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B Type Natriuretic Peptide as a Prognostic Marker in Acute Exacerbation of Chronic Obstructive Pulmonary Disease, Asthma and Pneumonia

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Authors' contributions

This work was carried out in collaboration between all authors. Author SP wrote manuscript and analyzed the data. Authors SP and FH formulated the hypothesis. Authors RV, Dr. Saurav P. and Swati P. were involved in data collection. Authors FS, DE and JQ were involved in manuscript writing and approval. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Acute exacerbation of chronic obstructive pulmonary disease (COPD)/asthma and pneumonia are the major reason for the hospitalization and emergency room visit in the US. In 2011, chronic lower respiratory diseases and pneumonia were among top ten causes of mortality in 2011. Hospitalization and emergency room visit due to these morbidities account for high health care cost. B type natriuretic peptide level (BNP) of more than 400 is a prognostic and diagnostic marker for congestive heart failure (CHF). However, BNP can be raised in other conditions and significance of it is unknown.

Aims: To identify role of BNP in prognosticating asthma/copd exacerbation and pneumonia.

Study Design: Retrospective study.

Place and Duration of Study: Emergency room and Hospital at Interfaith Medical Center between January 2008 to July 2012.

Methodology: We retrospectively reviewed the charts of the patients admitted to our hospital with diagnosis of asthma, pneumonia and COPD in whom CHF had been ruled

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out. We collected data about BNP, length of stay, mortality and other demographic data.
Results: 461 patients met inclusion criteria - 28% had asthma, 31% had COPD exacerbation and 41% had pneumonia. 21% patients had BNP > 100 pg/ml. Patient with BNP > 100 pg/ml had higher mortality as compared to patients with BNP < 100 pg/ml- 19% and 2% respectively (*P* value .0001). Mean length of stay for BNP > 100 group and BNP < 100 groups were 8.7 and 5.56 days. (*P* value .0001). These differences were seen across the subgroups of asthma, COPD and Pneumonia. Patients with BNP > 100 pg/ml were more likely to required ICU care as compared to patients with BNP < 100 pg/ml – 30% vs 9% (*P* value .0001).
Conclusion: Our study suggests that BNP can be used as prognostic marker for mortality and severity of the disease in Asthma, COPD and Pneumonia. Higher BNP levels can also predict the prolong length of stay in the hospital.

Keywords: B type natriuretic peptide; length of stay; mortality; intensive care unit; asthma; chronic obstructive pulmonary disease; pneumonia.

1. INTRODUCTION

Acute pulmonary diseases are major cause of morbidity and hospitalization. Chronic obstructive pulmonary disease (COPD) is a major cause of disability, and it's the fourth leading cause of death in the United States. Currently, more than 12 million people have diagnosed COPD with an additional 12 million with undiagnosed COPD [1]. During 2009, 2.1 million patients visited emergency room with asthma exacerbation [2]. In 2011, approximately 50,000 patients died of pneumonia as a primary diagnosis [3]. Considering high cost of hospitalization and mortality rates associated with severe exacerbation, a prognostic tool is required to stratify patients based on which length of hospitalization and ICU /medical ward management can be predicted.

B type Natriuretic Peptide (BNP) has been studied in several studies as prognostic marker for various outcomes of chronic lung diseases. Ventricular muscles secrets pro BNP in response to volume or pressure overload. Pro BNP is converted to BNP and N terminal BNP. BNP has diuretic, natriuretic and hypotensive effect and inhibits renin angiotensin system, endothelin secretion and systemic and renal sympathetic activity. Various studies have shown very excellent diagnostic utility on BNP in diagnosis of congestive heart failure (CHF). However, BNP values are increased although a bit to lesser extent than CHF in other conditions like sepsis, pulmonary embolism and chronic obstructive pulmonary disease with pulmonary hypertension etc [4].

In congestive heart failure, elevated level of BNP is associated with worse prognosis during admission and after discharge from the hospital and is used as prognostic tool to direct the therapy [5,6,7]. Very few studies are done to investigate the role of BNP for prognosticating non cardiac conditions. Goals of our study were 1) To investigate the role of BNP in determining severity of COPD, Pneumonia and Asthma 2) To identify the patient at high risk for mortality using BNP value 3) To identify the role of BNP in determining length of stay in the hospital.

2. MATERIALS AND METHODS

We retrospectively reviewed patients admitted to our hospital from January 2008 to July 2012 with diagnosis of acute exacerbation of bronchial asthma, acute exacerbation of COPD or pneumonia. Patients were included in study if they had a baseline BNP done on admission. Other inclusion criteria for the patients with above mentioned diagnosis include 1) Age of 18 year or older 2) no evidence of renal failure 3) Echocardiogram demonstrating absence of systolic and diastolic dysfunction within 6 months. Patients were excluded from the study if their BNP was > 400 pg/ml or were in septic shock. 461 patients met criteria for study.

COPD exacerbation was defined by Global initiative for chronic Obstructive Lung Disease (GOLD) criteria: Diagnosed by acute change in the symptoms (Dyspnea, cough and/or sputum production) that is beyond normal day to day variation in a patient with known or suspected COPD. Asthma exacerbation was defined by acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness—or some combination of these symptoms in a known asthmatic patient. Pneumonia was defined as acute infection of lung parenchyma from a community

BNP levels for each patient were collected. Also length of the hospital stay for each patient was obtained. Data of ICU/ward management and final outcome of each patient were obtained. ECHO report of each patients were reviewed.

Patients were divided into >100 pg/ml and <100 pg/ml. Categorical data were analyzed using either Chi square test or Fisher's Exact test. For analysis of continuous variable in two groups, student's T test was used. For 3 or more groups, Analysis of Variance test was used to analyze continuous variables. Significance level was 0.05. Patients were subdivided in asthma, COPD and Pneumonia subgroup and statistical analysis was done in subgroups. Statistical analysis software SPSS version 21 was used to analyze the data.

3. RESULTS

Table 1 shows baseline demographic characteristics of the patient. Mean age was 59.5 years with standard deviation (SD) of 15.82 years. Mean age (SD) in Asthma, COPD and Pneumonia subgroups were 44.75 (11.97), 63.8 (13.35) and 59.62 (16.17) years respectively. 50% of the patients were male. 442 patients (96%) were African American. 120 patients (26%) had asthma, 143 patients (31%) had COPD and 188 patients (41%) had pneumonia.

Table 1 also shows demographics by BNP level. 364 patients (79%) had BNP <100 pg/ml. 82% of male and 76% of female patients had BNP level <100 pg/ml. Mean age were 57.4 year and 67.3 year for the group BNP <100 and >100 pg/ml respectively. 79% of African American patients and 73% of non African American patients had BNP <100 pg/ml.BNP level was <100 pg/ml in 85% of asthma patients, 74% of COPD patients and 76% of pneumonia patients. Thus BNP >100 group had higher proportion of patient with older age and less likely to had diagnoses of Asthma.

Table 1. Demographic Characteristics

	Subgroup (N, % of total)	BNP < 100 N (%)	BNP >100 N (%)	*P* value
Total	461	364 (79%)	97 (21%)	
Mean age		57.4	67.3	.0001
Sex	Male (n=231, 50%)	190 (82%)	41 (18%)	.08
	Female (n=230, 50%)	174 (76%)	56 (24%)	
Race	African American (n=442, 96%)	350 (79%)	92 (21%)	.57
	Non AA (n=19, 4%)	14 (74%)	5 (26%)	
Diagnosis	Asthma (n=130, 28%)	115 (88%)	15 (12%)	.0001
	COPD (n= 143, 31%)	106 (74%)	37 (26%)	
	Pneumonia (n= 188, 41%)	143 (76%)	45 (24%)	

Table 2 shows mean BNP and mean LOS for overall and by subgroups. Overall mean BNP was 75.12. Mean BNP for asthma, COPD and Pneumonia patients were 55.1, 86.96 and 79.96 pg/ml respectively. Mean Length of stay was 6.22 days. Mean length of stay for asthma, COPD and Pneumonia patients were 4.55, 6.52 and 7.11 days respectively.

Table 2. Mean BNP and Mean length of stay in different subgroups

	Asthma	COPD	Pneumonia	*P* value	Overall
Mean BNP (SD)	55.10 (67.19)	86.96 (83.42)	79.96 (82.72)	.002	75.12 (67.19)
Mean LOS (SD)	4.55 (2.79)	6.52 (4.85)	7.11 (8.78)	3.002	6.22 (6.48)

Table 3 shows that 29 out of 97 patients (30%) BNP >100 requires ICU admission as compared to 32 out 364 patients (9%) with BNP value <100 pg/ml (*P*= 0.0001). 18 out of 97 patients (19%) with BNP >100 pg/ml expired as compared to 7 out of 364 patients (2%) with BNP <100 (*P* = .0001). Mean length of stay for the group with BNP >100 pg/ml 8.7 days as compared to 5.56 days for the group with BNP <100 pg/ml (*P* = .0001)

Table 3. Mean length of stay, outcome and required intensity of care in sample population

		Overall		
Characteristics		**BNP < 100 N=364 (%)**	**BNP > 100 N=97 (%)**	***P* value**
Place	ICU	32 (9%)	29 (30%)	.0001
	Floor	332 (91%)	68 (70%)	
Outcome	Expired	7 (2%)	18 (19%)	.0001
	Survival	357 (98%)	79 (81%)	
Mean LOS		5.56	8.7	.0001

Subgroup analysis showed similar results in all groups. Table 4 shows that 3 out of 15 (20%) patients with BNP > 100 required ICU care as compared to 5 out of 115 (4%) with BNP <100 (Fisher exact test *P* =.049). Similarly 3 out of 15 patients (20%) with BNP >100 expired as compared to 0 out of 100 in BNP <100 group (*P* = .001). Mean length of stay in patients with BNP > 100 was 8.06 days as compared to 4.13 days in patients with BNP < 100 pg/ml (*P* < .0001).

Table 4. Mean length of stay, outcome and required intensity of care in Asthmatic subgroup

Asthma				
Characteristics		**BNP < 100 N= 115**	**BNP > 100 (n=15)**	***P* value**
Place	ICU	5 (4%)	3 (20%)	.049
	Floor	110 (96%)	12 (80%)	
Outcome	Expired	0 (0%)	3 (20%)	.001
	Survival	115 (100%)	12 (80%)	
Mean LOS		4.13	8.06	<.0001

Table 5 shows that 11 out of 37 patients (30%) with BNP > 100 required ICU care in COPD groups as compared to 14 out of 106 patients (1%) in BNP <100 pg/ml group. Mortality was also higher in BNP >100 pg/ml group as compared to BNP <100 pg/ml (14% and 3% respectively, *P* = .03). Mean length of stay was 7.95 days in BNP > 100 pg/ml group and 6.03 days in BNP <100 pg/ml group (*P* = .04).

Table 5. Mean length of stay, outcome and required intensity of care in COPD subgroup

COPD				
Characteristics		**BNP < 100 N=106 (%)**	**BNP > 100 N=37 (%)**	**P value**
Place	ICU	14 (1%)	11 (30%)	.02
	Floor	92 (99%)	26 (70%)	
Outcome	Expired	3 (3%)	5 (14%)	.03
	Survival	103(97%)	32 (86%)	
Mean LOS		6.03	7.95	.04

Table 6 shows that 15 out of 45 patients (33%) required ICU care in pneumonia group with BNP >100 pg/ml as compared to 13 out of 143 patients (9%) in BNP <100 pg/ml (*P* = .0001). Mortality was also higher in BNP >100 pg/ml group as compared to BNP <100 pg/ml (22% and 3% respectively, *P* = .0001). Mean length of stays were - 9.53 days and 6.36 days in BNP > 100 and BNP < 100 group (*P* = .04)

Table 6. Mean length of stay, outcome and required intensity of care in pneumonia subgroup

Pneumonia				
Characteristics		**BNP < 100 N=143**	**BNP > 100 (n=45)**	***P* value**
Place	ICU	13 (9%)	15 (33%)	.0001
	Floor	130 (91%)	30 (67%)	
Outcome	Expired	4 (3%)	10 (22%)	.0001
	Survival	139 (97%)	38 (78%)	
Mean LOS		6.36	9.53	.04

Table 7 shows correlation between BNP and Length of stay. As seen in table there was moderate correlation between length of stay and each diagnosis.

Table 7. Correlation coefficient between BNP and Length of stay

Group	Correlation Coefficient (BNP and Length of stay)
Overall	0.4
Asthma	0.34
COPD	0.45
Pneumonia	0.35

4. DISCUSSION

B type Natriuretic peptide (BNP) is a 32 amino acid hormone which is a physiologically active metabolite of Pro BNP. Increased mechanical load on right or left ventricle or neuro hormonal stimulation increases the release of pro BNP from ventricular myocyte. BNP has natriuretic, vasodilatory and antiproliferative effects. It also decreases the effect of sympathetic nervous system on heart.

B type natriuretic peptide level more than 400 pg/ml is considered highly suggestive of Congestive heart failure with positive predictive value of 86% while BNP value of less than 100 pg/ml rules out Congestive heart failure with negative predictive value of 90% [8]. Values between 100-400 pg/ml are considered gray area. Along with CHF, other conditions which can increase the strain on the ventricular muscles like sepsis, COPD exacerbation, pulmonary embolism and cor pulmonale need to be considered in differential diagnosis for the BNP value in this range.

Cargill RI et al. studied effect of BNP in hypoxic pulmonary vasoconstrictions in humans. Eight humans were given ANP, BNP or placebo and 30 minutes later were subjected to hypoxemia. Mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) were measured during hypoxic stimulus. Only those patients who received BNP had decreased mPAP and PVR response to hypoxemic stimulus [9].

Prognostic value of BNP has been well studied for pulmonary embolism where it predicts right ventricular overload and in combination with troponin I, it predicts higher mortality [10]. However, only few studies have been done to establish relationship between BNP and acute pulmonary diseases other than pulmonary embolism.

Ishii et al. measured BNP levels in COPD patients while receiving right sided cardiac catheterization and followed these patients for 12 months. BNP levels correlated well with mean pulmonary artery pressure [11].This study also showed that after stepwise multivariate Cox proportional-hazards regression analysis including age, sex, BNP, ANP, hemodynamic variables and the ratio of PaO2 to fraction of inspired oxygen, only BNP (P<0.05) was found an independent predictor of end-stage CRD death [11]. In another study of chronic stable lung disease patients BNP normalized ratio defined as measured BNP level/age and sex adjusted normal value was associated with risk ratio of 2.94 for mortality and in univariate and multivariate analysis it predicted mortality independent of lung function and hypoxia [12]. In a study of interstitial lung disease patients after adjustment for age, gender and disease severity (CPI), both BNP and right heart failure remained predictive of mortality. BNP was the most significant predictor of mortality (above CPI and right heart failure) [13].

Stolz et al. showed that in COPD patients, BNP levels were significantly elevated during the acute exacerbation compared to recovery, particularly in those patients requiring ICU treatment and accurately predicted the need for ICU care with increase in BNP of 100pg/ml but failed to predict short- and long-term mortality [14].

Christ Crain et al. found that patients admitted with Community acquired pneumonia, BNP levels were higher in non survivors and combining BNP with pneumonia severity index (PSI) increased the predictive value of PSI for mortality. BNP value also predicted treatment failure as accurately as PSI [15].

Similar results were reported by Nowak et al. In 341 patients admitted with pneumonia, NT pro BNP combined with PSI successfully predicted short term and long term mortality [16].

For asthma, we did not find any study documenting role of BNP as a prognostic marker. However, study done by Matera et al., showed that BNP had relaxant action on non sensitized and passively sensitized bronchial muscle of isolated human bronchi [17].Similar results were reported by Akerman et al. in humans. 8 humans with documented asthma underwent nesitiride infusion for 3 hours. Baseline and post infusion spirometry and Forced oscillation measurements were taken. After infusion, FEV1 and FVC increased by 2.41± 0.78 L and 3.65± 1.05 L respectively [18].

Our study shows that elevated BNP levels suggest higher severity of asthma, COPD and Pneumonia. Higher BNP were also associated with increased mortality in asthma, COPD and pneumonia and were associated with increased length of stay.

There were some drawbacks of study. First study was a retrospective review study. Second, we evaluated BNP as binominal value rather than continuous variable so that linear relationship between BNP and outcomes could not be established. Third, patients could not be stratified based on the demographic characteristics because of small population size. It has been well established that female has less BNP value as compared to male for same degree of ventricular volume overload. Also patients with higher BMI/Obesity has low BNP as compared to other population. Majority of our hospital patient population is African American. Representation from other race is very minimal. So this sample would not be representative of general population. Smoking status, compliance to medications at home, stage of asthma and COPD were not included in study. Other characteristics like APACHE II score or PSI score/SOFA score were not included as a part of data collection. Thus study tests could not be adjusted for these variables. So we could not establish risk model(s) for BNP with study outcomes. A larger study or metaanalysis is required to arrive any definite conclusion.

5. CONCLUSION

This retrospective study evaluated use of BNP as a prognostic marker for severity and mortality with predictor of length of hospital stay. From the study we can conclude that higher BNP values are associated with higher mortality and severity of the disease and requires increasing hospital stay.

CONSENT

Not applicable.

ETHICAL APPROVAL

IRB board reviewed study and was considered exempt because of retrospective nature of study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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