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ORIGINAL ARTICLE

N-Terminal pro-brain natriuretic peptide as a diagnostic and prognostic marker in patients with heart failure

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ABSTRACT

Keywords: NT-proBNP; Peptides; Congestive heart failure; Ejection fraction.

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Background: Heart failure is a common medical condition with a poor prognosis. Echocardiography is the gold standard for diagnosis, but it is not always available, especially in emergency situations. NT-pro-brain natriuretic peptide (NT-proBNP) is a novel marker for the diagnosis of heart failure that is being used to detect and predict presence of heart failure. **Objective:** The purpose of this study was to investigate the diagnostic and prognostic role of NT-proBNP in patients with congestive heart failure and correlate its levels with the clinical manifestations and echocardiographic findings. **Patients and methods:** This study was performed on 100 heart failure patients who were divided in two groups and subjected to history taking, medical examination, echocardiography and other related laboratory investigations (S.urea, creatinine, ALT, AST, GGT, Alkaline phosphatase). **Results:** There was a significant proportional relationship between NT-proBNP versus age and inverse versus ejection fraction. ROC curve analysis showed the ability of NT-proBNP to identify patients with HF Also, comparison between different Predictors of developing heart failure, showed that NT-proBNP and Ejection fraction are the most significant. **Conclusion:** Measurement of NT-proBNP can be used as a useful biochemical marker for detection of heart failure and is superior to other natriuretic peptides.

INTRODUCTION

Heart failure is a popular chronic stage of cardiac functional dysfunction secondary to multiple etiologies, and various symptoms impacting their life quality are encountered in patients with HF, including dyspnea, weakness, reduced exercise ability, and fluid retention.[(1)]

While the standard criterion for determining a diagnosis is echocardiography, waiting lists and times are lengthy. Biochemical markers of heart failure and natriuretic peptides, in particular, have been helpful in establishing the diagnosis of heart failure.[(2)]

Rapid measurement of B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) levels can aid clinicians in differentiating between cardiac and noncardiac causes of dyspnea.[3-8] That is, BNP is mostly limited to the differentiation of heart failure versus other causes of dyspnea in patients with an atypical presentation. While NT-proBNP had superior prognostic power for all cause mortality when compared with BNP and proBNP, suggesting that discharge values of NT-proBNP have the greatest diagnostic and prognostic potential of all natriuretic peptides [9]

This study aims to Correlate the diagnostic and prognostic evidence of NT-proBNP in patients with heart failure in relation to echocardiographic evidences and clinical manifestations.

Patients and methods

Our study included 100 patients with heart failure admitted at cardiology department – Aswan university hospital with different disease duration. An informed consent obtained from all participants.

The study was approved by the Ethical and Research committees in Aswan university hospital. All cases subjected to:

- History taking including personal history, special habits.
- Echo-Doppler study:

The echo-Doppler study was performed using the standard echocardiographic procedures of the hospital, as applied in routine clinical practice, with 2.5 MHz transducers. Cardiologists assessing left ventricular function were blinded to the results of the NT-proBNP.

- Blood sampling:

Venous blood was collected by venipuncture with the subject supine having rested quietly for at least 30 min. After centrifugation at 1300 rpm and 4 C for 10 min, plasma samples were separated and stored in cryotubes at -80 C until assayed for NT-proBNP which was performed on ethylenediamine tetra-acetic acid (EDTA) blood samples using PATHFAST. Spectrophotometric measurements of clinical chemistry performed on BT3500 and PENTRA C400 automated chemistry analyzer) for the following:

a) **Serum creatinine**: kinetic colorimetric assay; Jaffe method, Normal values: men: 0.9-1.5 mg/dl and women: 0.7-1.3 mg/dl.
b) **Urea**: kinetic UV assay. Normal values: 15-40 mg/dl.
c) **ALT, AST:** colorimetric assay.

Patient selection:

Inclusion criteria:

- Those Diagnosed with heart failure either clinically or by Echocardiography.
- Those with age above 25.
- Both sexes.

Exclusion criteria:

- Those with other causes for the heart failure symptoms.
- Those with renal impairment.
- Those with liver cell failure.

Statistical analysis

Analysis of data done by IBM computer; using SPSS (statistical program for social science) version (12), MedCalc and Graph Pad Prism as following:

Description of quantitative variables as mean, SD and range. Description of qualitative variables as number and percentage. Chi-square test used to compare qualitative variables between groups. Unpaired t-test was used for comparison of quantities variables, in parametric data (SD <50%) of mean. One-way ANOVA test used to compare more than two groups as regard quantitative variable. Spearman correlation was used to rank variables versus others positively or inversely. Logistic regression model was used to find out the most significant independent predictors for dependent variable.
P value: P value >0.05 was insignificant, P <0.05 was significant and P <0.01 was highly significant.

Results:

This study included 100 congestive heart failure patients admitted in the cardiology department of Aswan university hospital.

Cases were divided to two groups:

Group 1: 62 Chronic heart failure patients with reduced LV systolic function (represented by EF < 40%); they were 29(46.8%) males and 33(53.2 %) females; mean age of 66.4±6 years.

Group 2: 38 Chronic heart failure with preserved LV systolic function (represented by EF ≥ 40%); they were 26(68.4%) males and 12 (31.6%) females; Mean age is 62.2±7.6 years.

Using Chi-square test, no significant statistical difference is observed between males and females patients regards clinical criteria. Using unpaired t-test , There is a significant difference between means of ejection fraction and NT-proBNP between the two studied groups with and without clinical manifestations. Other variable showed non-significant difference of means. (Table 1)

Using Spearman correlation test., there is a significant proportional relationship between NT-proBNP versus age and inverse versus ejection fraction by using Spearman correlation test. (Table 2)
Scatter plot of Spearman correlation between Ejection fraction and NT-proBNP showing that there is an inverse relationship between them; (R = - 0.94, P<0.0001). (Figure 1)

Scatter plot of Spearman correlation between Age and NT-proBNP. Showing that there is a proportional relationship between them; (R=0.99, P<0.0001). (Figure 2)

Receiver operating characteristic (ROC) curve analysis shows the ability of N-terminal pro-brain natriuretic peptide (NT-proBNP) to identify patients with HF. Sensitivity and specificity determined by (ROC) curve. Area under the curve = 80.6% (P<0.001). Cut-off value of 6789 pg/ml has a sensitivity and specificity of 73.3 and 77.5 (Figure 3)

Receiver operating characteristic (ROC) curve of N-terminal pro-brain natriuretic peptide (NT-proBNP), Ejection fraction, for the detection of heart failure in which significant difference is noted regards AUC between both of them. (Figure 4, Table 3)

Comparison between different Predictors of developing heart failure shows that NT-proBNP and Ejection fraction are the most significant. (Table 4)

Logistic regression backward likelihood ratio shows the ability of NT-proBNP to predict developing heart failure. (Figure 5)

Discussion

In the present study we investigated the role of NT-proBNP as a screening tool for the identification of patients with normal and reduced left ventricular systolic dysfunction in 100 heart failure patients admitted in the cardiology department at Aswan university hospital.

We found that there is a significant proportional relationship between NT-proBNP versus age (R=0.99, P<0.0001), and inverse versus ejection fraction (R = - 0.94, P<0.0001). Other parameters were not related to NT-proBNP.

In accordance to our study**, Bay et al.** [(12)] found that Accounting for sex, age, a history of myocardial infarction, angina pectoris, and hypertension, the concentration of NT-proBNP showed a strong and significant (p < 0.001) diagnostic value in predicting a low LVEF. Thus the usefulness of NT-proBNP as a screening tool is clearly greater than the clinical information gained from the patient's history.

Bayés-Genís et al. [(13)] found that higher NT-proBNP values were found in patients with systolic LV dysfunction compared to those with diastolic LV dysfunction (1118±199 pmol/l vs. 848±297 pmol/l, respectively; P=0.054).

Maisel et al. [(14)] found that BNP levels increased with increasing age (P < .001). The difference between men and women was not significant (P = .756).

Marfianti, Fauziyati, and Hisyam [(15)] found that male NT-pro BNP levels were higher than female patients, and NT pro-BNP levels in those aged> 70 years were higher than those aged less than 70 years.

In another study , by logistic regression analysis, **Mueller et al.** [(16)] observed no relevant influences of age, sex, and renal function (eGFR) on the diagnostic value of BNP and NT-proBNP.

Januzzi et al. [(8)] found that among subjects with HF a modest, but significant, relationship existed between ventricular function and natriuretic peptide concentrations (r = -0.289, P < 0.001) and that subjects with HF but preserved left systolic function had lower NT-proBNP concentrations (3070 pg/mL, IQR = 1344–7974 pg/mL) when compared with those with impaired systolic function (6536 pg/mL, IQR = 2777–13407 pg/mL, P < 0.001 for difference). The overall sensitivity of NT-proBNP in subjects with preserved systolic function was 84% when compared with 92% in those with impaired systolic function. Of the subjects with non-systolic HF below the threshold for diagnosis, 2.4% had NT-proBNP concentrations <300 pg/mL. it was also observed that no significant gender-related differences in median or inter-quartile NT-proBNP levels were noted among patients with HF, and the addition of gender stratification to age added no further diagnostic value for evaluating subjects.

In the present study, the area under the ROC curve was 80.6%, while in the many studies it has been above 90% [(12, 17)] , some studies showed an AUC of 75% [(18)]

The optimum cut-off value in the present study was 6789 pg/mL; this was associated with a negative predictive power of 66 %, while in other studies this figure was >90%. The positive predictive power of the NT-proBNP level in the present sample was higher (83.01 %). This means that, in a population with the characteristics of the present sample, most of (83.01 %) those who present at an emergency room or outpatient clinic with NT-proBNP values of >6789 pg/mL have CHF. However, some (34%) of patients with lower values also have CHF.

Figal et al. [(19)] found an area under the curve 72% which is lower than that of the present study, although these authors obtained a higher negative predictive power (92%). The optimum cut-off proposed in this earlier study was 900 pg/mL.

Hammerer-Lercher et al. [20] noted that BNP was found to be the best marker to detect patients with reduced left ventricular ejection fraction (LVEF; <40%) with an area under the curve (AUC) of (0.83 ± 0.06), whereas NT-proBNP) showed only a slightly smaller AUC (0.79 ± 0.07), which are lower that obtained in the present study.

As **Bayés-Genís** [21] postulates, determining the levels of these peptides would be of greatest use in patients with dyspnea of doubtful origin, and least useful when the results of the physical examination and other initial findings clearly point towards a definite cause of dyspnea. Comparison between NT-proBNP,EF,Alkaline phosphatse and serum creatinine in predicting heart failure development showed that NT-proBNP and EF are the most significant predictors.

Maisel et al. [14] also found that in multiple logistic-regression analysis, NT-proBNP>115 pmol/L was the strongest independent predictor of ventricular dysfunction (odds ratio 45.4; 95% CI: 4.5–452.3).

Comparison of ROC curves of NT-proBNP and ejection fraction in detecting heart failure in patients revealed AUC of 80.6%,19.5% respectively.

Bayés-Genís et al. [13] reported that Decompensated and masked HF patients had significantly higher NT-proBNP values than patients with non-cardiac dyspnea (normal ventricular function)(920±140 and 978±363 vs. 50±15 pmol/L; P<0.001 and P<0.01, respectively). The mean area under the ROC curve for NT-proBNP was 0.957 (95% CI, 0.918 to 0.996, P<0.001).

Conclusion:

In patients with dyspnea, overlapping or even conflicting history, physical and radiographic findings often hinder the differentiation between cardiac and non-cardiac etiology. The primary value of BNP and NT-pro-BNP testing in the emergency department is its diagnostic value in the differential diagnosis of acute dyspnea and possible congestive heart failure. Levels of natriuretic peptides may also assist the emergency physician in appropriately triaging the patient with congestive heart failure. Studies have shown that measurements of BNP or NT-pro-BNP in the emergency department can be used to establish the diagnosis of congestive heart failure when clinical presentation is ambiguous or when confounding co-morbidities are present.[22]

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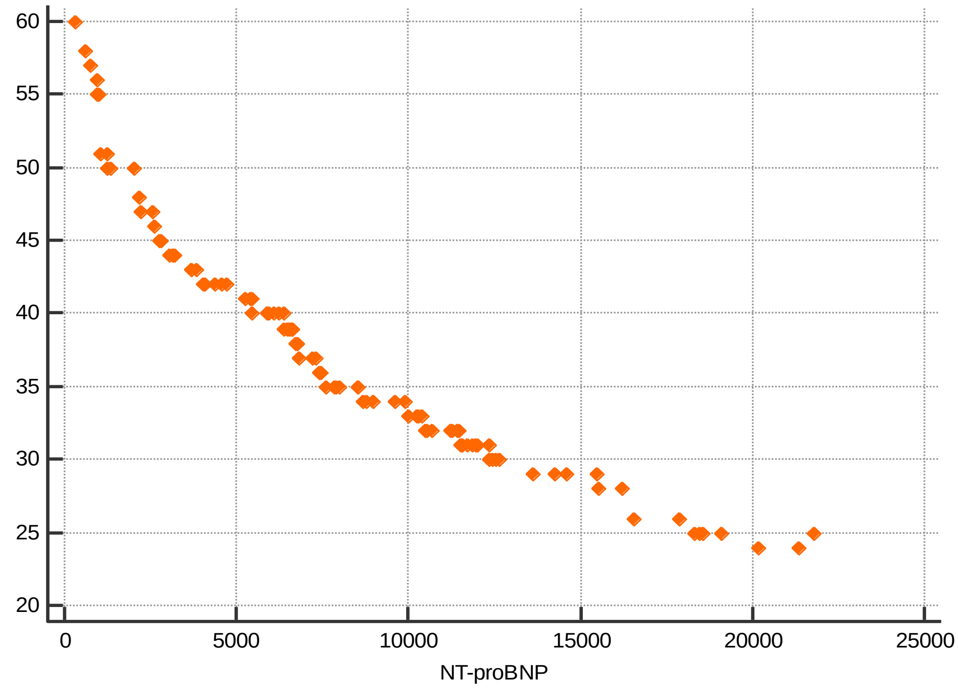

Figure (1): relationship between ejection fraction and NT-proBNP.

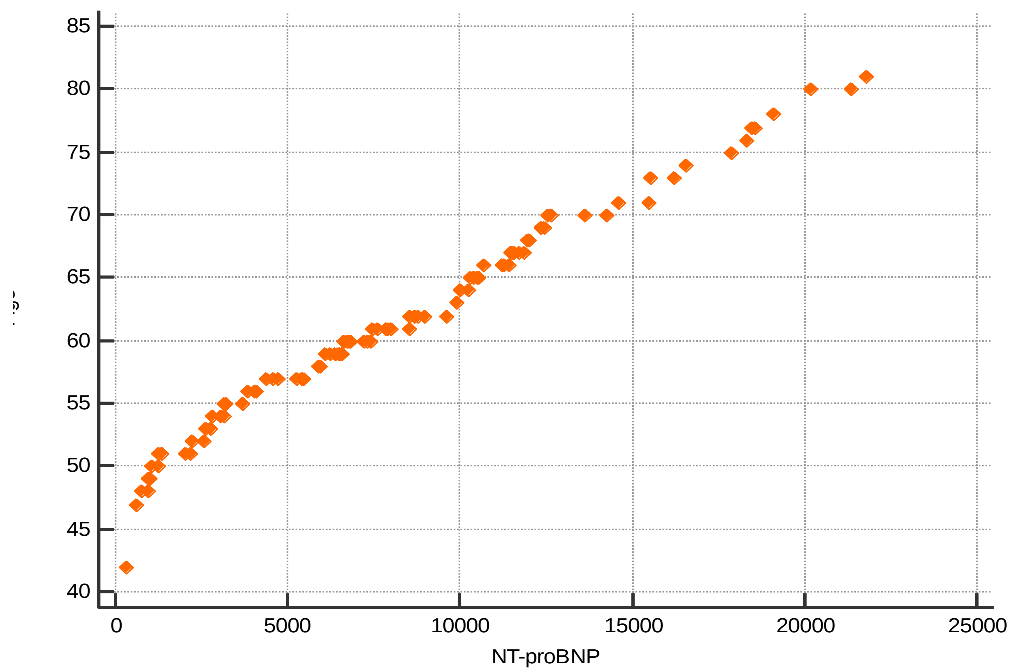

Figure (2): relationship between age and NT-proBNP.

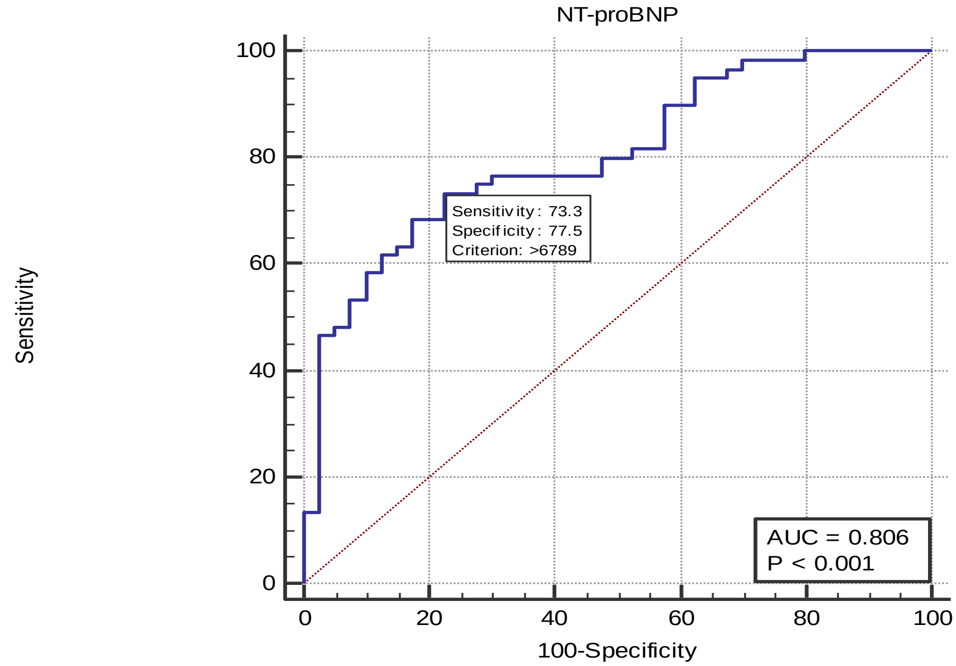

Figure (3):

ROC curve of NT-proBNP.

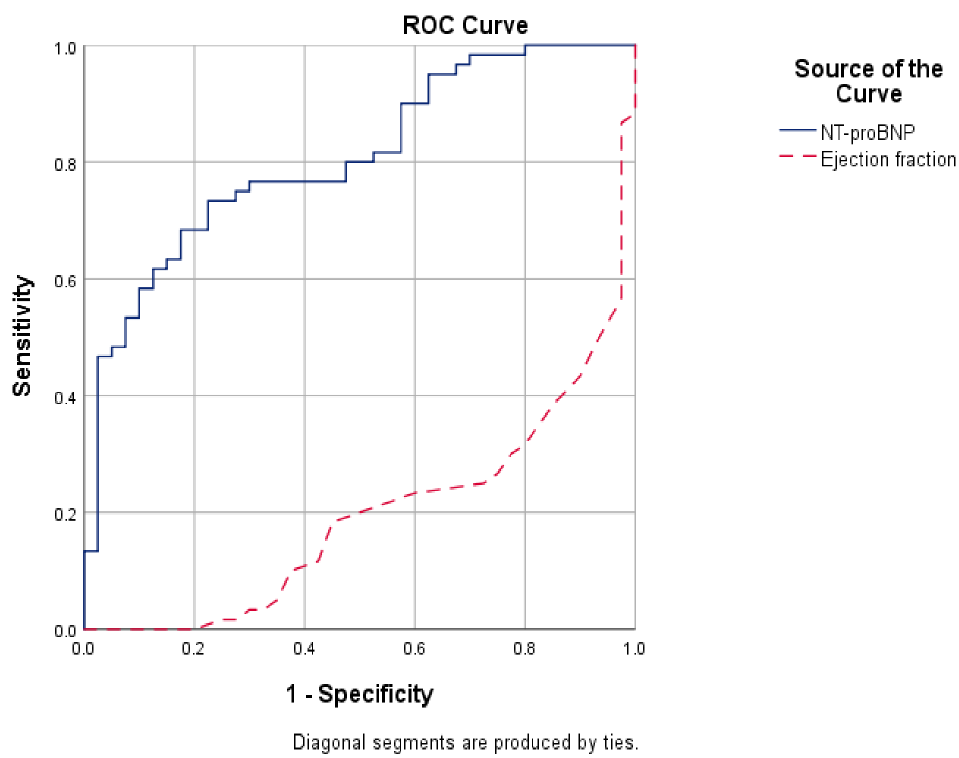

Figure (4): ROC curves of NT-proBNP and Ejection fraction.

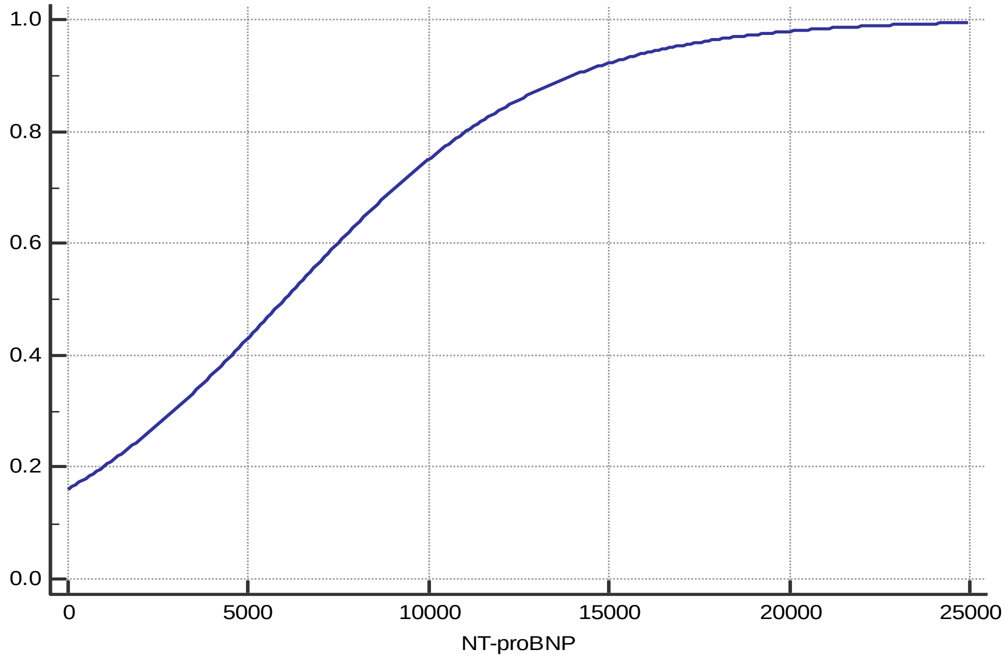

Figure (5): Logistic regression of NT-proBNP in heart failure.

Table (1): personal and clinical characteristics among two groups of patients with preserved and reduced ejection fraction.

Personal characteristics	Ejection fraction <40 (No =62)			Ejection fraction >=40 (No =38)		
Sex:	**No.**	**%**	**P**	**No.**	**%**	**P**
• Male	29	46.8%	0.3438	26	68.4%	0.6493
• Female	33	53.2%		12	31.6%	
Diabetes mellitus:						
• Diabetic	31	50%	0.5948	13	34.2%	0.6559
• Not diabetic	31	50%		25	65.8%	
Hypertension:						
• Present	46	74.2%	0.3901	18	47.4%	0.6180
• Absent	16	25.8%		20	52.6%	

Personal characteristics	**Ejection fraction <40 (No =62)**			**Ejection fraction >=40 (No =38)**		
Anemia :						
• Absent	30	48.4%		23	60.5%	
• Mild (10 g/dl : Lower normal limit)	18	29%	0.8216	13	34.2%	0.3915
• Moderate (7:10 g/dl)	10	16.1%		2	5.3%	
• Severe (<7 g/dl)	4	6.5%		0	0 %	
History of ischemic heart disease :						
• Present	26	41.9%	0.0003	15	39.5%	0.2638
• Absent	36	58.1%		23	60.5%	
Lower limb edema :						
• Present	32	51.6%	0.3511	26	68.4%	0.6493
• Absent	30	48.4%		12	31.6%	

Personal characteristics	**Ejection fraction <40 (No =62)**			**Ejection fraction >=40 (No =38)**		
Dyspnea ;						
• Absent	9	14.5%	0.2893	4	10.5%	0.7903
• Grade 1 – with unusual exertion	20	32.3%		11	28.9%	
• Grade 2 – with ordinary activity	9	14.5%		8	21.1%	
• Grade 3 – with less than ordinary activity	11	17.7%		8	21.1%	
• Grade 4 – at rest	13	21%		7	18.4%	

Table (2): Correlation between NT-proBNP versus age and ejection fraction among cases.

Variable	NT-proBNP	
	R	p
Age	0.99	<0.01
Ejection fraction	-0.94	<0.01
S. creatinine	-0.08	>0.05
Urea	0.05	>0.05
AST	-0.11	>0.05
ALT	0.13	>0.05
GGT	-0.09	>0.05
Alkaline phosphatase	-0.01	>0.05

Table (3) : Area under the curve of NT-proBNP and EF.

Area Under the Curve	
Variable(s)	Area
NT-proBNP	**0.806**
Ejection fraction	**0.195**

Table (4): Different predictors of development of heart failure.

Variable	Adjusted odds ratio (95% CI)	P
NT-proBNP	1.0003 (1.0002 - 1.0004)	<0.001HS
Ejection fraction	0.9925 (0.9796 - 1.0056)	<0.001HS
Alkaline phosphatase	0.8449 (0.7850 - 0.9093)	>0.05 NS
Serum Creatinine	0.7449 (0.1579 - 3.5134)	>0.05 NS