N-Terminal Pro-Brain Natriuretic Peptide: Prognostic Potential in End Stage Liver Cirrhosis in a Cohort Free of Heart Failure; an Egyptian Insight

Elham Ahmed Hassan[1]*, Abeer Sharaf EL-Din Abd El-Rehim[1], Zain EL-Abdeen Ahmed Sayed[2], Heba Ahmed Abdelhafez[3] and Muhamad Ramadan Abdelhameed[2]

[1]Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assiut University, Assiut, Egypt
[2]Department of Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt
[3]Department of Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt

Abstract

Background: Natriuretic Peptide (NP) system has emerged as one of the most important hormonal systems in control of cardiovascular homeostasis. Liver cirrhosis may affect NP levels that were well described in heart failure. NP prognostic evaluation was well established in many diseases.

Objectives: to measure serum and ascitic NT-proBNP levels in cirrhotic and cardiac Egyptian patients to diagnose a cut-off value for exclusion of heart failure, to assess if cirrhosis per se may contribute in NT-proBNP elevation and to assess the contribution of these levels as predictors of mortality in liver cirrhosis.

Patients and methods: A prospective cohort study was conducted in 80 patients (50 cirrhotics and 30 had heart failure). Serum and ascitic (if available) NT-proBNP were measured. Cirrhotic patients were followed for 1-year. Kaplan-Meier survival analysis was used to evaluate 1-year survival rates. Logistic regression analyses were performed with 1-year mortality as the dependent variable.

Results: Median serum and ascitic NT-proBNP levels in cirrhotics were 239.4 and 267pg/ml versus 10596.6 and 9771 pg/ml in heart failure patients (P<0.001). Serum and ascitic NT-proBNP cut-off values >1000 pg/ml resulted in sensitivity of 100% and 93.3% and specificity of 97.8% and 92.5% for exclusion of cardiac disease in cirrhotics. NT-proBNP was elevated in cirrhotics compared with age matched controls (P<0.001) and significantly correlated with severity of liver cirrhosis based on Child-Pugh and MELD (P=0.05, P<0.001 respectively). Higher NT-proBNP associated with increased 1-year mortality. NT-proBNP was an independent predictor for mortality in cirrhotics in addition to other conventional factors.

Conclusion: NT-pro BNP could be a powerful initial non-invasive diagnostic tool for exclusion of heart disease in cirrhotic patients. End stage cirrhosis per se may contribute to NT-proBNP elevation. NT-proBNP provided incremental information in 1-year mortality prediction in decompensated cirrhotics.

Keywords: Liver cirrhosis; 1-Year mortality; NT-proBNP; Prognosis

Introduction

In last decades, there are improving efforts to understand cardio-vascular changes in liver disease. Deterioration of liver function and portal hypertension with splanchnic vasodilatation was first associated with hyperdynamic circulation that characterized by increased cardiac output, decreased arterial pressure, peripheral resistance and marked activation of endogenous vasoactive systems that further aggravated the hyperdynamic circulation and cardiac strain [1,2]. Later, cirrhotic patients exhibited circulatory and cardiac dysfunctions predominantly governed by peripheral vasodilatation [2].

Cirrhotic cardiomyopathy has been observed in liver cirrhosis, it involves impaired cardiac contractility, systolic and diastolic dysfunction, and electrophysiological abnormalities without known cardiac diseases [3].

These cardio-vascular dysfunctions may affect the prognosis of cirrhosis and aggravate its course during invasive procedures such as surgery, insertion of a Transjugular Intrahepatic Porto-Systemic Shunts (TIPS), also, they are of great interest in prioritization of transplantation lists, during and post-transplant prognosis as liver transplantation has been shown to ameliorate the cardiac and circulatory disturbances [4,5].

In certain situations, there is a challenge in clinical judgment to distinguish primary liver disease or heart failure especially in the presence of ascites, as both diseases may have inconclusive traditional testing or diagnostic uncertainty. Hepatic patients may have symptoms resembling chronic heart failure like fatigue, dyspnea that was not proportional to liver affection. Also, cardiac patients may have picture simulating liver disease e.g. jaundice, unapparent jugular venous distension, lower limb edema, elevated liver enzymes and transudate ascites with SAAG > 1.1. Therefore, different investigative modalities may be needed to diagnose the etiology and assess cardiac function in liver cirrhosis such as echocardiology, hepatic venous pressure gradient and isotope ventriculography. However, these tests are more invasive,

expensive and highly technical that may not be available and have their share of potential complications.

Natriuretic Peptide (NP) system has emerged as one of the most important hormonal systems in the control of cardiovascular homeostasis and function via coordinated central and peripheral actions [6]. NPs promote natriuresis and diuresis, act as vasodilators and antagonise the vasoconstrictor effects of the renin–angiotensin–aldosterone system [7]. Ventricles become an important source of NPs, particularly Brain-Type Natriuretic Peptide (BNP) in response to myocardial ischaemia and stretch by volume and pressure overload [6]. N-terminal-proBNP (NT-proBNP) resulting from cleavage of ProBNP (a precursor of BNP) is more stable with longer half-life, it has been shown to be superior in predicting morbidity and mortality or hospitalization for chronic heart failure and an even better indicator of early cardiac dysfunction than BNP [8,9].

Previous studies revealed increased NP concentrations in patients with cirrhosis suggesting cardiac dysfunction [8,10,11]. However, few studies had demonstrated NP significance in prognosis of liver cirrhosis. So, lack studies in our locality encouraged us to do this work. Therefore, the aims of our study were to measure serum and ascitic NT-proBNP levels in cirrhotic and cardiac Egyptian patients to diagnose a cut-off value for exclusion of heart failure (especially in the presence of ascites), to assess if liver cirrhosis per se may contribute in NT-proBNP elevation and to assess the contribution of these levels as predictors of mortality in liver cirrhosis.

Patients and Methods

Study design

This was a single-central prospective cohort study with 1 year of follow-up carried out at Assiut University Hospital (AUH), Egypt, from October 2011 to October 2012. The study was approved by the Ethics Committee of AUH and informed consent was obtained from all the participants before enrollment.

Study population

A total of 80 patients (50 with liver cirrhosis and 30 with heart failure) were enrolled in this study. Cirrhotic patients had diagnostic criteria of liver cirrhosis (LC) by clinical, biochemical and ultrasonographic findings. The cause of liver dysfunction was hepatitis C. Severity of liver cirrhosis was assessed according to Child-Pugh classification and MELD scores. Diagnosis of heart failure was based on established clinical findings and imaging signs (chest X-ray, electrocardiography and echocardiography). Twenty four healthy individuals had no hepatic or cardiovascular diseases, they matched for sex and age with patients and they were served as controls. These patients were selected from outpatient clinics and inpatient wards of the departments of Tropical Medicine and Internal Medicine, Assiut University Hospital (AUH) and controls were selected randomly from outpatient clinic and relatives of the patients admitted to our department. All cirrhotic patients and controls had normal cardiac physical examination, absent signs of cardiomegaly on chest X-ray and fairly normal electrocardiography (ECG) findings. Exclusion criteria included

- Patients with renal, pulmonary disease, thyrotoxicosis, sepsis

- Patients with non-cardiac cause of heart failure (Heart failure that is not caused by a form of heart disease e.g. heart failure caused by anemia, decompensated cor pulmonale, renal failure)

- Cirrhotic patients with cardiac diseases, renal impairment and obesity were excluded.

At study entry, a thorough medical history was taken and measurement of NT-pro-BNP and other biochemical parameters were undergone. At the same time, echocardiography was performed. All cirrhotic patients were followed up prospectively for one year with emphasis on their survival status. Surveillance was made by direct contact or telephone with patients or relatives and observation of medical records.

Method

Venous blood and ascitic (if available) samples; 3-5 ml for each, were obtained from the stable participant at the same time. Samples were collected and centrifuged immediately. Serum and ascitic samples were frozen at -80°C until assayed. NT-proBNP levels were measured by enzyme immunoassay (using commercially available kits, purchased from Biomedica - Medizinprodukte GmbH & Co kG, Wein, Austria) in accordance with the protocol of the manufacturer.

Statistical Analysis

All statistical analyses were conducted using SPSS for windows version 17 (SPSS Inc., Chicago, IL. USA). Continuous data were expressed as means ± standard deviation (SD) or median and compared using Student's and ANOVA or Mann-Whitney U and Kruskal-Wallis tests for normally or abnormally distributed data respectively. Categorical variables were expressed as percentage and compared using chi-square ($\chi 2$) test. NT-proBNP values and severity of liver cirrhosis were correlated by means of Spearman correlation. Survival curve for cirrhotic patients was generated by means of Kaplan-Meier estimates and differences in survival were compared by the log-rank test. Multiple regression analysis was used to study the influence of independent variables on 1-year mortality. For all analyses, P value < 0.05 was considered statistically significant.

Results

Characteristics of the study population

The baseline demographic and biochemical characteristics of the study population were summarized in Table 1, where the study compromised 80 adult patients. Of these, 50 patients with liver cirrhosis were 14 females and 36 males with a mean age of 58 ± 5.6 years and 30 patients with heart failure were 8 females and 22 males with a mean age of 54.9 ± 13.4 years. While, control group formed of 6 females and 18 males with a mean age of 58 ± 6.6 years. There were no significant differences between studied groups as regard demographic data and between patients (LC, heart failure) regarding liver and renal functions.

There were 11 deaths within 1-year of follow up (one was Child B and 10 were Child C). The median serum and ascitic NT-proBNP levels in deceased patients were higher than survivors (964.5 and 292.6 pg/ml versus 268.6 and 223.3 pg/ml with $p < 0.001$ and $p > 0.05$ respectively).

Assessment of NT-pro BNP levels and its relation to severity of liver cirrhosis

Serum and ascitic NT-proBNP values in heart failure group were significantly higher than liver cirrhosis (LC) group ($p < 0.001$ for both) (Figure 1). As shown in our study, the lowest serum and ascitic NT-proBNP levels in patients with cardiac ascites was 1130 and 982 pg/ml, whereas the highest serum and ascitic NT-proBNP levels in patients with cirrhosis was 1494.4 and 1175.8 pg/ml respectively. Therefore using values greater than 1000 pg/ml, serum and ascitic NT-

	Cirrhosis (n = 50)	Heart failure (n = 30)	Control (n = 24)
Age	(50-76) 58 ± 5.6	(45-68) 54.9 ± 13.4	(50-76) 58 ± 6.6
Sex **Male (%)** **Female (%)**	36 (72) 14 (28)	22 (73.3) 8 (26.7)	18 (75) 6 (25)
Child-Pugh score	11.7 ± 1.3	-	-
Child-Pugh class **Child (A)** **Child (B)** **Child (C)**	10 (20%) 12 (24%) 28 (56%)	-	-
MELD score	17.5 ± 6.4	-	-
Serum creatinine (mg/dl)	1.6 ±1	1.9 ±1.4	1 ± 0.4
Serum bilirubin (mg/dl)	2.9 ± 2	2.2 ± 1.1	0.6 ± 0.2
Serum total protein	65.5 ± 6.7	69.6 ± 5.5	78.9 ± 5.3
Serum albumin	19.5 ± 5.2	21.1 ± 4.6	42.6 ± 2.2
AST	60.3 ± 56.7	54 ± 21	24.8 ± 8.6
ALT	36 ± 28.2	30.3 ± 15.6	22.2 ± 8.9
Prothrombin time (sec)	19.7 ± 4.2	18.4 ± 2.2	13 ± 1.1
INR	1.7 ± 0.4	1.6 ± 0.2	1.1 ± 0.1
Ascitic total protein (g/dl)*	1.2 ± 0.2	1.5 ± 0.9	-
Serum TN-proBNP (pg/ml) **Mean** **Median** **Range**	415.3 ± 383.4 239.4 62 – 1494.4	9168.8 ± 5101.7 10596.6 1130 – 14351.5	57.1 ± 18.9 61 28 – 86
Ascitic TN-proBNP (pg/ml) **Mean** **Median** **Range**	382 ± 330.3 267 8.5 – 1175.8	8088.6 ± 4131.6 9771 982.1 – 12781.7	

*SAAG in both groups were > 1.1

Table 1: Demographic and biochemical characteristics of the study population.

proBNP had sensitivity of 100% and 93.3%; specificity of 97.8% and 92.5%, positive predictive value was 93.8% and 90.3% respectively in predicting heart failure and excluding primary liver disease.

Serum NT-proBNP level was higher in patients with liver cirrhosis compared to age and sex matched healthy control ($p < 0.001$) (Figure 2). Although cirrhotic patients with Child C had higher serum and ascitic NT-proBNP levels than those with Child A and B, these differences were not significant ($p > 0.05$ for both) (Figure 3).

In addition, elevation of serum and ascitic NT-proBNP levels was positively correlated with the severity of liver cirrhosis based on Child-Pugh and MELD scores ($p = 0.05$, $p < 0.001$ respectively) (Table 2). Figure 4 showed significant positive correlation between serum and ascitic NT-proBNP levels in both cardiac and cirrhotic cases (r = 0.744, $p < 0.001$ and r = 0.897, $p < 0.001$ respectively).

Determination of the survival analysis

Figure 5 showed Kaplan–Meier survival estimates of cirrhotic patients stratified by median of serum and ascitic NT-proBNP levels predicting increased 1-year mortality in patients with higher levels compared with those with lower levels ($p = 0.003$ and $p > 0.05$ respectively).

### Assessment of NT-proBNP as a risk factor for 1-year mortality

To choose the factors that can independently predict the survival in cirrhotic group, multiple regression analysis was applied; using the variables from univariate analysis that had to be significantly ($P < 0.05$) associated with 1-year mortality, where, increasing serum and ascitic NT-proBNP levels were independent risk factors for mortality ($p=0.004$ and 0.05 respectively) in addition to other conventional factors such as hypoalbuminemia and high serum bilirubin and creatinine levels and severity of liver cirrhosis (Table 3).

Discussion

In this cohort study both serum and ascitic NT-proBNP levels were measured in advanced cirrhotic and cardiac Egyptian patients to diagnose a cut-off value for exclusion of heart failure and to assess the contribution of these levels as predictors of mortality in liver cirrhosis.

Cardiac patients could be misdiagnosed when they presented with a picture simulating liver disease e.g. hepatomegaly, transudate ascites with SAAG > 1.1, etc. They could even be missed with a non conclusive cardiac function assessment, especially in elderly with normal left ventricular ejection fraction or when invasive methods were not available, expensive or requiring specialized clinical staff.

In the present study, serum NT-proBNP level was higher in patients with heart failure compared to that with liver cirrhosis. This results matched with several studies [12,13]. Our study was in agreement with Sheer et al. [12] where serum and ascitic fluid NT-proBNP concentrations were found to be closely related and had similar
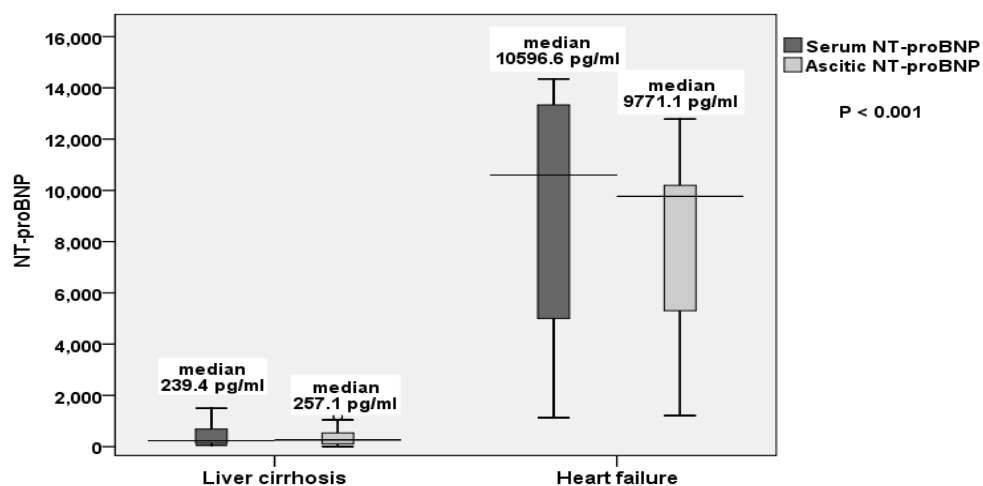
Figure 1: Serum and ascitic NT-proBNP levels in heart failure group were significantly higher than that in liver cirrhosis group (P < 0.001 for both).
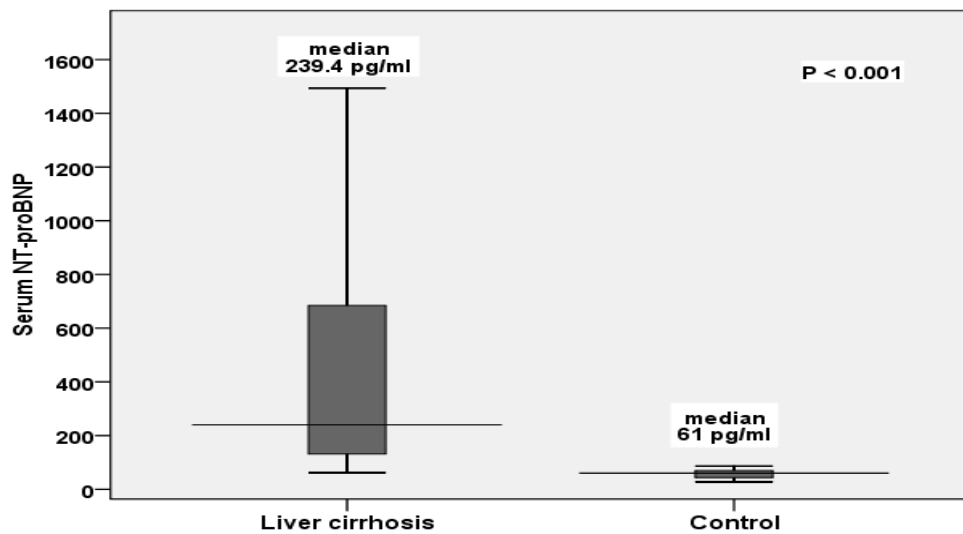
Figure 2: Serum NT-proBNP level in liver cirrhosis group was significantly higher than that in control group (P < 0.001).
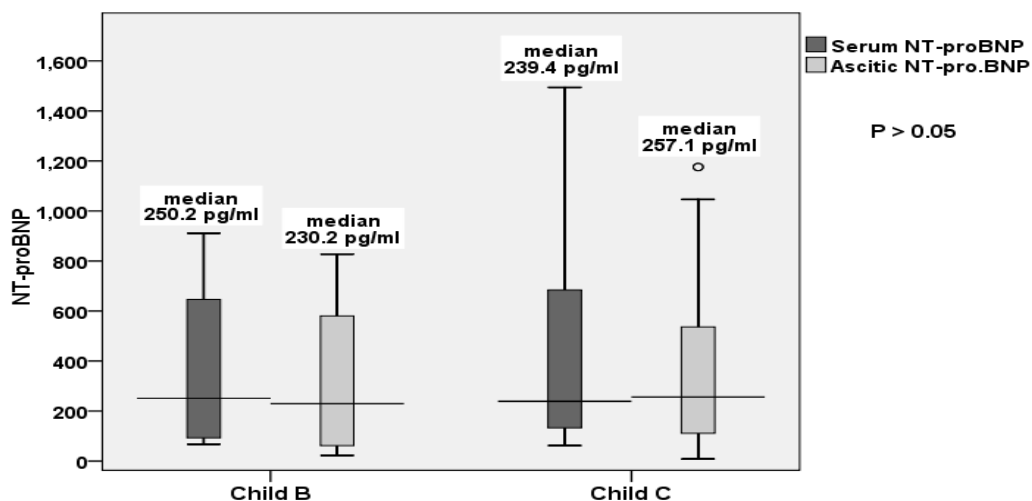

Figure 3: Serum and ascitic NT-proBNP levels in Child (C) group were higher than that in Child (B) group but these differences were not significant (P = 0.07 and 0.1 respectively).

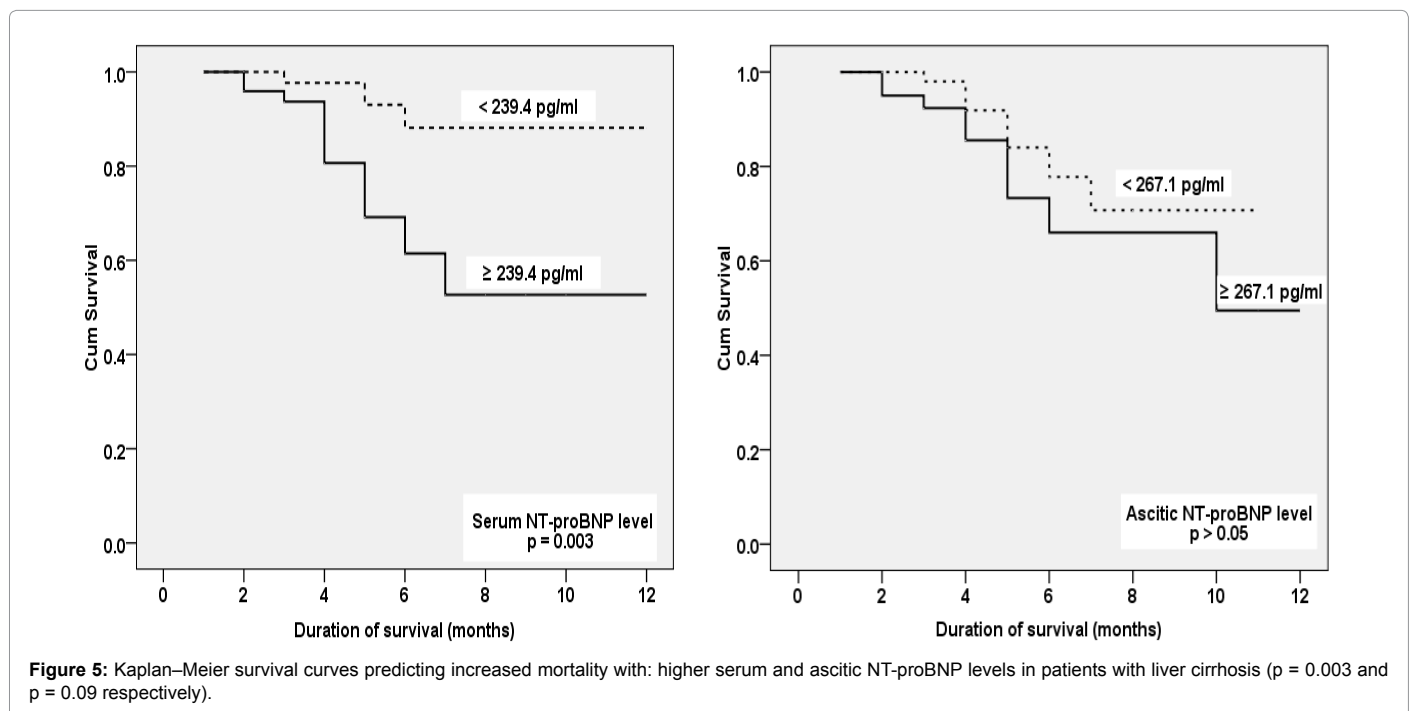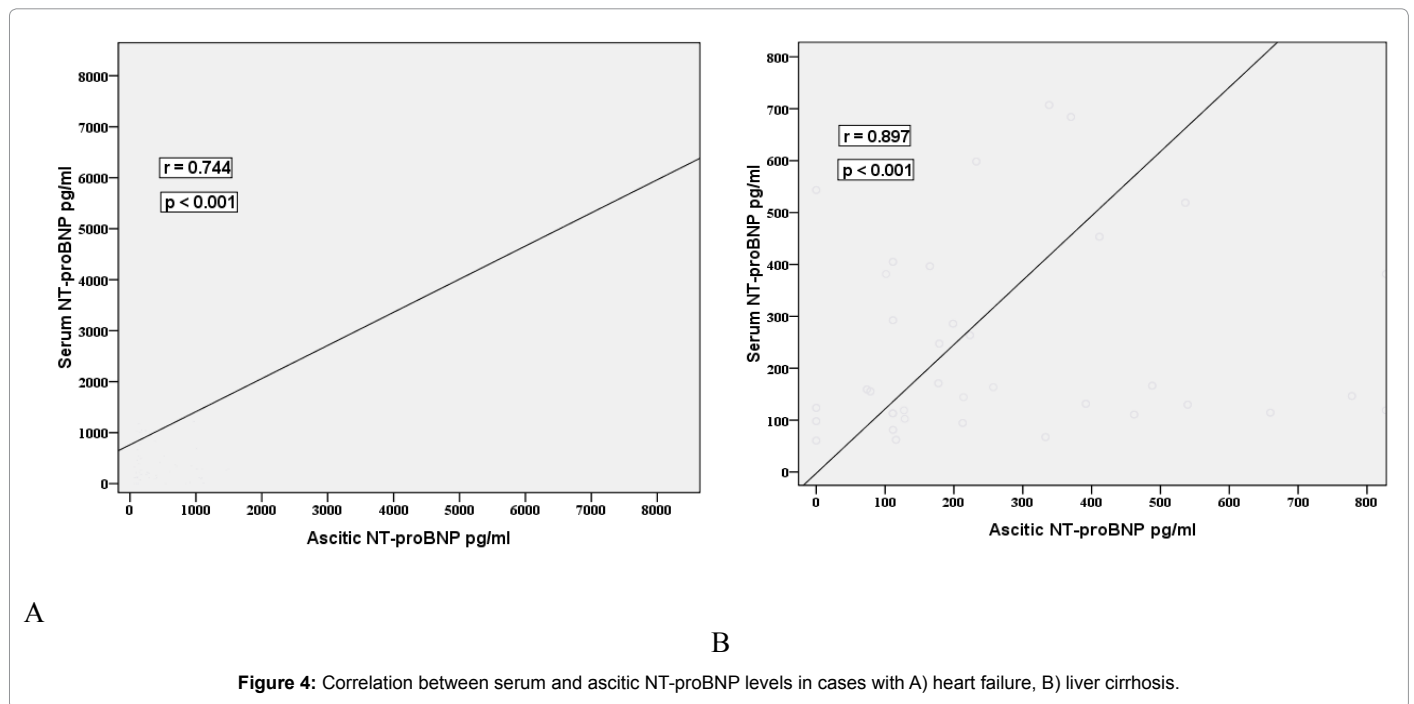|	Serum NT-proBNP		Ascitic NT-proBNP	
	Correlation Coefficient	P	Correlation Coefficient	P
Child-Pugh score	0.317	0.002	0.380	0.05
MELD score	0.615	< 0.001	0.350	0.001
Serum albumin	- 0.427	0.02	- 0.405	< 0.001
Prothrombin time	0.463	< 0.001	0.300	0.01
Serum bilirubin	0.637	< 0.001	0.035	0.8

Table 2: Correlation between serum and ascitic NT-proBNP levels and severity of liver cirrhosis.

diagnostic accuracy. Hence, ascitic fluid as well as serum NT-proBNP concentrations were useful in the differential diagnosis of cardiac and non-cardiac origins of ascites.

Our results were in a concordance with previous studies [12,14] that serum and ascitic fluid NT-proBNP levels with cut-off value greater than 1000 pg/ml was sensitive and specific in distinguishing patients with heart failure from those with concurrent extracellular volume overload in decompensated liver cirrhosis. Bursi et al. this peptide is

an effective biomarker in heart failure diagnosis and risk stratification, independent of ejection fraction [15].

We also found that both serum and ascitic NT-proBNP levels were elevated in cirrhotic patient but not as high as in heart failure. This was attributed to the direct relation of elevated peptide to diastolic dysfunction and central hypervolemia in patients with advanced cirrhosis and large ascites [3,15,16]. In addition, this significant raising may be explained by their correlation with ventricular wall stress [17].

Figure 4: Correlation between serum and ascitic NT-proBNP levels in cases with A) heart failure, B) liver cirrhosis.

Figure 5: Kaplan–Meier survival curves predicting increased mortality with: higher serum and ascitic NT-proBNP levels in patients with liver cirrhosis (p = 0.003 and p = 0.09 respectively).

In the present study, our results were comparable to several studies [8,10,11], where NT-proBNP levels were raised in cirrhotic patients in comparison to non-cirrhotic, non-cardiac age matched healthy controls. In addition, we noticed that these levels were positively correlated with Child-Pugh and MELD scores as demonstrated in the reported studies [11,17,18].

NT-proBNP elevation in liver cirrhosis may be multifactorial; as the possible cardiovascular changes in cirrhotic patients varied from subtle cardiac dysfunction to severe cirrhotic cardiomyopathy. These

were accompanied by hyperdynamic circulation, increased cardiac output and plasma volume [19]. However, previous studies had shown that increased ventricular generation of these peptides indicating the presence of cardiac dysfunction, rather than being caused by the hyperdynamic circulatory changes [8,11,20]. Also, it may be partially explained by the physiological increased NT-proBNP levels with increasing age of the studied patients [21].

Moreover, the increased intravascular volume in cirrhosis may be attributed to porto-pulmonary hypertension [22] that leads to

Variable	Hazard ratio (95% CI)	P value
Age	1.02 (0.98 - 1.06)	0.6
Serum albumin	0.92 (0.86 - 0.98)	0.007
Serum bilirubin	1.17 (1.07 - 1.28)	0.001
Prothrombin time	0.91 (0.81 - 1.01)	0.09
Serum creatinine	1.01 (1.002 - 1.011)	0.002
Child-Pugh score	1.04 (0.81 - 1.33)	0.02
MELD score	0.96 (0.88 - 1.09)	0.05
Serum NT -proBNP	1.001 (1 - 1.002)	0.004
Ascitic NT -proBNP	1.001 (1.001 - 1.002)	0.05

Table 3: Multiple regression analysis of risk factors affected 1-year mortality in liver cirrhosis group.

ventricular remodeling and myocyte stretch, which consequently elevates NT-proBNP levels in both serum and ascites [23].

Increased levels of NT-proBNP in the majority of our cirrhotic population having hepatitis C infection with no history of previous cardiac disease may declare that they suffered from cardiac abnormalities, structural or functional changes. This was supported by other authors reported that these changes correlated with increased blood levels of NT-proBNP [11,24,25].

Our data showed that higher serum and ascitic NT-proBNP levels were independent predictors of 1-year mortality in cirrhotic patients with normal cardiac assessment (no heart failure). These results agreed with Wang et al. [26] who reported that elevated levels of NT-proBNP had been regarded as a risk factor for death. This predictive power of NT-proBNP for mortality in cirrhotic patients may be explained partially by its relation with extracellular volume expansion (congestive state) apart from cardiac morphology and function [27]. Also, increased BNP level in cirrhotic patients may have a role in fibrosis. Tsuruda et al. [28] explained that besides cardiac myocytes, fibroblasts secrete BNP which leads to hepatic fibrosis and vascular remodeling through induction of matrix metalloproteinases.

Our study results recommend the estimation of either serum or ascetic NT-proBNP preoperative or intraoperative to predict the cardiac complications outcome of Liver Transplantation (LT) postoperatively. Thus, reduce the need for other more expensive and invasive diagnostic tests. In spite several studies recommended preoperative cardiac function evaluation in cirrhotic patients before (LT) in order to predict cardiac dysfunctions, 10% of hepatic patients with normal cardiac function suffered major complications in the post-transplant phase [29-31].

Our limitation was small sample sized study, and needs to be supported by further large number prospective studies to evaluate its association with cardiac changes especially before OLT to improve postoperative outcomes.

Conclusion

In conclusion, NT-pro BNP could be a powerful initial non-invasive diagnostic tool to be used in clinical practice for exclusion of cardiac dysfunction in decompensated cirrhotic patients as a part of the workup to overcome missed or misdiagnosis. End stage liver cirrhosis per se may contribute to NT-proBNP elevation which contributes as incremental information for the prediction of 1-year mortality in end stage liver cirrhosis.

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