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STUDY OF BRAIN NATRIURETIC PEPTIDE LEVELS IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

INTRODUCTION: Chronic Obstructive Pulmonary Disease (COPD) is currently the fourth leading cause of death in the world.Acute exacerbation of COPD are most commonly triggered by respiratory infections predominantly viral although bacterial infections as well as environmental triggers can initiate these events.Recent studies have indicated.B-type natriuretic peptide(BNP) is a valuable asset in predicting the severity of chronic obstructive pulmonary disease and outcomes as well.

OBJECTIVES: The objectives of this study are to measure the levels of Brain Natriuretic Peptide (BNP) in patients experiencing acute exacerbations of chronic obstructive pulmonary disease (COPD) and to evaluate the relationship between BNP levels, the staging of COPD, and in-hospital outcomes.

METHODOLOGY: The Study is a hospital based prospective study conducted on 110 patients presenting with Acute exacerbation of COPD satisfying inclusion and exclusion criteria admitted in hospitals attached to Bangalore Medical College & Research Institute. All necessary investigations were done.Plasma BNP levels were measured during initial presentation and patients were followed up until discharge or death.

RESULTS: Among 110 patients with acute exacerbation of COPD,20 (18.2%) were females and 90 (81.8%) were males. The mean plasma BNP level was 121.31 pg/ml (SD-48.29).The present study shows that BNP levels in acute exacerbation of COPD increases as the severity of COPD increases (r-0.786) (p= <0.01). The mean duration of hospitalization was 5.18 days. The mean BNP was higher in patients who were managed with non invasive (163.7pg/ml) and invasive ventilation(271.7pg/ml) than on just oxygen supplementation via face masks (107.0 pg/ml).BNP levels during acute exacerbation was significantly higher among non-survivors (286.7pg/ml) than survivors (119.8pg/ml).

INTERPRETATION AND CONCLUSION:BNP levels are elevated during acute exacerbation of COPD and can be used as an indicator of severity of COPD exacerbations. BNP levels are can be used for prediction of poor prognosis and mortality during acute exacerbation of COPD.

KEY WORDS: Chronic Obstructive Pulmonary Disease; Acute Exacerbations of Chronic Obstructive Pulmonary Disease; B-type natriuretic peptide

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is currently the fourth leading cause of death in the world.(1) It also is the ninth leading in the global years of life lost (YLLs) ranks. COPD today is one of the most important public health problems that can be both prevented and treated.The Global Burden of Disease Study reports a prevalence of 251 million cases of COPD globally in 2016.As per World Health Organization, it is estimated that 3.17 million deaths were caused by the disease in 2015 (5% of all deaths globally in that year). With most deaths occurring in low- and middle-income countries.(2)

COPD is a multifactorial disease and has multisystemic manifestations. Although smoking is one of the most common risk factor associated with COPD, other genetic factors as well as environmental factors play a key role. COPD is now widely accepted as a heterogeneous and multisystemic disease.

GOLD defines Acute exacerbation of COPD as acute worsening of respiratory symptoms that require additional therapy.(1) The predominant symptom being increased dyspnoea, other symptoms include increased sputum purulence and volume, increased cough and wheeze. Exacerbations are most commonly triggered by respiratory infections predominantly viral although bacterial infections as well as environmental triggers can initiate these events. B-type natriuretic peptide, which is also called brain-type natriuretic peptide (BNP), was isolated from porcine brain in 1988. However, it was soon found to originate mainly from the heart, representing a cardiac hormone. It is a 32-amino acid polypeptide synthesized and secreted predominantly from the right and left ventricles. The main stimulus for BNP secretion is ventricular stress with pressure or volume overload. Other triggers of BNP secretion are proinflammatory cytokines such as IL-1β, TNF-α, and IL-6.(3,4) Recent studies have indicated BNP is a valuable asset in predicting the severity of chronic obstructive pulmonary disease and outcomes as well.

Objectives

1. To estimate the BNP levels in acute exacerbation of chronic obstructive pulmonary disease
2. To assess the correlation between BNP levels and staging of COPD, in hospital outcomes.

Methodology

The Study is a hospital based Prospective study in a tertiary care referral hospital. After obtaining ethical clearance and approval from the Institutional Ethics Committee of BMCRI, written informed consent taken from the patients. Clinical examination and investigations was done and Data collected using proforma.Blood samples were obtained at the initial examination, and plasma BNP levels were measured.Staging of COPD done using GOLD criteria . Outcome was assessed using various measures given below.

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Assessment tools:

Classification Of Airflow Limitation Severity in COPD (Based on Post bronchodilator FEV_1)[1]

In patients with $FEV_1/FEC < 0.70$		
GOLD 1	**Mild**	**$FEV_1 \geq$ 80 % Predicted**
GOLD 2	**Moderate**	**50% $\leq FEV_1 \geq$ 80% Predicted**
GOLD 3	**Severe**	**30% $\leq FEV_1 \geq$ 50% Predicted**
GOLD 4	**Very Severe**	**$FEV_1 <$ 30 % Predicted**

Outcome measures:

1. Noninvasive ventilation
2. Invasive mechanical ventilation
3. Failure of NIV (continued hypoxemia, severe respiratory acidosis, and/or signs of clinical distress, and all these patients who receive subsequent endotracheal intubation and mechanical ventilation)
4. Reintubation at 48 hours,
5. Duration of NIV and/or MV,
6. Length of stay in the ICU and in the hospital
7. In-hospital mortality.

STATISTICAL ANALYSIS:

Data was entered into Microsoft excel data sheet and was analysed using SPSS 24 version software.

RESULTS AND OBSERVATIONS

It was observed that t maximum number of patients in our study were more than 50 years of age with a mean age of 62.42 years (SD -10.79). The lowest age encountered was 30 years whereas the oldest patient was 88 years in our study.The study had20 (18.2%) females and 90 (81.8%) male. The male to female ratio (M:F) was 4.5:1.In our study population 27 (25 %) individuals were non-smokers and 83 (75%) individuals were smokers. The average pack years among the smokers being 39 (SD – 18.08) pack years.Among the 110 patients, 18 (16.36%) had hypertension, 20 (18.18%) had diabetes mellitus, 3 (2.72%) had hypothyroidism and 70 (63.63%) patients had no comorbidities.

Out of the 110 patients, 26 (23.64%) patients presented with cough, 36 (32.72 %) patients presented with breathlessness and 48 (43.64 %) patients had both cough and breathlessness.Out of the 110

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patients, 21 (19.09%) patients presented with MMRC grade 1, 46 (41.81%) patients presented with MMRC grade 2, 36 (32.73) patients presented with MMRC grade 3 and 7 (6.36%) patients presented with MMRC grade 4.

In our study out of 110 Chronic Obstructive Pulmonary Disease patients 13 (11.82%) patients belonged to GOLD stage 1, 49 (44.54%) belonged to GOLD stage 2, 39 (35.45) belonged to GOLD stage 39 and 9 (8.18%) belonged to GOLD stage 4.The mean brain natriuretic peptide levels among the 110 individuals in our study was found to be 121.31pg/ml (SD-48.29) .BNP levels in acute exacerbation of COPD increased as the severity of COPD increased. (r-0.786) (p= <0.01) (Table 1)

		BNP (in pg/ml)			
		Mean	Standard Deviation	r value (pearson correlation)	p value
GOLD STAGING	1	69.5	15.9	0.786841	<0.01*
	2	100.5	19.5		
	3	140.1	35.3		
	4	228.2	39.9		

*Correlation is significant at the 0.01 level (2-tailed).

Table 1

		BNP			
		Mean	Standard Deviation	r value (pearson correlation)	p value
MMRC GRADING	0	84.6	18.2	0.486953	<0.01
	1	89.7	22.2		
	2	118.2	40.9		
	3	125.9	40.5		
	4	217.8	62.1		

*. Correlation is significant at the 0.05 level (2-tailed).

TABLE 2

The mean BNP value increases as the MMRC grading increases (Table 2). Among MMRC grade 0 patients mean BNP value was 84.6 pg/ml (SD - 18.2). The mean BNP value in MMRC grade 1 patients was 89.7 pg/ml (SD- 22.2). The mean BNP value in MMRC grade 2 patients was 118.2 pg/ml (SD-40.9). The mean BNP value in MMRC grade 3 patients was 125.9 pg/ml (SD-40.5). The mean BNP value in MMRC grade 4 patients was 217.8 pg/ml (SD-62.1)

In the present study there is a positive correlation between pack years among smokers (n=77) and BNP levels during acute exacerbation of COPD. The above graph shows that as the pack years

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increase the BNP levels during acute exacerbation of COPD also increases and is statistically significant. (r= 0.289) (p= 0.011)

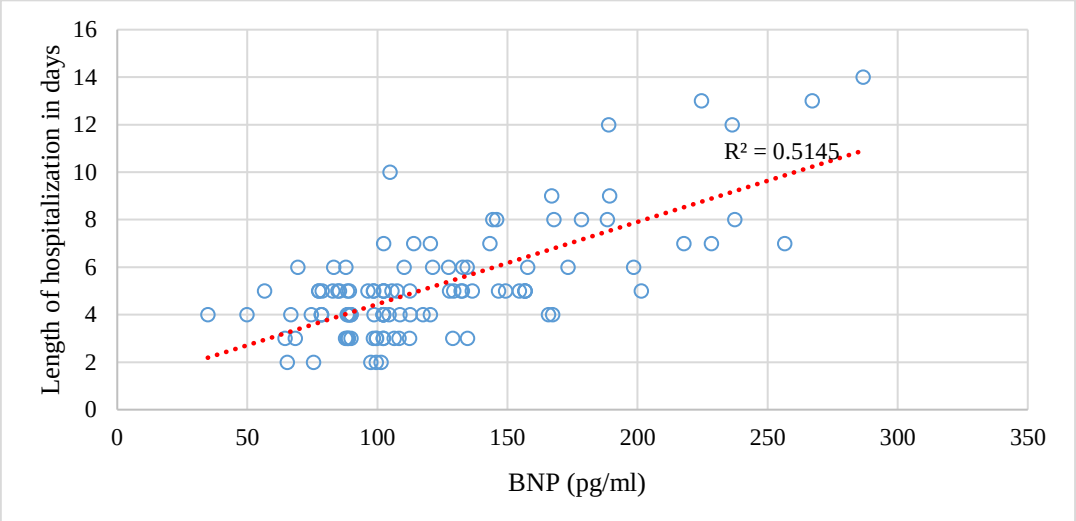

FIGURE 1

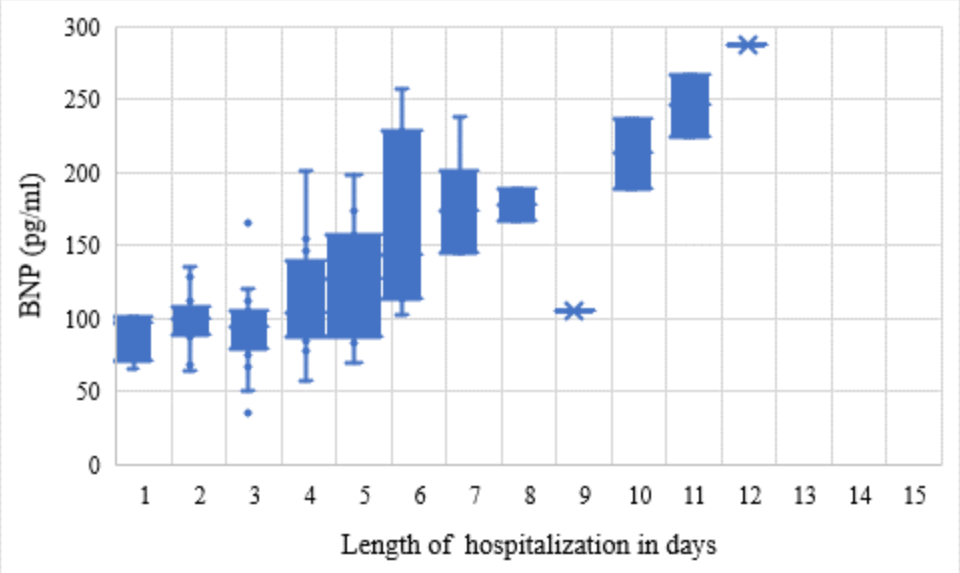

FIGURE 2

The study found a positive correlation between BNP levels during acute exacerbation of COPD and length of hospitalization.(Figure 1,2))The mean duration of hospitalization was 5.18 days. The pearson correlation coefficient between BNP levels during acute exacerbation of COPD and length of hospitalization is r= 0.717313 (p= <0.01).

	BNP Mean (pg/ml)	One way ANOVA f	P value
OXYGEN	107.0	36.052359	<0.01
NON INVASIVE VENTILATION	163.7		

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INVASIVE VENTILATION	271.7		

TABLE 3

Among the 110 patients 86 patients (78.2%) were managed with oxygen supplementation via face mask, 22 (20%) patients were managed with non-invasive ventilation and 2 (1.8%) patients were managed with invasive ventilation. The mean BNP was higher in patients who were managed with non invasive and invasive ventilation and is statistically significant. (Table 3)

	BNP Mean (pg/ml)	One way ANOVA f	P value
DISCHARGE (n=108)	119.8	13.155	<0.01
DEATH (n=2)	286.7		

TABLE 4

Among the 110 patients, 108 (98.2%) patients were discharged after treatment and 2 (1.8%) patients succumbed to death. BNP levels during acute exacerbation is significantly higher among non-survivors.(Table 4)

DISCUSSION

The mean age of the study population was 62.42 years(SD -10.79), maximum number of patients in our study were more than 60 years of age (54.54%). The least age encountered was 30 years whereas the oldest patient was 88 years in our present study series. The age group in our study is slightly lower compared to the study of Nishimura et al (2014) (75.4±7.6) with a similar study design.(5) Another similar study by Abdelnaby NK et al (2019) had a mean age of 62.9±6.6 years comparable to our study.(6)In the present study 20 (18.2%) patients of the study population were females and 90 (81.8%) were males.The male to female ratio (M:F) is 4.5:1.A similar sex distribution was found in the study by Abdelnaby NK et al (2019) with a male to female ratio (M:F) of 4.5:1.(6)

In the present study population, 27 (25 %) individuals were non-smokers and 83 (75%) individuals were smokers. The average pack years among the smokers being 39 (SD – 18.08) pack years.Nishimura et al (2014) study on BNP had a mean pack year of 76±41.(5)Abdelnaby NK et al (2019) had a mean pack year of 52.5±13.7 years. Our study population had a slightly lower pack years when compared to the other studies.(6)

Among the 110 patients, 18 (16.36%) had hypertension, 20 (18.18%) had diabetes mellitus, 3 (2.72%) had hypothyroidism and 70 (63.63%) patients had no comorbidities. Majority of the patients had no comorbidities.Patients presented with both cough and breathlessness most commonly. In the present study patients' maximum patients presented with MMRC grade II-III symptoms. Similarly, majority of the patients belonged to COPD stage II and stage III in the present study.However in another similar study by Stolz et al (2008) BNP levels did not discriminate between different GOLD classes and exacerbation.(7)

In the present study the mean brain natriuretic peptide levels were found to be 121.31pg/ml (SD-48.29) in patients with acute exacerbations of COPD. In a similar study by Nishimura et al (2014) the mean brain natriuretic peptide levels were found to be 126.8pg/ml (SD- 177.5), which correlates with our present study.(5) Another study by Abdelnaby NK et al (2019) the mean BNP levels were 204.0pg/ml slightly higher when compared to the present study.(6)

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In our study there is a positive correlation between pack years and BNP levels during acute exacerbation of COPD with a correlation coefficient of 0.289.In a similar study by Abdelnaby NK et al (2019) there is a positive correlation between pack years and BNP levels during acute exacerbation of COPD with a correlation coefficient of 0.533.(6)

In the present study 86 patients (78.2%) were managed with oxygen supplementation via face mask, 22 (20%) patients were managed with non-invasive ventilation and 2 (1.8%) patients were managed with invasive ventilation. In the study by Nishimura et al (2014) similar results was found with 51 (83.6%) managed with oxygen supplementation via face mask, 23 (37.7%)patients were managed with non-invasive ventilation and 1 (1.6%)patients were managed with invasive ventilation.(5) However in a study by Refaie et al the BNP level was elevated in both intubated and non intubated groups with COPD exacerbation and it was not related to the severity determined by the need for mechanical ventilation.(8)

The mean length of hospitalization was 5.18 days in our study population. In a similar study by Nishimura et al (2014) the mean length of hospitalization was 21.5 days, higher than our present study.(5) Another study by Abdelnaby NK et al (2019) the mean length of hospitalization was 8.5 days similar to our study.(6)In another similar study by Stolz et al (2008) median length of hospital stay was 9 days.(7)There is apositive correlation between BNP levels during acute exacerbation of COPD and length of hospitalization in our present study.In a study by Adrish et alpatients with elevated NT-pro-BNP levels were more likely to require intensive care (63% vs 43%) and had a longer hospital length of stay . There were no differences noted in the study in the need for non-invasive positive pressure ventilation or mechanical ventilation or in regard to in-hospital mortality.(9)

The result of this study showed that the serum BNP level is significantly elevated as the severity of COPD increases. The mean BNP was higher in patients who were managed with non-invasive and invasive ventilation. In the study done by Abdelnaby NK et al (2019) mean BNP was significantly elevated in patients admitted in ICU (835 pg/ml) when compared to patient admitted in wards (67.5 pg/ml).(6) Similarly, our study showed that increased BNP is associated with worse outcome. There were 2 (1.8%) deaths among the 110 patients. In the study done by Nishimura et althere were 2(3.4%) deaths, similar to our study.(5) In the study done by Abdelnaby NK et al (2019)89 there were 6(6.8%) deaths, higher than that of our present study.(6) The mean BNP among survivors was 119.8 pg/ml and among non survivors was 286.7 pg/ml in our study. In the study done by Nishimura et al BNP levels were found to be significantly higher in patients with unsuccessful discharge (median - 260.5 pg/ml). (5)In another similar study by Stolz et al (2008) BNP levels were significantly higher in patients requiring ICU treatment and correlated with the duration of the ICU and in-hospital stay.(7)In asimilar study done by Bucsa et alBNP level was significantly higher in severe exacerbations compared with moderate and mild forms.(10)

Among the other parameters age, urea and creatinine shows statistically significant positive correlation with BNP levels during acute exacerbations. FEV1/FVC had statistically significant negative correlation with BNP levels during acute exacerbations. Stolz et al (2008) study showed significant correlations between BNP levels on hospital admission and age, C-reactive protein and procalcitonin.(11)In another study by Bozkanat et al BNP levels were significant in diagnosis of cor pulmonale in patients with COPD.(12)

CONCLUSION

1. BNP levels are elevated during acute exacerbation of COPD and can be used as an indicator of severity of COPD exacerbations.
2. There is a positive correlation between pack years and BNP levels during acute exacerbation of COPD.
3. BNP levels are can be used for prediction of prolonged hospital stay, requirement for invasive ventilation.

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4. BNP levels are can be used for prediction of prognosis and mortalityduring acute exacerbation of COPD.

LIMITATIONS

1. Serial monitoring of BNP levels could have yielded better result.The present analysis has its ownlimitations, in its ability to elucidate, whether decreasing BNP levels would correlate with better outcomes.
2. Considering that the subjects were taken from a single hospital facility, we cannot make generalization based on the result.
3. Lack of a control group with BNP levels with stable COPD were not compared in this study.

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