Cirrhotic Cardiomyopathy: a cross-sectional study to know the frequency and its correlation with the severity of cirrhosis and other factors

[1]Dr. Kailash Mishra, [2]Dr. Purti Agrawal Saini, [3]Dr. Poonam Mishra, [4]Mr. Piyush Kumar Mishra

[1]Consultant Gastroenterologist, Jabalpur Hospital and research center, Jabalpur, (M.P)
[2]Associate Professor, Department of Pathology, Nandkumar Singh Chauhan Government Medical College, Khandwa, (M.P)
[3]Demonstrator, Department of Pathology, NSCB Medical College, Jabalpur, (M.P)
[4]Statistician, Department of Community Medicine, Nandkumar Singh Chauhan Government Medical College, Khandwa, (M.P)

Corresponding Author:
Dr. Poonam Mishra

ABSTRACT:
Background: Cirrhotic cardiomyopathy (CCM) is a cardiac dysfunction in the patients of cirrhosis. It is associated with increased morbidity and mortalitybecause of heart failure following invasive procedures. The present study aimed to determine the frequency of cirrhotic cardiomyopathy and its correlation with the spectrum of disease severity, Pro-BNP levels & other factors.
Material and Method: This cross-sectional study included 50 cirrhotic patients**.** All the demographic variables, biochemical test results and ECG findings were noted. Cardiac functions were assessed by echocardiography.The severity of cirrhosis was assessed by Child-Turcotte-Pugh(CTP) score and Model for end-stage liver disease (MELD) score. All the collected continuous and categorical data was represented as mean/standard deviation and frequency/percentage. The association between CCM and different parameters were assessed by Chi-square test and ANOVA test.
Results: Among 50 cirrhotic patients, systolic dysfunction was observed in 52% (n=26), diastolic dysfunction in 72% (n=36) and prolonged QTc in 78% cases (n=39)of cirrhotic patients. A total of 34 patients (68%) had CCM. The raised Pro-BNP level was observed in 70% (n=35) of patients. The CTP stage A, B and C was observed in 14%, 48% and 38% of cases respectively. Frequency of CCM was significantly increased with severity of cirrhosis as it was most frequent in CTP-C stage (p=0.001). Demographic variables (such as age, gender and BMI), etiologies and other biochemical parameters were not significantly different in patient with or without CCM. However, CCM patients had a significantly higher CTP score, MELD score and Pro -BNP level.
Conclusion: The Cardiac dysfunctions were more prevalent in higher stages of cirrhosis. The presence of CCM was not related to etiology of cirrhosis whereas; it is directly correlated with higher CTP score, MELD score and Po-BNP levels.
Keyword: Cirrhotic cardiomyopathy, CTP score, MELD score, QTc interval, Pro-BNP.

INTRODUCTION:

In 2005, World Conference of Gastroenterology defined cirrhotic cardiomyopathy (CCM) as "a chronic cardiac dysfunction in patients with cirrhosis characterized by blunted contractile responsiveness to stress (systolic dysfunction) and/or altered ventricular relaxation (diastolic dysfunction) with electrophysiological abnormalities in the absence of known cardiac disease". [1] Liver cirrhosis is characterized by a sustained peripheral vasodilatation which leads to decreased systemic vascular resistance resulting in a reduction of effective circulating plasma volume and blood pressure, and increased heart rate, cardiac output and sympathetic tone, with an eventual sustained reduction of cardiac afterload. [2]

This may be associated with a group of subclinical cardiovascular abnormalities, like resting tachycardia and baseline increased cardiac output, reduced myocardial contractility with a blunted systolic and diastolic response to inotropic and chronotropic stimuli and down-regulation of adrenergic receptor function. There is an increase in levels of brain natriuretic peptide (BNP) and an impaired electric "recovery" of ventricular myocardium.[3,4] This cardiac dysfunction may increase the morbidity and mortality following invasive procedures.[5]Thus, the early management of cardiac complications may change the prognosis and improve the quality of life in cirrhotic patient.

The prevalence of liver cirrhosis is also difficult to estimate, because many persons with compensated cirrhosis do not exhibit signs or symptoms of the disease and because non-invasive studies lack sensitivity to detect cirrhosis at early stages.The objective of this study was to determine the frequency of cardiomyopathy in cirrhotic patients. The present study also conducted to know the correlation between CCM and severity of cirrhosis, etiologies of cirrhosis, and Pro BNP level in northern Indian population.

MATERIALS AND METHODS

After the approval of Institutional Ethics Committee, this cross-sectional study was carried out in the Department of Gastroenterology and Hepatology, M.L.N. Medical College and Swaroop Rani Nehru Hospital, Allahabad for two-year (2014-2015) period.This study included 50 cirrhotic patients.

Inclusion criteria: All cirrhotic patients were included in the study. Diagnosis was done on the basis of history, clinical examination, biochemical and Ultrasonographic (USG) finding, and liver biopsy.

Exclusion criteria: Patients with prior history of myocardial infarction, valvular heart disease, conduction abnormalities, cardiac failure, hypertension, diabetes, severe pulmonary diseases, renal diseases, hepatocellular carcinoma, thyroid diseases, electrolyte imbalance, history of drug intake such as calcium channel blockers, antiarrhythmics and digoxin were excluded.

Data collection: The demographic variables such as age,gender and body mass index (BMI) of all cirrhotic patients were recorded.The base line investigations such as liver function test, serum creatinine and complete hemogram, ascitic fluid analysisesophago-gastroduodenoscopy (EGD) and USG abdomen were done and findingswererecorded. The severity of cirrhosis was assessed by Child-Turcotte-Pugh(CTP) score and Model for end-stage liver disease (MELD) score.

Resting ECG was performed by certified ECG technician in all the patients and the value of corrected QT interval (QTc) of > 0.44 sec was considered as prolonged.Presence of prolonged QTc and >100 heart rate was labeled as 'abnormal ECG'.[6]The two-dimensional echocardiography and color doppler was used to asses systolic and diastolic function. The diagnostic criteria applied forsystolic dysfunction (SDF) was <55% left ventricle ejection fraction (LVEF) and for diastolic dysfunction (DDF) abnormal early diastole/late diastole (E/A) ratio. The grading of diastolic dysfunction was done according to the American Society of Echocardiography. [7,8]

The Pro B type Natriuretic Peptide (pro-BNP) level was determined via Elecsys NT proBNP assay (Roche diagnostics, Mannheim–Germany). The cut-off level was 125 pg/ml.

CCM was diagnosed if evidence of systolic and/or diastolic dysfunction, with supporting criteria of prolonged QTc present. [7]

Statistical analysis: The Continuous variables such as age, BMI, QTc interval (sec), pro-BNP and E/A ratio were expressed as mean with standard deviation (SD).Categorical variables such as gender, etiology, Child-Pugh Class, and elevated pro BNP, increased E/A ratio, prolonged QTc were expressed as frequency and percentage. Chi-square test was applied for comparing categorical variables. ANOVA test and t-test was applied for comparison of continuous variables. A p-value < 0.05 (5%) was considered as statistically significant. All calculations were done using SPSS version 16 (Chicago, IL, USA).

RESULTS:

A total of 50 cirrhotic patients were enrolled in the study during the study period.Out ofthese, 48% of patients were in 41 to 50 years age group. Majority of patients (66%) were males. The demographic variables and baseline parameters were summarized in table -1.

Table-1: Demographic profile and baseline parameters of study population

Variable	Mean ±SD
Age (years)	44.86 ± 15.90
BMI (Kg/m^2)	22.43 ± 2.5
Sr Bilirubin (mg/dL)	5.48 ± 3.43
Sr ALT (IU/L)	129.58 ± 153.99
Sr AST (IU/L)	129.08 ± 113.47
Sr Albumin (g/dL)	3.05 ± 0.731
Prothrombin time (PT)	20.60 ± 8.458
INR	1.77 ± 0.828
S. Creatinine (mg/dL)	0.98 ± 0.311
CTP score	8.94 ± 2.06
MELD score	17.26 ± 13.65
Pro BNP level (pg/ml)	363.5 ± 323.2
Heart rate	86.66 ±13.16
QTc interval (seconds)	0.474 ± 0.066
LVEF	57.28 ± 6.02
E/A ratio	0.89 ± 0.22

The most common cause of cirrhosis was Alcohol (32%). The other causes were post necrotic (24%) due to Hepatitis B and C, wilson's disease (4%) and autoimmune hepatitis (2%). Rest 28% of patients had cryptogenic cirrhosis.The most common presenting symptom was abdominal distension (90%), followed by jaundice (48%), hemetemesis/melena (28%) and altered sensorium (18%). Among 50 cirrhotic patients, CTP stage A, B and C was observed in 14%, 48% and 38% of cases respectively.

According to the diagnostic criteria, SDF was observed in 52% (n=26), DDF in 72% (n=36) and prolonged QTc in 78% (n=39) of cirrhotic patients. All the three abnormalities were seen in 22% (n=11) of cases whereas prolonged QTc with SDF or DDF was found in 46% (n=23) of cases. Thus, among 50 cirrhotic patients, 34 patients (68%) had CCM. The raised Pro-BNP level was observed in 70% (n=35) of cirrhotic patients.

The cardiac parameters such as heart rate, QTc interval and Pro-BNP level were compared among the CTP stages of cirrhotic patient. Systolic function and diastolic function were significantly reduced with severity of cirrhosis. Frequency of CCM was significantly increased with severity of cirrhosis as it was most frequent in CTP-C stage (Table-2).

Table-2: Comparison of cardiac parameters with severity of cirrhosis

Parameter	Cirrhosis Stage			F value/χ2 value	p-value
	CTP-A (n=7)	CTP-B (n=24)	CTP-C (n=19)		
Heart rate (beats/ min)	79.57±11.40	86.63±13.64	89.32±12.80	1.43	0.250
QTc interval (sec)	0.43±0.07	0.47±0.08	0.49±0.04	2.34	0.107
LVEF (%)	60.31±3.88	58.45±6.3	54.70±5.56	3.38	0.042*
E/A ratio	1.11±0.34	0.97±0.14	0.71±0.14	17.35	0.000*
Pro-BNP (pg/ml)	140.43±299.48	360.5±345.42	449.47±273.98	2.48	0.094
CCM % (n)	28.57 (2)	58.33(14)	94.74 (18)	12.71	.001*

*denotes significant value <5%

Demographic variables (such as age, gender and BMI) , etiologies and other biochemical parameters were not significantly different in patient with or without CCM. However, higher CTP score, MELD score and Pro -BNP level were significant associated with presence of CCM. (Table-3)

Table-3 Comparison of demographic and clinical parameters in cirrhotic patients with cardiomyopathy and without cardiomyopathy

Parameter		CCM		χ2 value / t- test	p-value
		Present (n=34)	Absent (n=16)		
Age (years)		42.02±14.74	50.87±16.58	-1.90	0.063
Gender	Male n (%)	22 (64.7)	11 (68.8)	0.079	0.778
	Female n (%)	12 (35.3)	5 (31.3)		
BMI (Kg/m^2)		24.66±2.10	24.60±2.13	0.106	0.916
Etiology	Alcoholic n (%)	12 (35.3)	4 (25.0)	0.462	0.533
	Post-necrotic n (%)	8 (23.5)	4 (25.0)	0.013	0.910
Sr Bilirubin (mg/dl)		1.01±0.35	0.91±0.19	2.78	0.008*
AST (IU/L)		152.06±125.15	80.25±55.56	2.80	0.007*
ALT (IU/L)		156.82±175.54	71.69±58.45	2.54	0.014*
Albumin (g/dl)		2.99±0.67	3.17±0.83	-0.80	0.424
INR		1.88±0.78	1.54±0.88	1.37	0.177
Sr Creatinine (mg/dl)		1.01±0.35	0.91±0.19	1.05	0.299
CTP score		9.65±2.02	7.44±1.26	4.70	0.000*
MELD score		18.97±7.14	13.63±6.09	2.58	0.013*
Pro-BNP (pg/ml)		469.12±317.38	139.06±203.22	4.43	0.000*

*denotes significant value <5%

DISCUSSION:

In the present study, CTP stages A, B, and C were found in 14%, 48%, and 38% of the study population, respectively. The present cross-sectional study observed CCM in 68% of cirrhotic patients. The frequency of CCM varied from 28% to 45% in different studies.[9-11]This difference in frequency of CCM may be due to the fact that more cirrhotic patients in the present study (86%) belong to the higher CTP stage.

In the present study, SDF was observed in 52% of patients with low LVEF (<55%). Hammami et al.[12] found that 17.5% of patients out of 80 cirrhotic patients had SDF, whereas Dash et al.[10] found SDF in 25% of patients. The present study, similar to Dash et al.[10] found significantly reduced systolic function (LVEF) with advanced stages of cirrhosis (p=0.042). The DDF in the present study was seen in 72% of patients and had a significant fall in form of E/A ratio in CTP -C stage (p=0.00). DDF among cirrhotic

patients in literature varied from 30% to 70%.[10,12,13]. Many studies did not find correlation between DDF and severity of cirrhosis in contrast to the present study. [10, 12, 13]

The QTc prolongation and raised pro-BNP level were seen in 78% and 70% of patients respectively. In the current study, the QTc interval and pro-BNP level were not significantly differ in different CTP stages. However, previous studies found a significant association between prolongation of QTc and the severity of cirrhosis.[10,12,14]

Similarly, Sheikh et al.[11], Woo JJ et al.[15] and Mihailovici et al.[16] found levels of pro-BNP rose markedly in patients with CTP- C stage than A and B. The frequency of CCM was significantly increased with CTP stages of cirrhosis (p=0.001) similar to the literature.[9,10]It was present in 28.57% patients in Child's A, 58.33% patients in Child's B and 94.74% patients with Child's C cirrhosis.

The present study did not find any significant difference between patients with CCM and without CCM with respect to the age, gender, BMI and etiology of cirrhosis, similar to the study by Dash et al. [10] However, Kaoushik et al.[9] in their study on 100 cirrhotic patients observed a significantly different frequency of CCM among alcoholics and non-alcoholics.

The present study found a statistically significant higher CTP and MELD score in CCM patients in contrast to without CCM patients (p<0.005). This finding was in accordance with Dash et al. [10] and Hammami et al.[12] The pro-BNP level was also significantly raised in CCM patients (p=0.000) in the current study. In a study by Pentiuket al.[17], NT-pro-BNP levels were higher in patients with refractory ascites, severe esophagus varices, hepatorenal syndrome, hypoalbuminemia, and the lowest in pre-ascitic patients. Thus, we can conclude that elevated levels of pro-BNP may be a good indicator of cardiac dysfunction in patients with cirrhosis.

CONCLUSION:

CCM is highly prevalent in cirrhotic patients irrespective of the etiology and demographic variables. It is positively correlates with pro-BNP level, and degree of liver dysfunction. Diastolic dysfunction was more frequent than systolic dysfunction among cirrhotic patients and they significantly altered with stages of cirrhosis.

REFERENCES:

1. Pozzi M, Ratti L, Guidi C, Milanese M, Mancia G. Potential therapeutic targets in cirrhotic cardiomyopathy. Cardiovasc hematoldisord drug targets 2007;7(1):21-6
2. Liu H, Ma Z, Lee SS. Contribution of nitric oxide to the pathogenesis of cirrhotic cardiomyopathy in bile duct-ligated rats. Gastroenterology. 2000; 118:937–944.
3. La Villa G, Romanelli RG, Casini Raggi V, Tosti-Guerra C, Feo ML, Marra F, et al. Plasma levels of brain natriuretic peptide in patients with cirrhosis. Hepatology. 1992;16:156–161.
4. Wong F, Siu S, Liu P, Blendis L. Brain natriuretic peptide, is it a predictor of cardiomyopathy in cirrhosis? Clin Sci. 2001; 101:651–657.
5. Gines P, Uriz J, Calahorra B, Garcia-Tsao G, Kanath PS, Del Arbol LR, et al. Transjugular Intrahepatic posrtosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology 2002;123:1839–47.
6. Trevisani F, Merli M, Savelli F, Valeriano V, ZambruniA,Rriggio O et al. Qt interval in patients with non-cirrhotic portal hypertension and in cirrhotic patients treated with transjugular intrahepatic porto-systemic shunt. J hepatol2003;38:461-467.
7. Mandell MS, Tsou MY. Cardiovascular dysfunction in patients with end-stage liver disease. J chin med assoc 2008;71(7):331-335.
8. Rabie RN, Cazzaniga M, Salerno F, Wong F. The use of e/a ratio as a predictor of outcome in cirrhotic patients treated with transjugular intrahepatic portosystemic shunt. Am j gastroenterol 2009;104(10):2458-2466.
9. Koushik AK, Ganesh P, Shanmuganathan S. Incidence of Cirrhotic Cardiomyopathy among Hundred Patients of Tamil Nadu, India-A Cross-sectional Study. Journal of Clinical and Diagnostic Research 2020;14(11): OC31-OC33.
10. Dash SC, Beeravelli R, Behera SK, Sundaray NK, Patil P. Is Cirrhotic Cardiomyopathy Related to Cirrhosis Severity? Rambam Maimonides Medical Journal 2023;14(1): e0001.
11. Shaikh S, Abro M, Qazi I, Yousfani A. Frequency of cirrhotic cardiomyopathy in patients with cirrhosis of liver: A tertiary care hospital experience. Pak J Med Sci 2011;27(4):744-748.
12. Hammami R, Boudabbousb M, Jdidi J, et al. Cirrhotic cardiomyopathy: is there any correlation between the stage of cardiac impairment and the severity of liver disease? Libyan J Med 2017;12:1283162.
13. Somani PO, Contractor Q, Chaurasia AS, Rathi PM. Diastolic dysfunction characterizes cirrhotic cardiomyopathy. Indian Heart J 2014;66:649.
14. Huang CH, Wu LS, Jeng WJ,Cheng YF, Ko YS, Sheen ISet al. In HCV-related liver cirrhosis, local pulse wave velocity increases and in decompensated patients correlates with poorer survival. PLoS ONE 2019;14(3):e0212770.
15. Woo JJ, Koh YY, Kim HJ, Chung JW, Chang KS, Hong SP. N-terminal Pro B-type natriuretic peptide and the evaluation of cardiac dysfunction and severity of disease in cirrhotic patients. Yonsei Med J 2008;49(4):625–631.
16. MihailoviciAR, Donoiu I, Gheonea DI, Mirea O, Târtea GC, Buşe M, Calborean V, Obleagă C, Pădureanu V, Istrătoaie O. NT-proBNP and Echocardiographic Parameters in Liver Cirrhosis - Correlations with Disease Severity. Med PrincPract.
17. Pentiuk N, Mostovoy Y, Motsiuk V, Demchuk A, Nekrut D. NT-pro-BNP level in patients with liver cirrhosis: relation to portal hypertension and cardiovascular changes. Georgian Med News 2019;(292-293)