RESEARCH
www.commprac.com
ISSN 1462 2815

CLINICAL UTILITY OF NT-PRO BNP IN PATIENTS WITH ACUTE CARDIAC FAILURE: AN OBSERVATIONAL STUDY

Dr. Devipriya Surapaneni [1], Dr. Bhubaneshwar N [2] and Dr. Suhail Amir [3]

[1] Post Graduate, Department of General Medicine, Saveetha Medical College, Chennai, Tamil Nadu, India.
[2,3] Assistant Professor, Department of General Medicine, Saveetha Medical College, Chennai, Tamil Nadu, India.

DOI: 10.5281/zenodo.12651267

Abstract

Background: BNP along with its inactive N-terminal fragment, NT-pro BNP, plays a crucial role as serum biomarkers in the management of heart failure (HF). Increased levels indicate various pathophysiological processes such as cardiac structural and functional abnormalities, myocardial stretching caused by heightened filling pressure, and activation of neuro-hormones. **Aim:** To evaluate the clinical use of NT-Pro BNP in cases of suspected cardiac failure and its effectiveness in distinguishing between cardiac and respiratory dyspnea. **Materials and Methods:** The research was carried out at Saveetha Medical College in Chennai, Tamil Nadu, India, as a case-control study. One hundred patients, between the ages of 40 and 70, who were suspected of having Acute cardiac failure, were recruited for the study from January 2023 to January 2024. **Results:** The proportion of people with cardiac dysfunction as evaluated by Echocardiography was 69% in the study population, and the mean NT pro-BNP was significantly higher among the cardiac dysfunction group as compared to the pulmonary dysfunction group. The NT PRO BNP's predictive validity was shown to be good (AUC 0.871, 95% CI 0.780 to 0.961, p-value <0.001). **Conclusion:** The current study has tested the sensitivity and various cut-off values of NT Pro BNP and found the cut-off level of ≥ 1000 may be the ideal cut-off level, as it provided a better combination of sensitivity and specificity (87% and 74.2% respectively). A lower cut-off value (500) leads to an increase in sensitivity (98.6%), at the cost of specificity (64.5%).

Keywords: NT-Pro BNP, Cardiac Failure.

BACKGROUND

Heart failure is a growing issue on a global scale, impacting over 20 million individuals. It is a clinical condition that arises in patients who experience a range of symptoms and signs due to aberrations in the structure as well as the function of the heart, whether inherited or acquired. This leads to a lower life expectancy, more hospital stays, and a lower quality of life. Because there are no symptoms and a wide range of clinical manifestations, diagnosing HF accurately can be difficult. Patients affected are typically older, with other health conditions, mild symptoms, and limited access to echocardiography. [1] A large body of research has demonstrated the over diagnosis of HF in the general population, suggesting that a very small proportion of patients who are suspected of having heart failure are really diagnosed with the condition by general practitioners. [2]

It is evident that the diagnostic algorithm of HF requires additional components for improvement. Currently, there are readily available and straightforward tests that can assist in clinical assessment. In these tests, natriuretic peptides in blood or urine samples are “measured, particularly BNP (B-type Natriuretic Peptide) and N-terminal pro-B-type natriuretic peptide (NT-proBNP”).

Despite the significant advancements made in diagnosing and treating this illness, the prognosis remains bleak. This disorder serves as the ultimate pathway to death for patients with cardiovascular disease. When faced with acute dyspnea, the presence

of diagnostic uncertainty leads to prolonged hospital stays, extensive diagnostic and therapeutic efforts, increased healthcare expenses, and a higher likelihood of recurring heart failure hospitalizations or death. Although echocardiography is regarded as the standard method for evaluating decreased left ventricular function, it may not always be feasible in emergency scenarios.

Hence, there exists an urgent requirement for a dependable, easily obtainable, swift, and economical examination. As a result, the goal of the present investigation is to evaluate the effectiveness of cardiac biomarkers (NT-Pro BNP) in identifying the cardiac cause of dyspnea in critical situations, thus reducing the likelihood of enduring complications like illness and death in the long run.

MATERIALS AND METHODOLOGY

Study Design and Setting: The Saveetha Medical College's outpatient department in Chennai, Tamil Nadu, is where this case-control study was carried out. The study ran from January 2023 to January 2024, a period of six months. A well-known medical center with 1600 beds, Saveetha Medical College is located “in Kuthambakkam, southwest of Chennai.

Study Population: Participants in the investigation included acute ischemic stroke patients hospitalized to the Department of General” Medicine.

Sample Size Calculation: Based on the assumption that 24% of patients presenting with dyspnea have cardiac dyspnea, the sample size was determined. It was determined that the serum NTpro BNP had a sensitivity and specificity of 96% and 67% in distinguishing between cardiac and respiratory dyspnea, respectively. Additional factors considered in the sample size computation were a 95% confidence level and an eleven percent margin of error. According to the calculation, a total of 93 subjects would be needed for the required sample size. To accommodate for a non-participation rate of approximately 5%, an additional 5 subjects were included, resulting in a rounded sample size of 100.

Inclusion and Exclusion Criteria: The study includes patients aged 40-70 years hospitalized due to acute shortness of breath suspected to be caused by acute heart failure. Exclusion criteria encompass patients with liver cirrhosis, renal failure requiring dialysis, sepsis, current use of diuretics, and morbid obesity.

Method of Data Collection: Data collection for the study involved documenting all relevant parameters using a structured study proforma. After obtaining informed written consent, participants underwent a comprehensive evaluation, including sociodemographic data collection, detailed clinical history assessment, standard 12 Lead ECG, hemoglobin, “total count (TC), differential count (DC), erythrocyte sedimentation rate (ESR), chest X-ray in posteroanterior (PA) view, blood” urea, serum creatinine, lipid profile, random blood sugar, urine routine examination, echocardiography, electrolyte analysis, thyroid profile testing, and, if clinically indicated, CKMB and Trop I analysis. Blood samples were collected from each participant for NT-Pro BNP level analysis at the SAH Laboratory using tubes without additives, followed by centrifugation and analysis utilizing the Enzyme-Linked Fluorescent Assay (ELFA) technique, which integrates a one-step immunoassay sandwich method with fluorescent detection in the final stage.

Ethical Considerations: Before the research started, ethical clearance (SAV/AP/22/99) was received by Saveetha Medical College's Committee on Human Research Publication and Ethics in Chennai. Participants submitted written informed “onset before the typical structured questionnaire and blood samples. To ensure participant confidentiality and anonymize data, eligible participants had to sign or thumbprint a consent form before enrolling in the research.

Statistical Analysis: One potential predictive variable was NT-Pro BNP. The two main outcome factors were the kind of dyspnea and the left ventricular ejection fraction. The following explanatory factors were” included: demographic age, gender, pedal edema, substance addiction, and comorbidities.

Diagnostic testing utilized dyspnea type as the reference standard, while NT pro-BNP served as the initial screening tool. The investigation calculated 95% CI for each metric to assess NT pro-BNP's “sensitivity, specificity, predictive value, and diagnostic accuracy. The screening test's reliability was assessed using the kappa statistic, which gave a confidence interval of 95% and a p-value. ROC analysis was used to assess NT pro-BNP's dyspnea prediction capacity. The area under the curve, a confidence interval of” 95%, and a p-value were given. ROC analysis determined cutoff values of 500, 1000, 1500, & 2000. NT pro-BNP sensitivity, specificity, predictive values, and diagnostic accuracy at these cutoffs were given with a confidence interval of 95%.

RESULTS

The current research population's average age was 57.11, with 72% of participants being over 50. Additionally, there were more female participants than male participants (54% vs. 46%). 65% of participants in the current investigation had diabetes mellitus. The proportion of hypertension, CAD and RHD was 47%, 56% and 20% respectively. Among the study population, 35% people had smoking and 22% people had alcoholic. In the current study, 69% of people had been diagnosed with CHF. Out of 100 people had type of dyspnea, 69% people had cardiac dysfunction and another 31% people had pulmonary dyspnea in the study population. Out of 100 people, 20% of people were class 3 of NYHA HF and another 80% of people had class 4 of NYHA HF in the study population. Among the participants in the investigation, forty-three percent “had a left ventricular ejection fraction below 40%, 35% had a left ventricular ejection fraction between 40 and fifty percent, and twenty-two percent had a left ventricular ejection fraction above 50%.

In Table 1, individuals with a lower left ventricular ejection fraction (<40) had a median NT pro-BNP of 12100 (IQR 7995 to 18780). For patients with a borderline preserved left ventricular ejection fraction (40–50), the median NT pro-BNP was 1770 (916, 4430), while for those with a preserved fraction (>50), it was 179. Significant differences in NT pro-BNP levels were found between left ventricular ejection fraction” groups (P< 0.001).

Table 2 shows that among people with cardiac dysfunction, 68 (98.55%) people had high NT PRO BNP (≥500) and 1 (1.45%) people had low NT PRO BNP. The number of high (≥500) and low NT PRO BNP was 11 (35.48%) and 20 (64.52%) in the pulmonary dyspnea group. According to the kind of dyspnea group, there was a statistically significant difference in the proportion of NT PRO BNP (P value <0.001).

Table 3 demonstrates that the sensitivity of NT PRO BNP (≥500) in diagnosing HF, was 98.6% (95% CI 95.73% to 100 %). Specificity was 64.5% (95% CI 47.67% to

81.4%). The false positive rate was 35.5% (95 CI 18.64% to 52. 3%). The false negative rate was found to be 1.4% (95% CI: 1.00% to 4.3%), while the positive predictive value was determined to be 86.1% (95% CI: 78.44% to 93.7%). On the other hand, the negative predictive value was calculated to be 95.2% (95% CI: 86.13% to 100%), and the overall diagnostic accuracy was measured at 88.0% (95% CI: 81.63% to 94.4%).

Table 4 shows Among people with cardiac dysfunction, 60 (86.96%) people had high NT PRO BNP (≥1000) and 9 (13.04%) people had low NT PRO BNP. The number of high (≥1000) and low NT PRO BNP was 8 (25.81%) and 23 (74.19%) in the pulmonary dyspnea group. The statistical analysis indicated a notable difference (p-value <0.001) in the proportion of NT PRO BNP between the various dyspnea groups.

Table 5 demonstrates that, in comparison to the kind of dyspnea, the sensitivity of NT PRO BNP (Off value ≥1000) in diagnosing heart failure was 87.0% (95% CI 79.01% to 94.9 %). 74.2% (95% CI 58.79% to 89.6%) was the specificity. The false positive rate stood at 25.8% with a 95% confidence interval ranging from 10.40% to 41.2%. Conversely, the false negative rate was 13.0% with a 95% confidence interval between 5.10% and 21.0%. The positive predictive value was calculated at 88.2% with a 95% confidence interval from 80.58% to 95.9%. On the other hand, the negative predictive value was 71.9%, and the diagnostic accuracy was reported at 83% with a confidence interval of 75.64% to 90.4%.

Table 6 shows that among people with cardiac dysfunction, 53 (76.81%) people had high NT pro-BNP, and 16 (23.19%) people had low NT PRO BNP. The pulmonary dyspnea group had 7 (22.58 percent) nor 24 (77.42 percent) high and “low NT pro-BNP. There was a significant variation in the percentage of NT pro-BNP between the dyspnea groups, as indicated by the statistical analysis (p < 0.001).

The effectiveness of NT PRO BNP (≥1500) in identifying HF is observed in Table 7. It was determined that the specificity was 77.4% (95% CI 62.70% to 92.1%) and the sensitivity was 76.8% (95% CI 66.85% to 86.8%). It was discovered that the false negative rate was 23.2% (95 CI 13.23% to 33.1%) while the false positive rate was 22.6% (95% CI 7.86% to” 37.3%). Furthermore, 88.3% (95% CI 80.21% to 96.5%) was the positive predictive value and 60.0% (95% CI 44.82% to 75.2%) was the negative predictive value. According to reports, the overall diagnosis accuracy was 77% (95% CI 68.75% to 85.2%).

Table 8 presents the findings regarding individuals with cardiac dysfunction. It reveals that out of the total sample, 51 individuals (73.91%) exhibited “high levels of NT PRO BNP, while 18 individuals (26.08%) had low levels of NT PRO BNP. In the pulmonary dyspnea group, there were 7 individuals (22.58%) with high NT PRO BNP and 24 individuals (77.41%) with low NT PRO BNP. The difference in NT PRO BNP levels between dyspnea groups was significant (P < 0.001).

Table 9 illustrates that the sensitivity of NT PRO BNP” (≥2000) for diagnosing HF was 73.9% (95% CI 63.55% to 84.3%). The specificity was 77.4% (95% CI 62.70% to 92.1%). There was a 22.6% false positive rate (95 CI 7.86% to 37.3%) and a 26.1% false negative rate (95 CI 15.73% to 36.4%). 57.1% (95% CI 42.18% to 72.1%) was the negative predictive value and 87.9% (95% CI 79.55% to 96.3%) was the positive predictive value. According to calculations, the overall diagnosis accuracy was 75% (95% CI 66.51% to 83.5%).

Table 1: Comparison of median NT PRO BNP between studygroups (N=100)

Left ventricular ejection fraction (in %)	NT PRO BNP Median (IQR)	P value
Low (<40)	12100 (7995, 18780)	<0.001
40 to 50	1770 (916, 4430)	
High (>50)	179 (107, 520)	

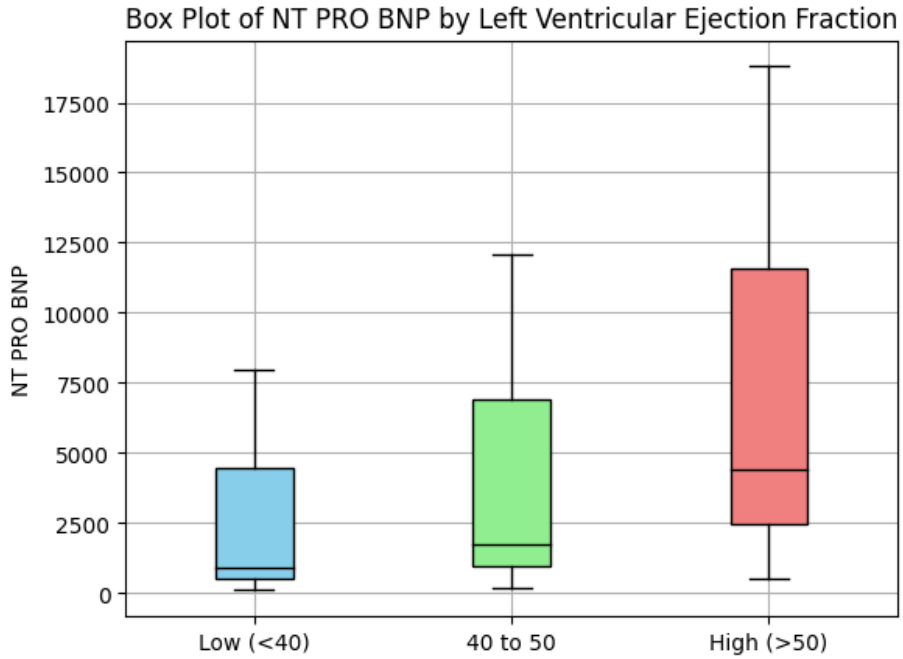

Table 2: Comparison of type of dyspnea with NT PRO BNP of the study population (N=100)

NT PRO BNP (*≥500)*	Type of dyspnea		P Value
	Cardiac dysfunction	Pulmonary dyspnea	
High (*≥500)*	68 (98.55%)	11 (35.48%)	***<0.001***
Low (499 or less)	1 (1.45%)	20 (64.52%)	

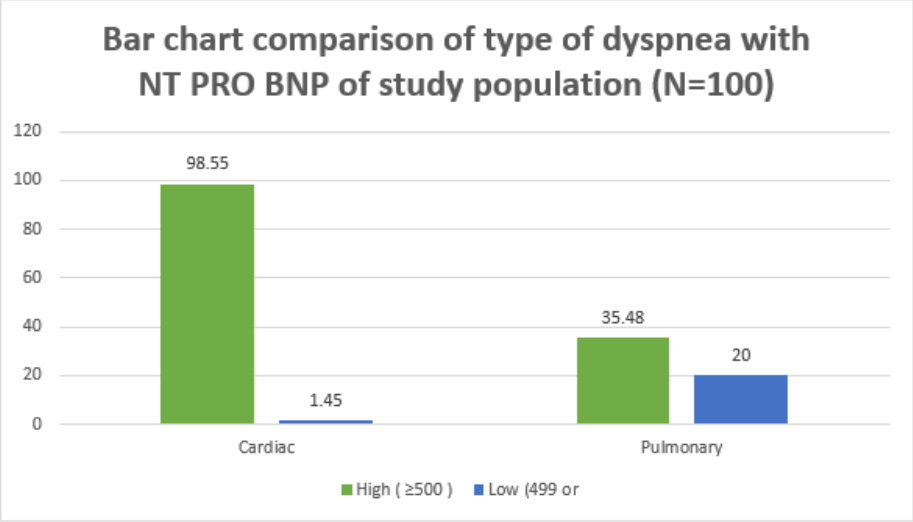

Table 3: Predictive validity of Type of dyspnea as compared to NT PRO BNP

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	98.6%	95.73%	100.0%
Specificity	64.5%	47.67%	81.4%
False positive rate	35.5%	18.64%	52.3%
False negative rate	1.4%	1.00 %	4.3%
Positive predictive value	86.1%	78.44%	93.7%
Negative Predictive value	95.2%	86.13%	100.0%
Diagnostic accuracy	88.0%	81.63%	94.4%

Table 4: Comparison of type of dyspnea with NT PRO BNP of the study population (N=100)

NT PRO BNP (1000)	Type of dyspnea		P value
	Cardiac dysfunction	Pulmonary dyspnea	
High (≥*1000*)	60 (86.96%)	8 (25.81%)	***<0.001***
Low (999 or less)	9 (13.04%)	23 (74.19%)	

Table 5: Predictive validity of Type of dyspnea as compared "to NTPRO BNP (1000) (N=100)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	87.0%	79.01%	94.9%
Specificity	74.2%	58.79%	89.6%
False positive" rate	25.8%	10.40%	41.2%
False negative rate	13.0%	5.10%	21.0%
Positive predictive value	88.2%	80.58%	95.9%
Negative predictive value	71.9%	56.30%	87.5%
Diagnostic accuracy	83.0%	75.64%	90.4%

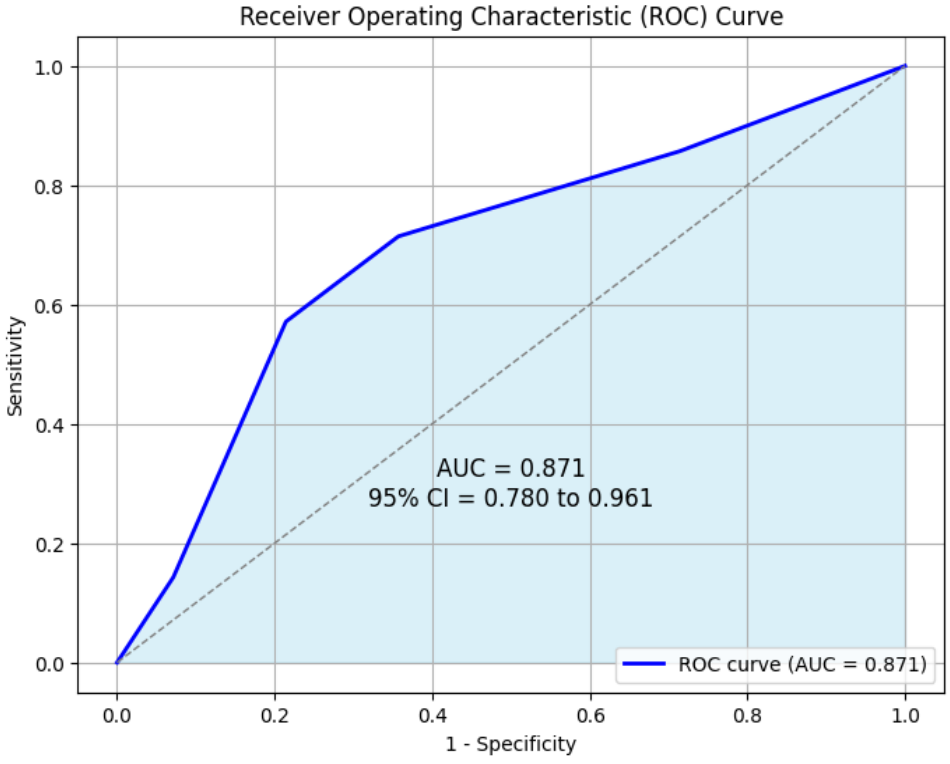

Table 6: Comparison of type of dyspnea with NT PRO BNP of the study population (N=100)

NT pro-BNP(1500)	Type of dyspnea		P value
	Cardiac dysfunction	Pulmonary dyspnea	
High (≥1500)	53 (76.81%)	7 (22.58%)	
Low (1499 or less)	16 (23.19%)	24 (77.42%)	***<0.001***

Table 7: Predictive validity of the type of dyspnea as compared "to NTpro-BNP (1500) (N=100)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	76.8%	66.85%	86.8%
Specificity	77.4%	62.70%	92.1%
False positive" rate	22.6%	7.86%	37.3%
False negative rate	23.2%	13.23%	33.1%
Positive predictive value	88.3%	80.21%	96.5%
Negative predictive value	60.0%	44.82%	75.2%
Diagnostic accuracy	77.0%	68.75%	85.2%

Table 8: Comparison of type of dyspnea with NT PRO BNP of the study population (N=100)

NT PRO BNP	Type of dyspnea		P- Value
	Cardiac dysfunction (N=69)	Pulmonary Dyspnea (N=31)	
High (*≥2000)*	51 (73.91%)	7 (22.58%)	
Low (1999 or less)	18 (26.08%)	24 (77.41%)	<0.001

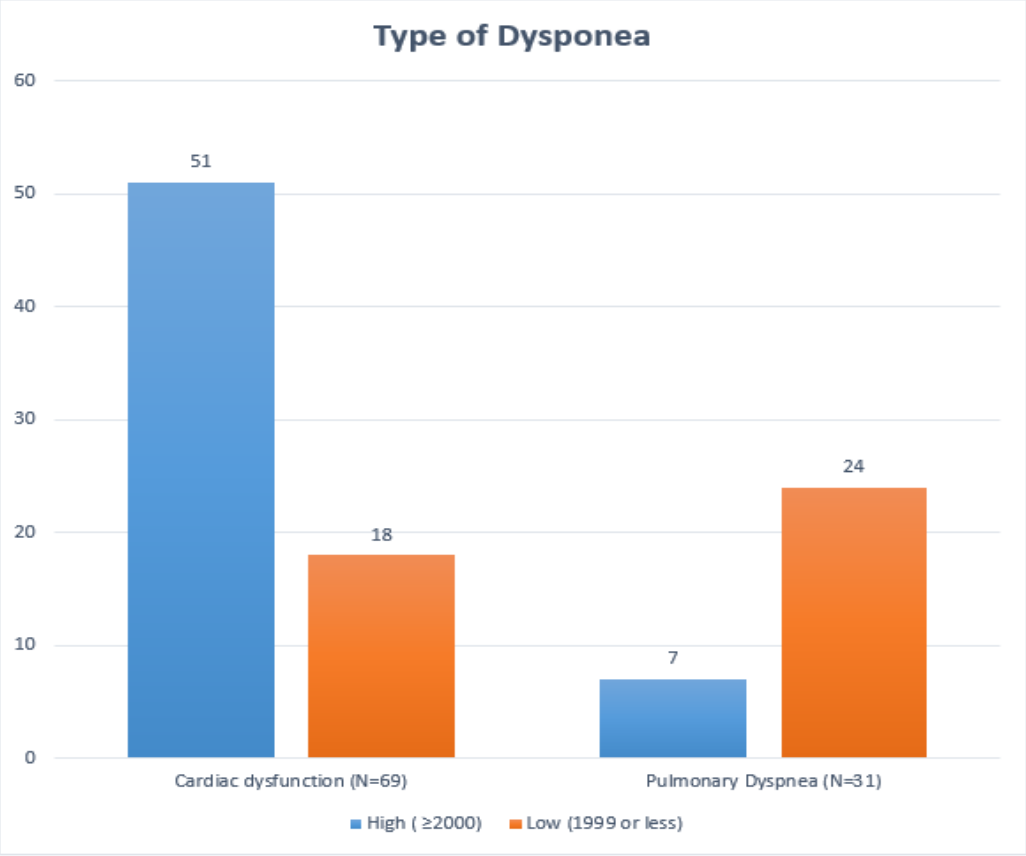

Table 9: Predictive validity "of NT PRO BNP *(≥2000) when* compared with the type of dyspnea (N=100)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	73.9%	63.55%	84.3%
Specificity	77.4%	62.70%	92.1%
False positive" rate	22.6%	7.86%	37.3%
False negative rate	26.1%	15.73%	36.4%
Positive predictive value	87.9%	79.55%	96.3%
Negative predictive value	57.1%	42.18%	72.1%
Diagnostic accuracy	75.0%	66.51%	83.5%

DISCUSSION

Dyspnea is becoming more often caused by HF, particularly because coronary heart disease and other underlying cardiac problems are becoming more common. Dyspnea has been found to be significantly influenced by heart failure, which makes it necessary to accurately identify its underlying cause at various healthcare levels. This precise diagnosis is necessary for the successful management of the condition and the prevention of unfavorable consequences.

Furthermore, it is crucial to recognize individuals who are at an elevated likelihood of advancing to decompensated heart failure, in order to promptly direct them to the suitable level of medical attention. Consequently, there exists a necessity for a dependable indicator that can assist in the identification and categorization of patients with HF.

Various markers have been investigated for their capability to forecast outcomes, with NT Pro BNP standing out as a commonly used marker in this population. Nevertheless, due to the continuously changing characteristics of individuals with congestive HF, it is essential to confirm the continued significance of NT proBNP in CHF patients and identify the optimal threshold for diagnosis and risk assessment.

The study included a cohort of one hundred individuals, ages 40 to 70, who presented for treatment of acute dyspnea with suspected HF at Saveetha Medical College in Chennai's outpatient department of the Department of General Medicine.

The present research "was a prospective observational investigation performed at a tertiary care teaching hospital to determine the NT pro-BNP values in patients with dyspnea and evaluate its effectiveness in identifying the cardiac etiology of dyspnea. The investigation also aimed to assess the predictive values, sensitivity, and specificity of various NT Pro BNP" levels.

In the present study, diabetes mellitus was observed in 65% of individuals. The prevalence of hypertension, CAD, and RHD was found to be 47%, 56%, and 20% respectively. Within the study cohort, 35% of the participants reported smoking, while 22% reported alcohol consumption.

The current study population's mean age was 57.11, with 72% of participants being over 50. Additionally, there were more female participants than male participants (54% against 46%). Gustafsson F et al[3] conducted their study in a population with a mean age, of 68.8 years.

The present study showed the mean NT pro-BNP of the cardiac dysfunction group was 9340.33 ± 7864.39 pg/ml and the pulmonary dyspnea group was 2408.65 ± 5370.6.

Nielsen, LS., et al.[4] reported the mean (S.D.) concentration of NT pro-BNP in individuals with HF was notably elevated at 189pmol/l (1598.373 Pg/ml) compared to those with noncardiac dyspnea, who had a concentration of 17 pmol/l (143 Pg/ml) (P<0.001). For patients 50 or older, NT-proBNP readings < 11pmol/l for men and 17pmol/l for women ruled out HF with a 97 percent negative predictive value. However, sensitivity was 95 percent, specificity 68 percent, and PPV 53 percent.

Verdu, JM., *et al*[5]. discovered that N-terminal pro-BNP levels were 715pg/mL (interquartile range 510.5-1575) in heart failure patients and 77.5 (58-179.75) in patients without HF.

The current investigation demonstrated that NT PRO BNP exhibited strong predictive capability in determining the type of dyspnea, with an area under the curve (AUC) of 0.871 (95% CI 0.780 to 0.961, p-value <0.001). The most effective threshold for attaining the best prognostic accuracy in mortality prediction was found by Kubler, P., et al. (2006) to be a 65% decrease in NT pro BNP (sensitivity: 90percent specificity: 37percent, AUC=0.65, 95percent CI: 0.54-0.74).

Compared to BNP and proBNP, the “admission and discharge levels of NT-proBNP exhibited a better predictive power for all-cause mortality, according to a study by Waldo et al. 7. The corresponding AUC values for NT-proBNP and BNP were 0.788 and 0.834, 0.644 and 0.709, and 0.653 and 0.666 for proBNP, respectively. With p< 0.01, these differences were statistically significant.

The best plasma NT-proBNP cut-point for in-hospital mortality was 3500 pmol/L, with 70.3% sensitivity, 72.0 percent specificity, 71.9 percent accuracy, 17.8 percent positive predictive value, and 96.6 percent negative predictive value. Wei, B. Q., et al.[8] predicted in-hospital death to be 0.772 (95 percent CI: 0.718 - 0.825, P<0.01). Wright” SP et al.[9] stated that when the cut-off was set at 40 pg/ml, they performed better, achieving an NPV of 88%. In contrast, NT proBNP demonstrated a 92% NPV when the cut-off was established at 150 pg/ml. If the 40pg/ml and 150pg/ml BNP and NT pro-BNP cut-offs had been implemented, it might have saved 24% & 25% of clinic referrals, respectively.

Goode et al. [10] managed to evade the need for thirty-eight percent of echocardiograms, while Aspromonte et al.[11] documented a 31% reduction in usage. Nevertheless, it is important to note that natriuretic peptide determination cannot fully substitute echocardiography. Echocardiography not only confirms the clinically suspected diagnosis of heart failure (HF) but also offers valuable insights into myocardial morphology and function.

Hence it can be said the NT-proBNP cut-off levels of ≤ 500 or ≤ 1000 may be considered suitable cutoffs depending on the type of setting, screening protocol of the institution, etc. In emergency departments and primary care settings, a lower cut-off level with higher sensitivity may be preferred. In centers where definitive treatment is provided and further diagnostic evaluation and definitive management are done, a higher cut-off value, with better specificity shall be preferred.

CONCLUSION

The sensitivity and different cut-off values of NT Pro BNP were examined in the current study, and it was discovered that the cut-off level of ≥1000 may be the best cut-off level since it offered a better combination of sensitivity and specificity (87% and 74.2%, respectively). A lower cut-off value (500) leads to an increase in sensitivity (98.6%), at the cost of specificity (64.5%). Whereas a higher cut-off value (1500) has led to a minimal increase in specificity (77.4%) at the cost much decline in sensitivity (76.8%).

References

1) Fonseca C, Morais H, Mota T, Matias F, Costa C, Gouveia-Oliveira A, et al. The diagnosis of heart failure in primary care: value of symptoms and signs. Eur J Heart Fail. 2004;6(6):795-800, 21-2.

2) Hobbs FDR, Doust J, Mant J, Cowie MR. Diagnosis of heart failure in primary care. Heart. 2010;96(21):1773-7.

3) Fuat A, Murphy JJ, Hungin AP, Curry J, Mehrzad AA, Hetherington A, et al. The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. Br J Gen Pract. 2006;56(526):327-33.

4) Nielsen LS, Svanegaard J, Klitgaard NA, Egeblad H. N-terminal probrain natriuretic peptide for discriminating between cardiac and noncardiac dyspnoea. Eur J Heart Fail. 2004;6(1):63-70.

5) Verdu, JM., et al. 22 reported that the median values of N-terminal pro-B-type natriuretic peptide were 715 pg/mL [interquartile range 510.5- 1575] and 77.5 pg/mL [interquartile range 58-179.75] for patients with and without heart failure respectively.

6) Kubler P, Jankowska EA, Majda J, Reczuch K, Banasiak W, Ponikowski P. Lack of decrease in plasma N-terminal pro-brain natriuretic peptide identifies acute heart failure patients with very poor outcome. Int J Cardiol. 2008;129(3):373-8.

7) Waldo SW, Beede J, Isakson S, Villard-Saussine S, Fareh J, Clopton P, et al. Pro-B-type natriuretic peptide levels in acute decompensated heart failure. J Am Coll Cardiol. 2008;51(19):1874-82.

8) Wei BQ, Yang YJ, Zhang J, Dou KF, Zhang YH, Huang XH, et al. [Predictive value of admission amino-terminal pro-B-type natriuretic peptide on in-hospital mortality in patients with decompensated heart failure]. Zhonghua Xin Xue Guan Bing Za Zhi. 2009;37(6):481-5.

9) Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ, et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. J Am Coll Cardiol. 2003;42(10):1793-800.

10) Goode KM, Clark AL, Cleland JG. Ruling out heart failure in primary-care: the cost-benefit of pre-screening using NT-proBNP and QRS width. Int J Cardiol. 2008;130(3):426-37.

11) Aspromonte N, Feola M, Scardovi AB, Coletta C, D'Eri A, Giovinazzo P, et al. Early diagnosis of congestive heart failure: clinical utility of B-type natriuretic peptide testing associated with Doppler echocardiography. J Cardiovasc Med (Hagerstown). 2006;7(6):406-13.