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STUDY OF N-TERMINAL PRO B-TYPE NATRIURETIC PEPTIDE VALUES IN PATIENTS WITH SHORTNESS OF BREATH ATTENDING TO EMERGENCY DEPARTMENT

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ABSTRACT:

Shortness of breath is defined as the feeling, that one cannot breathe well enough or difficulty in breathing. It is generally caused by disorders of the cardiac or respiratory system. NT-pro-BNP test values are used to identify the patients with the cardiac cause or non-cardiac cause of Shortness of breath. This test is useful in the detection, diagnosis, prognosis, evaluation, and severity of heart failure.

Materials and Methods: Prospective observational study was conducted from October 2019 to March 2020 with 70 patients of shortness of breath attending to the emergency department.

Observation: Out of 70 patients; 39were males and 31were females. NT-pro-BNP values were found to be 5785 pg/ml for cardiovascular cause (43) and 297 pg/ml for the non-cardiovascular cause of Shortness of breath. The mean NT-pro-BNP values were found to be 5785.25 pg/ml-HF likely (n=43), 377 pg/ml-HF unlikely (n=10), 452.25 pg/ml -grey zone (n=8) and 70 pg/ml -NAHF (n=9). The review rate within 6 months was found to be increased with increased NT-pro-BNP values.

Conclusion: The plasma concentrations of NT-pro-BNP levels are useful in differentiating the exact cause of Shortness of breath. It is a study to improve the awareness among people and physicians about the importance of the NT-pro-BNP test and its role. Increased NT-pro-BNP levels grossly correlate with the severity of left ventricle dysfunction. It is a good biomarker with high sensitivity and a cost-effective test.

KEYWORDS: Shortness of breath, NT-pro-BNP Test, Good biomarker, Sensitivity, Cost-effective test.

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INTRODUCTION:

Shortness of breath is also known as dyspnoea. It is the feeling that one cannot breathe well enough or difficulty in breathing. SOB is generally caused by disorders of the cardiac or respiratory system. The most common cardiovascular causes are acute myocardial infarction and congestive heart failure. While common respiratory causes include COPD, Asthma, pneumothorax, pulmonary edema and pneumonia[1]. NT-pro-BNP test refers to N-terminal pro B type natriuretic peptide test. This test measures the levels of the protein BNP in blood. NT-pro-BNP is a substance produced by the left ventricles of the heart which helps to relax the blood vessels to maintain smooth blood flow. NT-pro-BNP values increases in presence of cardiac dysfunction. Patients with SOB grade III and IV are tested and the NT-pro-BNP test values are used to identify the patients with cardiac cause or non cardiac cause of SOB. In patients with cardiac cause of SOB it is useful in prognosis of heart failure. This test is done to help in the detection, diagnosis and evaluation of the severity of Heart Failure.

Natriuretic peptides {NP} - are a family of hormone/ paracrine factors that are structurally related. It consists of Atrial natriuretic peptide (ANP), B type natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and Urodilatin.

Brain natriuretic peptide (BNP):

BNP was first segregated from the porcine brain in 1988. In humans, the majority of BNP is formed in ventricular cardiomyocytes in the heart ventricles in response to stretching caused by increased blood volume[2].

Production: The initial molecule is a 134-amino acid protein, pre-pro-BNP. After cleavage of a signal peptide of (26 amino acid), a 108 amino acid, pre-hormone called pro-BNP remains. Before release into the bloodstream, pro-BNP is cleaved into two parts, the biologically active 32-amino acid chain BNP and the inactive 76-amino acid neuro-hormone NT-pro-BNP (N-terminal pro-B-type natriuretic peptide) [3]. BNP and NT-pro-BNP differ concerning their biological half-life. As both are biologically separate [4], BNP and NT-pro- BNP are usually used in the assessment of cardiac functions and have an essential role in the regulation of natriuresis, dieresis, and vascular tone [5], (Table 1).

Role of BNP & NT-pro-BNP as a diagnostic marker:

NT-pro BNP testing solitarily was superior to clinical judgment for diagnosis of acute HF; NT-pro BNP along with clinical judgment was superior to NT-pro-BNP or clinical judgment alone. NT-pro BNP measurement is a valuable addition to definitive clinical assessment for the recognition and to ostracize acute CHF in the emergency department setting [6].

ACC/AHA guidelines recommend the use of BNP and NT-pro-BNP for the exclusive diagnosis of heart failure.BNP and NT-pro-BNP testing is a very valuable diagnostic and prognostic tool for heart failure. NT-pro-BNP, which has a longer half-life of 2 hours and a more consistent blood concentration than BNP, is indicated by recent data as a better marker in detecting the early stage of heart failure [7-10].

In the 2009 ACCF/AHA heart failure guidelines, Jessup et al .suggest that measurement of natriuretic peptide (i.e. BNP and NT-pro-BNP) can be useful in the evaluation of patients in an emergency care setting in whom the clinical diagnosis of HF is uncertain [11] .

Various guidelines and recommendations are accessible for the use of natriuretic peptides in the diagnosis of heart failure. As it is known that old age may foremost elevate natriuretic peptide levels in the absence of heart failure; it is compatible to resolve certainly, to use or not to use age-dependent reference ranges for clinical biochemistry parameters.

Heart failure overview:

Heart failure (HF) is a chronic condition, which mainly affects the elderly. Prevalence is about 0.8-2% in the general population and 10-20% among those people aged >70 years. With an ever-aging population, prevalence is increasing. In the US, HF presently affects 5.8 million; an estimate prognosticates that this will rise to more than 8 million by 2030.

HF is a conglomerate syndrome with many potential causes that result in impaired ability of the left ventricle to either fill with blood during the diastolic phase or eject blood during the systolic phase of the cardiac cycle. The diseased heart is unable to pump a sufficient amount of blood volume to meet the oxygen demands of the body. Heart imaging (echocardiography) will assess the left ventricular ejection fraction (LVEF).

This is the percentage of the total blood volume in the left ventricle that is ejected during systole and is normally around 50-70%. HF due to impair ventricular ejection fraction is associated with reduced ejection fraction (rEF), i.e. <50% and is referred to as HFrEF or systolic heart failure. HF due to impair ventricle filling is associated with preserved EF (i.e.>55%) and is referred to as HFpEF or diastolic heart failure. Heart Imaging will be

distinguished left ventricular dysfunction (either systolic or diastolic) before symptoms of heart failure occur [12].

Fundamental symptoms of HF include: SOB with mild exertion (dyspnoea); exercise intolerance, weakness, and eventually ankle bump/pain due to local fluid (edema) accumulation. HF is a progressively debilitating condition. The New York Heart Association (NYHA) Functional Classification is extensively used to classify the severity of HF from one to four classes based on the extent to which physical activity is limited [13].

NHYA Class I is asymptomatic HF, and NHYA Class IV is relevant to patients with most severe HF who are "unable to carry on their physical activities without discomfort." These Class IV HF patients will experience symptoms (SOB, fatigue, etc.) at rest.

Typically, patients with periods of chronic stable HF, punctuated by acute exacerbation called acute (decompensated) heart failure (AHF). While symptoms of the hemodynamic condition worsen, significantly requiring emergency admission to the hospital. AHF, which may occur in those with HF, is associated with high mortality. Around 12- 15% of patients who are hospitalized with decompensated heart failure die within 12 weeks, and 30% of patients die within 12 months of admission.

Enhanced ventricle wall stretch/stress is a characteristic feature of heart failure which accounts for the increased release of circulating natriuretic peptides i.e. BNP and NT-pro-BNP [14].

Diagnosis of HF:

BNP and NT-pro-BNP are the best-established and best evaluated markers to help in proper diagnosis and exclusion of HF.

Copious studies have analyzed the value of BNP and NT-pro-BNP in the diagnosis of HF; two large meta-analyses summarized this data. These adequately illustrate that these blood tests will improve the diagnosis of HF, AHF in both primary care and hospital room setting. The most widely used diagnostic application of BNP/NT-pro-BNP is to examine the patients with dyspnoea, the most usual (but non-specific) symptom of heart failure.

Role of BNP as a prognostic biomarker in HF patients:

BNP & NT-pro-BNP as a marker of left ventricular systolic function provides independent prognostic information regarding the estimated risk of disease progression, hospital-readmission, and mortality.

Determining the severity of HF:

Copious studies have entrenched that BNP and NT-pro-BNP values resemble the severity of HF assessed by NYHA functional classification along with imaging measures of cardiac dysfunction in HF. Generally, the higher the value the more severe is the HF. Elevated values are suggestive of worse clinical outcomes and greater risk of death.

Admission NT-pro-BNP is also strongly predictive of outcome for patients admitted to hospital with acute decompensated HF [15].

The 2017 update guideline task force recommended the use of BNP or NT-pro-BNP to help establish prognosis or disease severity in chronic HF [16].

The aim of this study is to determine the importance of the NT-pro-BNP test in differentiating a cardiac cause or non-cardiac cause of shortness of breath in patients attending to the emergency department. With the objectives of Comparison of NT-pro-BNP values in Heart failure reduced ejection fraction (HFrEF) and Heart failure preserved ejection fraction (HFpEF), to observe NT-pro-BNP levels and readmission rate.

MATERIALS AND METHODS:

This prospective observational study was done from October 2019 to March 2020 in department of cardiology, Hitam cardiac care centre located in Hanamkonda, Warangal. The study was conducted with 70 patients of shortness of breath attending to emergency department. The patients were included in the study after applying the inclusion and exclusion criteria. Data was collected using a proforma meeting the required objectives of the study. Every individual's data was collected including the demographics, vital signs at the initiation of hospitalization, serum NT-pro-BNP values drawn within 24 hrs upon hospitalization using Roche diagnostic values. Other diagnostic tests which include electrocardiogram, echocardiography, left ventricular ejection fraction and other blood tests were also included.

The NT-pro-BNP test procedure is done by drawing blood from a vein in your arm using a hypodermic needle. A machine (Roche diagnostics) then measure the levels of NT-pro-BNP in the blood sample. The results from the test are usually ready in 20-30 minutes

These values of NT-pro-BNP test were collected and assessed for the cause of SOB. Depending on the cause of SOB, other investigations are done (lung function test or ECG, 2d Echo).For the cardiac cause of SOB, echocardiography findings are collected and noted their ejection fraction which aid in prognosis and severity of HF. The data was collected throughout 6months from 70 patients. Patients were categorized based on their test values and assessed for the cause of SOB.

Data was analyzed using appropriate statistical tests like mean, sensitivity, specificity, positive predictive value, negative predictive value.

Inclusion Criteria were, Adult patients (age >18 years), Shortness of breath grade 3 and grade 4 patients. Exclusion Criteria were, Age <18 years, Shortness of breath grade 1 and grade 2, Diagnosed case of heart failure.

RESULTS AND OBSERVATIONS:

In our prospective observational study, data were collected from 70 patients who presented with the chief complaint of shortness of breath to the emergency department.

Demographic analysis of this study revealed that, out of 70 patients; 39(56%) were males and 31(44%) were females.

Table 2 and figure 1 shows the comparison of age and gender i.e. <50 years-male 15 (21%), female 16 (22%). 50-75 years –male 23 (32%), female 13 (18%) and >75 years – male 1 (1%), female 2 (3%).

Based on the NT pro BNP values, the patients were categorized into 4 groups

- NAHF-<125 pg/ml
- HF Unlikely<300 pg/ml
- Grey zone->300 pg/ml and under "rule in" criteria
- HF likely->450pg/ml and under "rule in" criteria

Table 3 and figure 2 shows cardiovascular and non-cardiovascular cause of shortness of breath i.e. cardiovascular cause of SOB was seen in 43 (61%) patients and non-cardiovascular cause of SOB was seen in 27(39%) patients and table 4 shows their mean NT-pro-BNP values were found to be5785 pg/ml for the cardiovascular cause of SOB and 297 pg/ml for the non-cardiovascular cause of SOB.

Table 5 shows the correlation between gender and mean NT-pro-BNP i.e. 3714 pg/ml –males and 3611 pg/ml –females.

All SOB patients were categorized according to NYHA classification, of which stage III and stage IV were selected for our study (Table 6 & fig 3). NT-pro-BNP test was conducted for those stage III and stage IV SOB patients. NT-pro-BNP test values were obtained from the laboratory data and the mean NT-pro-BNP is found to be-3668pg/ml. Along with NT-pro-BNP test, echocardiography was also done and their mean ejection fraction (EF %) was found to be 42.5% (Table 7)

Based on grouping the patients were diagnosed as 43 (62%) were HF likely, 10 (14%) were HF unlikely, 8 (11%) were grey zone and 9 (13%) were NAHF (Table 8 & Figure 4) and their mean NT pro BNP values were found to be 5785.25 pg/ml -HF likely, 377 pg/ml –HF unlikely, 452.25 pg/ml –grey zone and 70 pg/ml –NAHF (Table 9 & Figure 5). While the mean EF % was found to be 39.46%-HF likely, 51.5% - HF unlikely, 54.25% - grey zone and 60% - NAHF (Table 10 & Figure 6) .

Table 11 and figure 7 shows the echocardiography values for HFrEF and HFpEF i.e.31 (65%)-HFrEF and17 (35%) –HFpEF. Table 12 shows the mean NT-pro-BNP values with HFrEF and HFpEF i.e. 6660.5pg/ml (13) female,6083 pg/ml (18) male and 3281 pg/ml (7)female,3101 pg/ml(10) male. In our study, we also compared the review rate within 6 months and it was found to be increased with increased NT-pro-BNP values (Table 13 & Figure 8).

The statistical analysis of our study shows that; 72.85% of prevalence, 84.31% of sensitivity 47.36% of specificity, 81.13% of positive predictive value, and 52.9 % of negative predictive value (Table 14 & Figure 9). Which were compared with age groups and are shown in table 15 and depicted in (figure 10).

Table 1 : BNP versus NT-pro-BNP

Characteristics	BNP	NT-pro-BNP
Amino acid	32	76
Molecular weight, kDa	3.5	8.5
Half-life, min	20	120
Clearance mechanism		
Primary mechanism	Neutral endopeptidase	Renal
Clearance receptor	NPR-C	Renal
Hemodialysis	No	No
Correlation with GFR	Moderate	Strong
Biologically active	Yes	No
Clinical range (pg/ml)	0-5000	0-35000

BNP: B-type natriuretic Peptide; NT-pro-BNP: N-terminal pro B-type natriuretic peptide; NPR-C: Natriuretic peptide receptor -C

Table 2 : Age wise and gender wise distribution

Age in years	Male	Female
<50 years	15	16
50-75 years	23	13
>75 years	1	2
Total	39	31
Sub total		70

Table 3 : Etiology of Shortness of Breathe

Etiology	No of patients
Cardiovascular	43
Non-cardiovascular	27

Table 4 : Correlation between Mean NT-pro-BNP and Cause of Shortness of Breathe

Causes	Mean NT-pro-BNP
Cardiovascular	5785 pg/ml
Non cardiovascular	297 pg/ml

Table 5 : Correlation between Gender and Mean NT-pro-BNP values

Gender	Mean NT-pro-BNP (pg/ml)
Male	3714(39)
Female	3611(31)

Table 6: Staging of SOB Patients according to NYHA Classification

Stage	Total no patients
IV	29
III	41

Table 7 : NT-pro-BNP findings and ECHO findings in SOB Patients

Study	Mean findings
NT-pro-BNP (pg/ml)	3668
ECHO -EF%	42.5

Table 9 : Correlation between grouping of SOB Patients and Mean NT-pro-BNP values

Group	Mean NT-pro-BNP(pg/ml)
HF likely	5785.25
HF unlikely	377
Grey zone	452.25
NAHF	70

Table 10 : Correlation between grouping of SOB patients and Mean EF %

Group	Mean EF%
HF likely	39.46
HF unlikely	51.5
Grey zone	54.25

Table 8 : Grouping of SOB Patients according to NT-pro-BNP values

Group	Total no of patients
HF-likely	43
HF unlikely	10
Grey zone	8
NAHF	9
Total	70
NAHF	60

Table 11 : Comparison of HFrEF and HFpEF

Group	Total no of patients
HFrEF	31
HFpEF	17

Table 12 : Comparison of HFrEF and HFpEF with Mean NT-pro-BNP values and Mean EF%

Group	Gender	Mean NT-pro-BNP(pg/ml)	Mean EF%
HFrEF	Female	6660.5(13)	36.84
	Male	6083(18)	32.5
HFpEF	Female	3281(7)	54.57
	Male	3101(10)	53.1

Table 13 : Comparison of NT-pro-BNP value and Review rate within 6 months

NT-pro-BNP (pg/ml)	Readmission rate
>1000	1
>2000	3
>4000	5
>6000	6
>9000	8

Table 14 : Statistical analysis of NT-pro-BNP test study

Prevalence (%)	72.85
Sensitivity (%)	84.31
Specificity (%)	47.36
Positive predictive value (%)	81.13
Negative predictive value (%)	52.94

Table 15 : Age wise NT-pro-BNP test Statistical analysis

Age (years)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
<50	30.23	36.84	72.3	58.34
50-75	62.79	10.52	84.37	40
>75	6.97	0	100	0

Figure 1: Age wise and gender wise distribution

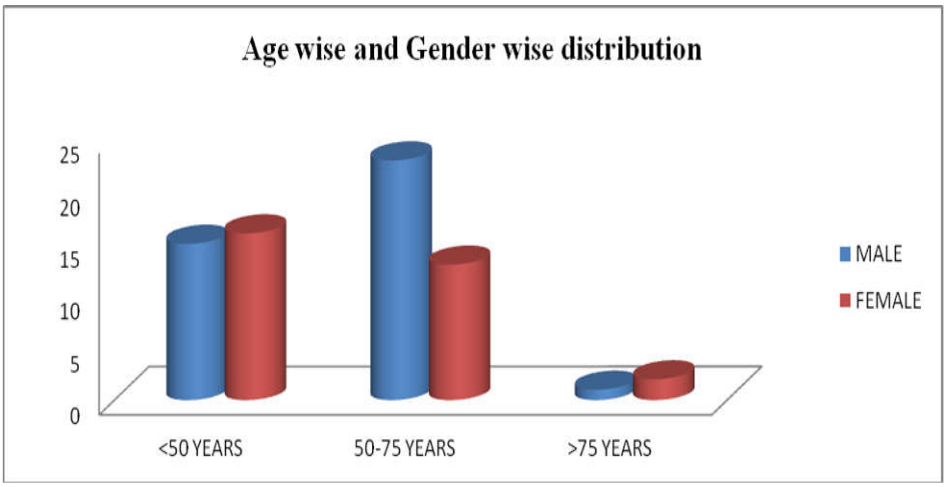


Figure 2: Etiology of SOB Patients

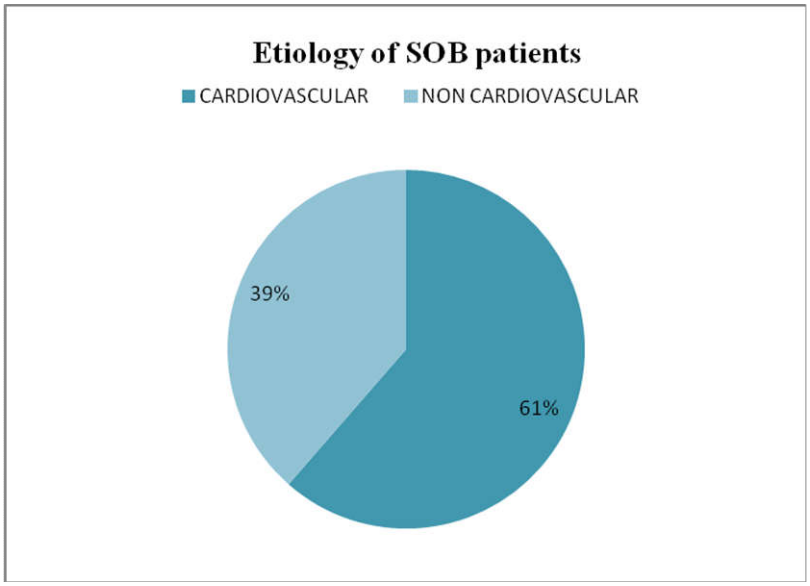


Figure 3: Staging of SOB patients according to NYHA Classification

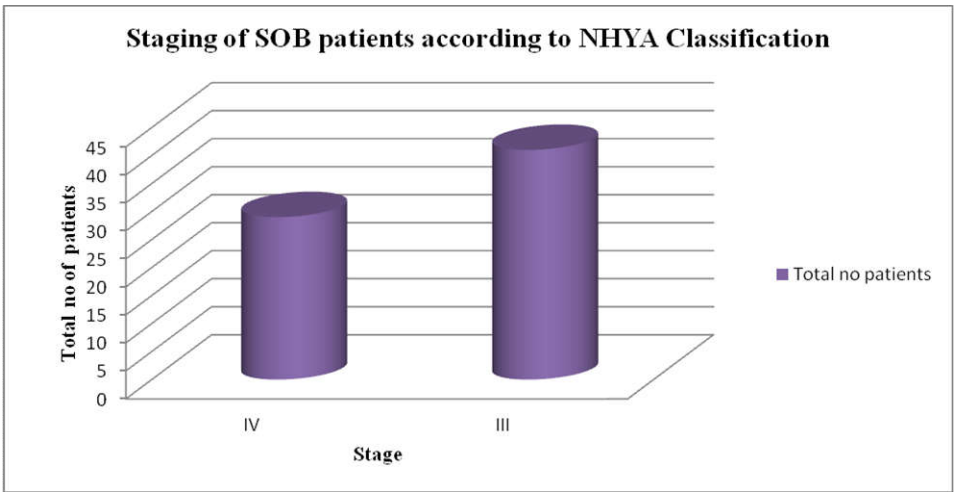


Figure 4: Grouping of SOB patients according to NT-pro-BNP values

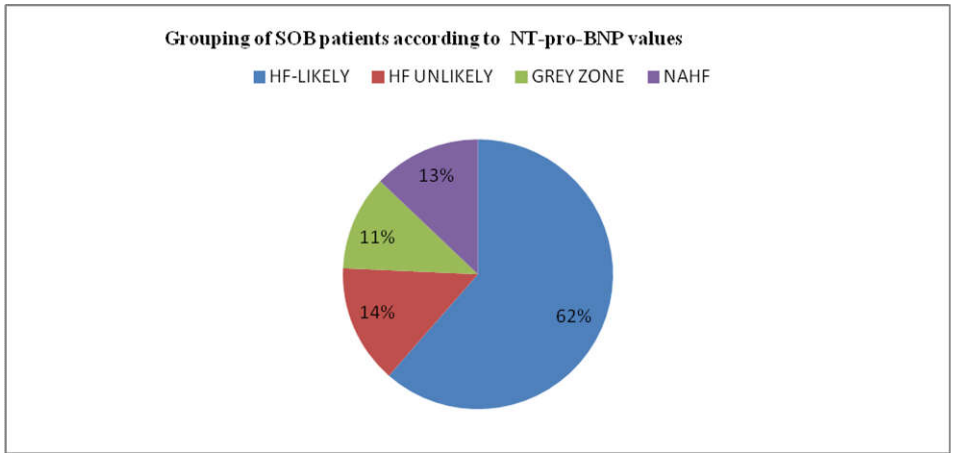


Figure 5: Correlation between grouping of SOB patients and their Mean NT-pro-BNP

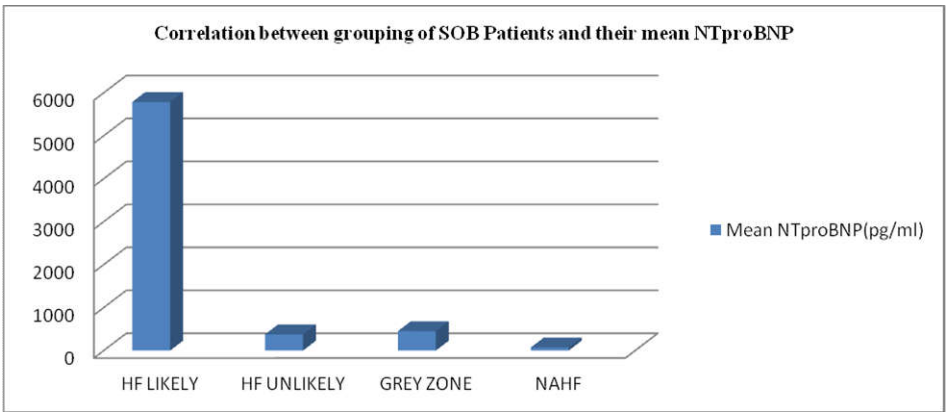


Figure 6: Correlation between grouping of SOB patients and Mean EF%

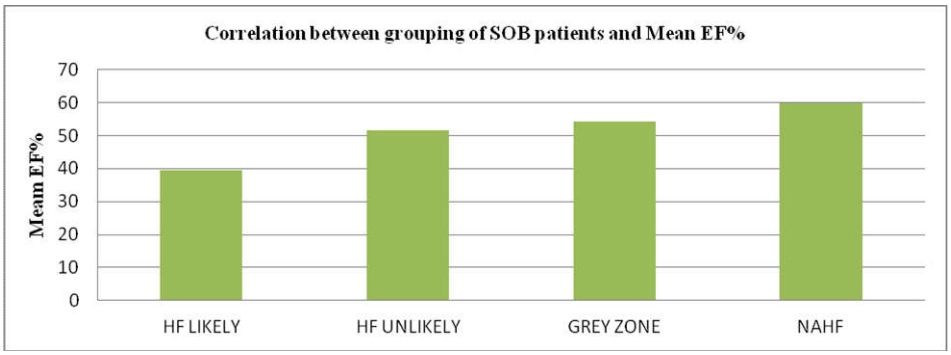


Figure 7: Comparison of HFrEF and HFpEF

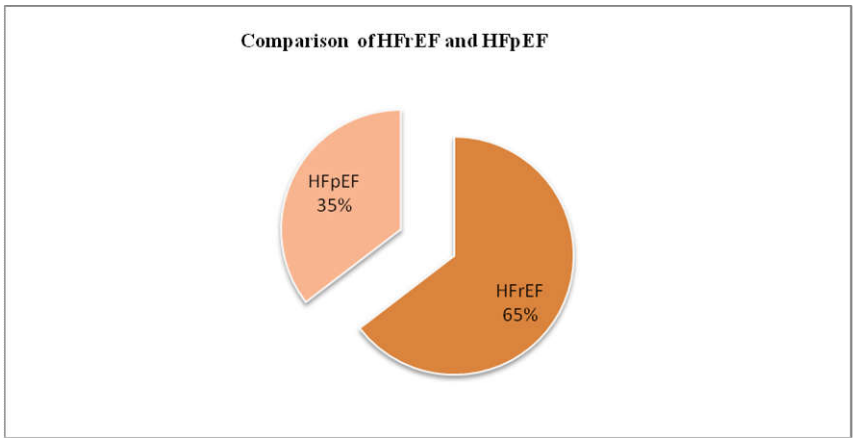


Figure 8: Comparison of NT-pro-BNP value and patient review rate

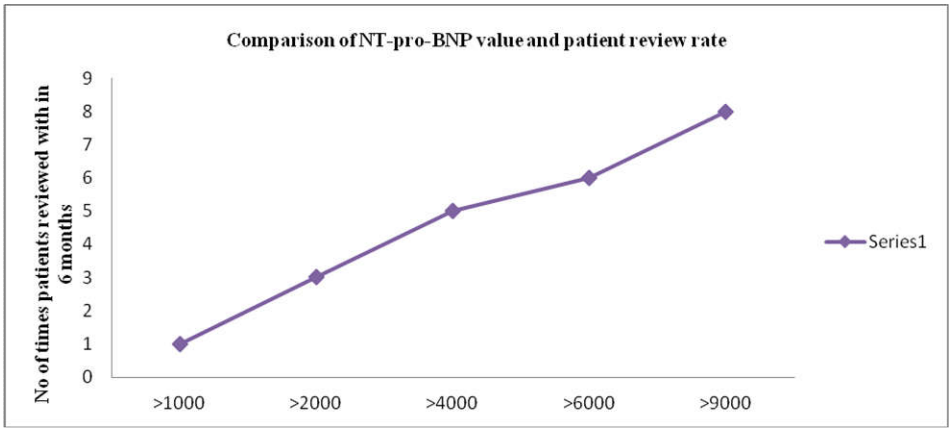


Figure 9: Statistical analysis

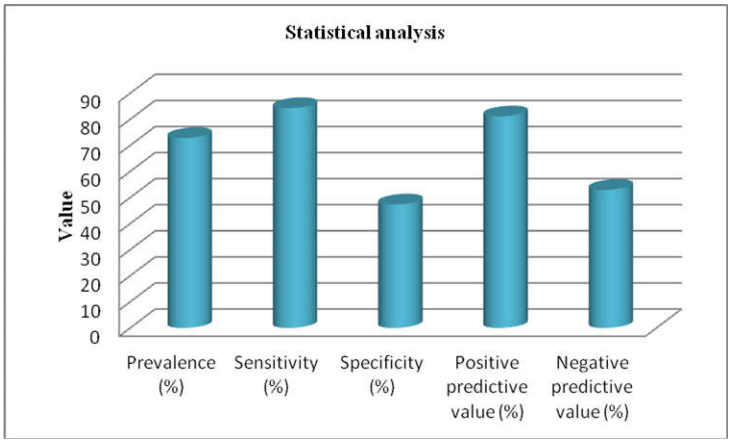
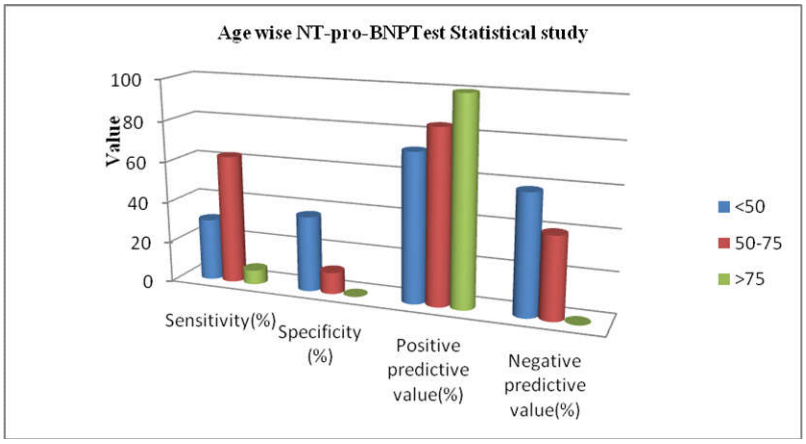


Figure 10: Age wise NT-pro-BNP test statistical study



DISCUSSION:

Shortness of breath is a common clinical condition diagnosed in the emergency room, often has unknown specific causes, and is frequently made complicated by other illnesses. Pulmonary and cardiac diseases are two major causes of dyspnoea, which have high morbidity and mortality rates. Therefore, accurate diagnosis of dyspnoea is essential to prescribe effective treatments and to achieve better patient outcomes.

Echocardiography is the most common tool in evaluating the proper functioning of the heart. However, an expensive machine and specially trained physicians are necessary for implementing echocardiography. Since not many hospitals have such resources in their emergency departments, applications of echocardiography in an emergency setting are often limited. Also, patients with mild heart failure or slightly higher ventricular tension may not show abnormalities in their echocardiography results. Among patients with severe heart failure or dyspnoea, the accuracy of echocardiography may be significantly affected by the patient's body position during the examination. Therefore, fast, specific, and sensitive methods for differential diagnosis of dyspnoea are important in managing the condition of patients and in reducing the mortality rate.

In recent decades, NT-pro-BNP has emerged as a cardiac biomarker of ventricular dysfunction. Many studies have undergone in recent years to investigate and support the role of NT-pro-BNP in identifying the exact cause of shortness of breath, mainly in differentiating between the cardiovascular and non-cardiovascular causes of an SOB.

Overall, in our study, it was found that the NT-pro-BNP values will aid in differentiating the cause of SOB i.e. cardiac cause of SOB or non-cardiac cause of SOB. NT-pro-BNP levels in the cardiovascular

cause of SOB were above the age-related "Rule In" reference level of NT-pro-BNP.

In our study, it was found that as the mean EF % decreases, Mean NT-pro-BNP levels increase non-linearly, and HFrEF has a higher mean NT-pro-BNP value. We also monitored the review rate of patients; the greater the NT-pro-BNP level the greater is the review rate i.e. higher indicates the greater complaints frequently.

The statistical analysis of our study shows that the test has high sensitivity and a high positive predictive value.

CONCLUSION:

In our study, the patients presenting with acute shortness of breath to the emergency department are managed based on their history and physical examination findings, aided by basic laboratory tests and investigations like chest-x-ray, electrocardiogram, and echocardiography. But in some emergencies, it is difficult to differentiate between the cardiac or non-cardiac cause of SOB. To rule out the exact cause of SOB, NT-pro-BNP Test is done. Due to the limited accuracy and availability of current laboratory, clinical criteria in emergency care demands for a sensitive and specific biomarker reflecting the hemodynamic changes due to cardiac conditions of dyspnoea.

In the present study, plasma NT-pro-BNP levels will provide specific information about the cardiac involvement in an acute SOB and so it is of value to clinicians in making the differential diagnosis between the cardiac and non-cardiac cause of SOB. It is also observed that elevated NT-pro-BNP levels correlate with a higher risk of HF.

In our study, we conclude that the plasma concentrations of NT-pro-BNP levels are useful in differentiating the exact cause of SOB. The mean NT-pro-BNP levels were higher in the cardiovascular cause of SOB and were above the age-related "Rule in" reference level of NT-pro-BNP. It also shows that as the NT-pro-BNP level increases the EF% decreases, and the review rate is also increased with an increase in plasma NT-pro-BNP level.

It is a study to improve the awareness among people and physicians about the importance of the NT-pro-BNP test and its role. It is a useful test in differentiating the exact cause of SOB. It is a valuable tool in determining the severity of the disease and prognosis of clinical outcomes in patients with heart failure. Increased NT-pro-BNP levels grossly correlate with the severity of left ventricle dysfunction. It is a good biomarker with high sensitivity and a cost-effective test.

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ABBREVIATIONS:

SOB: Shortness of breathe

COPD: Chronic obstructive pulmonary disease

MI: Myocardial infarction

CHF: Congestive heart failure

NP: Natriuretic peptides

ANP: Atrial natriuretic peptide

BNP: Brain natriuretic peptide

Pro BNP: Pro b-type natriuretic peptide

NT-pro-BNP: N-terminal pro b-type natriuretic peptide

CNP: C-type natriuretic peptide

HF: Heart failure

ACC: American college of cardiology

AHA: American heart association

LVEF: Left ventricular ejection fraction

HFrEF: Heart failure with reduced ejection fraction

HFpEF: Heart failure with preserved ejection fraction

NYHA: New York heart association

AHF: Acute heart failure

NAHF: Non acute heart failure

2D ECHO: 2dimensional Echocardiography

CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE REPORTED