

2D Echocardiographic Findings, NT-ProBNP Levels, and Outcomes in Dyspnoeic Patients: Results from the Pro-BNP Investigation of Dyspnoea in the Emergency Department- a Single Centre Experience

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Authors' contributions

This work was carried out in collaboration among all authors. Author DB did the data collection and manuscript preparation. Authors VK and CK did the literature search. Author HSSNS designed the study. Author JK did the data collection. Author LSS did the data interpretation. Author RP did the reference collection. Author CNM did the final approval. All authors read and approved the final manuscript.

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ABSTRACT

Background: Dyspnoeic in the emergency department with multiple co-morbidities is a diagnostic challenge. Approximately 15-20% of acute dyspnoeic in the Emergency Department due to ADHF (acute decompensated heart failure) are misdiagnosed. B-type peptide (BNP) and its amino-terminal fragment (NT-proBNP) accurately identify HF in dyspnoeic patients. In the general population with dyspnoea, plasma pro-BNP concentrations are increased in left ventricular dilatation, hypertrophy, systolic dysfunction, or diastolic dysfunction but are unaffected by pulmonary dysfunction.

Aims and Objectives: To study the relation between NT pro-BNP & echocardiographic findings in acute dyspnoeic patients, and the relation between NT pro-BNP and In-hospital Mortality.

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Materials and Methods: Source of data- Patients admitted to the Emergency Room or cardiac intensive care unit with a history of acute dyspnea in a tertiary cardiac care center in south India, meeting inclusion & exclusion criteria, were studied.

Results: The study population is predominantly constituted of the elderly population. The most common co-morbid condition was hypertension. The present study uses an NT pro BNP level of 900pg/ml as the cut-off level. 78 patients were positive for the test. Echocardiography showed that 58% had LV systolic dysfunction, 60% had diastolic dysfunction. 42 patients had EF >55%, 10 patients between 55-45%, 33 patients between 44-30% and 15 patients had EF < 30%. Mortality rate was 6% in the whole study population. However, Mortality was seen in only NT pro-BNP positive group it was not statistically significant (p=0.46).

Conclusions: NT pro-BNP correlates well with the worsening of LV systolic function; as the EF decreases, NT pro-BNP increases. Increase in NT pro-BNP levels has to be interpreted in the clinical context, and it is not a substitute for echocardiography for assessing cardiac abnormalities and dysfunction.

Keywords: Dyspnoeic; 2D-echocardiography; NT pro-BNP.

1. INTRODUCTION

“Dyspnoeic in the emergency department with multiple co-morbidities is a diagnostic challenge. Relying solely on history, physical examination, and chest radiography to delineate dyspnea’s cardiac versus noncardiac etiology is traditionally problematic” [1]. “Approximately 15-20% of acute dyspneic in the Emergency Department due to ADHF (acute decompensated heart failure) are misdiagnosed”. [2] “Heart failure is among the most common cause of acute onset dyspnoea. The left ventricular injury due to these causes leads to left ventricular remodeling, reduced ejection fraction, arrhythmias, and sudden cardiac death” [3]. “Hence, it is essential to establish the diagnosis of cardiac failure early in the course of the disease to prevent Mortality and morbidity from this condition. Several investigations, including X-ray chest and 2D Echo, serve as a valuable guide to distinguish between the causes of dyspnoea. Evaluating patients with dyspnoea is often challenging because of the wide variety of cardiovascular and non-cardiovascular causes to be considered. With its ability to identify or exclude abnormalities in cardiac structure and function, echocardiography is a mainstay of the diagnostic work-up of dyspnoeic patients. In patients with heart failure (HF) symptoms, echocardiography often reveals a low left ventricular ejection fraction (LVEF). Up to 50% of symptomatic patients have a preserved LVEF, and abnormal diastolic function is assumed if no valvular lesions are identified in this regard; echocardiography may be helpful in confirming diastolic dysfunction” [4].

“B-type peptide (BNP) and its amino-terminal fragment (NT-proBNP) accurately identify HF in dyspnoeic patients [5]. BNP correlates with echocardiographic indices of diastolic function and right ventricular (RV) systolic function. Still, the relationships between NT-proBNP and echocardiographic findings have not been established” [6]. “Over the years, BNP–brain natriuretic peptide has gained much attention due to its high negative predictive value in dyspnoea of cardiac origin. The suspicion that the heart may have an endocrine function was raised approximately 50 years ago. At that time, it was shown that dilatation of cardiac atria produced natriuresis” [7]. “Initially, BNP was proposed as a simple diagnostic tool to aid in the clinical assessment of decompensated heart failure; studies have now shown that this hormone offers enormous diagnostic as well as prognostic information in a variety of settings, including cardiomyopathy, congestive heart syndromes, ischemic heart disease, and even pulmonary thromboembolism” [8]. “In the general population with dyspnoea, plasma pro-BNP concentrations are increased in left ventricular dilatation, hypertrophy, systolic dysfunction, or diastolic dysfunction but are unaffected by pulmonary dysfunction” [9]. Furthermore, the value of measuring natriuretic peptides for long-term prognostication above echocardiography is unclear.

The present investigation is to better understand the integrative value of NT-proBNP testing with respect to the information gained from echocardiography in dyspnoeic emergency department patients.

1.1 Aims and Objectives

1. To study the relation between NT pro-BNP & echocardiographic findings in acute dyspnoeic patients.
2. To study the relation between NT pro-BNP and In-hospital Mortality.

2. MATERIALS AND METHODS

2.1 Methodology

Source of data- Patients admitted to the Emergency Room or cardiac intensive care unit with a history of acute dyspnea in a major tertiary care center in south India, meeting inclusion & exclusion criteria, were studied.

Study duration - May 2013 to April 2015

Sample size- 100 patients.

2.1.1 Inclusion criteria

1. Patients with acute onset dyspnea above 18 yrs with or without prior history of cardiac failure and on anti-cardiac failure measures.

2.1.2 Exclusion criteria

1. CKD
2. Trauma
3. COPD

In all patients, an initial history, complete physical examination & necessary relevant investigations like Complete blood count, Renal function tests, Chest x-ray, and Electrocardiogram were done. NT pro BNP levels were measured in all patients on presentation & 2D echocardiography was done in all patients after consent. Data were collected in a pre-tested proforma. The echocardiographer was blinded to the result of NT-pro BNP.

2.2 Statistical Analysis

The Statistical software latest version of SPSS 22.0, used for the data analysis, and Microsoft Word and Excel have been used to generate graphs and tables. As appropriate, comparisons were made using the student t-test, χ^2 test, and Pearson's correlation coefficient.

3. RESULTS

We studied 100 patients with acute dyspnea who visited ER or were admitted to ICU in a major tertiary care center. Among the study population, 75 % of patients were > 50 yrs old. The age

group of 61- 70 yrs was the largest group, with 33 patients [Table 1 & Chart 1]. The elderly population predominantly constitutes the study population. Male constituted 56%, and females constituted 44% of the study population [Chart 2]. 64% were known hypertensives, 56 % were diabetic, and 51% were on treatment for coronary artery disease [Table 2]. The most common co-morbid condition was hypertension. 62% of patients were in NYHA class III, and 30% were in NYHA class IV on presentation. 8% of the study population presented with NYHA class II [Table 3 & Chart 3]. The most common presentation class was NYHA class III, irrespective of NTpro BNP levels. The present study uses an NT pro BNP level of 900pg/ml as the cut-off level. With a median level of 3833 pg/ml, 78 patients tested positive; with a median value of 202 pg/ml, 22 patients tested negative [Table 4]. 23% patients had NT pro BNP in the range of 900 – 3000, 23% in the range of 3000-5000, 16% in 5000- 10000 ,10% in 10000-20000 and 6% in >20000 pg/ml respectively [Table 5 & Chart 4]. In the current study, echocardiography showed that 58% had LV systolic dysfunction, 60% had diastolic dysfunction, LVH was found in 46%, and E/e'>15 was found in 46% of the study population, respectively [Table 6]. 58 Patients had LV systolic dysfunction, and 54 had elevated NT pro-BNP. 42 patients had normal LV systolic function. A statistically significant correlation was found between the presence of LV systolic dysfunction and elevated NT pro-BNP ($p<0.001$) [Table 7 & Table 7.1]. 42 patients had EF >55%, 10 patients between 55- 45 %, 33 patients between 44-30% and 15 patients had EF < 30 % [Table 8]. When compared with mean NTpro BNP, there is a statistically significant correlation ($p<0.001$) between the reduction of EF and elevated NT pro-BNP levels. Diastolic dysfunction (DDF) was present in 60 and absent in 40 patients. Among the NT pro-BNP group, DDF was present in 52 and absent in 26 [Table 9 & Chart 5]. There is a statistically significant correlation between the presence of DDF and elevated NT pro-BNP [Table 9.1]. In the current study, 48 patients had E/e'>15. Among the positive NT pro-BNP group, 42 patients had E/e >15, and 36 had E/e < 15 [Table 10 & Chart 6]. There is a statistically significant correlation between the elevated filling pressure (E/e'>15) and positive NT pro-BNP [Table 10.1]. Elevated PASP was found in only 16 patients. 84 patients had normal PA pressures [Table 11 & Chart 7]. And statistically, no correlation was found between elevated PA pressure and NT pro-BNP ($p=0.1$) [Table 11.1].

In the current study, 19 patients had a history of previous hospitalization for heart failure, 17 in the NT pro-BNP positive group and 2 in the opposing group. The Mortality rate was 6% in the

whole study population; although Mortality was seen in only NT pro-BNP positive group, it was not statistically significant (p =0.46).

Table 1. Age-wise distribution

Age Group	No. of patients/ percentage
<30 yrs.	3
31-40 yrs.	8
41-50 yrs.	14
51-60 yrs.	20
61-70 yrs.	33
>70 yrs.	22
Total	100

Table 2. Comorbid conditions

Co-morbid diseases	No. of patients
Hypertension	64
Diabetes mellitus	56
Coronary artery disease	51

Table 3. NYHA class

NYHA class	No. of patients/%	NT pro BNP>900 pg/ml	NT pro BNP>900 pg/ml
I	0	0	0
II	8	7(87%)	1(13%)
III	62	47(69%)	15(31%)
IV	30	24(80%)	6(20%)
Total	100	78	22

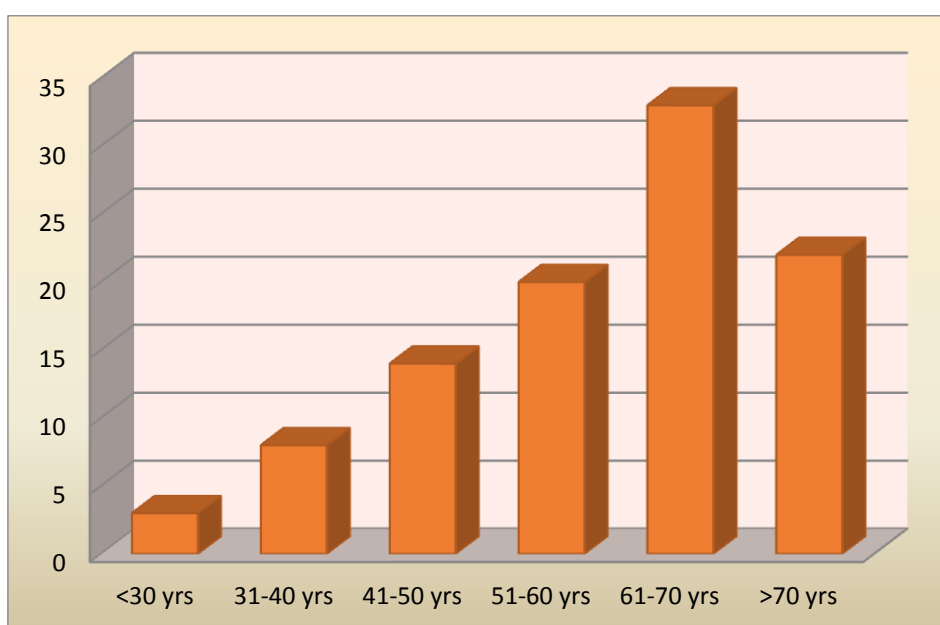


Chart 1. Age-wise distribution

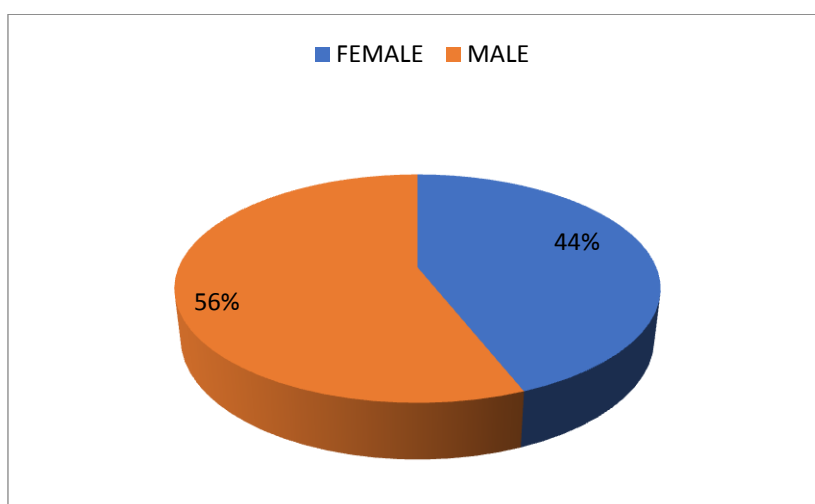


Chart 2. Sex distribution

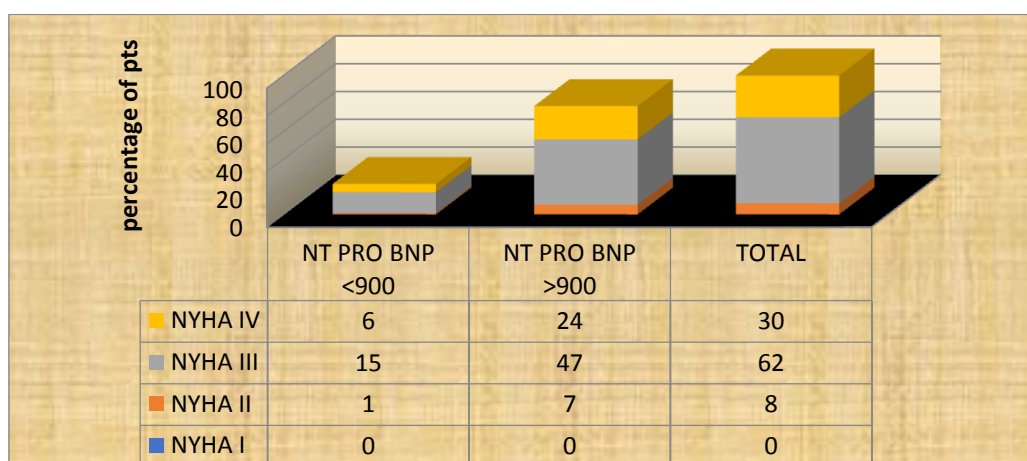


Chart 3. NYHA class

Table 4. Median & mean of NT pro-BNP

NT pro-BNP	No of Pts	Median	Mean
>900 pg/ml (Positive)	78	3833 pg/ml	8479 pg/ml
<900 pg/ml (Negative)	22	202 pg/ml	287 pg/ml
TOTAL	100	3247.44 pg/ml	6676 pg/ml

Table 5. Distribution of NT pro BNP

NT PRO BNP Level pg/ml	No of patients	Percentage
<900	22	22%
900-3000	23	23%
3000-5000	23	23%
5000-10000	16	16%
10000-20000	10	10%
>20000	6	6%
Total	100	100%

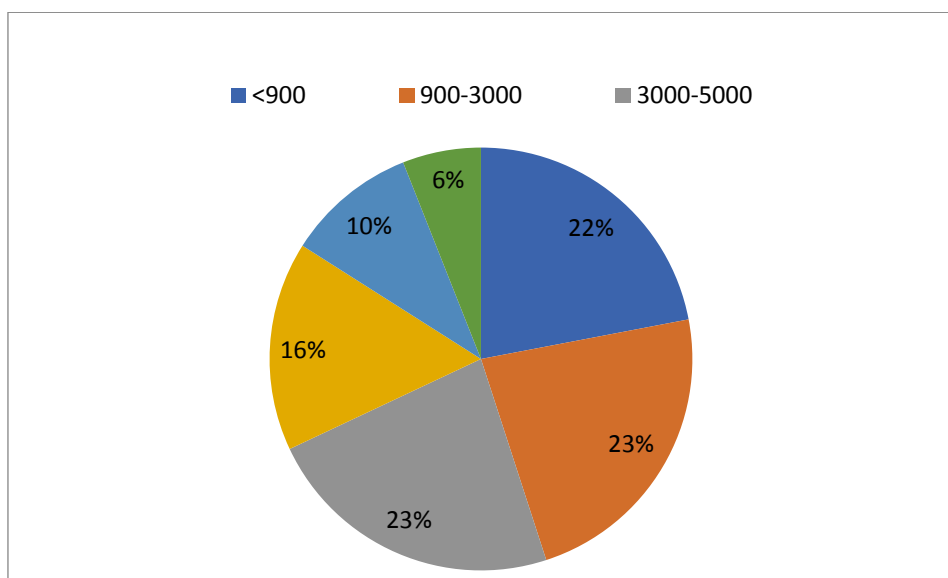


Chart 4. NT pro BNP distribution

Table 6. Echocardiographic findings

Echo Findings	No of patients
Left atrial enlargement	26
LVH	48
LV systolic dysfunction(low EF)	58
LV diastolic dysfunction (ddf)	60
High- PASP	16
E/ e'>15	46

Table 7. LV systolic dysfunction & NT pro-BNP

EF	NT PRO BNP (pg/ml)		Total
	>900	<900	
Low	54	4	58
Normal	24	18	42
Total	78	22	100

Table 7.1. Correlation between LV dysfunction and NT pro-BNP

Chi-square tests	Value	df	p-value	Association
Pearson chi-square	18.345	1	1.8E-05	Significant
Continuity correction	16.322	1	<0.0001	Significant
Fisher's s exact test			4.2E-05	Significant

Table 8. Correlation between EF and NT pro-BNP

Ejection Fraction	No. of patients	Mean EF (CI-95 2 SD)	Mean NT pro BNP pg/ml	p-value	Significance
>55	42	61.43	1590	<0.001	SIGNIFICANT
45- 55	10	47.2	3477	<0.001	SIGNIFICANT
30-44	33	34.5	6186	<0.001	SIGNIFICANT
<30	15	25.9	24142	<0.001	SIGNIFICANT

Table 9. Diastolic dysfunction & NT pro-BNP

Diastolic dysfunction	NT Pro BNP(pg/ml)		Total
	>900	<900	
Present	52	8	60
Absent	26	14	40
Total	78	22	100

Table 9.1. Correlation between diastolic dysfunction and NT pro-BNP

Chi-square tests	Value	Df	p-value	Association
Pearson chi-square	6.5	1	0.01	Significant
Continuity correction	5.34	1	0.01	Significant
Fisher's exact test			0.01	Significant

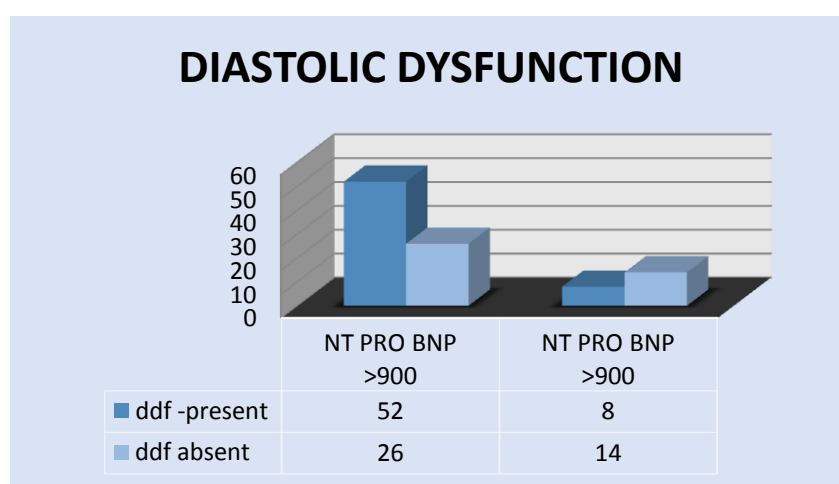


Chart 5. Diastolic dysfunction and NT pro-BNP

Table 10. E/e' and NT pro-BNP

E/ e' > 15	NT Pro BNP (pg/ml)		Total
	>900	<900	
Present	42	4	46
Absent	36	18	54
Total	78	22	100

Table 10.1. Correlation between E/e' and NT pro-BNP

Chi-square tests	Value	df	p-value	Association
Pearson chi-square	8.787	1	0.003	Significant
Continuity correction	7.410	1	0.0065	Significant
Fisher's exact test			0.0035	Significant

Table 11. PASP & NT pro BNP

PASP	NT Pro BNP (pg/ml)		Total
	>900	<900	
High	10	6	16
Normal	68	16	84
Total	78	22	100

Table 11.1. Correlation between PASP and NT pro-BNP

Chi-square tests	Value	DF	P- Value	Association
Pearson chi-square	2.668	1	0.102	Not significant
Continuity correction	1.7	1	0.19	Not significant
Fisher's exact test			0.112	Not significant

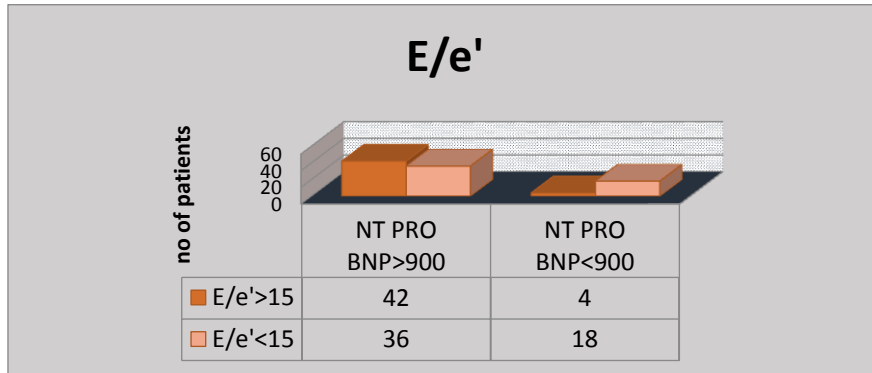


Chart 6. E/ e' and NT pro-BNP

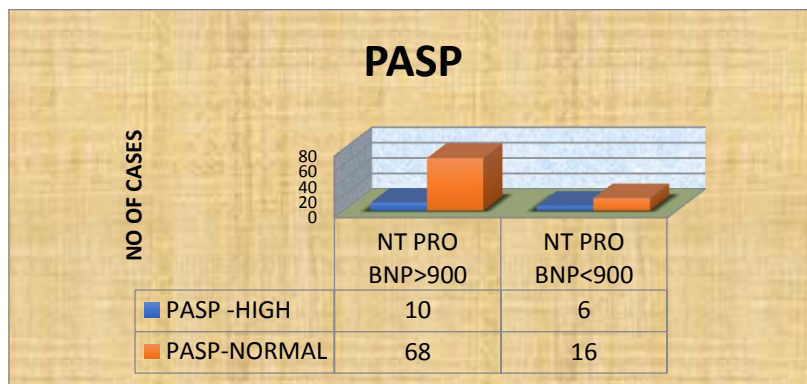


Chart 7. PASP and NT pro BNP

4. DISCUSSION

Dyspnea in the emergency department with multiple co-morbidities is a diagnostic challenge. Relying solely on history, physical examination, and chest radiography to delineate a cardiac versus noncardiac etiology of dyspnea is traditionally problematic. Approximately 15-20% of acute dyspneic in the Emergency Department due to ADHF are misdiagnosed. Heart failure is among the most common cause of acute onset dyspnoea.

In the present study population, 64% had hypertension, 56 % were diabetics, and 51 % were known cases of coronary artery disease. Concomitant diseases are widespread in patients hospitalized with AHF, reflective of the elderly population. These co-morbid conditions not only represent diseases that are risk factors for heart

failure development but can also complicate diagnosis and management. Hypertension is the most prevalent of the concurrent conditions and is present in approximately two-thirds of the study population. Coronary artery disease causes systolic and diastolic dysfunction; hence it is one of the most common causes and co-morbid conditions associated with heart failure syndromes.

8% of patients presented with NYHA Class II, 62 % with NYHA class III, and 30 % with NYHA class IV dyspnea. Compared PRIDE echo sub-study [10] numbers of patients in NYHA class III were more in the present study [Table 12].

NT proBNP was positive in 78 patients (>900 pg/ml) and negative in 22 patients (<900). Among the negative group, 9 patients' final

diagnosis was AHF. The reason for negative NT pro-BNP may be, obesity or euvolemic status.

The present study's median value of NT pro-BNP is 3833pg/ml, comparable to median values found in the PRIDE study and Januzzi et al. [11] (Table 13).

In the present study, 54 patients had LV systolic dysfunction & there is a significant correlation between LV systolic dysfunction and NT pro-BNP levels ($p < 0.001$). Worsening or decreasing ejection fraction was associated with increasing NTpro BNP values ($p < 0.001$). In the present study, patients with EF < 30 % had higher median values of NT pro-BNP as the LV dilation and reduced systolic function increased NT pro-BNP levels. Amulya C. Belagavi Medha Rao and Aslam Y. Pillai studied 100 patients who presented to the emergency department with acute dyspnea, and the NT proBNP was measured in all 100 patients. The level was compared with echocardiographic findings to assess ejection fraction (EF) correlation (Table 14). The NT proBNP values increased significantly as the functional severity of heart failure (HF) increased ($P < 0.001$). The NT proBNP levels had a good correlation with worsening LVEF [13]. Significant differences were found between patients with LVEF < 25 % and patients with moderate ventricular impairment (LVEF = 26 - 40%) and mild ventricular impairment (LVEF = 41-60%, $p < 0.001$). The group of patients with LV dilation, had significantly higher BNP levels than those with normal LVEDD (12416 ± 1060 pg/ml vs. 6113 ± 960 , $p = 0.009$) and LVESD (10416 ± 1160 vs. 4513 ± 960 pg/ml, $p = 0.008$). The study concluded that NT-proBNP is strongly associated with the two-dimensional echocardiographic determination of left ventricular dimensions and EF in identifying CHF in patients with acute dyspnoea.

In the present study, 52 Patients had diastolic dysfunction. Diastolic dysfunction was positively correlated with increasing levels of NT pro-BNP ($p < 0.001$), the main reason being the increase in the incidence of HFPEF, which almost constitutes 40% of CHF. PRIDE echo substudy

showed, as increasing severity of diastolic dysfunction, from normal (1703 pg/mL, IQR= 476–6605pg/mL) to Stage I (2264pg/mL, IQR=352–11862), stage II (2590 pg/mL, IQR=1874–8284) and Stage III (7835 pg/mL, IQR=3684–16635; $P < 0.05$ for trend across groups (Table 15).

In the present study, 46 patients had $E/e' > 15$. Out of them, 42 had positive NT proBNP levels. As $E/e' > 15$ indicates elevated LV filling pressures, patients coming to the emergency department with pulmonary edema and acute heart failure syndromes correlate well with elevated filling pressures. And it is helpful to assess the hemodynamic congestion also. The present study shows a positive correlation between the elevated $E/e' > 15$ i.e. elevated LV filling pressure and positive NT pro-BNP. The relationship between natriuretic peptides and TDI velocities (E/e') is controversial. Ioanna Zacharopoulou et al. showed the E/Ea ratio had a moderate correlation with NTproBNP levels (Table 16). The positive correlation found in the current study may be due to more patients being in higher NYHA classes with higher PCWP.

The current study did not show any correlation between LVH, PASP, and NT pro-BNP levels, similar to Sonal Virani et al. [Table 17 and 18]. However, the PRIDE study showed a weak correlation between TR velocity and NT pro-BNP.

In the current study, 19 patients had a history of previous hospitalization for heart failure, 17 in the NT pro-BNP positive group and 2 in the opposing group. 21 % of patients in the NT pro-BNP positive group had previous hospital admission and were under treatment for heart failure. In this group, NTpro BNP s were > 5000 pg/ml, higher than the median values. It is well documented that NT pro-BNP levels increase with each hospital admission, usually on the higher side, irrespective of fluid status. The mortality rate was 6 % in the whole study population. Although Mortality was observed only in the NT pro-BNP positive group with previous hospital admission and NT pro-BNP > 10000 pg/ml, it was statistically insignificant.

Table 12. Comparison of NYHA class

NYHA class	Present study	PRIDE echo substudy
I	0	6%
II	8%	21%
III	62%	31%
IV	30%	42%

Table 13. Comparison of median NT pro-BNP

NT pro-BNP median values pg/ml			
Present study	PRIDE echo sub-study	Januzzi et al.	Pride study
3833	2450	4639	4054

Table 14. LV systolic dysfunction and NT pro-BNP comparison of studies

Correlation between LV systolic dysfunction and NT pro-BNP		
Present study	Pride echo sub-study	Amulya c [12]
Present	Present	Present

Table 15. Diastolic dysfunction and NT pro-BNP comparison of studies

Correlation between LV diastolic dysfunction and NT pro-BNP		
Present study	Pride echo substudy	Sonal Virani et al. [14]
Present	Present	Present

Table 16. E/e' and NT pro-BNP comparison of studies

Correlation between E/e' and NT pro-BNP		
Present study	Pride echo substudy	Ioanna Zacharopoulou et al. [15]
Present	Inconclusive	Present

Table 17. PASP and NT pro-BNP comparison of studies

Correlation between PASP and NT pro-BNP	
Present study	Sonal Virani et al.
Absent	Present

Table 18. LVH and NT pro-BNP comparison of studies

Correlation between LVH and NT pro-BNP	
Present study	Sonal Virani et al.
Absent	Absent

5. CONCLUSIONS

The NT pro-BNP provides a rapid and reliable marker for accurate and early diagnosis of acute heart failure. NT pro-BNP correlates well with the worsening of LV systolic function. As the EF decreases, NT pro-BNP increases. It correlates well with the severity of diastolic dysfunction and elevated filling pressure. There is no correlation between PASP, LVH & NT pro-BNP in acute dyspnea. A single measurement of Nt pro-BNP on admission lacks prognostic value in acute dyspnea. Without Echocardiography in ER, the NT pro BNP level gives indirect clues to LV systolic and diastolic dysfunction. Any increase in NT proBNP levels has to be interpreted in the clinical context, and it is not a substitute for echocardiography for assessing cardiac abnormalities and dysfunction.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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