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"Cardiac dysfunction and N-terminal pro BNP in Chronic liver disease"

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ABSTRACT
INTRODUCTION :*N-Terminal prohormone brain natriuretic peptide (NT-pro BNP) is a prohormone of brain natriuretic peptide produced primarily within heart and released into circulation in response to increased wall tension. Previous studies have shown increased plasma concentration of BNP in some patients of liver cirrhosis where renin angiotensin system is activated even in absence of LV clinical dysfunction. Because they seem to be related to severity of liver disease and cardiac dis-function, they could be useful markers to identify cirrhotic patients with increased cardiovascular risk and therefore poor prognosis.*
MATERIALS AND METHODS :*100 patients with chronic liver disease of any etiology admitted in medicine department of Gauhati medical college were evaluated using ECG,2D Echocardiography, NTpro-BNP and severity of liver disease according to CTP class.Data from the case record proforma was entered into Microsoft excel spreadsheet version 2021 and analysed using IBM-SPSS version 26.*
RESULTS :*Majority of patients (50%) were in age group of 41-50 yrs. Most common etiology was alcohol (85%) . Significant corelation was noted between Child class and cardiac dysfunction (A<B<C, p=0.001), NT-proBNP and child class . A NT- pro BNP cut off of 100ng/ml showed a sensitivity of 80% and specificity 95% as a predictor of cardiac dysfunction in patients with chronic liver disease.*
CONCLUSION :*Cardiac dysfunction is common in chronic liver disease. Serum NT-pro BNP levels were significantly elevated in chronic liver disease patients with cardiac dysfunction and it is related to severity of the liver disease. There is positive corelation between CTP class, cardiac dysfunction and serum NT-pro BNP levels. NT pro-BNP can be used as clinical predictor of underlying cardiac dysfunction.Further studies are required to evaluate prevalence of cardiac dysfunction in chronic liver disease and to evaluate the role of NT-pro BNP as a predictor of cardiac dysfunction in chronic liver disease through larger population and multicentric studies all over India.*

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I. AIMS AND OBJECTIVES

1 To identify cardiac dysfunction among patients with chronic liver disease
2 To study NT-pro BNP in patients with chronic liver disease
3 To study if there is a probable corelation between cardiac dysfunction and NT-pro BNP in chronic liver disease.

II. MATERIALS AND METHODS

Place Of Study : Department of General Medicine ,Gauhati Medical college and Hospital ,Guwahati
Duration of Study :One year
Study population : all patients of cirrhosis of liver, admitted in the department of medicine in gauhati medical college and hospital, guwahati during periodof one year from 1st june 2021 to 31st may 2022
Study design : hospital based observation study
Sample size : 100 sample size is calculated using formula, sample size $=z^2*p*(1-p)/(me)^2$where, z is critical value based on normal distribution, p prevalence and me is margin of error, here z is 1.95, p is 7% me is 5%

Inclusion criteria
1 Patients with cirrhosis with age > 12years irrespective of etiology were evaluated for presence of cardiac dysfuntion
2 Patients with proven cirrhosis diagnosed by
a altered liver function test for > 6 months with esophageal varices or ultrasound showing coarse hepatic echo texture with features of portal hypertension

b biopsy if available showing cirrhosis
Exclusion criteria
1 Patients with primary cardiac or pulmonary disease.
2 Patients with hypertension and severe anemia(hb<7gm)
3 Patients with active infections

Methods of collection of data
The study enrolled 100 liver cirrhosis patients selected according to inclusion and exclusion criteria. Patient's demographic details were noted. Biochemical test for liver function and prothrombin time, NT-pro BNP; abdominal ultrasonography was performed along with clinical assessment for degree of ascites and hepatic encephalopathy. CTP scoring was done for each patient. Resting ECG was done in all patients. The QTc interval > 0.44 sec was defined as prolonged. Then cardiac structural and functional assessment was performed non-invasively using transthoracic echocardiography to determine cardiac dysfunction among the patients.
Diagnosis of cardiac dysfunction :
Systolic dysfunction was defined as resting Ejection fraction<55%
Diastolic dysfunction was defined as early diastole(E)/late diastole(A) ratio less than 1.0

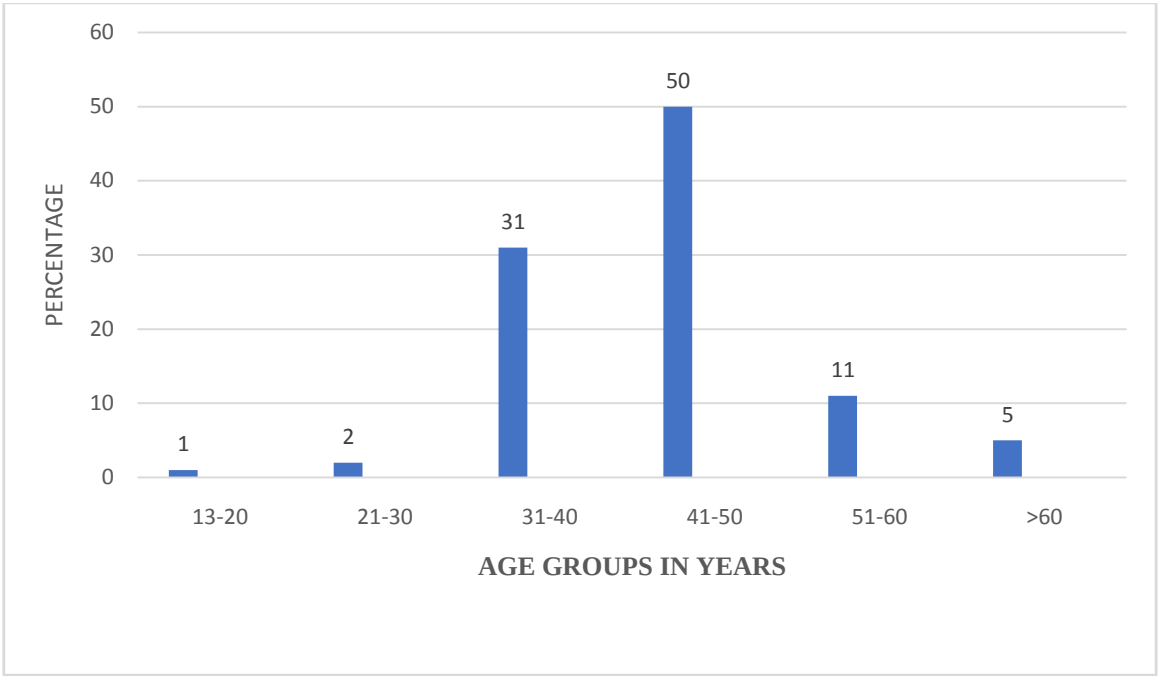
Statistical Analysis
Data from the case record proforma was entered into Microsoft excel spreadsheet version 2021 and analysed using IBM-SPSS version 26.

III. RESULTS AND OBSERVATIONS

During this duration of 1 year study, total number of 100 hospitalized patients were taken for the study, fulfilling the inclusion criteria. The details of each cases were studied and consolidated into below mentioned results.

AGE WISE DISTRIBUTION OF PATIENTS WITH CHRONIC LIVER DISEASE

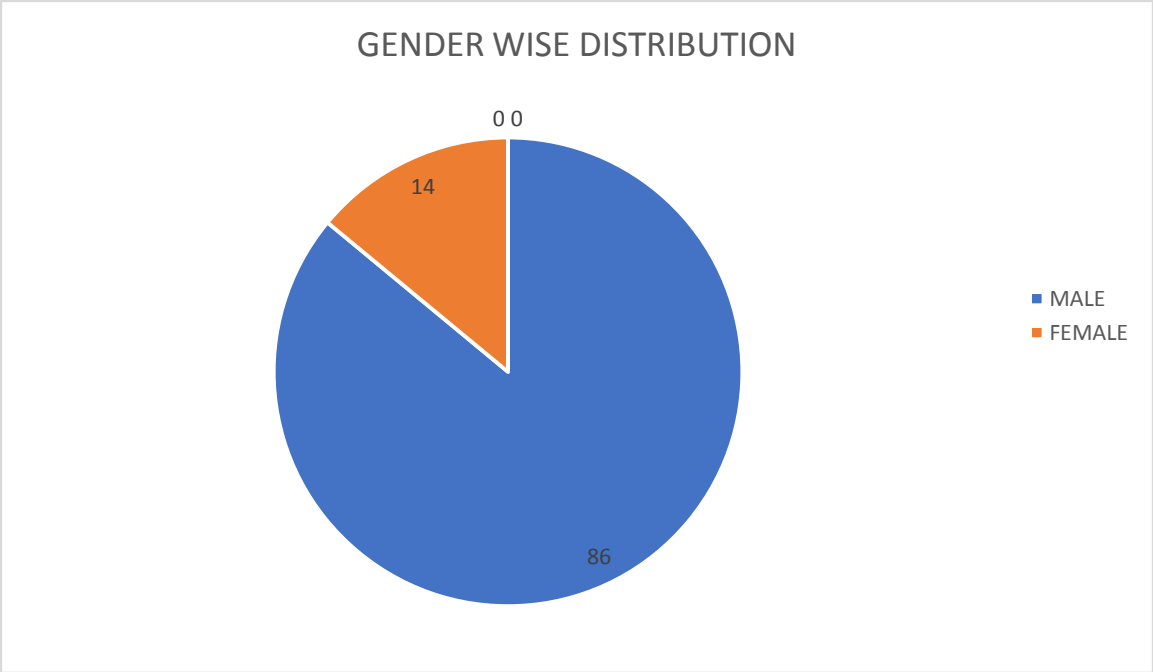
AGE GROUP(YEARS)	NO OF PATIENTS
12 - 20	1
21 - 30	2
31 - 40	31
41 - 50	50
51 - 60	11
>60	5
Mean +/- SD	43.7+/-8.7



The above table and graph show that maximum patients, (n= 50) are in the age group 41-50

GENDER WISE DISTRIBUTION OF PATIENTS WITH CHRONIC LIVER DISEASE

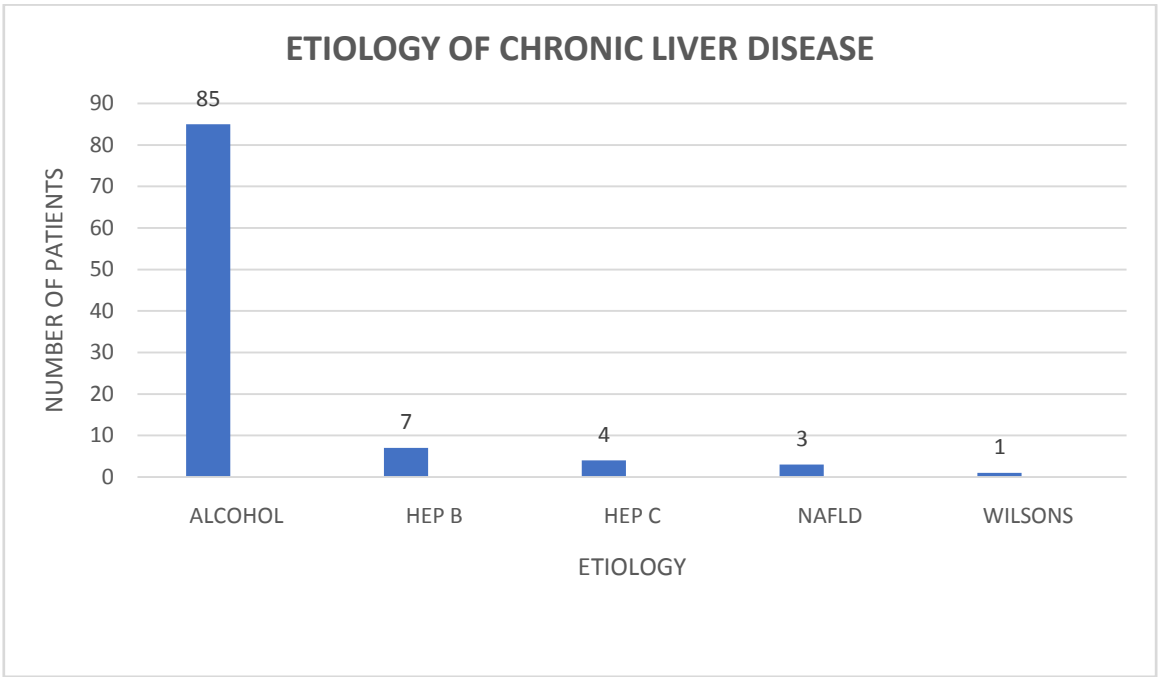
GENDER	NUMBER OF PATIENTS
MALE	86
FEMALE	14
TOTAL	100



From the above table, it can be seen that there is male predominance in cirrhosis of liver. Here male comprises of 86% and female 14%

ETIOLOGY OF CHRONIC LIVER DISEASE

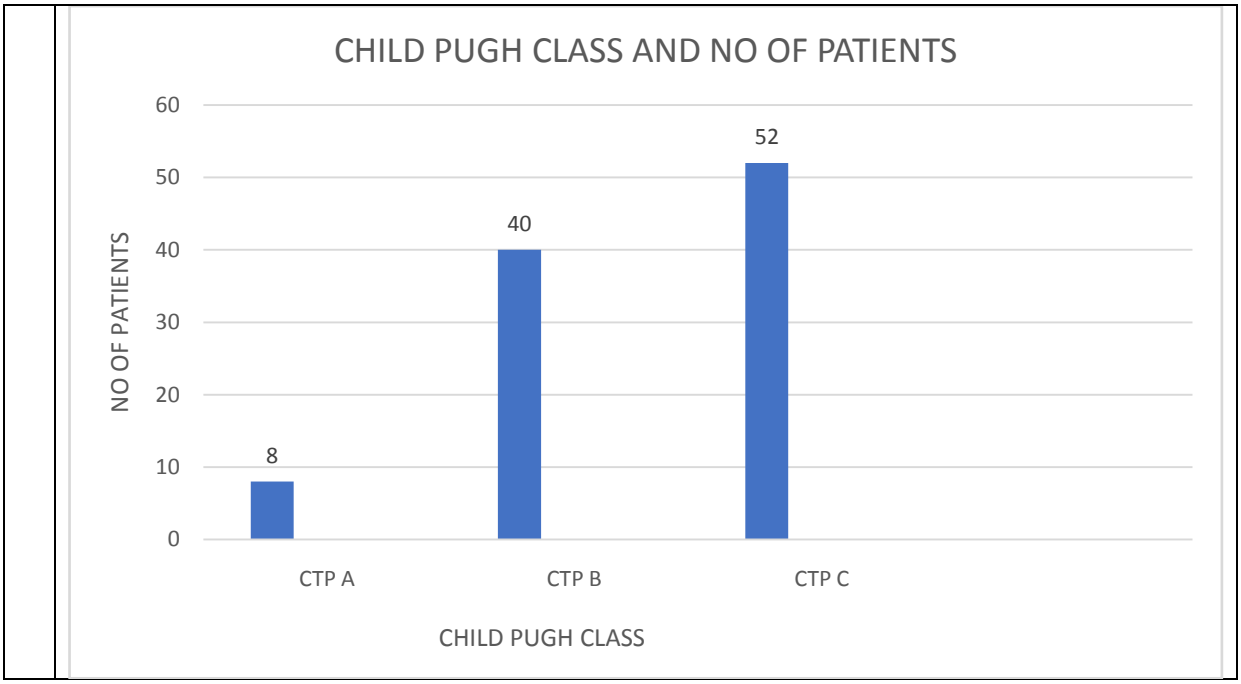
ETIOLOGY	NO OF PATIENTS
ALCOHOL	85
HBV	7
HCV	4
NAFLD	3
WILSON'S DISEASE	1



In the table it can be seen that most common etiology of CLD in the study group was alcohol which comprised 85 patients of all cases.

CHILD PUGH SCORE OF PATIENTS WITH CHRONIC LIVER DISEASE

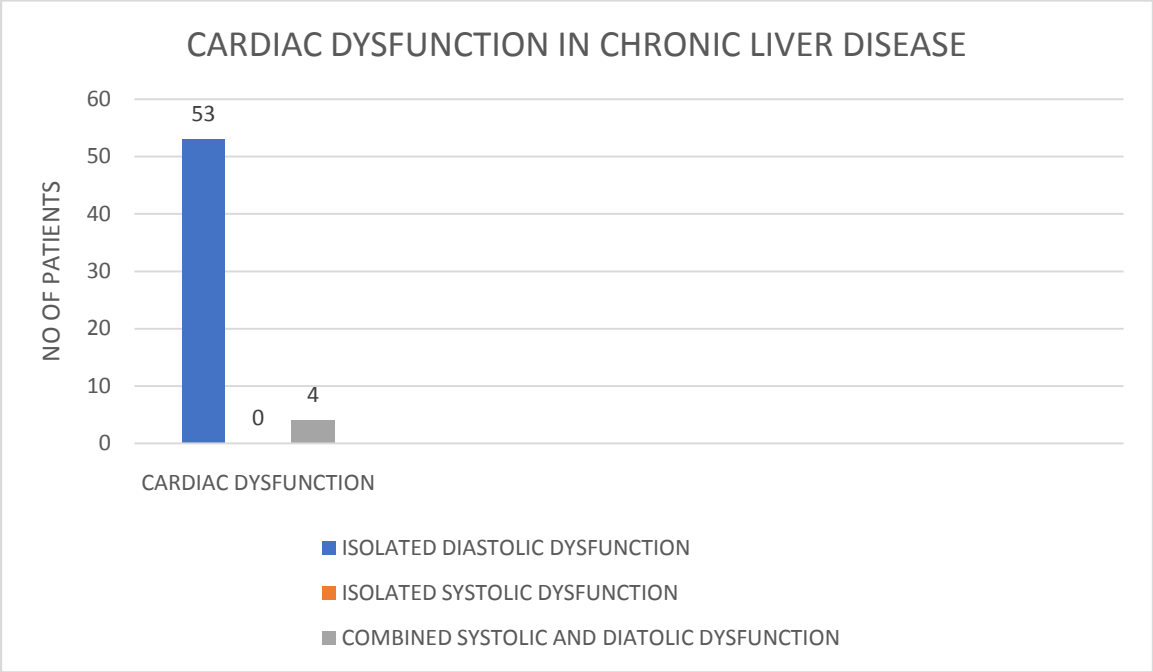
CHILD PUGH SCORE	NO OF PATIENTS
A	8
B	40
C	52



In this table it can be seen that most of the patients 52 are in child pugh class C at time of admission.

CARDIAC DYSFUNCTION IN CHRONIC LIVER DISEASE

CARDIAC DYSFUNCTION	NO OF PATIENTS
ISOLATED DIASTOLIC DYSFUNCTION	53
ISOLATED SYSTOLIC DYSFUNCTION	0
COMBINED SYSTOLIC AND DIASTOLIC DYSFUNCTION	4
TOTAL	57

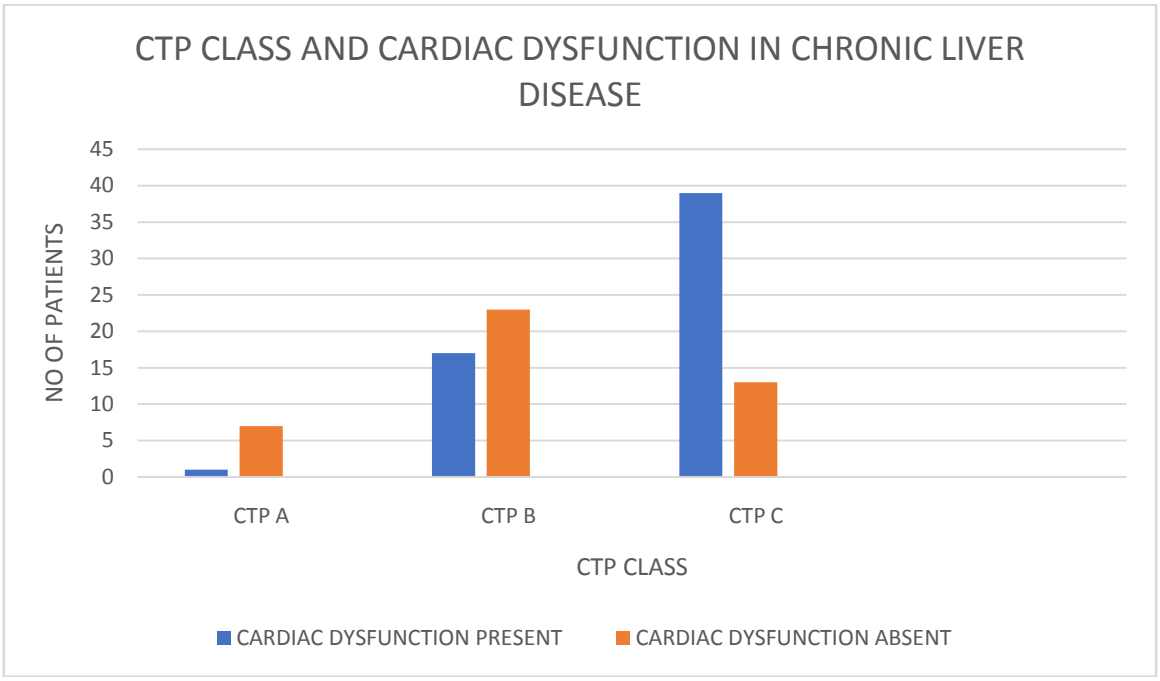


From the table it is seen that out of 100 patients studied 57 patients had cardiac dysfunction.
Diastolic dysfunction is more common compared to systolic dysfunction.

CTP CLASS AND CARDIAC DYSFUNCTION IN CHRONIC LIVER DISEASE

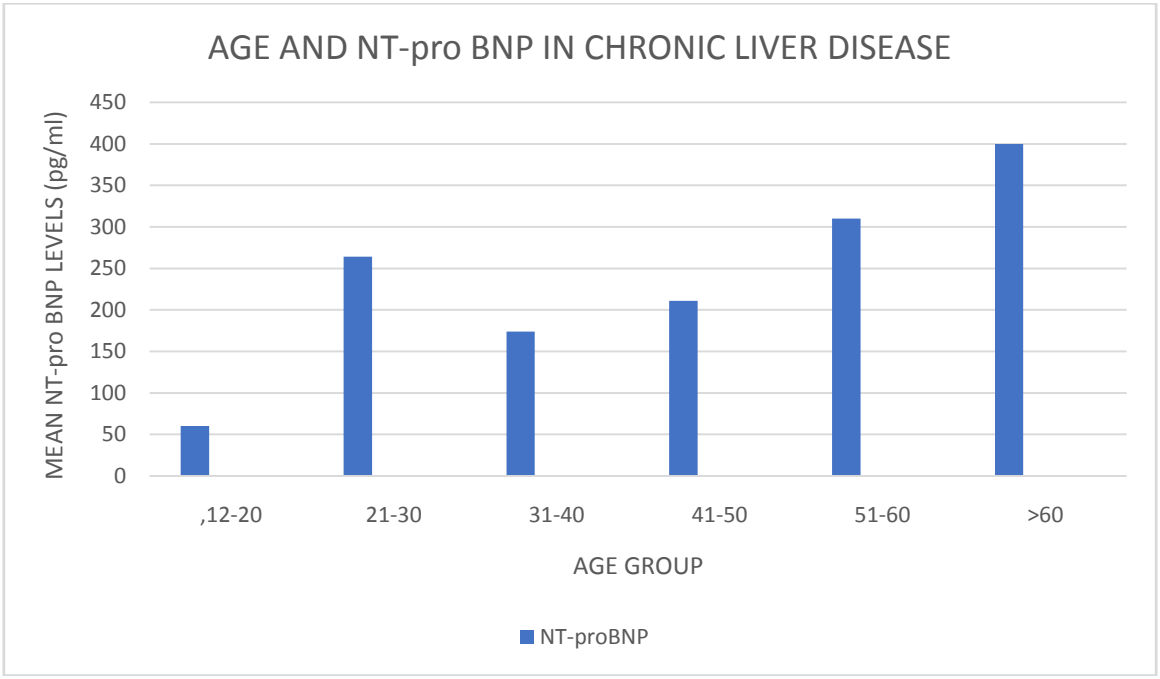
CTP CLASS	CARDIAC DYSFUNCTION			p- value
	ABSENT N (%)	PRESENT N (%)	TOTAL N (%)	
A	7 (16.3%)	1 (1.8%)	8 (8%)	0.001
B	23 (53.5%)	17 (29.8%)	40 (40%)	
C	13 (68.4%)	39 (68.4%)	52 (52%)	

From the above table it is seen that maximum no of patients with cardiac dysfunction in chronic liver disease belongs to CTP class C.
There is significant relationship between cardiac dysfunction and CTP class.



AGE AND NT-pro BNP IN CHRONIC LIVER DISEASE

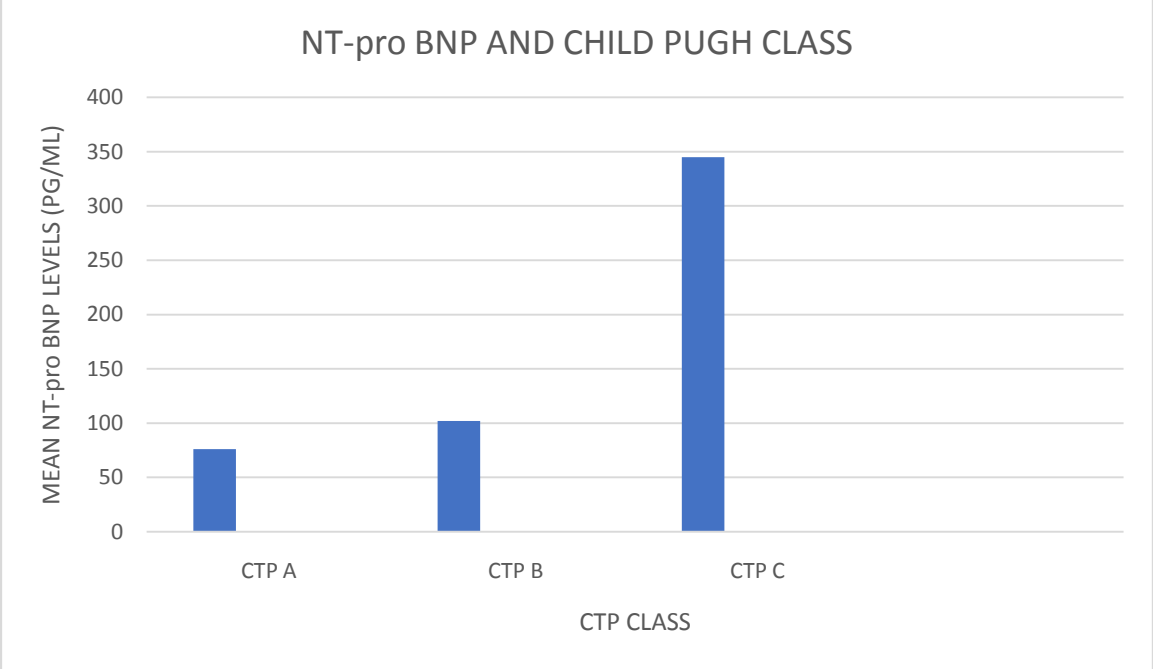
AGE	NT-pro BNP (Mean ±SD)
12-20	60
21-30	264 ±156
31-40	174 ±125
41-50	211 ± 285
51-60	310 ±399
>60	400 ± 457



From the graph and table it is seen that NT-pro BNP was maximum in age group >60

NT-pro BNP AND CTP CLASS

CTP CLASS	NT-pro BNP (MEAN ±SD)
A	76 ±18
B	102 ±91
C	345 ±329

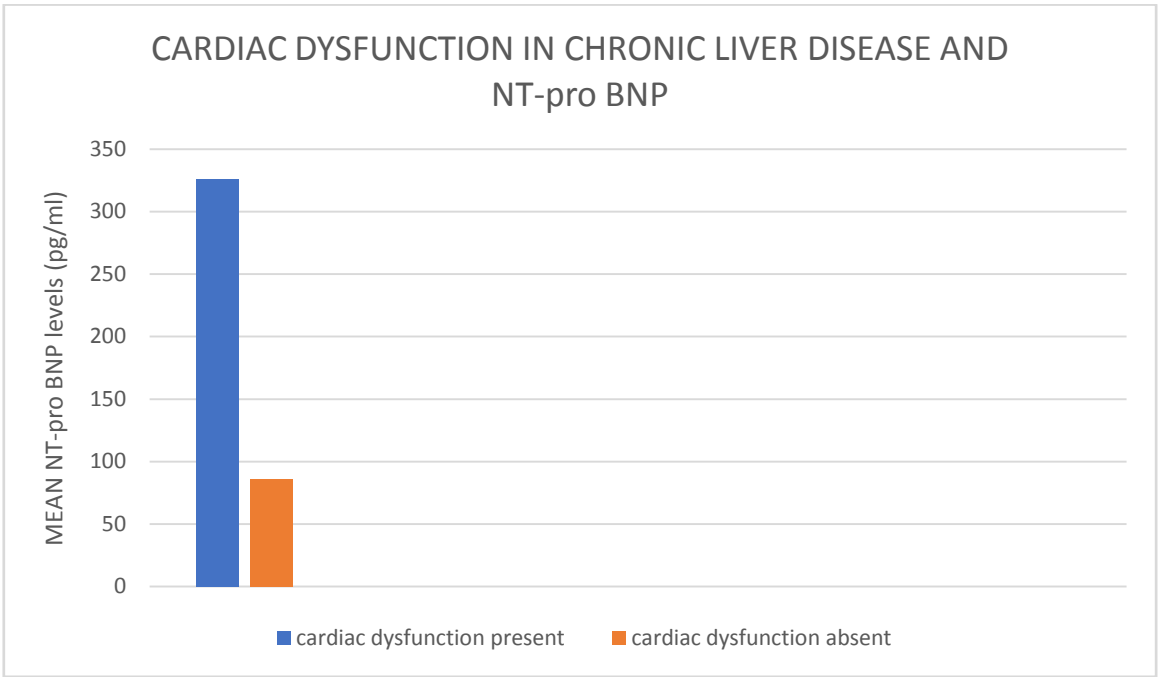


From the graph it is seen that NT-pro BNP levels are maximum increased in CTP CLASS C.

NT-pro BNP AND CARDIAC DYSFUNCTION IN CHRONIC LIVER DISEASE

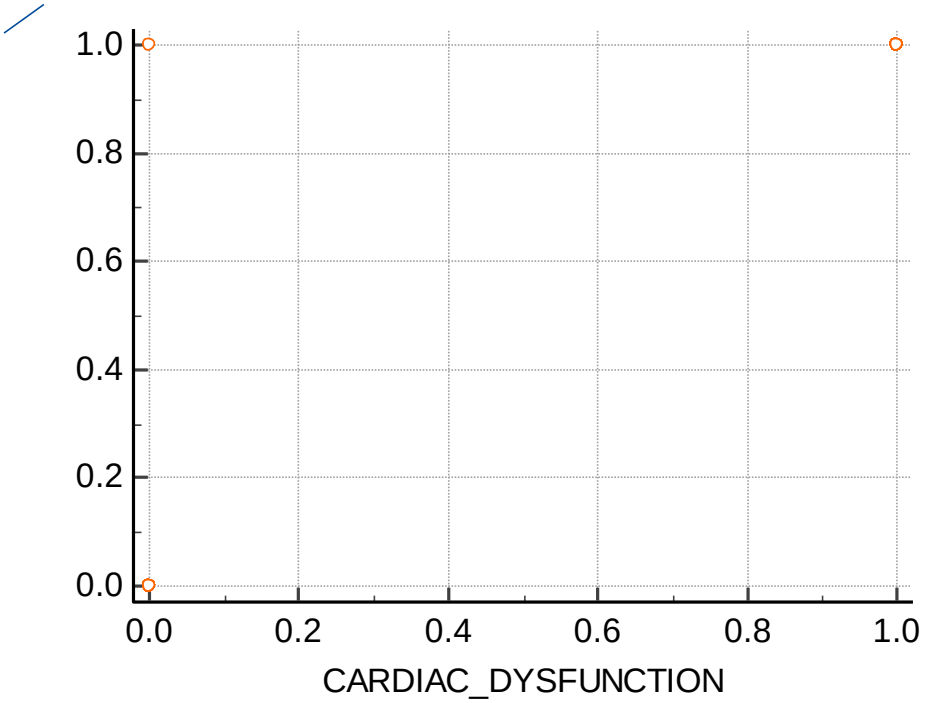
	CARDIAC DYSFUNCTION			p-value
	PRESENT	ABSENT	TOTAL	
	MEAN±SD	MEAN±SD	MEAN ±SD	
NT-pro BNP LEVELS	326 ± 327	86 ± 68	223 ± 277	0.001

From the above table it is seen that NT-pro BNP levels are higher in chronic liver disease patients with cardiac dysfunction as compared to those without cardiac dysfunction and since p value is less than .05 the relation between cardiac dysfunction in CLD and NT-pro BNP is significant.



Variable Y	BNP_LEVEL
Variable X	CARDIAC_DYSFUNCTION

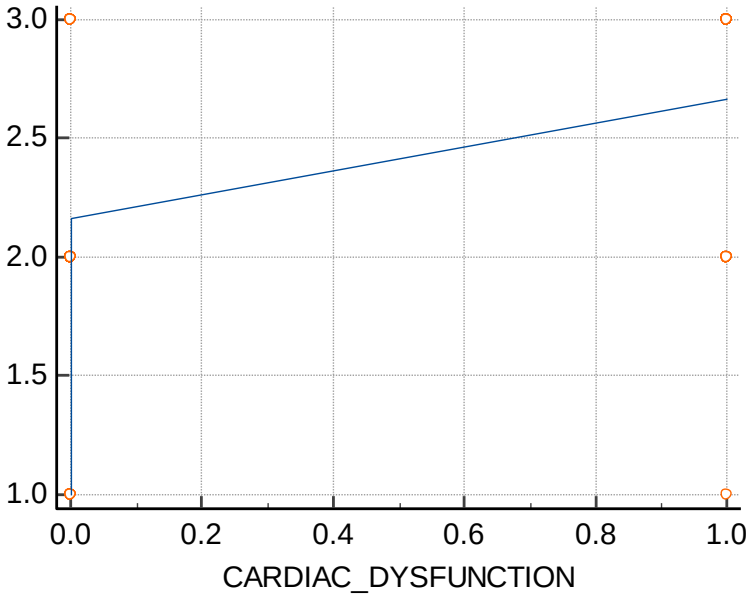
Sample size	100
Correlation coefficient r	0.9598
Significance level	P<0.0001
95% Confidence interval for r	0.9407 to 0.9728



Significantly strong positive corelation was found between BNP levels and cardiac dysfunction. r =0.9598 and p<0.05

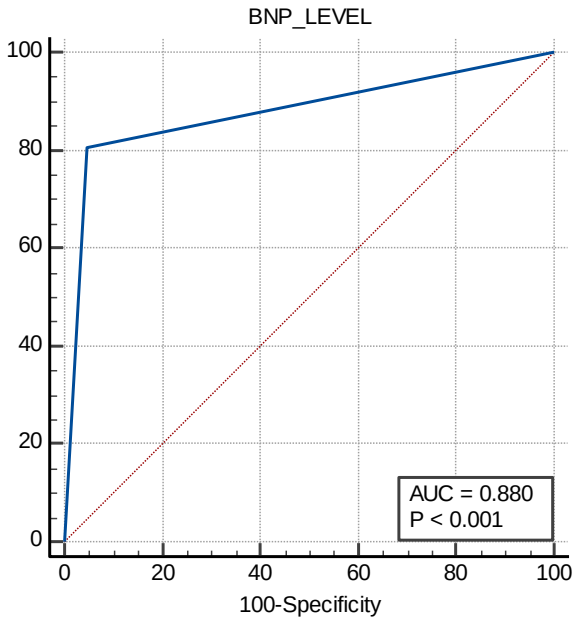
Variable Y	CTP_SCORE
Variable X	CARDIAC_DYSFUNCTION

Sample size	100
Correlation coefficient r	0.4094
Significance level	P<0.0001
95% Confidence interval for r	0.2316 to 0.5607



Significantly positive moderate corelation was found between CTP score and cardiac dysfunction. r=0.494 and p<.0.05

Taking 100 as cut off



Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.880
Standard Error [a]	0.0310
95% Confidence interval [b]	0.800 to 0.937
Significance level P (Area=0.5)	<0.0001
Associated criterion	>0
Sensitivity	80.70
Specificity	95.35
NPV	95.8
PPV	75.8

We used a cut off of 100ng/ml given by FDA to find out it's role as a predictor of cardiac dysfunction in patients with chronic liver disease. It showed a sensitivity of 80% and specificity 95%.

IV. SUMMARY

The study titled "CARDIAC DYSFUNCTION AND N-TERMINAL PRO HORMONE BRAIN NATRIURETIC PEPTIDE IN CHRONIC LIVER DISEASE" was conducted at Gauhati Medical College and Hospital from June1st 2021 to May 30 2022. The study was conducted with the aim to study cardiac dysfunction and NT-pro BNP levels in chronic liver disease patients and to determine whether there is any possible relation between two in chronic liver disease patients. The study included a total of 100 chronic liver disease patients admitted in department of medicine, Gauhati Medical College and Hospital, who were taken up for detailed history recording, clinical examination and appropriate investigation as per protocol. Available literature both from India and abroad were reviewed and discussed with the observations made in our study. The results of the studies are as follows

1 The age group ranged from 14-68 years. The mean age of patients with cirrhosis of liver studied was 43.7±8.7 years. Maximum patients were in the age group 41-50 which comprises of 50% of the patients.
2 Male patients constituted 86% of study population
3 Alcohol was the most common etiology for chronic liver disease, 85% followed by Hep B virus comprising 7%.
4 In our study, we found that 52% of patients belonged to Child Pugh class C ,40% of the patients belonged to class B and rest 8%belonged to class A. It suggests that patients having chronic liver disease have severe disease at presentation.
5 The prevalence of cardiac dysfunction in chronic liver disease patients in our study was 57%.
6 In our study it was seen that 68% of patients with chronic liver disease have cardiac dysfunction in CTP class C compared to 1.8% in CTP class A. it suggests that patients with CTP class C are more likely to have cardiac dysfunction compared to class A and B. Significant corelation was found between CTP class and cardiac dysfunction.
7 NT-pro BNP was found to be maximum elevated in age group >60 years.
8 NT- pro BNP was found to be more elevated in CTP class C compared to class A and B.
9 There is positive corelation between CTP class , cardiac dysfunction and NT-pro BNP levels .

V. DISCUSSION

The present hospital based observational study was carried among 100 patients of cirrhosis of liver in department of medicine, Gauhati medical college and hospital. All subjects were aged 13 or more and were admitted in the department of medicine, Gauhati medical college and hospital, Guwahati, during the period from 1st June 2021 to 31st May2022. All the cases fulfilled the inclusion and exclusion criteria as per methodology of the study.

The study was primarily aimed at detecting cardiac dysfunction and estimating NT-pro BNP levels in cirrhosis patientsand to find out any corelation between NT-pro BNP and cardiac dysfunction and severity of liver disease.

AGE DISTRIBUTION

In our study, maximum patients were in the age group [41-50] comprising 50 patients, followed by 31 patients in the age group of (31-40). Mean (±SD) age in this study group was 43.7±8.7.

In an another study carried out by **Mishra et al** on 4331 patients, Mean age of the study subjects was 46.35 ± 13.22 years.

In a study carried out by**Kothari et al.** in India on 202 patients with cirrhosis of liver, mean (±SD) age of the study group was 43.77±9.95 years.

In another study carried out by **Brito-Azevedo et al.**, on 54 patients with cirrhosis of liver, the mean(±SD) age

of the study group was found to be 53 ± 8 years.

Here it can be seen that there is a difference in the mean age group between Indian and western population developing cirrhosis of liver. This could be due to difference in the racial, geographical, socioeconomic background of the two populations.

SEX DISTRIBUTION

In this study of total 100 patients, 86 cases were male whereas 14 cases were female.

In an another study carried out by **Acharya et al.**, on 171 patients with cirrhosis of liver in which 143 (83.62%) were males and 28 (16.37%) were females.

In an another study carried out by **Gao et al.**, out of 865 patients, 576 patients were male accounting for 66.6% of all cases, whereas rest 289 patients were female comprising 33.4%.

In our study shows that there is a male preponderance of Cirrhosis of liver cases, which is found similar to other studies.

ETIOLOGY OF CIRRHOSIS OF LIVER

In our study, most common etiology of Cirrhosis of liver was Alcohol which accounted for 85 cases (85%), followed by Hepatitis B in 7cases, Hepatitis C 4 cases, NAFLD a for 3 cases and Wilsons disease for 1 case.

In another study carried out by**Mishra et al.** in India,a total of 4,331 patients with Cirrhosis of liver, of whom 2,742 (63.3%) had alcohol-related cirrhosis, 858 (19.8%) had viral hepatitis-related cirrhosis, and 731 (16.9%) had cirrhosis of liver due to nonalcohol and nonviral cause.

In an another study carried out by **Sharma et al.**in India on 178cirrhosis of liver patients, Alcohol was the leading cause of cirrhosis (62.9%), followed by Hepatitis B (10.1%), Non-Alcoholic Steatohepatitis (NASH) (7.9%), Autoimmune (3.9%), Hepatitis C (2.8%). Cardiac cirrhosis and wilson disease were present in one patient each. In 9.6% patients the cause was

In an another study carried out by **Wani et al.** Hepatitis B is a major cause of CLD amounting to 28% followed by Non Alcoholic Fatty Liver Disease (NAFLD) 23%. Whereas Alcohol related CLD disease is almost non-existent.

In most parts of the world, hepatotropic viruses are the leading cause of end-stage liver disease.[161] In developed countries, as well as in some parts of India, alcohol is a major cause of end-stage liver disease.

There was significant interregional differences (hepatitis C in North, hepatitis B in East and South, alcohol in North-east, Non-alcoholic Fatty Liver Disease in West) in the predominant cause of chronic liver disease.Alcohol related CLD is rare in the northern part of India, whereas **Alcohol is the most common cause of cirrhosis of liver in north-eastern part of India.** Our study showed that alcohol was the major cause of cirrhosis of liver in this region.

CHILD-PUGH SCORE OF PATIENTS WITH CIRRHOSIS OF LIVER.

In our study, it can be seen that most patients 52 are in child pugh grade C at the time of admission, while only 8 patients are in grade A and 40 patients in grade B.

In another study carried by **Gao et al.**, out of 865 patients with cirrhosis of liver, 383 (45.1%)patients are in Child pugh B at the time of admission, followed by 314 (36.9) patients are in Child pugh C and 153 (18.0) patients were in child pugh A.

In a study carried by**Trimukhe et al.** on 125 patients with cirrhosis of liver in india, the maximum mortality was noted in class C

In an another study carried out by **Chaurasia et al.** on 216 patients CTP score were higher (12.44 ± 1.07) in expired cases than who improved and discharged (11.32 ± 1.28), with significant p-value (<0.001).

In our study, most patients were in Child Turcotte Pugh class C category followed by class B. It indicates that most patients presenting as cirrhosis of liver have severe disease on admission. Patients tend to present at an advanced stage of disease with high Child- pugh score studied by **Bhattacharyya et al.** in north-eastern part of India.

CARDIAC DYSFUNCTION IN CHRONIC LIVER DISEASE

In our study, out of 100 patients studied 57% patients had cardiac dysfunction and 53% patients had diastolic dysfunction and 4%had combined systolic and diastolic dysfunction.

In a study conducted by Karki et al.cardiac dysfunction in chronic liver disease was found to be 51.4%.

In a study conducted by Vasilios et al.cardiac dysfunction in chronic liver disease was found to be 59%

In a study conducted in India by Singh AJ et al. cardiac dysfunction in chronic liver disease was found to be 42%

In a study conducted in south India by Varun Bogadi et al. cardiac dysfunction was found in 44.7%.

In our study we noted higher prevalence of cardiac dysfunction in CTP class C (68%) compared to CTP

class A (1.8%) and CTP class B (29.8%).

A study by Eldeeb et alshowed prevalence of cardiac dysfunction as 78%,66%and 50% in CTP class C, B, A respectively.

A study by Vasilios et al.showed prevalence of cardiac dysfunction as 10.3%, 12.8%, 45.8% respectively in CTP class A, B, C respectively.

A study by Varun Bogadi et al.showed prevalence of cardiac dysfunction as 11%, 38.6%, 75% respectively in CTP class A, B, and C.

In our study no corelation was found between etiology of chronic liver disease and cardiac dysfunction. Similar findings were seen in studies by Lunzer et al and Torregrossa et al.

NT-pro BNP and CHRONIC LIVER DISEASE

In our study it was found that NT-pro BNP increases with age and mean NT-pro BNP levels were maximum in age group> 60years. Similar findings were seen in studies done by Goetze JP et al and C Meune et al.

In our study we found that patients with CTP class C have higher serum NT-pro BNP values compared to CTP class A and B.

Similar results were seen in studies by Woo JJ et al and Henriksen JH et al.

In India studies conducted by Singh AJ et al and Varun Bogati et al showed similar results.

In our study it was found that mean NT-pro BNP levels were higher in chronic liver disease patient with cardiac dysfunction as compared to those without cardiac dysfunction. Similar findings were seen in studies conducted by Eldeeb et al, Licata et al, Woo JJ et al and Henriksen JH et al. Similar findings were seen in Indian studies conducted by Singh AJ et al and Varun Bogati et al.The variation in the mean NT-pro BNP levels as observed by different authors could be because of varied ethnicity, assay used to measure NT- pro BNP levels and cofounding factors like use of diuretics and beta blockers, which are likely to alter pro BNP levels.

We found a negative correlation (p-value 0.001) between serum albumin levels and cardiac dysfunction. Similar relation was noted by Yilmaz et al.

We found a positive correlation (p- value 0.001) between CTP class and NT-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. and Ziada et al.

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 80.7% and a high specificity of 95.35%. Saner et al. used a cut-off of 391ng/ml and found a sensitivity of 100% in predicting cardiac dysfunction. Ziada et al. used a cut-off of 265 ng/ml and found a sensitivity of 91.7% and specificity of 86.6%. In a study conducted in India by Varun Bogati et al taking cut off 100 pg/ml, found sensitivity to be 97 % and specificity to be 46%.

LIMITATIONS OF STUDY

1 Since this study was a hospital based observational study on small population, further prospective long-term studies with large no of cases are required to validate our findings.

2 Beta blockers and diuretic therapy used by chronic liver disease patients can lower serum NT-pro BNP levels.

VI. CONCLUSION

Cardiac dysfunction is common in chronic liver disease. Diastolic dysfunction is most common abnormal cardiac manifestation in patients with chronic liver disease. There is significant corelation found between CTP class and cardiac dysfunction.

Serum NT-pro BNP levels were significantly elevated in chronic liver disease patients with cardiac dysfunction and it is related to severity of the liver disease.

There is positive corelation between CTP class, cardiac dysfunction and serum NT-pro BNP levels. Patients with higher CTP score are more likely to have cardiac dysfunction and elevated serum NT-pro BNP levels. NT pro-BNP can be used as clinical predictor of underlying cardiac dysfunction.

Further studies are required to evaluate prevalence of cardiac dysfunction in chronic liver disease and to evaluate the role of NT- pro BNP as a predictor of cardiac dysfunction in chronic liver disease through larger population and multicentric studies all over India.

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