

## Evaluation of Cirrhotic Cardiomyopathy in Patients with Liver cirrhosis by Brain Natriuretic Peptide and Echocardiography Pre and Post Liver Transplantation.

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**Abstract:** Cirrhotic cardiomyopathy (CCM) is a chronic cardiac dysfunction in patients with liver cirrhosis. Cirrhotic patients undergoing living donor liver transplantation (LDLT) may show signs of cardiac dysfunction. Brain natriuretic peptide (BNP) could be an indicator of cirrhotic cardiomyopathy. **The aim** of this study was to evaluate the presence of cirrhotic cardiomyopathy in patients with chronic liver disease candidate for liver transplantation by measuring BNP and echocardiography before and after liver transplantation. **Patients and methods:** This study was conducted on 25 patients with liver cirrhosis. They were divided into 2 groups: **Group 1:** Included 15 Patients candidate for Living donor liver transplantation (LDLT) as patient group. **Group 2:** Included 10 patients with Chronic liver disease (child A) as control group. Evaluation of cirrhotic cardiomyopathy in patient group (group 1) was done by measuring BNP level by ELIZA and performing echocardiography before and after LDLT by one month. **Results:** S.BNP levels showed a significant difference between patient group (before liver transplantation) and control group (child A) ( $P=0.000$ ) but there was no significant difference before and after LDLT ( $P=0.369$ ). There was also a significant difference between patient group (before liver transplantation) and control group (child A) as regard ejection fraction (EF%) ( $P=0.000$ ). Also there was a significant difference between EF% in patient group before and after liver transplantation ( $P=0.032$ ). There was also a significant difference between echocardiographic findings (E/A ratio and Deceleration time) before and after LDLT in patient group ( $P=0.008$ ,  $P=0.034$ ). **Conclusion:** Echocardiographic findings and S.BNP level might be a non invasive investigation for evaluation of CCM in chronic liver disease before and after living donor liver transplantation.

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**Key words:** Brain natriuretic peptide (BNP), Living donor liver transplantation ( LDLT), Cirrhotic cardiomyopathy (CCM).

### 1. Introduction

Cirrhotic cardiomyopathy is a clinical syndrome in patients with liver cirrhosis characterized by an abnormal and blunted response to physiological, pharmacological or pathological stress but normal to increased cardiac output and contractility at rest (**Zardi et al., 2010**). Although some etiologies (e.g., iron overload and alcohol consumption) further impact on myocardial structure and function. Yet this syndrome is considered to be related to both portal hypertension and cirrhosis and is characterized by intrinsic alterations in myocardial function (**Donovan et al., 1996**).

Stresses such as liver transplantation, infection and procedures such as insertion of Tran jugular intrahepatic portosystemic stent-shunts (TIPS) can convert latent to overt heart failure. Indeed, heart failure is responsible for 7%–15% of mortality following liver transplantation (**Myers and Lee, 2000 & Therapondos et al., 2004**).

In the setting of liver cirrhosis and portal hypertension, a wide spectrum of factors, such as volume expansion and hyperdynamic circulation, contribute to systolic and diastolic dysfunction. Cardiomyocyte plasma membrane abnormalities, cytokines, growth factors, and autonomic impairment are also implied in this process. With advanced liver disease, these factors can lead to cardiac failure (**Zardi et al., 2010**).

Several studies suggest that some level of diastolic dysfunction exists in most patients with cirrhosis therefore, it would be expected that this and other cardiac abnormalities would disappear after liver transplantation (LT). However, results from previous studies have been conflicting regarding this point (**Torregrasa et al., 2005**).

Portal hypertension is an important and common complication of liver cirrhosis. Pathophysiology of portal hypertension include two important factors, vascular resistance and blood flow. Endothelin, angiotensin 2 and alpha adrenergic

stimulus increase hepatic vascular resistance (**Theodorakis et al., 2009**).

Cirrhotic cardiomyopathy presents mainly by:

- 1- High output failure (with normal EF% measured by echocardiography) but with blunted response to stress.
- 2- Diastolic dysfunction as evaluated by Doppler of the mitral flow and presenting by reversed E/A ratio, prolonged deceleration time(>200ms).
- 3- Elevated serum BNP level (**Moller and Henriksen, 2009**).

Brain natriuretic peptide (BNP) is a biological active peptide of 32 amino acids, released from cardiac ventricles in response to stretching chambers. Its release appears to be in direct proportion to ventricular volume expansion and pressure overload. BNP decreases after effective treatment of heart failure. It is used in routine assessment for differentiating acute heart failure from other causes of dyspnea (**Hobbs et al., 2002**).

Cardiac natriuretic peptides, namely atrial natriuretic peptide and BNP, have long been known to be elevated in cirrhotic patients as a consequence of increased cardiac release and not because of impaired hepatic extraction (**Gines et al., 1988 & La Villa et al., 1992**).

BNP levels increase markedly in Left ventricular dysfunction and the level in heart failure is correlated with symptoms severity (**Jankowski, 2008**).

SBNP levels of  $\geq 100$  pg /mL have a greater than 95% specificity and greater than 98% sensitivity in patient with congestive heart failure (CHF) (**Hobbs et al., 2002**).

Liver transplant is a treatment option for people who have end-stage liver failure that can't be controlled using other treatments and for some people with liver cancer. Liver failure can occur rapidly, in a matter of weeks (acute liver failure), or it can occur slowly over months and years (chronic liver failure). Liver failure has many causes, including: liver cirrhosis, biliary duct ectasia, cystic fibrosis, early stage liver cancer, hemochromatosis, primary liver cirrhosis, primary sclerosing cholangitis, Wilson's disease (**Martin, 2010**).

In cirrhotic patients, increased levels of BNP correlate with the severity of liver disease and cardiac dysfunction (**Yildiz et al., 2005**).

## 2. Patients and Methods

This study was conducted on 25 patients with chronic liver disease selected from El Demerdash hospital and Ain Shams Center for Organ Transplantation (ASCOT) in the period from July

2011 till October 2012. They were divided into 2 groups:

Group 1: Included 15 Patients candidate for living donor liver transplantation (LDLT) as patient group.

Group 2: Included 10 patients with Chronic liver disease (child A) as control group.

Evaluation of cirrhotic cardiomyopathy was done by measuring serum BNP level and performing echocardiography before and after living donor liver transplantation by one month.

### Exclusion Criteria

Patients with the following diseases were excluded from our study:

- 1- Diseases that may increase serum BNP as Heart failure, Cardiomyopathy, Ischemic heart disease, Rheumatic heart disease, Hypertension, Atrial fibrillation, Diastolic dysfunction, Pulmonary embolism, Chronic Renal failure and Thyrotoxicosis.
- 2- Contraindications to liver transplantation as uncontrolled sepsis, large hepatocellular carcinoma (HCC), advanced cardiopulmonary diseases....etc.

### Both groups were submitted to the following

1. Full history taking and clinical examination.
  2. Complete blood count (CBC).
  3. Renal function test [Blood urea nitrogen (BUN), Serum Creatinine, urine analysis].
  4. Serum Electrolytes (S. Na, S.K).
  5. Liver function test [Serum Albumin, Total Bilirubin, Direct Bilirubin, Alanine transaminase (ALT), Aspartate transaminase (AST)].
  6. Prothrombin time (PT), Partial thromboplastin time (PTT), International normalized ratio (INR).
  7. Fasting and postprandial blood sugar, glycosylated hemoglobin (HbA1c).
  8. Tumour markers including Alpha fetoprotein, Carcinoembryonic antigen.
  9. Viral markers for hepatitis C, hepatitis B, cytomegalovirus and ebstein- barr- virus (HCV antibody, HBs antigen, HBs antibody, HB core antibody IgM, CMV antibody, EBV antibody).
  10. Polymerase chain reaction (PCR) for HCV and HBV.
  11. Lipid profile [LDL (Low density lipoprotein), HDL (High density lipoprotein), Serum cholesterol, Serum Triglycerides].
  12. Thyroid function test (FT3, FT4 & TSH).
  13. Abdominal ultrasound and portal vein Doppler.
  14. Upper and lower GIT endoscopy.
  15. Electrocardiography (ECG), Chest X-ray (CXR).
  16. Echocardiography to evaluate a- Systolic function, Ejection fraction was measured using the modified simpson technique.
- a- Assessment of diastolic function:

Transmitral flow profile was assessed by 2-D guided pulsed wave Doppler from the apical 4-chamber view by positioning a 3 - mm - sized sample volume between the tips of the mitral leaflets in diastole and recording at a sweep velocity of 100 mm/s. Mitral flow parameters included peak velocities during early diastole (E) and late diastole (A), their ratio (E/A ratio), as well as the deceleration time (DT) of the early filling wave (E-wave). This echocardiographic evaluation was done before and after liver transplantation by one month. (Rakowski H *et al*, 1996).

17-Serum cardiac marker → Brain natriuretic peptide (BNP) by ELISA technique which was measured in patient group pre and post living donor liver transplantation by one month and in control group.

## Methods

### Blood samples

15ml was sampled from peripheral veins from both patients and controls were collected into two tubes ; 5 ml of heparinized blood for separation of mononuclear cells for detection of virus B by realtime PCR and another 10ml in plain tubes for serum separation for BNP detection and for other laboratory investigation.

### Isolation of peripheral blood mononuclear layer:

Peripheral blood mononuclear cells (PBMCs) were isolated from blood by density gradient centrifugation using ficoll-hypaque 1077 ml in (sigma, USA ) at 1200 g for 30 minutes at 4 C°. the interface cells were removed, washed twice with 25 ml of sterile PBS (pH 7.3 ), pelleted, and resuspended in 1ml of PBS. The cells were pelleted again at 1200 g for 2 minutes. The cell pellets were kept at -80 C° until nucleic acid extraction.

### Nucleic acid Extraction:

- Viral RNA extraction for virus C was done using viral RNA extraction kit supplied by (Qiagen) according to the manufacturer instruction.
- Viral DNA extraction for virus B was done using the QIAamp DSP virus DNA extraction kit supplied by (qiagen) according to the manufacturer instruction
- All DNA and RNA preparation and handling took place in a biosafety level 2 laminar flow hood.
- The isolated DNA and RNA were resuspended in molecular grade water and stored at - 80 C° until assay. Both THE RNA and the DNA concentrations were assessed by absorbance reading at 260 nm with UV spectrophotometry (Beckman ; Du series 650, INC USA ).

### REALTime PCR:

IN Real-time PCR the amplified product is detected via fluorescent dyes. These are usually linked to oligonucleotide probes which bind specifically to the amplified product. Monitoring the fluorescence intensities during the PCR run (i.e in real-time ) allows the detection and quantitation of the accumulating product without having to re-open the reaction tubes after the PCR run.

The artus HBV TM PCR Kit and the artus HCV RT-PCR kit supplied by QIAgen was used for the detection of HBV and HCV. Programming of the applied biosystems apparatus (ABI PRISM 7500 FAST) was done according to the manufacturer instruction.

### Immunoassay for Detection of BNP:

Circulating BNP was determined by commercially available ELISA and STANDARDS. The BNP ELISA kit allows for the in vitro quantitative determination of BNP concentrations in serum. The microtitre plate provided has been precoated with an antibody specific to BNP .Standards and samples were added to microtitre plate wells with a biotin-conjugated polyclonal antibody preparation specific for BNP.Next , avidin conjugated to horseradish PEROXIDASE (HRP) was added to each well and incubated ,then a substrate solution was added to each well.Only those wells that contained BNP ,biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in colour.The colour change was measured spectrophotometrically at a wavelength of 450 nm. The concentration of BNP in samples was determined by comparing the O.D of the samples to the standard curve.

### Statistical analysis

Data was analyzed on IBM personal computer, using Statistical Package for Special Science (SPSS) software computer program version 15.The following tests were used as mean ± standard deviation (SD), frequency & percentage Independent Student t test, Paired t test Chi-square test, Pearson correlation coefficient, Significance level (P) value:

- $P \leq 0.05$  is significant (S).
- $P < 0.01$  is highly significant (HS).
- $P > 0.05$  is nonsignificant (NS).

## 3. Results

This study included 25 patients with chronic liver disease. They were divided into 15 patients prepared for LDLT as patient group and 10 patients with chronic liver disease (child A) as a control group. The patient group were 15 males (100%) and the control group were 9 males (90%) and 1 female (10%) with no significant difference in sex. As regard age patient group had mean ±SD 47.93±6.67 years while

control group had mean  $\pm$ SD 50.30 $\pm$ 7.70 years and there was no significant difference as regard age.

**Table (1): Aetiology of living donor liver transplantation.**

Number of patients	Diagnosis	Child pugh score
3	HCC+ Cirrhosis	A,B
1	HCC+ Cirrhosis	C
9	HCV+ Cirrhosis	C
1	Budd Chiari Syndrome	C
1	Cryptogenic Cirrhosis	C

HCC: Hepatocellular carcinoma. (Child and Turcotte, 1964).

**Table (2): Comparison between EF % in patient group (before liver transplantation) and control group.**

Variable	Groups				Values		Sig.
	Patients		Control		t	P value	
	Mean	$\pm$ SD	Mean	$\pm$ SD			
EF%	74	$\pm$ 3.66	63.50	$\pm$ 3.89	6.84	.000*	S

EF%: Ejection fraction

There was statistical significant difference between both groups as regard EF%.

**Table (3): Correlation between liver function tests and EF% before liver transplantation in patient group.**

Variable	T.Bil		S.Albumin		ALT		AST	
	R value	Sig.	R value	Sig.	R value	Sig.	R value	Sig.
EF% Before	.211	.451 NS	-.022	.937 NS	.1	.722 NS	-.016	.95 NS

There was no significant correlation between liver function tests and EF% before liver transplantation in patient group.

**Table (4): Comparison between S.BNP levels in patient group (before liver transplantation) and control group.**

Variable	Groups				Values		Sig.
	Patient		Control		t	P value	
	Mean	$\pm$ SD	Mean	$\pm$ SD			
BNP (Pg/ml)	1064.58	$\pm$ 84.24	901.15	$\pm$ 96.55	-4.3	.000*	S

S.BNP: serum Brain Natruretic Peptide

There was statistical significant difference between both groups as regard S.BNP levels.

**Table (5): Correlation between liver function tests and S.BNP level before liver transplantation in patient group.**

Variable	T.Bil		S.Albumin		ALT		AST	
	R	Sig.	R	Sig.	R	Sig.	R	Sig.
BNP Before	.01	.969 NS	-.077	.784 NS	.176	.531 NS	.08	.75 NS

There was no significant correlation between liver function test and S.BNP level before liver transplantation.

**Table (6): Comparison between S.BNP level before and after liver transplantation.**

Variable	Mean	$\pm$ SD	t	P value	Sig.
BNP Before	901.15	$\pm$ 96.55	.929	.369	NS
BNP After	860.89	$\pm$ 131.82			

There was no statistical significant difference between BNP value before and after liver transplantation in patient group.

**Table (7): Comparison between EF% before and after liver transplantation in patient group.**

Variable	Mean	±SD	t	P value	Sig.
EF% Before	74	±3.66	2.37	.032*	S
EF% After	68.33	±7.06			

There was statistical significant difference between EF% before and after liver transplantation.

**Table (8): Correlation between EF %and BNP before and after liver transplantation in patient group.**

Variable	EF after		BNP before		BNP after	
	R value	Sig.	R value	Sig.	R value	Sig.
EF Before	-.419-	.120 NS	-.202-	.470 NS		
EF After					-.222-	.426 NS
BNP Before					-.057-	.840 NS

There was no statistical significant correlation between EF% and BNP levels before and after liver transplantation in patient group.

**Table (9): Comparison between Echocardiographic findings before and after liver transplantation in patient group.**

Variable	Number	Z	P value	Sig	
E/A ratio before	>1	-2.64	.008*	HS	
	<1				15(100%)
E/A ratio after	>1				8(53.3%)
	<1				7(46.7%)
Deceleration time before	Normal	-2.12	.034*	S	
	Prolonged				9(60%)
Deceleration time after	Normal				6(40%)
	Prolonged				3(20%)
		12(80%)			

HS: highly significant

There was statistical significant difference between E/A ratio before and after liver transplantation.

There was statistical significant difference between deceleration time before and after liver transplantation.

**Table (10): Correlation between E/A ratio and Deceleration time with S.BNP level before and after liver transplantation.**

Variables	N	Mean	±SD	F	P value	Sig.
BNP before	E/A ratio before					
	>1	15	901.15	±96.55	.815	.379
	<1	0				
BNP after	E/A ratio after					
	>1	8	849.61	±100.63	2.36	.148
	<1	7	873.78	±168.43		
BNP before	Dec. time before					
	Normal	9	906.47	±115.98	2.09	.171
	prolonged	6	893.16	±66.73		
BNP after	Dec. time after					
	Normal	3	767.43	±41.50	2.63	.129
	prolonged	12	884.25	±137.20		

There was no significant correlation between E/A ratio and Deceleration time with S.BNP level before and after liver transplantation.

#### 4. Discussion

Cirrhosis is the end result of chronic liver damage caused by chronic liver diseases. Common causes of chronic liver disease include Hepatitis C infection, Hepatitis B (long-term infection), Long-term alcohol abuse, Autoimmune inflammation of the liver, Disorders of the drainage system of the liver (the biliary system), such as primary biliary cirrhosis and primary sclerosing cholangitis, Medications, Metabolic disorders of iron and copper (hemochromatosis and Wilson's disease), Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) (**Franco et al., 1988**).

Although overt cardiac failure is uncommon in cirrhosis, unexpected cardiac deaths have occurred following surgery in patients with cirrhosis (**Rayes et al., 1995, Lebrech et al., 1996 & Franco et al., 1988**), suggesting that better assessment of cardiac function is needed in these patients. CCM has been reported to be a major cause of morbidity and mortality in cirrhotic patients after they have liver transplantation (**Therapondos et al., 2004**).

When there is a rapid hemodynamic change (e.g., after TIPS or liver transplantation), the increased filling pressure may favor the development of congestive heart failure. That is due both to the impaired diastolic relaxation, already present but still unrevealed, that causes elevated ventricular pressure thus favoring left atrium dilation, and to the impaired heart rate and intrinsic alterations of myocardium contractility (**Ma et al., 1997**).

Cardiac natriuretic peptides have been generally regarded as markers of volume overload rather than markers of cardiac dysfunction. Recently, Wong and colleagues proposed that BNP could be an indicator of cirrhotic cardiomyopathy (**Wong et al., 2001**).

In our study evaluation of presence of cirrhotic cardiomyopathy in patient group was done by measuring serum BNP level and performing echocardiography before and after living donor liver transplantation by one month.

As regards age and sex there was no significant difference between both groups. **Henrisken et al. (2003)** study measured BNP levels in 51 cirrhotic patients and 13 controls. Circulating BNP concentrations increased with age. The increase was weak in subjects less than 70 years but in elderly subjects beyond this age BNP increased substantially. This may in part reflect unmasked heart failure but in elderly healthy individuals with normal exercise test and echocardiography, BNP levels higher than younger subjects therefore age matched controls was important.

Agreeing with **Henrisken et al. (2003)** study that showed higher EF% in severe liver disease, there was a statistically significant difference in EF% between patient (before living donor liver transplantation) and control (Child A) groups in our study which is lower in control group. This result can be explained by high selection of patients with high ejection fraction for LDLT with its stressful factors (anaesthesia, bleeding, postoperative drugs,.....).

As regards S.BNP levels between patient (before LDLT) and control groups, we found in this study a statistical significant difference which was higher in patient group and this agreed with **Henrisken et al. (2003)** who showed that circulating BNP concentration was significantly increased with degree of liver cirrhosis. Also this was agreeing with **Yilmaz et al. (2010)** that evaluated relationship of increased S.BNP levels with hepatic failure and Portal hypertension.

In this study there was no significant correlation between liver function tests and BNP levels in patient group before LDLT that may need serial evaluation for longer periods, this disagreed with **Yilmaz et al. (2010)** who found a significant positive correlation between BNP levels and liver function test. It showed BNP levels increased with higher grades of Child Pugh score indicating that BNP related to severity of liver cirrhosis. The rise of S.BNP in advanced liver cirrhosis can be considered as independent laboratory marker in evaluating those patients as it is not dependant on liver functional reserve but it is related to cardiac muscle dysfunction. This high level and increased release from cardiac muscle is related to hyperdynamic circulation in cirrhosis more than hepatic functional reserve.

In the current study there was increase in BNP levels in 5 patients and decrease in 10 patients after liver transplantation by one month but it was statistically insignificant and this disagreed with **Bernal et al. (2012)** who evaluated Cardiac function and aminoterminal pro-brain natriuretic peptide in liver transplanted cirrhotic patients. It was done on 60 cirrhotic patients without cardiovascular disease. Clinical data, echocardiography and NT-ProBNP level were analyzed before and after liver transplantation and showed deterioration in diastolic function in the form of decrease E/A ratio and decrease NT-ProBNP significantly 6 month after liver transplantation compared to pre transplantation values. This also was consistent with **Acosta et al. (1999)** and **Therapondos et al. (2002)** who reported impairment of diastolic function with increase ventricular hypertrophy after orthotopic liver transplantation.

Other study observed normalization of cardiac function after liver transplantation (**Torregrasa et al., 2005**). These contradictory results

may be explained by differences in protocol and time sequences for evaluating cardiac function. Moreover cardiovascular risk factors such as hypertension, hyperlipidemia and diabetes mellitus commonly occur in liver transplant recipients, so all these factors might worsen preexisting cirrhotic cardiomyopathy (**Hunt et al., 2005 & Adams et al., 2006**).

This study evaluated S.BNP level one month after living donor liver transplantation and may be serial measuring of BNP for longer duration can better evaluate the cardiac function.

Indeed this study showed that post transplant patient group suffered from structural cardiac changes in the form of lower EF%, E/A ratio <1 and prolonged Deceleration time than pre transplant patients group (statistically significant) indicating impairment of systolic and diastolic function. This was agreeing with **Bernal et al. (2012)** study which reported lower E/A ratio and prolonged Deceleration time indicating impairment in diastolic function after liver transplantation but it was different in time of evaluation by echocardiography (1 month in our study and 6 months in that study). So we need further longer prospective studies to evaluate cardiac function post transplantation by echocardiographic findings and S.BNP level to monitor the changes in cardiac function and assess the risk on those patients with their survival in a better way furthermore this may express the global effect of liver cirrhosis on cardiac muscle structure and function and may allow better evaluation of those patients when surgical intervention is attempted.

### Conclusion

Echocardiographic findings and S.BNP might be non invasive investigations for evaluation of cirrhotic cardiomyopathy in chronic liver disease before and after living donor liver transplantation.

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