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Role of NT-Pro BNP as a Predictor of Morbidity and Mortality among Patients of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (COPD) with Hypercapnic Respiratory Failure

Yashasvi Tyagi[1], Ghubdee Ramakrishna Vishnu Pant[2]

[1]Post Graduate Resident, Department of Pulmonary Medicine, Teerthanker Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh.

[2]Professor & HOD, Department of Pulmonary Medicine, Teerthanker Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh.

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ABSTRACT

Background: NT-ProBNP is a cardiac biomarker which is seen to increase in patients of AECOPD. This study aims to find the correlation between higher levels of this biomarker in serum and outcomes in terms of length of ICU stay and 30 day mortality in such patients. **Methods:** We enrolled patients in acute exacerbation and subjected them to a series of investigations. Data from 40 of these patients was recorded and subjected to statistical analysis. **Result:** As the mean NTPro BNP increases the ICU stay also increases, When NTProBNP was compared statistically according to ICU stay using anova test, statistically significant difference was seen as $p<0.05$.Mean NTPro BNP was found to be 3356.36±2469.21 and 685.86±791.27 in the subjects who expired and alive respectively with statistically significant difference as $p<0.05$. **Conclusion:** The results of the present study concluded that elevated levels of NT-proBNP predict the need for invasive mechanical ventilation, length of ICU stay and deaths in subjects with AECOPD autonomously of other recognized predictive reasons.

Keywords: COPD, Respiratory Failure.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a global menace, causing poor quality of life and deaths,[1] impacting >5% of the world's population.[2,3] In the US, it has become the 4th reason for mortality, with >one lakh twenty thousand people being killed annualy.[4] Due to its high occurrence and chronicity, COPD leads to regular out department visits, regular admission in hospitals, economic burden, and a prescription for long term medical and supplemental oxygen therapy.[5] The GOLD guidelines has described COPD as:[6]

"COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases".

Chronic airway inflammation changes the structure in the form of small-airways narrowing and parenchymal destruction. This may contribute to mucociliary dysfunction & airflow limitation which is a characteristic of COPD.[6]

Researches have found that more than 50% of people during adulthood with stumpy lung function are unaware regarding the presence of COPD, signifying that, real estimations may be much more.[7] Studies had found that COPD ultimately affects patients' daily activities, varying from 27-63% days limited daily work annually in comparison to adults without COPD.[8]

COPD aggravation is described as: "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD".[9]

Pulmonary infections accounted for 50-70% of COPD aggravations, with environmental pollution being responsible for an additional 10%. Out of all COPD aggravations etiology of approximately 30% are unknown.[10,11] Out of all infections, 45% occurs due to typical bacteria, 5-10 % by atypical bacteria, and 30% by viruses.[12-14] An additional significant issue in ECOPD might be Cardiac dysfunction.[15-17]

COPD might be a significant co-morbidity among subjects having heart disease: recognized among 7-16 % and up to 52% of the subjects with acute MI and heart failure respectively. This leads to increased hospital readmission as well as deaths.[18] As such,

Name & Address of Corresponding Author
Dr. Ghubdee Ramakrishna Vishnu Pant,
Professor & HOD,
Department of Pulmonary Medicine,
Teerthanker Mahaveer Medical College &
Research Centre,
Moradabad, Uttar Pradesh.

subjects having cardiac abnormality co-morbidity and COPD are rarely given β blockers for myocardial dysfunction or β agonists for air tract obstruction [Figure 1].[19-21]

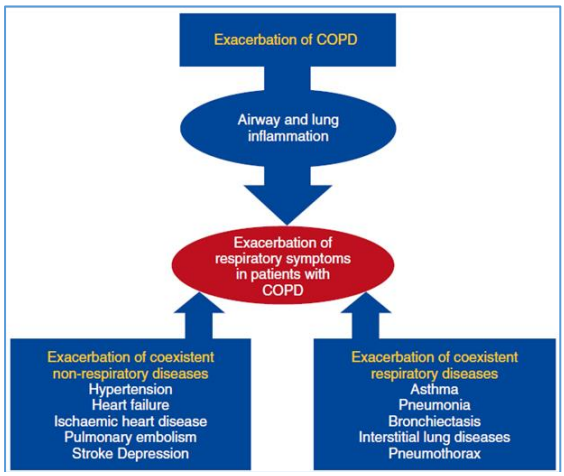


Figure 1: the schema of the primary etiologies leading to the development of exacerbation in C.O.P.D.[21]

The results of earlier researches found a minimum 30% greater risk of cardiovascular deaths among subjects having compromised lung-function, after adjusting for smoking status, age and other conventional cardiovascular risk factors.[22,23] After meticulously reviewing the causes of death, cardiovascular diseases seem responsible for 25% of the deaths.[24]

Heart disease may be found among approximately 55% of subjects admitted due to aggravations of COPD. Moreover, approximately 20% of COPD aggravations might be because of acute non-compensated heart failure and cardiac arrhythmias.[25] Heart failure, ischaemic heart disease, and arrhythmias were linked with poor survival in exacerbations of COPD, mostly with early inpatient death. Previous researches had found that 8-25% of subjects having COPD aggravation have irregular serum cardiac troponin concentrations.[26,27]

It is now clear that heart problem is the leading reason for mortality among subjects with COPD during its various stages. Such links might be because of common risk factors, like cigarette smoking that leads to inflammatory changes. Clinically, distinguishing between respiratory and heart disease as a cause of dyspnea is never easy. In this regard, the analysis of brain natriuretic peptide (BNP) and its fragments might be valuable.[28]

Bold A et al 1981 tested the endocrine heart by infusing anesthetized rats with extracts from atrial tissue. The infusion induced rapid water and sodium renal excretion, lower blood pressure, raised hematocrit. Consequently, this material was logically referred to as the atrial natural variable.[29] Shortly after, this element was isolated and classified as a peptide of 28 residues of amino acids and more correctly referred to as an atrial natriuretic peptide (ANP). The discovery of this new peptide paved the way for a separate but structurally similar peptide to be later identified in the porcine brain: brain natriuretic peptide (BNP).[30] Though it was found that BNP was found to be primarily made in heart, hence the term “brain natriuretic peptide" is now often replaced by" B-type natriuretic peptide.[31]

It has also been found that N-terminal fragments from the cardiac precursor peptides proANP and proBNP circulate in plasma and provide new molecular markers for biochemical detection of heart failure. Physiologically atrial myocytes produce secretory granules for pro BNP, while myocytes of the ventricles don't appear to be developing such granules in the healthy heart.[32]

These peptides (BNP and N-terminal proBNP (NT-pro-BNP) were also found to be high in patients with COPD without heart failure, possibly secreted from both sides of the heart. Cor-pulmonale, hypoxemia, and secondary PAH are some important causes for the right side of the heart to release these natural peptides and also increase the expression of BNP genes.[33]

Multiple pieces of research documented the use of NT-pro-BNP in envisaging the consequences in COPD including early cardiac dysfunction, length of ICU stay (LOS), and 30-day mortality.

Aim:

To study the role of serum NT-Pro BNP levels as a predictor of morbidity and mortality among patients of Acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD) with hypercapnic respiratory failure.

Objectives:

To evaluate the correlation of NT- Pro BNP levels in patients of AECOPD in hypercapnic respiratory failure with respect to-

a) Length of ICU stay.
b) 30-day mortality.

MATERIALS AND METHODS

This prospective observational research was done among subjects either visiting OPD or being admitted (Inpatient Department) in the department of Pulmonary medicine after taking clearance from the ethical committee. The study comprised 40 COPD cases in acute exacerbation having a hypercapnic respiratory failure having >40 years of age of either sex [Figure 1]. COPD's diagnosis was based on GOLD guidelines. Exacerbations have been identified through the aggravation of respiratory symptoms, elevated inflammation markers, and antibiotic and/or oral steroid requirements.

Study duration: 1 year

Type of study: Prospective observational study

Study center: Department of Pulmonary Medicine, TMMCRC

Sample size: 40

Inclusion Criteria:

1. Patients who gave positive consent.
2. Cases of AECOPD of more than 40 years of age of either sex.
3. PaCo2 values in ABG higher than 45 mmHg.

Exclusion Criteria:

1. Any pre-existing cardio-vascular comorbidity like CAD, Stroke, Acute Myocardial Infarction.
2. Symptoms of another acute respiratory condition (like acute asthma) or if COPD exacerbation was not the main reason for hospitalization.
3. Chronic liver disease, chronic kidney disease patients.
4. Active Tuberculosis.
5. ARDS patients.

Case selection:

The data was collected by a preformed structured open-ended questionnaire that was pretested with modifications made prior to its use in the study. Subjects underwent full history, detailed medical review focusing on COPD symptoms, respiratory failure, and heart failure.

Investigations

1. Each subject underwent ECG. Electrocardiography and 2-D Echo was done within 24 hours of the admission to assess the cardiac status and to look for signs of failure and pulmonary hypertension. Any patient showing signs of acute coronary syndrome, MI or Systolic failure was excluded.
2. An arterial blood sample was drawn from the radial artery to analyze for hydrogen ion concentration (pH), the partial pressure of arterial oxygen (PaO2), the partial pressure of arterial carbon dioxide (PaCO2), oxygen saturation and bicarbonate (HCO3) level.
3. N-terminal pro B-type natiuretic peptide (NT-pro BNP) level

   A peripheral venous sample withdrawn and tested for plasma NT-pro BNP level. NT-proBNP was measured with VID(A) S® NT-proBNP2. That uses Enzyme-Linked Fluorescent Assay technique. The cut off value to label as "high" was considered to be 450pg/ml on the basis of the manufacturer settings as governed by the general consensus and previous studies which included general healthy population vs the patients.

   Serum NT-ProBNP levels were noted at the time of admission from a peripheral vein. Patients were managed according to their clinical state and outcomes were noted with respect to the length of ICU stay, need for mechanical ventilation and followed up for 30-day mortality. Any mortality because of a non cardiogenic or respiratory failure cause was excluded for 30-day mortality data.

   Only first admission was registered for patients getting admitted more than once during the study period. The age-adjusted serum NT-ProBNP values were then compared to find any significant correlation if any to the patient outcomes.

   Data was collected and subjected to statistical analysis.

ICU management:

Noninvasive mechanical ventilation (NIV) was applied with an ICU ventilator via an oronasal mask to facilitate respiratory muscle resting in patients with severe dyspnea and tachypnea. Decision for the same was made according to ABG values, such as pH <7.35, pCO2 >45 mmHg, and paO2/FiO2 <200. ABG analysis was performed 2 and 4 hours after the initiation of NIV, at least two times a day. Improvement in dyspnea and alertness, decrease in heart and respiratory rate and PaCO2, increase in pH, rise of SaO2 to 85% or above indicated NIV success.

Patients who had contraindications for NIV application or who did not respond to it and worsening (NIV failure) were immediately intubated and put on mechanical ventilator.

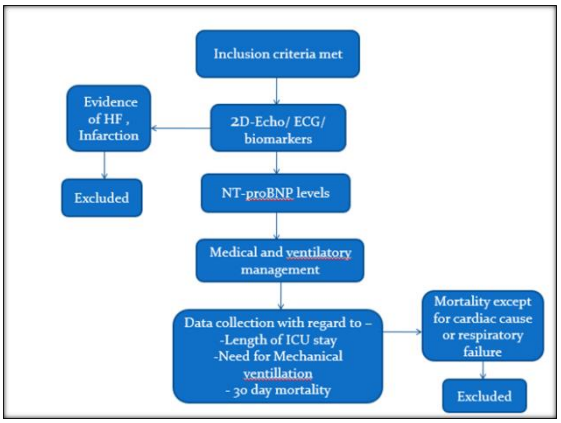
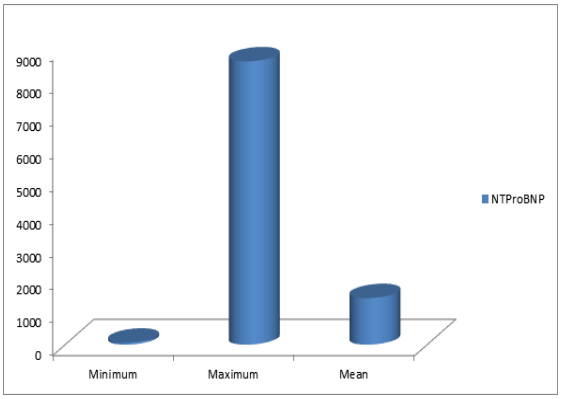


Figure 1: Flowchart of the study

RESULTS

Table 1: Mean distribution of NTProBNP

	Minimum	Maximum	Mean	SD
NTPro BNP	61	8637	1420.25	1863.104

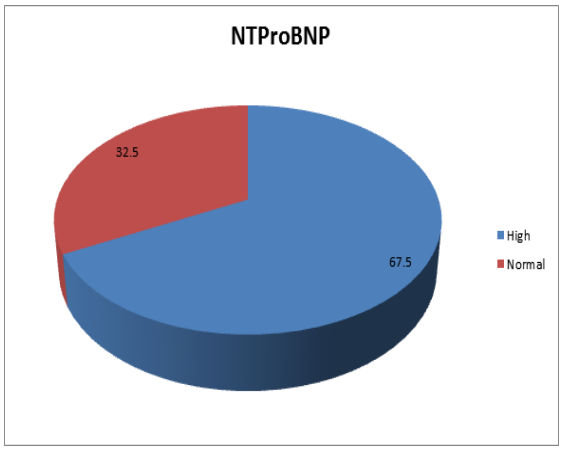


Graph 1: Mean distribution of NTProBNP

The mean NTProBNP of the study population was 1420.25±1863.104 with minimum and maximum NTProBNP of 61 and 8637 respectively [Table 1, Graph 1].

Table 2: Distribution of NTProBNP

Category	N	%
High	27	67.5
Normal	13	32.5

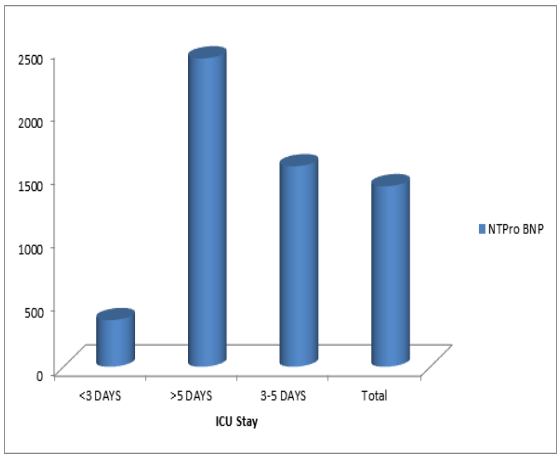


Graph 2: Distribution of NTProBNP

Table 3: ICU Stay in relation to mean NTPro BNP

ICU Stay	N	Mean	SD
<3 DAYS	15	366.73	357.28
3-5 DAYS	11	1576.91	1206.92
>5 DAYS	14	2425.93	2600.94
Total	40	1420.25	1863.11
Anova test		5.51	
p value		0.008*	

*: statistically significant

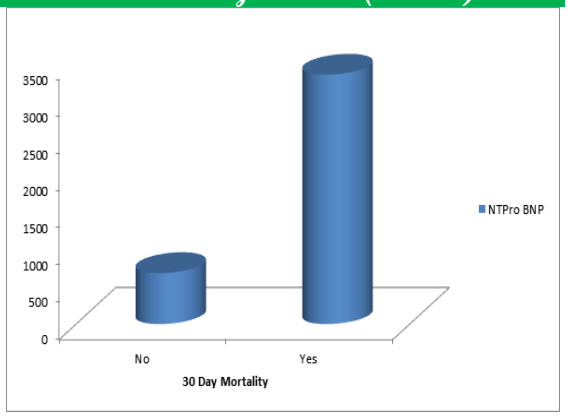


Graph 3: ICU Stay in relation to mean NTPro BNP

Table 4: 30 day mortality in relation to mean NTPro BNP

30 Day Mortality	NTPro BNP	
	Mean	SD
No	685.86	791.27
Yes	3356.36	2469.21
t test	27.53	
p value	<0.01*	

*: statistically significant



Graph 4: 30 day mortality in relation to mean NTPro BNP

High and normal NTProBNP was found in 67.5% and 32.5% of the subjects respectively in the present study [Table 2, Graph 2].

[Table 3, Graph 3] shows the ICU stay in relation to mean NTPro BNP. It can be appreciated from the table that as the ICU stay increases, mean NTPro BNP also increases. When NTProBNP was compared statistically according to ICU stay using anova test, statistically significant difference was noted as $p<0.05$.

[Table 4, Graph 4] shows the 30 day mortality in relation to mean NTPro BNP. Mean NTPro BNP was found to be 3356.36±2469.21 and 685.86±791.27 in the subjects who were expired and alive respectively. When NTProBNP was compared statistically according to the mortality, statistically significant difference was noted as $p<0.05$.

DISCUSSION

COPD is now a leading reason for death and poor quality of life worldwide along with a significant addition to the economic burden. For individual patients, there are some important extrapulmonary pathologies that might add to the graveness of the disease. Airflow restriction, which is not fully reversible, characterizes the pulmonary portion of the disease. Typically, this airflow restriction is associated with an unusual inflammatory response of the lung to gases or noxious particles. A combination of two main components-small airway disease (obstructive bronchiolitis) and parenchymal damage (emphysema)-causes chronic airflow restriction in COPD, with relative contributions varying from individual to individual.[34]

Compared to the general population, these symptoms are clearly more common in COPD patients, even after adjustment for cigarette smoking and other important confounders.[35] In fact, heart disease in such patients sometimes goes undiagnosed. This might be because of signs and symptoms of heart failure and MI that might impersonate AECOPD, but also to the classic signs and symptoms of MI, i.e. Changes in ECG and chest

pain during AECOPD are poorly associated with myocardial injury.[36]

Therefore the current study was done to evaluate the correlation between serum NT-Pro BNP levels and outcomes among patients of AECOPD with hypercapnic respiratory failure. The study comprised of 80% males and 20% females. 52.5% of the subjects were having age between 56-65 years. The mean age of this study population was 63.10±8.72 yrs.

Mean NTProBNP

The mean NTProBNP of the study population was 1420.25±1863.104 with minimum and maximum NTProBNP of 61 and 8637 respectively in the present study. High and normal NTProBNP was found in 67.5% and 32.5% of the subjects respectively in the present study. Approximately similar results were revealed by Muhammad Adrish et al,[37] where NTProBNP was higher among 62% of the subjects and normal among 38% of the subjects.

ICU stay and need for invasive mechanical ventilation in relation to mean NTPro BNP

Mean NTPro BNP was found to be 2360.87 in the subjects who undergo invasive mechanical ventilation while it was 855.88 among the subjects who did not require invasive mechanical ventilation. When NTProBNP was compared statistically according to the need for invasive mechanical ventilation, statistically it was also found to be significant. In the current study, as the ICU stay increases, the mean NTPro BNP also increases. When NTProBNP was compared statistically according to ICU stay using ANOVA test, it was found to be statistically significant as $p<0.05$.

30-day mortality in relation to mean NTPro BNP

Mean NTPro BNP was found to be 3356.36±2469.21 and 685.86±791.27 in the subjects who were expired and alive respectively. When NTProBNP was compared statistically according to the mortality, it was found to be statisticallysignificant as $p <0.05$ in the present study. Catherina L Chang et al,[38] reported that in the unselected group of individuals who were admitted to the hospital with COPD exacerbations, there were elevated NT-proBNP, being strongly associated with increased early mortality. Patients with NT-proBNP abnormalities had a 15-fold higher 30-day mortality compared to patients with normal values. It is unclear the pathophysiological mechanisms that underlie these derangements in such biomarkers, and how they relate to an increase in deaths in COPD exacerbations. Muhammad Adrish et al,[37] reported that patients with AECOPD with higher levels of NTpro-BNP were highly likely to be admitted to ICU than patients with normal levels of NT-pro-BNP (70% vs 43%), although the total ICU LOS was similar between the two classes. Nevins et al,[39] assessed 60 COPD aggravated patients who needed MV; the mean length of MV and median LOS were 8.9 days and 14 days respectively. Patients having higher levels of NTpro-BNP also had a longer length of stay than those with NTpro-BNP levels within the normal range, regardless of them requiring ICU admission or not.

The benefits of this research include the prospective design. This is the first time, to our knowledge, that ventricular overload markers (NT-proBNP) are together tested in a population of subjects having acute COPD exacerbations specifically presenting in hypercapnic respiratory failure. No subjects were diagnosed with acute coronary syndromes or acute heart failure medically or previously treated. Finally, since there are no specific guidelines as of now regarding comprehensive management of AECOPD with Cardiac involvement, this study will provide data for any such future prospects by researchers and clinicians.

CONCLUSION

The results of the present study concluded that elevated levels of NT-proBNP predict the need for invasive mechanical ventilation, duration of ICU stay and deaths in subjects with AECOPD autonomously of other recognized predictive reasons. The main patho-physiological foundation of this relation is still unidentified, still, the outcomes strongly specify the significance of heart abnormality among these subjects. NT-proBNP may be used as an available, valuable, low-cost, and noninvasive predictor for the severity grading of COPD exacerbations, specifically for patients with hypercapnic respiratory failure. NT-proBNP is higher in hospital admitted patients with AECOPD who are admitted to the ICU. Therefore NT-proBNP might assist practitioners to evaluate severity and prospects in exacerbations of COPD, still more studies are required to find if they affect treatment or not.

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