JMSCR Vol||05||Issue||10||Page 29438-29445||October 2017

www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i10.164

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Early Detection of Cirrhotic Cardiomyopathy Using Cardiac Bio-Markers: A Cross Sectional Study

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Abstract

Introduction: *Cirrhosis is well known to be associated with severe hemodynamic changes like hyperdynamic circulation, increased cardiac output, increased heart rate and decreased systemic vascular resistance resulting in cirrhotic cardiomyopathy (CCM). Patient with CCM are at higher risk for complications during surgeries and liver transplantation. Hence early detection may be beneficial in offering treatment even in patients asymptomatic for heart disease.*

Objectives: *To determine the presence of elevated cardiac biomarkers in patients with chronic liver disease and to study the relationship between these cardiac biomarkers and severity of chronic liver disease.*

Methods: *Cross sectional study including 50 adult patients diagnosed with chronic liver disease. Patients were subjected to detailed history and physical examination, basic biochemical profile, and cardiac biomarkers (Troponin I, CK MB, BNP). Severity of liver disease was assessed using Child-Pugh and MELD scores. The levels of cardiac markers in the study population, and their correlation with disease severity were evaluated using appropriate statistical methods.*

Results: *In the present study of 50 patients with chronic liver disease (CLD) the mean age was 46.48 years and 84%were male. 68% had alcohol related CLD, and 4% had chronic Hepatitis B. Troponin I was elevated in 12(24%) patients, CKMB in 46(92%) and BNP in 20(40%) patients. The elevation in cardiac enzymes demonstrated a linear correlation with severity of liver disease, Troponin I correlated significantly with Child Pugh score (p= 0.001) and Meld score(p=0.015); BNP with Child Pugh score(p=0.001) and*

MELD score(p=0.022). There was no statistically significant relationship between CKMB and severity of liver disease.

Conclusion: *Troponin I may prove to be an useful marker of myocardial injury in chronic liver disease patients and elevated BNP may reflect an underlying cardiac dysfunction. Use of these biomarkers for screening patients with advanced liver disease may aid in early detection of cirrhotic cardiomyopathy.*

Introduction

Liver cirrhosis is associated with severe hemodynamic changes that include hyperdynamic circulation with altered cardiac output, increased heart rate and reduced systemic vascular resistance. Cirrhotic cardiomyopathy is an entity reported in patients with advanced cirrhosis, which is characterised by reduced contractile responsiveness to stress, altered diastolic relaxation and electrophysiological abnormalities (QT interval prolongation) all occurring in the absence of existing cardiac disease. At present there is evidence that compromised liver function and portal hypertension along with splanchnic vasodilatation lead to the development of these hyperdynamic changes[1]. Other factors like increased sympathetic activity, increased blood flow and presence of arteriovenous communications can play a significant role in pathogenesis. Many pathophysiological mechanisms like reduced beta-receptor action seem to be involved in the cardiac and autonomic dysfunction.

Cirrhotic cardiomyopathy is best demonstrated by pharmacological or physical stress. Investigations such as electrocardiography (ECG), 2D echocardiography, and cardiac serum markers (Troponin I, NT pro BNP) also play a role in diagnosis. Elevation of Troponin I is increasingly accepted to be a marker of cirrhotic cardiomyopathy[2].

Invasive procedures such as surgery, insertion of a transjugular intrahepatic portosystemic shunting and liver transplantation may adversely affect the prognosis of patients with cirrhotic cardiomyopathy, and result in worsening of the smoldering cardiac failure. Therefore, patients with this complication of cirhhosis need to be detected early, even if they are asymptomatic, in order to prevent mortality and prognosticate the patients.

Objectives

- To determine the presence of raised cardiac biomarkers in patients with chronic liver disease.
- To study the relationship between these cardiac biomarkers and severity of chronic liver disease.

Materials and Methods

The study was a prospective cross sectional study carried out in the Department of Internal medicine at a semi urban tertiary care centre in South India over a period of twelve months (June 2015 to May 2016) after obtaining necessary approval from the institutional ethics committee. Informed consent was obtained from all the participants prior to initiation into the study.

Inclusion Criteria

All patients with chronic liver disease, aged above 18 years, who agreed to give informed consent were recruited for the study.

Exclusion Criteria

Patients with acute liver disease, those aged below 18 years, patients with pre-existing congenital and acquired heart disease, patients with chronic kidney disease, those with active infection and those who refused informed consent were excluded from the study.

Sample Size

Based on previous studies, prevalence of elevated Troponin I was 32% in patients with cirrhosis[3]. Sample size calculation was done at 80% power, with an alpha error of 0.05, and minimum sample size of 50 was calculated.

Data Collection

The patients were subjected to detailed history (age, sex, alcohol intake and duration of alcohol intake, duration of liver disease and co-existing conditions like Diabetes Mellitus and Hepatitis B, if any, were noted) and clinical examination (pallor, icterus, edema, splenomegaly, ascites and encephalopathy). The baseline investigations like liver function tests, coagulation parameters, renal function tests and electrolytes were performed according to the treating clinicain. For the purpose of study, 5ml of additional blood was collected and cardiac bio-markers were analyzed. Troponin I was measured by CLIA method, CK MB by IFCC method and BNP by Fluorescence Immune Assay.

Statistical Analysis

Severity of liver diseases as assessed by Child Pugh classification was considered primary explanatory variable. Presence of elevated cardiac markers like troponin I, CK-MB, NT pro BNP were considered as primary outcome parameters. The other liver disease related factors like duration of liver disease, MELD score, variables like age, gender, history of alcohol intake, and duration of alcohol intake were considered as other explanatory variables.

Initially descriptive analysis of explanatory and outcome variables was done using mean and standard deviation for quantitative variables, frequency and percentages for categorical variables. The association between the explanatory and outcome variables was assessed by cross tabulation and chi square test for categorical variables. ANOVA was used to compare the mean values of quantitative variables across categorical exposure variables. The correlation between two quantitative variables was assessed by Pearson's correlation coefficient. IBM SPSS version 21 was used for statistical analysis. p value < 0.05 was considered as statistically significant.

Results

The baseline parameters along with physical examination characteristics, laboratory parameters and cardiovascular parameters were analysed to obtain the relationship between chronic liver disease and cardiac function. The major baseline characteristics are represented in Table 1.

The mean age of the study population was 46.48± 11.51 years (mean±SD). Majority of the study population (56%) fell in the age group of 41 to 60 years, followed by 32% participants between 21 to 40 years of age and 12 % patients were above 60 years. 42(84%) were males, and 68% were alcohol consumers. The mean duration of liver disease in the present study was 10.19 ± 8.29 years. With regard to physical examination findings, 23 patients (46.0%) had pallor, 36 (72%) were icteric, and 12 (24%) had edema. Splenomegaly was noted in 24 patients (48%), 8(16%) had encephalopathy and 27 (54%) had ascites [19 patients (38%)with mild ascites and 8 (16%) with moderate to severe ascites]. The summary of laboratory parameters including liver, renal function and coagulation tests is shown in Table 2. Among the study population, only 2 patients (4%) were found to be positive for HBsAg and none were detected to have hepatitis C. The severity of liver disease was assessed based on the Child-Pugh scoring system. The majority of

patients in the study population were found to have moderate to severe liver disease (Child A-24%, Child B – 30% and Child C –28%). MELD (Model of End stage Liver Disease) score is used to calculate prognosis and survival rate of the cirrhotic patients, especially to categorise for liver Transplantation. The mean MELD score was 15.08±5.37 in our study population.

After ascertaining the baseline parameters, the cardiac biomarkers were studied, and compared with the severity of liver disease. Troponin I values >0.01 ng/ml, CK MB >25 IU/L and BNP >100 pg/ml were regarded as significant. The mean value of Troponin I was 0.017±0.06 ng/ml, CK MB was 40.78±22.26 IU/L, and that of BNP was 226.5±352.8 pg/ml in the study population. Overall, CKMB was elevated in more than 90% of the patients (Table 3). The association between cardiac markers against all classes of Child Pugh and MELD scores was analyzed to determine whether the severity of liver disease had any correlation with the elevation of cardiac markers. The results are shown in Table 4 (Cardiac biomarkers with Child Pugh score) and Table 5 (Cardiac markers with MELD score). It can interpreted from these data that Troponin I and BNP have a linear correlation with increasing severity of liver disease, whereas CKMB seems to have no such relationship (Figures 6, 7).

Table 1: Baseline Characteristics

Parameter		Mean ± SD /Frequency	Percentage
Age (years)		46.48± 11.51	
Sex	Male	42	84
	Female	8	16
History of alcohol		34	68
Duration of alcohol intake (years)		15.20± 9.171	
Duration of liver disease (years)		10.19 ± 8.29	
Type 2 Diabetes Mellitus		13	26

Table 2: Laboratory parameters at admission

Parameter	Mean±SD
Total Bilurubin (mg/dl)	3.344 ± 3.732
Direct Bilirubin (mg/dl)	1.364 ± 2.005
AST (U/L)	68.16 ± 35.72
ALT (U/L)	68.16 ± 18.36
Serum Alkaline Phosphatase (U/L)	133.4 ± 96.23
GGT (U/L)	97.06 ± 113.4
Total protein (g/dl)	6.998 ± 1.126
Albumin (g/dl)	3.552 ± 1.045
PT(Test) (seconds) INR (ratio)	15.90 ± 2.556 1.303 ± 0.197
aPTT (seconds)	41.91 ± 3.107
BUN (mg/dl)	10.38 ± 3.833
Serum creatinine (mg/dl)	1.049 ± 0.282
Sodium (mEq/L)	137.1 ± 18.90
Potassium (mEq/L)	3.756 ± 0.428

Table 3: Distribution of Cardiac biomarkers

Cardiac Biomarker	Mean±SD	Frequency positive n(%)
Troponin I (ng/ml)	0.017±0.06	12 (24)
CKMB (IU/L)	40.78±22.26	46 (92)
BNP (pg/ml)	226.5±352.8	20 (40)

Table 4: Correlation between Child- Pugh score and cardiac markers

Severity of liver disease		Cardiac biomarker					
		Troponin I		CKMB		BNP	
		Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)
Child Pugh score	A	2 (16.7)	10 (83.3)	12 (100)	0 (0)	2 (16.7)	10 (83.3)
	B	2 (8)	23 (92)	24 (96)	1 (4)	7 (28)	18 (72)
	C	8 (61.5)	5 (38.5)	10 (76.9)	3 (23.1)	11 (84.6)	2 (15.4)
p value		<0.001		0.061		<0.001	

Table 5: Correlation between Meld score and cardiac biomarkers

Cardiac biomarkers		MELD score (Mean ± SD)	p value
Troponin I	Positive	18.33 ± 3.9	0.015
	Negative	14.06 ± 5.4	
CKMB	Positive	14.77 ± 5.49	0.164
	Negative	18.69 ± 3.82	
BNP	Positive	17.19 ± 3.94	0.022
	Negative	13.68 ± 5.79	

Figure 6: Correlation between MELD score and Troponin I

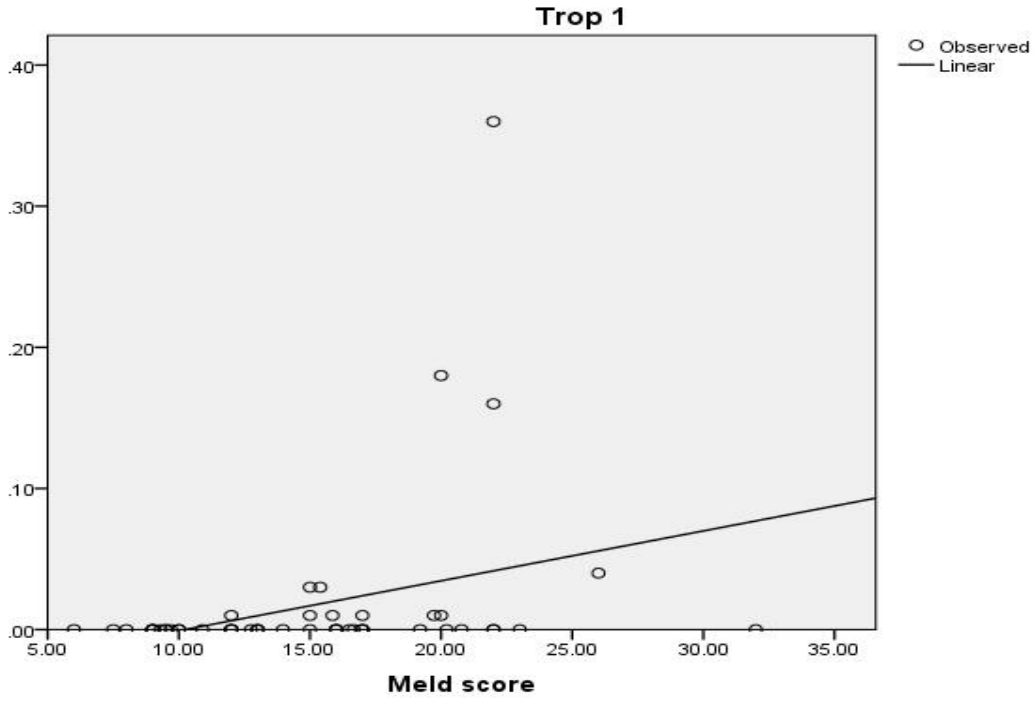
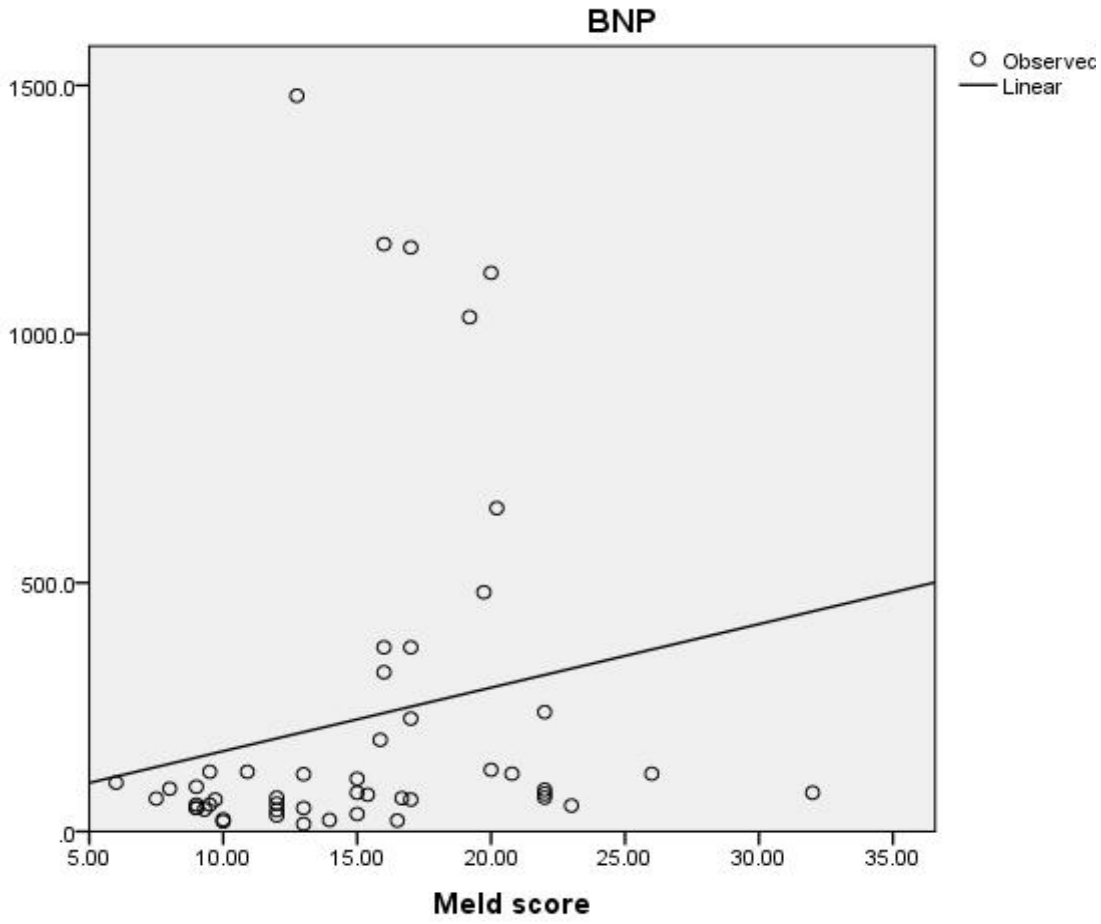


Figure 7: Correlation between MELD score and BNP



Discussion

Cardiac function and impending cardiac failure need to be recognised early and treated effectively. Failure to address the presence of early cirrhotic cardiomyopathy may carry a poor prognosis in patients with chronic liver disease, especially following TIPS and liver transplantation. Very few studies have been done in the Indian population to assess the relationship between cardiac biomarkers and the severity of liver disease. The present study aims to detect cardiac dysfunction and myocardial injury in patients with cirrhosis who are asymptomatic for heart disease, by using cardiac biomarkers namely troponin I, CKMB and BNP.

Troponin I:

In the present study an elevated troponin I was seen in 12 patients (24%). This was similar to a study by Pateron D et al[3] which showed elevated serum value of Troponin-I in 32% of cirrhotic patients, especially in those with alcoholic cirrhosis. In the present study population, higher values of Troponin I were obtained in severe liver cirrhosis as evidenced by Child Pugh score as well as Meld score, which was statistically significant (P= 0.001). The present study also demonstrates that also exists a linear co-relation between sub-clinical myocardial injury and severity of liver cirrhosis

CK MB:

There was no demonstrable correlation between CKMB and the severity of liver disease in the studied population of cirrhotic patients. Interestingly, there appeared to be a decline in

CKMB as the severity scores increased, although this was not statistically significant (p=0.06). A possible explanation would be that the muscle mass and consequently the total CK levels would be decreased in those with advanced liver disease as a result of protein malnutrition. There are no studies which show otherwise or supporting the observed results in the present study, to the best of our knowledge[6].

BNP:

The results of this study indicate that there is a rise in BNP levels in severe liver disease demonstrating a linear co- relation with the severity of cirrhosis. A study by Florence WO et al[5] also showed significantly higher BNP levels in patients with cirrhosis and ascites (P = 0.05). Licata et al[7] observed in their study, that BNP levels rose liniearly in those with high Child Pugh and MELD scores. Similarly Metwaly et al found that BNP is correlated both with severity of liver disease and morpho-functional cardiac changes in patients with hepatitis C and fatty liver related cirrhosis[8]. Wong et al have propsed based on the results of their study that levels of BNP may be useful in screening patients with cirrhosis for the presence of cirrhotic cardiomyopathy[9]. The significance of BNP elevation has also been shown in the pediatric age group by Fattouh et al[10].

The present study therefore establishes that even asymptomatic patients with advanced liver disease have subclinical myocardial injury in the form of elevated Troponin I and ventricular dysfunction as reflected by increase in CKMB. Screening of patients for cirrhotic cardiomyopathy should be undertaken, especially in those with higher Child-Pugh and MELD scores. This may aid in early detection of cardiac dysfunction, especially prior to surgical procedures, TIPS and liver transplantation.

Conclusion

Cirrhotic cardiomyopathy is an under-recognized complication of chronic liver disease. Early detection and prompt treatment may help in improving the prognosis of patients especially after major surgeries and liver transplantation. Increase in cardiac markers such as Troponin-I and Brain Natriuretic Peptide (BNP) correlates with the severity of liver disease. Therefore, it may be prudent to screen patients with advanced liver disease for evidence of cirrhotic cardiomyopathy.

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