Original Research Paper

Volume - 14 | Issue - 12 | December - 2024 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

General Medicine

A PROSPECTIVE STUDY OF ASSOCIATION OF SERUM PRO BRAIN NATRIURETIC PEPTIDE (BNP) LEVEL AS A MARKER OF SEVERITY AND CARDIAC DYSFUNCTION IN CIRRHOSIS OF LIVER

Dr Noor Fathima — Junior Resident, Department of General Medicine, Al-Ameen Medical College, Vijayapura.

Dr Basavaraj PG — Professor, Department of General Medicine, Al-Ameen Medical College, Vijayapura.

Dr Taranath Sitimani — Professor, Department of General Medicine, Al-Ameen Medical College, Vijayapura.

Dr Zaheer Ahamed P — Junior Resident, Department of General Medicine, Al-Ameen Medical College, Vijayapura.

Dr Raghavendra D* — Assistant Professor, Department of Community Medicine, Sri Chamundeshwari Medical College, Hospital & Research Institute, Channapatna. *Corresponding Author

ABSTRACT **Background:** Liver disease doubles the risk of cardiovascular disease (CVD), with cirrhosis—often from alcoholism or hepatitis—causing fibrosis and disrupting liver architecture, which impairs cardiac function. Reduced cardiac index, lower systolic volume, and increased vascular resistance lead to renal dysfunction and fluid retention. Elevated NT-proBNP levels, indicative of cardiac stress, correlate with cirrhosis severity. Our study examines the prevalence of subclinical cardiac dysfunction in cirrhotic patients and its correlation with NT-proBNP levels to enhance early diagnosis and management. **Methods:** Our study, conducted at Al-Ameen Medical College, Vijayapura, from May 2022 to April 2024, investigated the link between serum NT-proBNP levels and cardiac dysfunction in liver cirrhosis patients. This cross-sectional study included 100 patients aged 20 to 60 years diagnosed via ultrasonography. Exclusions included pre-existing heart disease and diabetes. Participants underwent clinical assessments, including Child-Pugh scoring, liver function, and NT-proBNP via Enzyme-Linked Fluorescent Assay, alongside ECG, echocardiography, and ultrasound. Data were analyzed using SPSS, employing statistical tests like Chi-square and ANOVA, with significance set at $p<0.05$. **Results:** Our study found alcohol (57%) and viral infections (34%) as primary causes, with 72% male participants and 47% in Child-Pugh Class C, indicating severe liver dysfunction. Elevated NT-proBNP levels (mean: 517.38 pg/ml) correlated with higher Child-Pugh scores, prolonged QTc (mean: 420.04 ms), and increased LVEDD (mean: 5.84 cm), suggesting cardiac stress. NT-proBNP levels were also associated with longer hospital stays (mean: 9.56 days) and higher mortality. These findings support NT-proBNP's role as a prognostic marker for cardiac complications in cirrhosis, advocating regular monitoring for improved early detection and management. Study survival was 89%. **Conclusion:** Our study demonstrates that serum NT-proBNP is an effective marker for assessing cardiac dysfunction severity in cirrhosis patients. Elevated NT-proBNP levels correlate significantly with severe liver dysfunction, prolonged QTc intervals, increased LVEDD, extended hospital stays, and higher mortality. These findings justify using NT-proBNP as a screening tool for early detection and management of cardiac complications in cirrhotic patients.

KEYWORDS : Prospective Study, Serum Pro Brain Natriuretic Peptide, Marker, Cardiac Dysfunction, Cirrhosis of Liver

INTRODUCTION:

Liver disease substantially raises cardiovascular disease (CVD) risk, with liver patients facing a two-fold higher CVD incidence than those without liver disease. Cirrhosis, marked by fibrosis and regenerative nodules, distorts liver architecture and presents life-threatening complications. Chronic alcoholism and hepatitis infections are key causes.[1-3] In cirrhosis, cardiac function declines, evidenced by a reduced cardiac index and systolic volume, increased peripheral resistance, and worsened renal dysfunction, with fluid retention adding strain. NT-proBNP, a cardiac stress biomarker, rises in response to these changes and correlates with liver and heart dysfunction severity.[4]

Cirrhotic patients often display hyperdynamic circulation and cardiac structural alterations, which raise NT-proBNP levels—a marker of ventricular overload and neurohormonal activation. Studies link NT-proBNP to advancing cirrhosis, lower ejection fractions, and chronic heart failure risk, indicating its potential as a screening tool for left heart failure in liver disease. Although the connection between liver disease and cardiac issues is recognized, specific mechanisms remain unclear. The role of NT-proBNP as an indicator for cardiac dysfunction in cirrhosis warrants deeper exploration, especially regarding how cirrhosis-related cardiac changes drive BNP elevation.[5,6]

With rising cirrhosis rates, understanding its cardiovascular impact is crucial. Our study explores NT-proBNP's relationship with cardiac dysfunction in cirrhotic patients, aiming to bridge knowledge gaps for early diagnosis and intervention. Investigating NT-proBNP's correlation with cirrhosis severity and cardiac parameters like QT prolongation and left ventricular dimensions could aid in early cardiac dysfunction detection, improving patient management and outcomes.

METHODOLOGY:

The cross-sectional study was conducted in the General Medicine Department at Al-Ameen Medical College, Vijayapura, from May 2022 to April 2024. It involved 100 patients, aged 20 to 60, diagnosed with liver cirrhosis based on ultrasonography. Exclusions included patients with cardiac disease, hypertension, diabetes, thyroid disorders, electrolyte abnormalities, arrhythmias, chemotherapy recipients, and those unwilling to participate. Data were collected using a structured proforma, including detailed histories focusing on medical conditions like diabetes, hypertension, and cardiac illnesses.

Patients underwent clinical examinations and biochemical investigations, including liver function tests, blood counts, serum electrolytes, and abdominal ultrasound. The Child-Pugh score, assessing ascites, bilirubin, albumin, prothrombin time/INR, and encephalopathy, categorized patients into Classes A, B, or C, reflecting liver function severity. NT-proBNP levels were determined using Enzyme-Linked Fluorescent Assay (ELFA), with reference ranges based on age. Cardiac function was further evaluated through ECG, measuring QTc intervals, and transthoracic echocardiography, focusing on left ventricular end-diastolic dimension (LVEDD).

Ultrasound findings for cirrhosis included liver shrinkage, coarse texture, surface nodularity, portal hypertension signs, and ascites. Additionally, hepatic encephalopathy was assessed based on symptoms like sleep disturbances, constructional apraxia, flapping tremor, and cognitive testing. Overall, NT-proBNP served as an indicator of heart failure severity in cirrhotic patients. Data analysis involved Microsoft Excel and SPSS (Version 26), using tests like Chi-square, Fisher's exact, ANOVA, and Pearson/Spearman correlation. A p-value <0.05 was considered significant, ensuring robust interpretation of NT-proBNP's relationship with cardiac dysfunction in liver cirrhosis.

RESULTS:

Our study involved 100 subjects aged 21-60 years, with a mean age of 44.8 years (SD 8.8). Most participants were in the 41-50 age range (48%), followed by those aged 51-60 (29%), 31-40 (16%), and under 30 (7%). Males comprised 72% of the cohort, highlighting a male predominance in liver cirrhosis cases, potentially due to higher alcohol consumption. This age and gender distribution suggest liver cirrhosis is prevalent in middle-aged men. (Table 1)

Table 1: Characteristics Of The Study Subjects

Subjects (N=100)		Frequency (N)	Percentage (%)
Age group	**≤30 years**	7	7.0%
	31 to 40 years	16	16.0%
	41 to 50 years	48	48.0%
	51 to 60 years	29	29.0%
Gender	**Male**	72	72.0%
	Female	28	28.0%

Among 100 subjects, alcohol was the leading cause of liver cirrhosis (57%), followed by viral infections (34%) and other causes (9%), emphasizing alcohol's significant role in cirrhosis development. This high rate of alcohol-related cirrhosis underscores the need for strong public health initiatives to reduce alcohol abuse and support early intervention and treatment for alcohol dependency to prevent cirrhosis. (Figure 1)

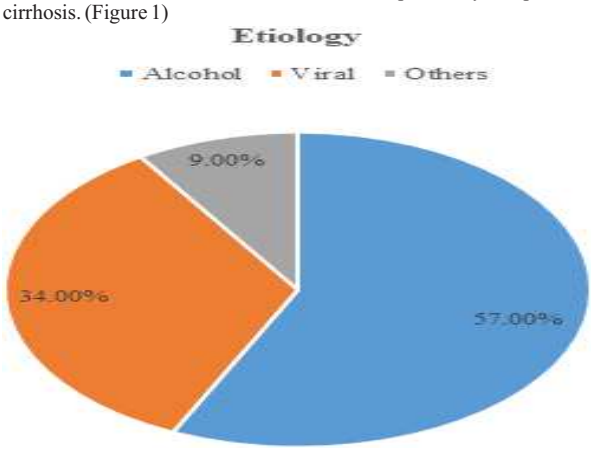

Figure 1: Distribution Based On Etiology

The Child-Pugh scores in our study revealed varied hepatic impairment among subjects. A majority (59%) had total bilirubin >3 mg/dL, indicating marked liver dysfunction, and 47% had serum albumin <2.8 g/dL, reflecting reduced synthetic function. Additionally, 30% had PT INR >2.3, signifying coagulation issues. Ascites and encephalopathy were absent in 58% and 66%, respectively. Child-Pugh classifications showed 47% in Class C (advanced impairment), 31% in Class B (moderate), and 22% in Class A (mild). The mean score was 9.42 (SD 3.23), underscoring a high prevalence of moderate to severe liver disease, highlighting the need for proactive management to improve outcomes. (Table 2 & Figure 2)

Table 2: Parameters of Child-Pugh Score

Subjects (N=100)		Frequency (N)	Percentage (%)
Total Bilirubin	**<2 mg/dL**	12	12.0%
	2 to 3 mg/dL	29	29.0%
	>3 mg/dL	59	59.0%
Serum Albumin	**>3.5 g/dL**	22	22.0%
	2.8 to 3.5 g/dL	31	31.0%
	<2.8 g/dL	47	47.0%
PT INR	**<1.7**	51	51.0%
	1.7 to 2.3	19	19.0%
	>2.3	30	30.0%
Grade of Ascites	**Absent**	58	58.0%
	Slight	27	27.0%
	Moderate	15	15.0%
Encephalopathy	**Absent**	66	66.0%
	Minimal (I & II)	29	29.0%
	Advanced (III & IV)	5	5.0%

The mean serum NT-proBNP level was 517.38 pg/ml (SD 239.00 pg/ml), ranging from 92.00 to 974.00 pg/ml, indicating variable cardiac stress levels and the need for regular cardiac monitoring in cirrhotic patients. The QTc interval averaged 420.04 ms (SD 34.29 ms), with a range of 364.00 to 480.00 ms, suggesting an arrhythmia risk in many subjects, underscoring the importance of ECG monitoring. The mean left ventricular end-diastolic dimension (LVEDD) was 5.84 cm (SD 0.36 cm), indicating possible cardiomyopathy, and necessitating comprehensive cardiac evaluation to manage potential dysfunction early. (Table 3)

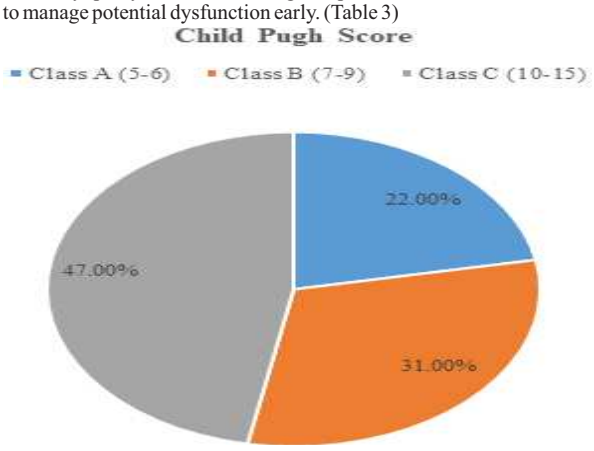

Figure 2: Distribution Based On Child Pugh Score

Table 3: Cardiac Parameters

Subjects (N=100)	Mean	SD	Minimum	Median	Maximum
Serum NT pro BNP	517.38	239.00	92.00	537.00	974.00
QTc Interval	420.04	34.29	364.00	421.00	480.00
LVEDD (in cm)	5.84	0.36	5.20	5.90	6.50

The mean hospital stay among 100 subjects was 9.56 days (SD 2.93), ranging from 4 to 14 days, with a median of 10 days, reflecting the severity of their conditions and need for extensive care. At the study's end, 89% were alive, while 11% had died, highlighting the mortality risk in advanced liver cirrhosis despite high survival rates. These findings emphasize the importance of continued advancements in treatment strategies to improve patient outcomes in liver cirrhosis. (Figure 3)

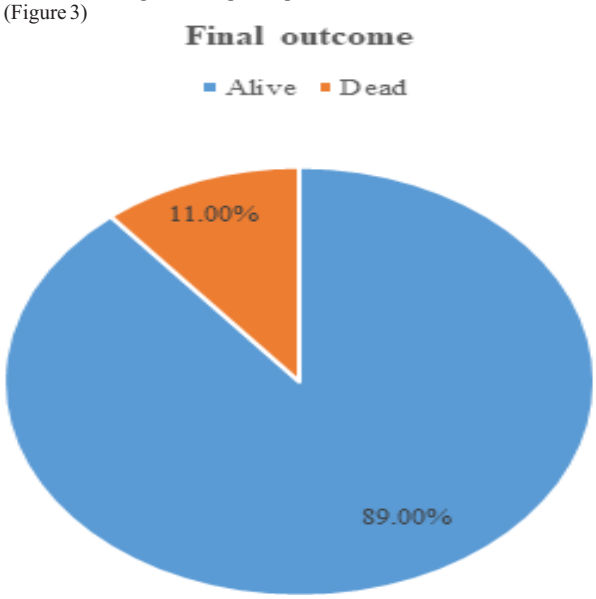

Figure 3: Distribution Based On Final Outcome

The association between Child-Pugh scores and NT-proBNP levels was significant ($p < 0.001$), with mean NT-proBNP levels rising across classes: 192.82 pg/ml in Class A, 421.26 pg/ml in Class B, and 732.70 pg/ml in Class C. This trend indicates that higher Child-Pugh scores, reflecting more severe liver disease, correlate with increased NT-proBNP levels, underscoring NT-proBNP's value as a marker for assessing cardiac dysfunction severity in liver cirrhosis patients. (Table 4)

Table 4: Association between Child Pugh Score and serum NT pro BNP levels

Subjects (N=100)	Mean	SD	Minimum	Median	Maximum
Class A (5-6)	192.82	45.45	92.00	191.50	260.00
Class B (7-9)	421.26	81.73	275.00	404.00	564.00
Class C (10-15)	732.70	116.88	572.00	714.00	974.00

One Way ANOVA, p-value <0.001 (Statistically significant)

Our study found strong positive correlations between serum NT-proBNP levels and QTc interval (r = 0.991), LVEDD (r = 0.995), and hospital stay (r = 0.989), all with p-values <0.001. Elevated NT-proBNP was linked to prolonged QTc intervals, increased LVEDD (indicating cardiac enlargement), and longer hospital stays, reflecting greater cardiac stress and disease severity. These findings underscore NT-proBNP's utility as a prognostic marker for assessing cardiac complications and predicting hospitalization duration, emphasizing the importance of careful monitoring in cirrhotic patients with elevated NT-proBNP levels (Table 5). Our study revealed a significant difference in NT-proBNP levels between survivors (mean = 474.49 pg/ml) and non-survivors (mean = 864.36 pg/ml; p < 0.001), indicating higher NT-proBNP is linked to poorer prognosis, underscoring its value in mortality prediction. (Figure 4)

Table 5: Correlation Of Cardiac Parameters With Serum NT pro BNP levels

Subjects (N=100)	Pearson Correlation	p-value
QTc Interval (in ms)	0.991	<0.001*
LVEDD (in cm)	0.995	<0.001*
Hospital Stay (in days)	0.989	<0.001*

* Statistically significant

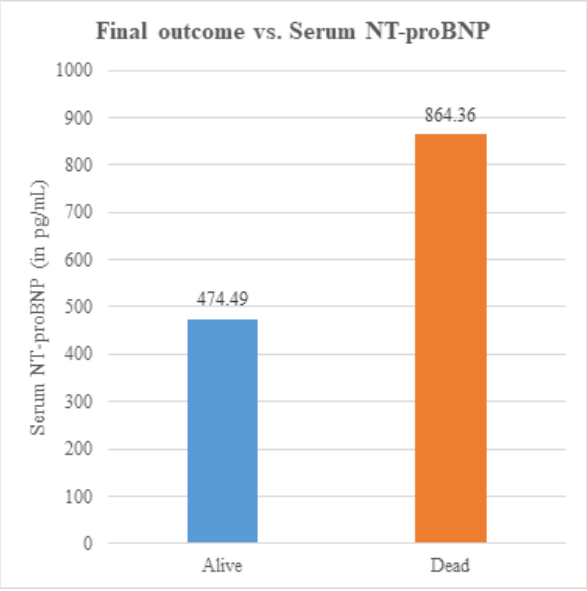

Figure 4: Association between final outcome and serum NT pro BNP levels

DISCUSSION:

Our study examined the link between serum NT-proBNP levels and cardiac dysfunction in liver cirrhosis patients. A total of 100 participants aged 20-60 years, diagnosed with cirrhosis via ultrasound, were included, while those with heart disease, hypertension, diabetes, or thyroid disorders were excluded to avoid confounding factors. Key clinical assessments included Child-Pugh scoring for liver function, biochemical markers (liver function tests, serum electrolytes, and prothrombin time), and NT-proBNP measurement through Enzyme-Linked Fluorescent Assay, with reference values segmented by age. Hemoglobin levels, lipid profiles, 12-lead ECG, and echocardiography (LVEDD measurements) were additional investigative components, with ultrasound confirming cirrhosis and examining ascites and portal hypertension.

Characteristics Of The Study Subjects

Our study centered around a middle-aged demographic, with most participants between 41-50 years and a mean age of 44.81 years, closely aligning with Metwaly A et al[7] and Singh AJ et al[8], who observed average ages around the mid-40s to late 40s. Other studies, like those by Licata A et al[9] and Mushtaq S et al[10], focused on slightly older cohorts, with mean ages of 63 and 55.4 years, respectively, suggesting a focus on older populations in specific research. This convergence highlights cirrhosis's impact on middle to older-aged adults, emphasizing targeted interventions for these age groups.

Gender analysis revealed that males predominated the study population, accounting for 72%, echoing findings from Metwaly A et al[7] (66.67% males) and Mushtaq S et al[10] (60% males). Singh AJ et al[8] reported an even higher male prevalence at 91%, attributed largely to higher alcohol consumption rates among men, a known risk factor for cirrhosis. Studies by Torhan et al[11] and Licata A et al[9] similarly reported higher male ratios, particularly in patients with ascites (84.3%), further substantiating the gender-specific pattern in liver cirrhosis, potentially due to lifestyle differences.

Etiology

Alcohol-related cirrhosis emerged as the primary etiology in this study (57%), followed by viral hepatitis (34%), consistent with findings by Licata A et al[9] and Singh AJ et al[8] Mushtaq S et al[10] noted a significant majority (74%) with alcohol-induced cirrhosis, reinforcing alcohol's role as a leading cause of liver disease. Contrasting studies, such as those by Metwaly A et al[7], highlight viral and metabolic etiologies like post-hepatitis C and NAFLD, while Torhan et al[11] focus on non-alcoholic cirrhosis due to hepatitis B and C. Despite these variances, alcohol and viral hepatitis remain central etiological factors across studies, stressing the need for focused public health measures addressing these risks.

Child-Pugh Score

Child-Pugh Score (CPS) played a crucial role in evaluating liver disease severity. In this study, 47% of patients were in Class C (advanced disease), 31% in Class B, and 22% in Class A. Similar severity distributions were noted in studies by Metwaly A et al[7], Mushtaq S et al[10], and Singh AJ et al[8], where higher prevalence in advanced CPS classes reflected severe liver dysfunction. CPS's utility in cirrhosis risk stratification and clinical decision-making is validated by consistent use across these studies, supporting its integration into routine assessments for prognostic and therapeutic purposes.

Investigations

Prolonged QTc intervals in cirrhotic patients were observed in this study, with similar findings reported by Licata A et al[9], Metwaly A et al[7], and Mushtaq S et al[10] These studies associate QTc prolongation with cardiac dysfunction and elevated NT-proBNP levels, highlighting an increased arrhythmic risk. Singh AJ et al[8] found QTc >440 ms in 26% of participants, underscoring its clinical importance. Torhan et al[11] corroborated this with a positive NT-proBNP and QT interval correlation, suggesting that QTc prolongation in cirrhotic patients is a significant indicator of cirrhotic cardiomyopathy risk, underscoring the importance of cardiac monitoring.

Increased LVEDD, indicating possible cardiac enlargement, was evident in our study, consistent with Licata A et al[9], Metwaly A et al[7], and Mushtaq S et al[10], who observed structural cardiac changes. Torhan et al[11] also reported higher LVED volumes in cirrhotic patients, pointing to similar cardiac adaptations. These findings suggest that liver cirrhosis can lead to structural cardiac changes, supporting regular echocardiographic evaluations to monitor heart health in these patients, especially those with advanced disease.

Outcomes

The average hospital stay in the present study was 9.56 days, implying prolonged hospitalization associated with advanced cirrhosis and cardiac dysfunction. While exact durations are often unspecified in previous studies, the severity of cirrhosis, as indicated by NT-proBNP levels, suggests a trend of extended hospital stays for advanced cases. Studies by Metwaly A et al[7], Mushtaq S et al[10], and Torhan et al[11] align with this implication, highlighting the benefit of early and effective management to potentially reduce hospital stays.

Survival analysis revealed an 89% survival rate, with higher mortality linked to elevated NT-proBNP levels. Licata A et al[9], Metwaly A et al[7], and Mushtaq S et al[10] similarly associate high NT-proBNP with poorer outcomes. Sanyal PK et al3 and Singh AJ et al[8] further support this association, demonstrating NT-proBNP's prognostic relevance. The

findings collectively underscore NT-proBNP's value in predicting cirrhosis prognosis, emphasizing its role in clinical risk assessment and patient management.

NT-proBNP as a marker of severity and cardiac dysfunction in cirrhosis of liver

Our study affirms NT-proBNP as a significant marker for cirrhosis severity and cardiac stress, with a mean level of 517.38 pg/ml. Licata A et al[9], Metwaly A et al[7], and Mushtaq S et al[10] report elevated BNP levels correlating with advanced liver disease, substantiating BNP's diagnostic and prognostic utility. Sanyal PK et al3 highlight BNP's association with echocardiographic markers of cardiac dysfunction, further supporting its role in identifying patients at risk of cardiac complications. Singh AJ et al[8] observe high BNP levels in advanced Child-Pugh classes, while Torhan et al[11] note correlations with MELD scores and cardiac output, reinforcing BNP's value in assessing cirrhosis severity.

Consistently elevated BNP levels across these studies highlight its role as a marker for cardiac dysfunction and cirrhosis severity. Integrating BNP measurement into cirrhosis management protocols would enhance risk stratification and inform therapeutic strategies, improving outcomes for cirrhotic patients at risk of cardiac complications.

CONCLUSION:

Our study on serum NT-proBNP levels in liver cirrhosis patients confirmed its utility as a marker for cardiac dysfunction severity. Conducted with 100 patients aged 20-60, predominantly male, and primarily affected by alcohol-induced cirrhosis, our study revealed that elevated NT-proBNP levels are strongly correlated with higher Child-Pugh scores, prolonged QTc intervals, increased LVEDD, longer hospital stays, and increased mortality risk. These findings align with the objectives of assessing NT-proBNP as a biochemical marker of liver cirrhosis severity and its correlation with cardiac dysfunction indicators. Regular monitoring of NT-proBNP can facilitate early detection and management of cardiac complications in cirrhotic patients, highlighting its importance in improving patient outcomes.

Acknowledgement: We extend our sincere gratitude to the study participants for their invaluable contributions and participation in this research.

Declarations

Funding: None

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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