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Relationship of Serum Brain Natriuretic Peptide Levels with Severity of Chronic Liver Disease

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Authors' contributions

This work was carried out in collaboration between both authors. Author SM designed the study, managed the literature searches, collect data and wrote the protocol. Author MM designed the study, performed statistical analysis and wrote the first draft of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine mean serum B-type natriuretic peptide (BNP) levels and their relationship with the severity of disease in patients with chronic liver disease (CLD).
Study Design: Descriptive cross-sectional study
Place and Duration of Study: Department of Medicine, Unit-2, Jinnah Hospital, Lahore, from 5th August 2015 to 4th February 2016.
Methodology: A study was done on 80 patients of Chronic liver disease. Under aseptic conditions, venous blood samples were obtained from cases at the time of presentation along with asking some questions related to disease and measure their weight and height. Serum albumin and BNP levels (outcome variable) were measured by using standard chemical analyzer in laboratory. Association between BNP levels with patients' personal and disease factors of patients were analyzed by SPSS 21.
Results: Mean age of the patients was 55.4±10.43 years. Out of 80 patients, 48 (60%) were male. Mean BMI was 21.89±5.45 kg/m^2, mean duration of CLD was 11.23±5.22 years and mean serum albumin and BNP was 3.18±1.05 g/dl and 393.13±289.36 pg/ml respectively. Upper gastro-

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intestinal bleeding observed in 22 (27.5%) patients, ascites was present in 60 (75%). Child Pugh class-A observed in 19 (23.8%) patients, class-B in 30 (37.5%) patients and class-C found in 31 (38.8%) patients. Serum BNP level was positively related with history of upper GI bleed (p=0.000), ascites (p=0.000) and Child Pugh classification (p=0.000) and negatively related with albumin level (p=0.000).

Conclusion: Elevated serum brain natriuretic peptide correlate with severity of chronic liver disease in cirrhotic patients. The use of this marker in cirrhotic patients should be cautiously interpreted for cardiomyopathy.

Keywords: Cross-sectional study; liver cirrhosis; B-type natriuretic peptide (BNP); chronic liver disease; cardiomyopathy.

1. INTRODUCTION

Chronic liver disease (CLD) is one of the leading causes of morbidity and mortality worldwide. The most common causes of CLD are chronic hepatitis due to hepatitis B and hepatitis C virus [1], alcoholic liver disease and non-alcoholic fatty liver disease [2]. Within last two decades, with the invention of effective anti-viral treatments, non-viral causes of CLD are becoming prevalent throughout the western world [3]. However, despite the tremendous amount of work done on it and number of sufferers of all types of hepatitis is increasing day by day especially in Middle East and Asia, indicating that much more aspects of this disease need to be explored [3, 4]. Still viral hepatitis is a global health issue taking the lives of 1.4 million individuals globally [1]. In Asia and Africa deaths due to viral hepatitis are highest than other parts of world and around 90% of this burden is due to chronic liver disease and hepatocellular carcinoma which occurred mainly due to hepatitis B and hepatitis C viruses [1].

Around 10 million individuals in Asia are affected with viral hepatitis [3,4], while non-viral causes are ten times more prevalent than viral causes [2,3]. Pakistan is among those countries with chronic liver disease is at its peak. Pakistan ranked sixth with respect to prevalence of hepatitis B (2.5%) and hepatitis C (4.8%) [3].

Chronic hepatitis leads to cardiovascular complications [5]. Around one third of worldwide mortality is due to coronary vascular disease with 7.4 million deaths are due to coronary heart diseases [6]. The systemic circulation in patients with cirrhosis is hyper dynamic with increased heart rate and cardiac output, reduced systemic vascular resistance and normal or low arterial blood pressure [7]. Many cirrhotic patients present with signs of fluid overload and limited exercise capacity without any history of previous heart disease [8]. All these conditions can be explained under one term, Cirrhotic Cardiomyopathy [5,9,10], which is not very uncommon complication of CLD [5].

In the recent past, newer techniques have been utilized to assess cardiovascular disturbances in patients of chronic liver disease. Natriuretic peptides (BNP and pro-BNP) are one of these newer modalities [7] that can be used as diagnostic as well as prognostic modalities for cardiac failure [11,12].

Pro-BNP in response to intracellular metabolism and under the effect of protease enzyme release active natriuretic peptide .i.e. BNP [13]. B-type natriuretic peptide (BNP) is a biological hormone that is released in response to cardiac ventricular pressure or volume. High concentration showed cardiac dysfunction [10]. In congestive heart failure BNP levels have high reliability in severity of disease [5].

The biological effects of BNP are natriuresis, diuresis, and vascular relaxation, but patients with cirrhosis, especially with advanced disease, may be partially resistant to these effects. Any pressure or volume stress to the heart leads to increase serum level of BNP, so this hormone is non-specifically stimulated in all type of heart disease. Therefore, there are multiple factors that can stimulate BNP secretion [12].

Natriuretic peptides have been used as diagnostic biomarker for heart failure over many years [7,11]. Their diagnostic as well as prognostic value in management of heart failure is already established [12], however it has been noted that their role can also be implicated in diseases other than heart failure like chronic liver disease [7,11,13].

However, not much work has been done in assessing the role of Brain Natriuretic Peptide

(BNP) in showing disease severity in cirrhotic patients [7]. The proposed reason for the raised levels of pro-BNP in severe form of chronic liver disease was due to the relative decrease in ejection fraction and systolic dysfunction after physical activity [14] and micro-vascular fibrosis in response to cirrhosis leading to thrombosis and ultimately triggering microvascular ischemia in multiple organs especially in heart muscles [15]. Ischemia in heart muscles stimulated excessive release of BNP [16]. This study finds out the mean BNP level in cirrhotic patients and its association with severity of chronic liver disease.

2. MATERIALS AND METHODS

The cross-sectional study was conducted from August 2015 to February 2016. After getting ethical approval from Research cell of Jinnah Hospital, Lahore and 80 patients of chronic liver disease of any etiology from emergency and outdoor patients department of Jinnah hospital were enrolled using the non-probability purposive sampling.

Those who meet the inclusion criteria were enrolled in the study. Those patients with age between 30 to 70 years, of both genders and had been treated for chronic liver disease for more than 5 years were included in study. NT-pro BNP levels changed as the age progresses due to decline in glomerular filtration rate, so normal values of BNP in blood changed after the age of 70 years [17]. Patients of chronic liver disease with history of diabetes mellitus, heart disease, hypertension (blood pressure > 140/90 mmHg), dyslipidemia, stroke, acute or chronic kidney disease, any malignancy, pregnancy, anemia with hemoglobin less 10 gm/dl, taken any medication including beta blockers which may effect the liver and heart functions or alcohol drinkers were excluded from this research. Chronic liver disease was operationalized by reduced liver span shrunken liver <8 cm with increased liver echo pattern, splenomegaly >13 cm and portal vein diameter > 13 mm, confirmed on ultrasonography as it was reliable, cost effective and valid method of diagnosing CLD. Patients diagnosed at least 5 years ago were included.

The subjects were diagnosed clinically as well as with lab tests and ultrasound. After evaluating the patients according to inclusion and exclusion criteria, informed consent was taken from the subjects before filling the self-administered the questionnaire, examining the patients and send their blood sample for this study.

Data was collected by researcher herself on self-structured questionnaire containing information about personal details of patient like age, gender, hospital registration number and history of CLD, encephalopathy, upper gastrointestinal bleed (G.I. bleed) irrespective of the source of bleeding due to lack of resources for endoscopy and sonographically examined the patient for the grade of ascites in which ascites responsive and refractory to treatment was labelled as mild to moderate and severe ascites respectively. Anthropometric measurement i.e. weight and height were done using digital weighing scale and inches tap respectively with patient standing in erect position.

Blood sampling was done from forearm vein by professional phlebotomist after 10 minutes resting in supine position and collected in standard blood tubes for lab analysis. Serum bilirubin, albumin, prothrombin time and serum BNP levels (measuring range 5 pg/ml to 35000 pg/ml) were using standard chemical analyzer in laboratory. Patients were categorized according to Child Pugh classification.

Collected data was entered and analyzed in the SPSS version 21 with continuous variables like age, BMI, BNP levels were expressed as mean and standard deviation and categorical variables like gender were recorded as frequency and percentage. Data was normally distributed (Kolmogorov-Smirnov test of normality, $p=0.064$. Data was stratified for age, gender, BMI, upper GI bleed, Child Pugh class and duration of chronic liver disease. Post-stratification albumin levels, grades of ascites and Child's classification are analyzed with BNP levels by using One-way analysis of variance (ANOVA) with Tukey post hoc test on ascites level and Child's classification and dichotomous variable like gender, duration of CLD are analyzed by independent sample t-test with p value ≤ 0.05 is considered significant.

3. RESULTS AND DISCUSSION

A total of 80 patients were included in the study during the study period of six months from 5th August, 2015 to 4th February 2016. Mean age of the participants was 55.4±10.43 years and mean albumin and BNP levels are 3.18±1.05 g/dl and 393.13±289.36 pg/ml (Table 1). Other personal characteristics are also shown in Table 1.

Table 1. Baseline characteristics of patients of chronic liver disease

	Mean	Standard deviation
Age of Patient (years)	55.4	10.43
Height of patient (meters)	1.67	0.09
Weight of patient (kg)	61.06	15.25
Body Mass Index (kg/m ^{2})	21.89	5.45
Duration of CLD (years)	11.23	5.22
Albumin level of Patient (g/dl)	3.18	1.05
BNP level (pg/ml)	393.13	289.36

Stratification with regard to age, gender, BMI, upper GI bleed, Child Pugh class and duration of CLD was carried out and presented in Table-2. Regarding age distribution, 39 patients (48.8%) were between 58 to 71 years of age and 48 (60%) were male while remaining 32 patients (40%) were females. Only 17 (21.3%) participants were overweight or obese while the rest of patients are either within normal BMI or were underweight. Around three-quarter of the patients (57, 71.3%) were suffering from chronic liver disease for 5 to 15 years, also, same frequency (58, 72.5%) was observed for no history of even a single episode of upper G.I. bleeding (Table-2).

Out of 80 participants, 20 (25%) patients had no ascites, 34 (42.5%) of patients with ascites had mild to moderate ascites .i.e. adequate natriuresis with dietary sodium restriction alone, or only respond to diuretic therapy while 26 (32.5%) had ascites diuretic resistant ascites. Nineteen (23.8%) participants had normal albumin level. According to Child Pugh classification, 19 (23.8%) patients were labeled as class-A, 30 (37.5%) patients as class-B and 31 (38.8%) patients as class C. Normal BNP level was observed in only 13 (16.3%) of subjects (Table 2).

Table 2. Frequency distribution of different characteristics of CLD patients

		Frequency	Percent
Age of patients	30 to 43 years	12	15
	44 to 57 years	29	36.3
	58 to 71 years	39	48.8
Gender of Patient	Male	48	60
	Female	32	40
BMI	Underweight (< 18.5 kg/m^2)	24	30
	Normal (18.5 to 24.9 kg/m^2)	39	48.8
	Overweight or Obese (≥ 25 kg/m^2)	17	21.3
Duration of CLD	5 to ≤ 15 years	57	71.3
	> 15 years to ≤ 30 years	23	28.8
History of G.I. bleeding	Yes	22	27.5
	No	58	72.5
Ascites in patient	None	20	25
	Mild to Moderate	34	42.5
	Severe	26	32.5
Albumin level	< 2.8 g/dl	31	38.8
	2.8 to 3.5 g/dl	30	37.5
	> 3.5 g/dl	19	23.8
Child Pugh Classification	Class A	19	23.8
	Class B	30	37.5
	Class C	31	38.8
BNP	Normal values (less than 100)	13	16.3
	Grey zone values (100 to 400)	35	43.8
	Critical values (More than 400)	32	40

Table 3 showed that demographic factors like age (*P=.25*), gender distribution (*P=.19*) and body mass index (BMI) (*P=.51*) were not found to be associated with serum BNP level. Among disease factors duration of disease (*P=.25*) has no role in raising levels of BNP, however, factors that showed stage of disease e.g. any episode of upper G.I. bleed (*P=.00*), severity of ascites (*P=.00*) with progressive increase in BNP levels (*P=.00* for none vs mild to moderate ascites and *P=.03* for mild to moderate to severe ascites) by Tukey post hoc test (Fig. 1) and albumin levels (*P=.00*) are linked with BNP level. Furthermore, Child Pugh classification (*P=.00*) has statistically significant association with BNP and class B had far more increase in BNP than class A while class C had significantly increase in BNP than in class B (Fig. 2).

3.1 Discussion

In current study, age, gender, BMI and duration of liver cirrhosis had no relationship with BNP levels, however, upper G.I. bleeding, grades of ascites, albumin levels and grades of Child-Pugh classification had direct relationship with increased BNP levels.

Present study showed no association of age with BNP (p=0.250), which is contrary to study done by Woo et al. [17] and Hamada et al. [18]. The data published by Hamada showed that BNP concentration is higher in females than male among healthy subjects [18] but current study showed no association between gender distribution and BNP (p=0.187) . This is due to the disease process that might be more significant in raising the BNP concentration in cirrhosis than gender difference.

High levels of natriuretic peptides were considered to be due to decreased visceral fats and increased fats in lower extremity regardless of age, gender, race and overweight condition. This showed that there might be a connection between fat distribution in heart and natriuretic

Table 3. Relationship between different characteristics of patient with the BNP levels in Chronic liver disease

		BNP level pg/ml		
Age of Patients	**N**	**Mean**	**Std. Deviation**	**p-value**
30 to 43 years	12	343.17	298.02	.25
44 to 57 years	29	464.62	301.87	
58 to 71 years	39	355.33	273.98	
Gender of Patient				
Male	48	358.15	284.34	.19
Female	32	445.59	293.36	
BMI				
Underweight (< 18.5 kg/m^2)	24	428.67	283.77	.51
Normal (18.5 to 24.9 kg/m^2)	39	401.72	305.29	
Overweight or Obese (≥ 25 kg/m^2)	17	323.24	262.77	
Duration of CLD				
5 to up to 15 years	57	369.16	281.65	.25
> 15 years to up to 30 years	23	452.52	305.90	
History of G.I. bleeding				
Yes	22	583.82	250.02	.00
No	58	320.79	271.40	
Ascites				
None	20	137.45	95.34	.00
Mild to Moderate	34	406.85	284.95	
Severe	26	571.85	254.42	
Albumin levels				
< 2.8 g/dl	31	639.61	224.22	.00
2.8 to 3.5 g/dl	30	306.07	200.94	
> 3.5 g/dl	19	128.42	165.56	
Child Pugh Classification				
Class A	19	83.63	27.97	.00
Class B	30	294.80	142.80	
Class C	31	677.97	214.80	

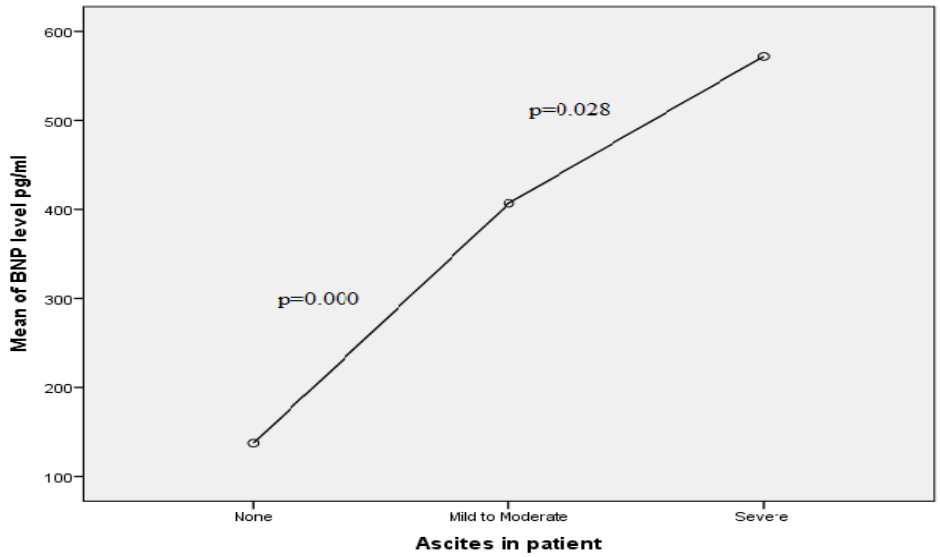

Fig. 1. Serum BNP levels in cirrhotic patients group according to the grades of ascites. Successive increase in BNP levels with severity of ascites

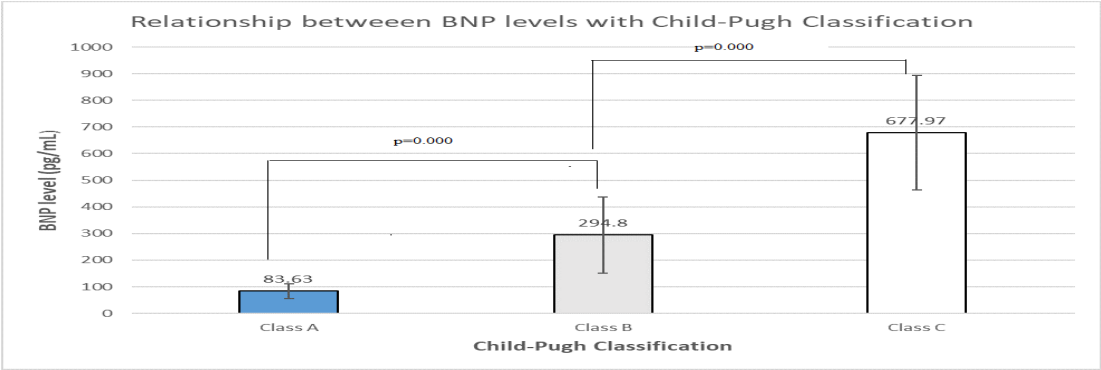

Fig. 2. Serum BNP levels in cirrhotic patients categorized as class A, B and C. BNP levels in class B was significantly raised than in class A and in class C was significantly raised in class B (Tukey post hoc test)

peptides [19]. So, BNP levels may be an indication of cardiac diastolic dysfunction in patients with liver cirrhosis [9]. Hamoudi showed that duration of liver disease had some impact in changing the histology of cardiac myocyte leading to cardiomyopathy [20]. Current study also agreed on it, in which BNP levels were raised as the duration of disease increased (369.16 pg/ml at 5-15 years vs 452.52 pg/ml at 16 to 30 years) but was not proved to be statistically significant (p=0.246)

Upper G.I. bleed in cirrhotic patients can be caused by gastro-esophageal varices, gastropathy due to portal hypertension and gastro-duodenal ulcers. Endoscopy is the primary investigation of choice in diagnosing the cause of bleeding [21]. Increase level of BNP in cirrhosis in response to hypervolemic states helps in decreasing portal hypertension especially in patients with esophageal varies [22] but the patients on the treatment of diuretics and beta-blockers, BNP level can be far low than actual due to the combined action of these drugs in decreasing BNP, so they must be stopped before measuring BNP concentration in blood [22, 23]. Ruyon et al. reported that history of upper G.I. variceal bleed was strongly associated with BNP levels and severity of cardiomyopathy [24]. Also, this study found that BNP levels were higher in patients who had at least one episode of upper G.I. bleed than those cirrhotic patients

who never had upper G.I. bleeding (583.82 vs 320.79 pg/ml, p=0.000).

Ascites along with upper G.I. bleed and hepatic encephalopathy is one of the three chief complications of chronic liver disease [24]. All these complications are used as indicators in Child–Pugh classification [22]. Even ascites is so common that around half of patients with compensated cirrhosis develop ascites within one decade of disease diagnosis without any other complication. Research showed that presence of ascites was an indicator for poor prognosis [24]. In 15% of patients with ascites, it is due to non-hepatic reasons like any underlying right heart failure, cancer, nephrotic syndrome, thyroid diseases and pulmonary infection. The serum-ascites albumin gradient (SAAG) ≥ 1.1 g/dl (11 g/L) differentiated ascites due portal hypertension from other causes of ascites [24, 25].

Normal hepatic sinusoids offer free communication of proteins with interstitial space so there is no osmotic gradient, but in cirrhosis due to lack of fenestrae, this transport is restricted, resulting in the restriction of protein transport [26]. So, ascites in cardiac failure, ascitic fluid total protein (AFTP) concentration was greater than 2.5 g/dl, which helps in discrimination of ascites due to cirrhosis with the ascites from cardiac cause [27].

According to Pimenta et al.[5], found that BNP levels in end-stage liver disease showed cardiac systolic function [9]. Study also showed that BNP was a subclinical symptom of a heart disorder that played a role in liver dysfunction. BNP levels were significantly associated with dilatation of left atrium and cardiac diastolic failure, indicating the structural as well as functional changes commonly seen in late liver disease [11]. Many previous studies showed some association between B-type natriuretic peptide (BNP) and cirrhotic cardiomyopathy but the prognostic or survival role of BNP in cirrhosis is still theoretical [5]. Results showed that severity of cirrhosis was significantly related with BNP. Grades of ascites and albumin levels were used in calculating Child-Pugh score. These parameters (albumin: p=0.000, ascites: p=0.000) along with the collective grades of Child Pugh score were significantly related with BNP levels (p=0.000). Also, BNP level was progressively raised in Class-C as compared to Class A and class B (677.97 pg/ml vs 83.63 and 294.80 pg/ml)

A study done by Yildiz et al. [22] showed that presence of ascites and hepatic encephalopathy were strongly correlated with increased concentration of BNP (p=0.033 and p= 0.014 respectively) [22]. Moreover, same studies proved good association with Child Pugh scoring and BNP levels (p=0.012) and specifically increasing grading of cirrhosis leads to successive increase in serum BNP (p<0.05). Similarly, Zhao et al. found that pro-BNP more than 900 pg/ml was present in 40% of patients, with pro BNP levels was significantly related with ascites (p=0.002), stage of cirrhosis according to Child Pugh score (p=0.045) as well as according to MELD scoring (p<0.001) and decreased survival rate (p=0.024) [16].

Woo et al. in their study showed that N-amino terminal pro-brain natriuretic peptide (NT pro-BNP) was significantly increased in patients with chronic liver disease as compared to healthy controls irrespective of the presence of ascites (155.9 pg /ml and 198.3 pg /ml in the presence and absence of ascites respectively , p<0.05). Moreover, Child Pugh grading of cirrhosis was associated with raised BNP levels (250.0 pg/ml in grade-C vs. 168.6 pg/ml in grade-B and 119.6 pg/ml in grade-A, p<0.05) [17]. Another study showed that pro-BNP levels was higher in cirrhotic patients (19 pmol/l) than healthy controls (<15 pmol/l, p=0.002) and was directly related with the stage of cirrhosis (p<0.01) [28]. Thus, ascites, variceal bleeding, hepatic encephalopathy as used in Child-Pugh classification and BNP levels had significant correlation with negative prognosis of patients [22].

According to Paganaa, normal serum levels of BNP should be less than 100 pg/ml, while the levels for diagnosing heart failure should be more than 400 pg/ml and the intermediate levels (100 to 400 pg/ml) needs clinical judgment as well as other investigation to discriminate between heart failure and other diseases in which BNP concentration can also be raised [29]. Raised levels of BNP in CLD patients and its detailed association with severity of disease and progressively decreased cardiac function can be explored in further studies.

Mihailovic and Radvan and also reported that in cirrhosis, serum BNP can range from 21 to 1078 pg/ml and was related with stage of patient's disease according to Child's Pugh classification (p=0.0009) as well as by MELD score (p=0.003). Also, BNP levels correlated with survival rate of

these patients [8, 30]. Many studies showed that BNP levels were directly proportional to the stage of liver disease [10, 22, 28, 31, 32].

Padillo's reported that increased level of BNP was strongly correlated with Child score and cardiac function impairment in chronic liver disease [33]. Shi's study showed that patients with high BNP concentration were linked with Child's classification, upper G.I. bleeding and level of ascites [34]. Mean BNP concentration was strongly correlated with severity of chronic liver disease and important poor prognostic factor with decreased 1 year survival [9, 34].

One thing should be kept in mind, BNP levels should be interpreted with great care as without any cardiac insult its value increase as the age progresses i.e. before 65 years of age more than 100 pg/ml BNP showed heart disease while after 65 years cut off was shifted to 155 pg/ml. Also, its concentration in serum also changes according to stages of disease. So, extreme values (very high or very low) of BNP helped as diagnostic role in heart failure while value in between showed the grey where BNP cannot differentiate heart disease from lung disease [12].

In this study current treatment of patients especially any diuretic was not taken into account that could be an important confounder and may lead to unexpectedly small serum concentration of BNP.

Secondly, in future, multiple center study should be required. Also, this study is cross-sectional study due to time restrains. Prospective study with serial measurement of BNP levels may give more promising results.

BNP can be raised in a number of disease states including congestive cardiac failure, chronic renal failure, hypertension, pulmonary edema [12] and cirrhosis [5]. As this study found that raised BNP levels and severity of CLD was related then future studies are required to find out effect of BNP levels on management plan and quality of life when measured at different time in the treatment of patient.

4. CONCLUSION

It is concluded that elevated serum brain natriuretic peptide correlates significantly with severity of chronic liver disease in cirrhotic patients as established by Child-Pugh classification and is a good prognostic marker in symptomatic as well as asymptomatic patients but the use of this marker in cirrhotic patients should be interpreted with caution.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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