum pro-BNP was analyzed by using an electrochemiluminescence sandwich immunoassay.

Patients were divided into two groups depending on the presence or absence of cardiac dysfunction (Diastolic and/or Systolic). Various clinical and lab indices were compared between the two groups. Patients were also divided into those with and without ascites, Alcohol and Non-alcohol groups for comparison. The data was compiled in an Excel sheet and was analysed using SPSS version 16 software. Data was expressed as Mean $\pm$ standard deviation. The probability level of $P < 0.05$ was set for statistical significance.

RESULTS AND ANALYSIS

Out of a total of 85 patients, majority of patients were in the age group of 30-50 years (60%) (Table 1). Most common cause of chronic liver disease in our study is alcohol related cirrhosis of liver followed by hepatitis B virus related chronic liver disease (Table 2). Out of total 85 patients 38 patients had diastolic dysfunction; out of 38 patients 3 had associated systolic dysfunction. None of the patient had isolated systolic dysfunction.

Significant co-relation between CTP class and cardiac dysfunction. Patients with CTP class C are more likely to have cardiac dysfunction as compared to CTP class A, B. P-value (For cardiac dysfunction and CTP Class) $\rightarrow 0.000$ (Table 3).

There is correlation between albumin levels and cardiac dysfunction. Patients with lower albumin levels are more likely to have cardiac dysfunction ($p=0.005$) (Table 4). There is correlation between serum Albumin levels and serum pro-BNP levels. Patients with lower Albumin levels are more likely to have higher pro-BNP levels ($p=0.000$).

With a cut-off of 167ng/ml for pro-BNP, there is correlation between its levels and presence of cardiac dysfunction. With this cut-off it has relatively low sensitivity (78.94%), but higher specificity (93.36%) when compared with a cut-off of 100ng/ml ($p=0.008$) (Table 5). With a cut-off of 100 ng/ml pro-BNP has high sensitivity (97.36%) and low specificity (47.08%) in detecting presence of cardiac dysfunction ($p=0.000$) (Table 6).

There is correlation between prolonged QTc and elevated pro-BNP levels. Patients with prolonged QTc are more likely to have elevated pro-BNP levels ($p=0.000$) (Table 7). INR more than 1.4, serum albumin <2.8 , mean arterial pressure ≤ 75 mmHg, QTc >0.44 , CTP score ≥ 10 , serum pro-BNP with a cut-off of 100 ng/ml and 167 ng/ml can be used as clinical predictors of underlying cardiac dysfunction. These patients should undergo detailed cardiac evaluation (Table 8).

DISCUSSION

In the presence of cirrhosis, cardiac dysfunction is defined as:

- Systolic incompetence in times of stress.
- Diastolic dysfunction related to altered diastolic relaxation.
- Electro-physiologic abnormalities in absence of primary cardiac diseases (prolonged QTc).

Patients with cardiac dysfunction are more likely to develop complications like arrhythmias, heart failure, myocardial ischemia, and acute pulmonary edema in post-transplant period and post TIPS. Exact prevalence of cardiac dysfunction in cirrhosis remains unclear. There are very few studies, which have attempted to find out the prevalence of cardiac dysfunction in patients with liver cirrhosis at rest. In our study, we tried to find out the prevalence of cardiac dysfunction on 2D-Echo in the form of diastolic and/or systolic dysfunction. We tried to find out the utility of serum pro-BNP in predicting the presence of cardiac dysfunction in patients with liver cirrhosis.

The prevalence of cardiac dysfunction in our study is 44.7%. For the sake of uniformity, cardiac dysfunction has been used to denote presence of systolic and/or diastolic dysfunction. Various other authors also reported more or less similar findings. The highest prevalence was reported by Merli et al.²⁰ (Table 9). We did not use stress echo in our study, which could have probably underestimated the actual prevalence of cardiac dysfunction. Wong et al. included largest number of patients in his study and reported a prevalence of 56.3%.²¹

We noted a higher prevalence of cardiac dysfunction in patients with CTP class C (75%) as compared to patients with CTP class A (11.11%) and CTP class B (45.8%). Similar results were noted by other authors as (Table 10). Bernardi et al. in their study found that the frequency of cardiac dysfunction was dependent on the severity of cirrhosis as assessed by Child Turcotte Pugh score.²² Similar observation was done by Rabie et al. in their study on diastolic dysfunction in cirrhotics.²³ In our study, similar correlation was found. Lunzer et al. and Torregrossa et al. found no correlation between etiology of cirrhosis and severity of cardiac dysfunction.^{24,25} In our study, similar findings were seen.

Taking a cut-off of 0.44, QTc prolongation was seen in 30 patients, (35.29%) in our study. Prolonged QTc interval correlated with presence of cardiac dysfunction, but has low sensitivity (55.26%) in detecting cardiac dysfunction. Similar findings were seen in other studies (Table 11). We noted that patients with cardiac dysfunction have higher mean pro-BNP levels as compared to patients without cardiac dysfunction. Similar observations were also made by other authors. The variation in the mean pro-BNP levels as observed by various authors could be because of varied ethnicity, inclusion and exclusion criteria, assay used to measure pro-BNP levels and other confounding variables like use of diuretics and β -blockers, which are likely to alter pro-BNP levels (Table 12).

We found a negative correlation (p-value 0.000) between serum albumin levels and serum pro-BNP levels. Similar relation was noted by Yilmaz et al. Patients with serum albumin <2.8 mg/dl are more likely to have higher mean pro-BNP levels.²⁶ We found a positive correlation (P value -0.001) between CTP class and pro-BNP levels. Patients with CTP class C are more likely to have higher pro-BNP levels compared to CTP class A and B. Similar observations were made by Yilmaz et al.²⁶ and Ziada et al.²⁷

We used a cut-off of 100 ng/ml given by FDA to find out its role as a predictor of cardiac dysfunction in patients with liver cirrhosis. It showed a high sensitivity of 97.36% and a low specificity of 46.08%. We also analyzed our data using a higher cut-off of 167 ng/ml. It showed a sensitivity of 78.94% and specificity of 93.36%. Saner et al. used a cut-off of 391ng/ml and found a sensitivity of 100% in predicting cardiac dysfunction.²⁸ Ziada et al. used a cut-off of 265 ng/ml and found a sensitivity of 91.7% and specificity of 86.6%.²⁷ We noted that a higher cut-off has more specificity, while lower cut-off has more sensitivity (Table 13).

CONCLUSION

Significant correlation found between CTP class and cardiac dysfunction. Patients with CTP class C are more likely to have cardiac dysfunction as compared to CTP class A, B. There is positive correlation between CTP class, cardiac dysfunction and pro-BNP levels. Patients with higher CTP score are more likely to have cardiac dysfunction and elevated pro-BNP levels. Higher cut off values for pro-BNP (167mg/ml) lead to increased specificity, but decreased sensitivity. INR more than 1.4, serum albumin <2.8, mean arterial pressure $\leq$ 75mmHg, QTc>0.44, CTP score $\geq$ 10, serum pro-BNP with a cut-off of 100mg/ml and 167mg/ml can be used as clinical predictors of underlying cardiac dysfunction.

LIST OF ABBREVIATIONS

CCM – Cirrhotic Cardiomyopathy.

LT – Liver Transplant.

ESLD – End Stage Liver Disease.

MELD – Model for End Stage Liver Disease.

UTI – Urinary Tract Infection.

RTI – Respiratory Tract Infection.

HBV – Hepatitis B Virus.

HCV – Hepatitis C Virus.

Age Group (Years)	Number of Patients (N=85)
10-20	6(7.05%)
21-30	11(12.94%)
31-40	25(29.41%)
41-50	26(30.58%)
51-60	17(20%)

Table 1: Age Group of the Patients

Etiology	Number of Patients (n=85)
Alcohol	41(48.23%)
HBV	11(12.94%)
Alcohol + HBV	8(9.41%)
Auto-immune liver disease	5(5.88%)
HCV	5(5.88%)
Cryptogenic	5(5.88%)
Wilson's disease	4(4.7%)
Budd-Chiari syndrome	3(3.52%)
Alcohol + HCV	1(1.17%)
HBV + HCV	1(1.17%)

Table 2: Etiology of Liver Disease

CTP Class	Number of Patients (N=85)	Cardiac Dysfunction (N=38)
A	18	2 (11.11%)
B	39	15(38.46%)
C	28	21(75%)

Table 3: Prevalence of Cardiac Dysfunction in Liver Cirrhosis as per CTP class

P-value (for cardiac dysfunction and CTP Class) $\rightarrow$ 0.000.

Albumin Level (mg/dl)	Number of Patients N=85	Cardiac Dysfunction N=38	Pro-BNP Mean +/-S.D
<2.8	31	19	534.58+/-480.75
2.8-3.5	48	18	228.58+/-459.69
>3.5	6	1	258.33+/- 470.03

Table 4: Correlation of Albumin Levels with Cardiac Dysfunction and Pro-BNP levels in Liver Cirrhosis

Cardiac Dysfunction→ Pro-BNP ↓	Present (N=38)	Absent (N=47)
Elevated (N=33)	30	3
Normal (N=52)	8	44

Table 5: Correlation of Cardiac Dysfunction and Pro-BNP Levels (Cut-off 167ng/ml) in Liver Cirrhosis

P-value→ .008.

SENSITIVITY →78.94%.

SPECIFICITY →93.36%.

Cardiac Dysfunction→ Pro-BNP ↓	Present (N=38)	Absent (N=47)
Elevated (N=62)	37	25
Normal (N=23)	1	22

Table 6: Correlation of Cardiac Dysfunction and Pro-BNP Levels (cut-off 100ng/ml) in Liver Cirrhosis

p-value : 0.000.

SENSITIVITY → 97.36%.

SPECIFICITY → 46.08 %.

Pro -BNP	Elevated (N=33)	Normal (N=52)
QTc		
Prolonged (N=30)	20	10
Normal (N=55)	13	42

Table 7: Correlation of pro-BNP and QTc Prolongation in Liver Cirrhosis

	Number of Patients	Cardiac Dysfunction	P-value
INR (>1.4)	28	2.3	0.004
Serum Albumin (< 2.8 mg)	31	19	0.007
Serum Na (<125)	15	10	0.05
Mean arterial pressure (≤ 75 mm of Hg)	13	11	0.002
Platelets (< 1lac/mm3)	52	26	0.157
QTc (> 0.44)	30	21	0.001
CTP score(≥10)	22	17	0.000
Serum pro-BNP (>167ng/ml)	33	30	0.000
Serum pro-BNP (>100ng/ml)	62	37	0.000

Table 8: Clinical Predictors of Cardiac Dysfunction in Liver Cirrhosis

Author	Total Patients	Cardiac Dysfunction	Percentage
Wong et al. ²¹	355	200	56.3%
Merli et al. ²⁰	74	47	64%
Sheikh et al. ²⁹	74	33	44.6%
Vasilios et al. ³⁰	92	55	59.8%
Present study	85	38	44.7%

Table 9: Prevalence of Cardiac Dysfunction in Liver Cirrhosis in Various Studies

Author	CTP class A	CTP class B	CTP class C
Eldeeb et al. ³¹	50%	66.66%	78%
Vasilios et al. ³⁰	10.3%	12.8%	45.8%
Our study	11.11%	38.46%	75%

Table 10: Prevalence of Cardiac Dysfunction in Liver Cirrhosis as per CTP class

Author	Percentage of Patients
Bernardi et al. ²²	46.8%
Henriksen et al. ³²	37%
Pothumana et al. ³³	45%
Mohammed et al. ³⁴	83%
Sheikh et al. ²⁹	21.6%
Our study	35.29%

Table 11: Prevalence of QTc Prolongation in Liver Cirrhosis in Various Studies

Author	No Cardiac Dysfunction (pg/ml)	Cardiac Dysfunction (pg/ml)
Eldeeb et al. ³¹	140.84 +/- 144.14	231.3+/-200.92
Licata et al. ³⁵	70.8+/- 70.6	365.2+/- 340
Our study	152.1+/-306.09	582+/-524.37

Table 12: Mean Pro-BNP Levels in Liver Cirrhosis in Various Studies

Authors	Cut-off (pg/ml)	Sensitivity	Specificity
Saner et al. ²⁸	391	100%	-
Ziada et al. ²⁷	265	91.7%	86.6%
Neven et al. ³⁶	101	87.6%	72.73%
Our study	100	97.36%	46.08%
Our study	167	78.94%	93.36%

Table 13: Cut-off of serum pro-BNP for Cardiac Dysfunction in Liver Cirrhosis in Various Studies

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