**Prognostic value of NT-pro Brain Natriuretic Peptide levels in patients with AECOPD in Intensive Care Unit .**

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**Abstract**

Background: The prognostic value of amino terminal pro-brain natriuretic peptide levels in patients with acute exacerbation of chronic obstructive pulmonary disease has not been fully established. Objectives: This work aimed to evaluate the prognostic value of amino terminal pro-brain natriuretic peptide levels in patients with acute exacerbation COPD who need ICU admission. Methods: This prospective observational study included 80 patients who were admitted in chest ICU at Benha university hospital from may 2020 to march 2021 due to acute exacerbation of chronic obstructive pulmonary disease . Demographic data, noninvasive mechanical ventilation application, need for invasive mechanical ventilation, amino terminal pro-brain natriuretic peptide level, duration of mechanical ventilation, intensive care unit and hospital stay, weaning success, and mortality rates were recorded. Results: A total of 80 patients (74 males and 6 females) were included in the study. The mean age of the participants was 69 (53-84) years, and the mean. The mean amino terminal pro-brain natriuretic peptide level was found to be lower in cases with noninvasive mechanical ventilation success than those with noninvasive mechanical ventilation failure (320.50 – 991.90). In addition, the mean amino terminal pro-brain natriuretic peptide level was significantly higher (1004.90 – 1188.30, p=0.001) in patients who needed invasive mechanical ventilation support than in patients who did not. The mortality rate was significantly higher in patients who had an increasing trend of amino terminal pro-brain natriuretic peptide levels during hospitalization in patients who were on IMV(12.5%,). Conclusion In cases of acute exacerbation of chronic obstructive pulmonary disease requiring mechanical ventilation, amino terminal pro-brain natriuretic peptide measurement and monitoring of its trend may be a valuable asset in predicting mortality, noninvasive mechanical ventilation, weaning success, and need for invasive mechanical ventilation.

**1.Introduction**

Chronic Obstructive Pulmonary Disease (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. (9)

COPD is a major cause of morbidity and mortality globally. It is the fourth leading cause of death in the world and has been projected to become the third leading cause of death. (9)

Acute exacerbation of COPD (AECOPD) is defined as “acute worsening of respiratory symptoms that needs additional therapies” (9).

Many patients require admission to an intensive care unit (ICU), and a substantial percentage (26%-74%) of patients need mechanical ventilatory support due to hypoxemic or hypercapnic respiratory failure. Viral and/or bacterial infections are the leading causes of AECOPD; nevertheless, up to one-third of these cases have an unknown etiology (17).

Cardiovascular diseases are the most common comorbidity in patients with COPD and affect up to 30% of the patients. These diseases are related to increased mortality and are consequently considered as important prognostic factors (15).

Natriuretic peptides, namely, brain natriuretic peptide (BNP) and amino terminal pro BNP (NT-pro BNP), are biomarkers released from ventricles in response to myocardial wall stress in case of impaired myocardial function. These peptides may be used as valid biomarkers for diagnosis of cardiac failure (19).

Increased BNP levels are associated with several conditions, such as primary pulmonary hypertension, myocarditis, right ventricle failure, and sepsis (2).

The right ventricle is mostly affected in COPD, whereas both ventricles may be affected in AECOPD. Hence, high levels of BNP and NT-pro BNP may have a prognostic value and are related to increased mortality in
AECOPD (4).

**2.Aim of the work**

The aim of this work is to evaluate the prognostic value of amino terminal pro-brain natriuretic peptide levels in patients with acute exacerbation COPD who need ICU admission due to their need to mechanical ventilation either invasive or non invasive**.**

**3.Patients And Methods**

This Prospective observational study Included 80 patients who were admitted to intensive care unit at Benha university hospital in the period from may 2020 to march 2021.

Approval from ethical committee in the faculty of medicine (Institutional Research Board IRB).

**Inclusion criteria**

* Patients with acute exacerbation COPD who were admitted at ICU due to their need for mechanical ventilation,

**NIMV**

* types of devices used include
* CPAP
* BIPAP
* Criteria suggestive use ofNIMV include

Acute hyper capnic repiratory failure with PH(7.25-7.35). **(3).**

* Criteria suggestive success of NIMV,
* Clinical improvement as regard(heart rate,respiratory rate,blood pressure).
* Laboratory improvement of ABG two hours after use.**(Ediboglu o et al.,2017).**

**IMV**

* Criteria suggestive use of IMV include,
* Major criteria (respiratory arrest, loss of consciousness, psychomotor agitation requiring sedation, hemodynamic instability with a systolic BP less than 70 or greater than 180 mmHg, HR less than 50 beats/minute with loss of alertness, gasping for air).
* Minor criteria(RR >35 breath/min, worsening acidemia or pH < 7.25, paO2 < 40 mmHg or paO2/FiO2 < 200 despite oxygen therapy, decreasing level of consciousness.) **(3).**

**Criteria of successful weaning,**

Weaning started once the cause of the exacerbation was adequately treated and the patient is hemodynamically stable.

Physiologic parameters must be followed intensively. It’s targeted MV < 15 L, RR < 30 breaths/minute, TV > 325 ml, rapid shallow breathing index (RSBI) <105, maximum inspiratory pressure (MIP) < −15**.(Gaprestad E et al., 2007).**

**Exclusion criteria**

* Myocarditis.
* Right ventricular failure.
* Renal failure.
* Sepsis.

**Study description**

**All patients were subjected to the following:**

1. **Full medical history**: age, sex, residence, occupation, smoking and other special habits of medical importance.
2. **Thorough physical examination:** general and local chest examination.
3. **Routine laboratory investigations in the form of:**
* Complete Blood picture, erythrocyte sedimentation rate (ESR), coagulation profile.
* Liver function tests: (ALT,AST and serum albumin).
* Kidney function tests: in the form of serum urea and serum creatinine.
* Arterial blood gases
* Level of NT-pro BNP;

It was measured before induction of mechanical ventilation.

By ELISA KIT supplied by **Shanghai Korain Biotech CO.,Ltd** **Cat.No E1239Hu**

**Assay Principle**

This kit is an Enzyme-Linked Immunosorbent Assay (ELISA). The plate has been pre-coated with Human NT-pro BNP antibody. NT-pro BNP present in the sample is added and binds to antibodies coated on the wells. And then biotinylated Human NT-proBNP Antibody is added and binds to NT-pro BNP in the sample. Then Streptavidin-HRP is added and binds to the Biotinylated NT-pro BNP antibody. After incubation unbound Streptavidin-HRP is washed away during a washing step. Substrate solution is then added and color develops in proportion to the amount of Human NT-pro BNP. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

**Intended Use**

This sandwich kit was used for the accurate quantitative detection of Human N-terminal pro-brain natriuretic peptide (also known as NT-pro .BNP) in serum.

Allow serum to clot for 10-20 minutes at room temperature. Centrifuge at 2000-3000 RPM for 20 minutes. Collect the supernatant without sediment.

* Sample concentrations was predicted before being used in the assay.
* Samples were used within 5 days were stored at 2-8°C.
* Samples should were brought to room temperature before starting the assay.
* Centrifugation were done to collect sample before used.
* When sediments occurred during storage, centrifugation were performed again.
1. **Radiological examination including:**
* Plain chest X-ray postero-anterior and lateral views.
* CT scan of the chest when indicated.
* Echocardiography.

**Data management and Statistical Analysis :**

All data were collected, tabulated and statistically analyzed using statistical package of special science SPSS version 22 (SPSS Inc. Chicago, IL, U.S.A) as follow:

1. Editing and coding
2. Data entry in computer.
3. Quantitative data were expressed as mean ± SD (standard deviation) for parametric data median and range for non- parametric data.
4. Qualitative data were expressed as frequencies and relative percentage.
5. Data were tested for normal distribution using Shapiro-Wilk’s test.
6. Data were handled using appropriate statistical tests of significance such as :
	1. Independent t-test and mann whitney test were used to calculate difference between quantitative variables in two groups.
	2. Paired t-test was used to compare between two dependent groups of normally distributed variables.
	3. Chi square test (χ2) and fisher exact was used to calculated difference between qualitative variables.
	4. All statistical comparison were two tailed with significance level of p-value $\leq $ 0.05 indicates significant, p- value <0.001 indicates highly significant difference while p-value > 0.05 indicates non significant difference.

**3.Results**

**Table 1:** Distribution of studied sample according to patient’s demographic data.

|  |  |  |
| --- | --- | --- |
|  | **Number** | **Percent** |
| **Age (years)** |  |  |
| Range | 53-84 |
| Mean±S.D. | 69.30±6.934 |
| **Sex** |  |  |
| Male | 74 | 92.5 |
| Female | 6 | 7.5 |
| **Smoking** |  |  |
| Smoker | 79 | 98.75 |
| Non smoker | 1 | 1.25 |
| **Smoking index** |  |  |
| Range | 400-1800 |
| Mean±S.D. | 994.94±331.623 |
| **Invasive Mechanical Ventilation** |  |  |
| No | 48 | 60.0 |
| Yes | 32 | 40.0 |

This Table shows demographic data of the studied group. Age ranged from 53-84 years with mean value 69.30±6.934 years. Male cases were 74(92.5%) while female cases were 6(7.5%). The majority of our cases were smoker (98.75%). Smoking index ranged between 400-1800 with mean value 994.94±331.623. Invasive Mechanical Ventilation were detected in 32 patients (40%).

**Table 2:** Distribution of studied sample according to patient’s arterial blood gases

|  |  |  |
| --- | --- | --- |
|  | **Min. – Max.** | **Mean±S.D.** |
| PaO2(mm Hg) | 40 – 56 | 47.49±5.166 |
| PaCO2(mm Hg) | 56 – 111 | 80.84±12.896 |
| PH | 2.28 – 7.33 | 7.15±0.563 |
| PaO2/FiO2 | 50 – 340 | 230.63±73.007 |

This table show patient’s arterial blood gases; PaO2 was ranged from 40 – 56 with a mean value of 47.49±5.166. Patient’s PaCO2 was ranged from 56 – 111 with a mean value of 80.84±12.896. Patient’s PH was ranged from 2.28 – 7.33 with a mean value of 7.15±0.563. Patient’s PaO2/FiO2 was ranged from 50 – 340 with a mean value of 230.63±73.007.

**Table 3:** Distribution of studied sample according to patient’s Duration of mechanical ventilation and I.C.U stay

|  |  |  |
| --- | --- | --- |
|  | **Mechanical Ventilation** | **P value** |
| **NIMV** | **IMV** |
| **Duration of mechanical ventilation** |  |  |  |
| Min. – Max. | 3 – 14 | 4 – 11 | 0.381 |
| Mean±S.D. | 8.15±2.858 | 7.53±1.665 |
| **Duration of ICU stay** |  |  |  |
| Min. – Max. | 4 – 21 | 4 – 14 | 0.255 |
| Mean±S.D. | 9.90±3.360 | 8.97±2.148 |

This table show patient’s Duration of mechanical ventilation and I.C.U stay and it show no statistically significant differences between IMV and NIMV.

**Table4:** Distribution of studied sample according to patient’s NT-Pro BNP

|  |  |  |
| --- | --- | --- |
|  | **Min. – Max.** | **Mean±S.D.** |
| NT-Pro PNP | 320.50 – 1188.30 | 874.53±233.998 |

This table show patient’s duration of ventilation and it was ranged from 320.50 – 1188.30 with a mean value of 874.53±233.998.

**Table 5:** Distribution of studied sample according to patient’s mortality in cases of IMV.

|  |  |  |
| --- | --- | --- |
| **Mortality** | **Number** | **Percent** |
| No | 70 | 87.5 |
| Yes | 10 | 12.5 |
| **Total** | 80 | 100 |

This table shows invasive ventilation of the studied group and it show that 10(12.5%) were died.

**Table 6:** Comparison between levels of NT-Pro BNP in patients who needed invasive mechanical ventilation and those who didn’t need invasive mechanical ventilation.

|  |  |  |
| --- | --- | --- |
| **NT-Pro PNP** | **Invasive Ventilation** | **P value** |
| **No** | **Yes** |
| Min. – Max. | 320.50 – 991.90 | 1004.90 – 1188.30 | <0.001\* |
| Mean±S.D. | 739.08±208.526 | 1077.71±50.903 |

This table shows comparison between levels of NT-Pro BNP in patients who needed invasive mechanical ventilation and those who didn’t need invasive mechanical ventilation and it show highly statistically significant difference between them.

**Table7:** Relation between NT-Pro BNP and mortality.

|  |  |  |
| --- | --- | --- |
| **NT-Pro PNP** | **Mortality** | **P value** |
| **No** | **Yes** |
| Min. – Max. | 320.50 – 1099.60 | 1102.50 – 1188.30 | <0.001\* |
| Mean±S.D. | 837.14±226.303 | 1136.25±31.840 |

This table shows relation between NT-Pro BNP and mortality and it show highly statistically significant difference between them.

**Table 8:** Correlation between levels of NT-Pro BNP and different patients parameters

|  |  |
| --- | --- |
|  | **NT-Pro PNP** |
| **R** | **P** |
| Age | -0.184 | 0.102 |
| PH | 0.321 | 0.004\* |
| PaO2 | 0.021 | 0.853 |
| PaCO2 | -0.252 | 0.024\* |
| PaO2/FiO2 | 0.309 | 0.005\* |
| ICU stay | 0.374 | 0.001\* |

Correlation between levels of NT-Pro BNP and different patients parameters show highly positive significant correlation between levels of NT-Pro BNP and each of PH (r=0.321 , P=0.004), PaO2/FiO2 (r=0.309 , P=0.005) and ICU stay (r=0.374 , P=0.001) and negative significant correlation between levels of NT-Pro BNP and PaCO2 (r=-0.252 , P=0.024)

**Table 9:** ROC curve analysis of NT-Pro BNP levels as a predictor of need for invasive mechanical ventilation and mortality

|  |  |
| --- | --- |
|  | **NT-Pro PNP** |
| Cut of Value | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **AUC** | **P** |
| IMV | >991.9 | 100% | 100% | 100 | 100 | 1.000 | <0.001\* |
| Mortality | >1099.6 | 100% | 100% | 100 | 100 | 1.000 | <0.001\* |

Table( 9) show that NT-Pro BNP levels was a best predictor of need for invasive mechanical ventilation and mortality at cut off point of >991.9 and >1099.6 respectively with high sensitivity and specificity 100% for each.

**4.Discussion**

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide and is associated with a significant economic burden. In 2014, 15.7 million Americans reported that they were diagnosed with COPD. Prevalence of COPD increases with age, ranging from 2.6% in adults aged 18–34 years of age to 12.3% in adults aged 75 years or older (**24).**

Studies show that >50% of adults with low pulmonary function do not know that they have COPD, suggesting that actual estimates could be higher. COPD not only leads to limitations in daily activities but also leads to increased economic burden. Work force participation estimates suggest a significant decline in adults with COPD as well as limitations in the type and amount of work that they can perform with restricted activity days ranging from 27 to 63 days per year compared with adults without COPD (**20).**

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a common cause of acute hospitalization and a great risk for morbidity and mortality. Since chronic obstructive pulmonary disease (COPD) is considered to be a systemic disorder, it has been reported that one of its multiple aspects is cardiovascular in nature. Although various cardiac diseases, including acute myocardial infarction and chronic heart failure (HF), may be associated with AECOPD, the typical presentation of a specific cardiac condition is rather exceptional in clinical practice (**12)**.

B-type natriuretic peptide (BNP) is derived from the pro-hormone pro-BNP, an intracellular, 108-amino acid precursor protein, which is cleaved into two fragments and released by myocytes, yielding BNP and the 76-amino acid N-terminal fragment of pro-BNP (NT-pro-BNP) (**5)**.

BNP and NT-pro-BNP are established biomarkers of heart failure (HF) and are primarily used for diagnosis, risk stratification, and management. Elevated natriuretic peptide levels have also been observed in patients with COPD without HF, likely originating from the left and right sides of the heart. Cor pulmonale, secondary pulmonary hypertension, and hypoxemia represent important stimuli for the release of natriuretic peptides from the right side of the heart and increase BNP gene expression (**8).**

Several studies have suggested the utility of BNP in predicting the outcomes of COPD. A prospective, single-center study of stable patients with COPD in the ambulatory setting suggested that NT-pro-BNP predicts survival in unadjusted survival plots; however, the association was not significant when adjusted for the presence of a dilated left atrium, aortic stenosis, and left ventricular systolic dysfunction. Another study of patients with AECOPD suggested an association between elevated NT-pro-BNP levels and 30-day mortality. That study was limited to include only those patients with known cardiovascular diseases. Hoiseth et al showed an association between NT-pro-BNP and long-term mortality in patients with AECOPD; however, ~12% of the patients in that study did not have Spiro metrically confirmed COPD. A meta-analysis by Buchan et al found that most of the studies correlating COPD with NT-pro-BNP levels included left ventricular dysfunction as a primary or secondary end point (**4)**.

The aim of this study was to evaluate the prognostic value of amino terminal pro-brain natriuretic peptide levels in patients with acute exacerbation COPD who need ICU admission due to their need to mechanical ventilation either invasive or non-invasive.

 This cross-sectional study was conducted, including eighty patients who were admitted to intensive care unit at Benha university hospital due to acute exacerbation COPD. The duration of the study ranged from 6-12 months.

**The main results of this study were as following:**

As regard demographic data of the studied group. Age ranged from 53-84 years with mean value 69.30±6.934 years. Male cases were 74(92.5%) while female cases were 6(7.5%). The majority of our cases were smoker (98.75%). Smoking index ranged between 400-1800 with mean value 994.94±331.623. Invasive Mechanical Ventilation were detected in 32 patients (40%).

Our results were supported by study of **(6)** as they reported that a total of 110 patients (75 male) from 1228 patients were included in the study. The median age was 69 (61-76) years, and the median APACHE II score was 19 (15-23).

Furthermore, **(7)** revealed that the patients’ characteristics of all 20 patients showed a mean ± SD age of 57.85 ± 9.37 years ranging from 47 to 76 years. Sixteen (80%) patients were males and four (20%) were females. Fifteen (75%) patients were smokers and five (25%) were nonsmokers. The mean ± SD duration of smoking was 32 ± 8.71 years ranging from 15 to 43 years.

Chronic obstructive pulmonary disease (COPD) is a common and disabling condition affecting hundreds of millions of people worldwide and the third leading cause of global mortality behind ischemic heart disease (IHD) and stroke. Comorbidities and exacerbations are recognized to contribute to the complexity of COPD and mortality from the disease (**14**).

Acute exacerbations of COPD are common and important events, usually related to airway infection and inflammation. A phenotype of patients suffering from more frequent exacerbations (frequent exacerbators) is seen across all grades of COPD severity. Frequent exacerbators also have a worse health-related quality of life and accelerated lung function decline than infrequent exacerbators (**12)**.

The present study showed that patient’s arterial blood gases; PaO2 was ranged from 40 – 56 with a mean value of 47.49±5.166. Patient’s PaCO2 was ranged from 56 – 111 with a mean value of 80.84±12.896. Patient’s PH was ranged from 2.28 – 7.33 with a mean value of 7.15±0.563. Patient’s PaO2/FiO2 was ranged from 50 – 340 with a mean value of 230.63±73.007.

Cardiovascular comorbidity in general and IHD in particular is prevalent and important in patients with COPD beyond shared risk factors, such as age and smoking. The presence of IHD in COPD negatively impacts health status, symptoms, exercise capacity, exacerbation recovery time, hospitalizations, and mortality (**20).**

Echocardiography is a useful tool to diagnose pulmonary hypertension and cor pulmonale. However, measurement cannot be achieved in all patients since hyperinflation of the chest will alter sound-wave transmission through the chest. Invasive measurements of pulmonary arterial pressure by right heart catheterization remain the “gold standard” measurement of the pulmonary arterial pressure (**17).**

COPD is the only major cause of mortality for which death rates continue to rise. There remains a lack of objective measures to risk-stratify patients, standardized management of comorbidities, and therapies that prolong life. One third of deaths in COPD relate to cardiovascular disease, equaling or exceeding pulmonary-related mortality. Cardiovascular therapies are proven to reduce morbidity and mortality, yet are underutilized because disease is unrecognized. Simple, generalizable and cost-effective strategies are therefore needed to identify cardiovascular disease (and particularly heart failure) to improve outcomes in COPD (**10)**.

In the study in our hands, patient’s Duration of mechanical ventilation and I.C.U stay and it show no statistically significant differences between IMV and NIMV. 10(12.5%) were died.

However, in the study of **(6)**, noninvasive mechanical ventilatory therapy was initiated in 69 patients due to type 2 respiratory failure. The noninvasive mechanical ventilatory success rate was 68.11%, and the median NT-pro BNP level was lower in cases with noninvasive mechanical ventilatory success than those with noninvasive mechanical ventilatory failure (2004 pg/mL vs. 3977 pg/mL, p=0.05). No differences in pH, pCO2, and PaO2/FiO2 ratio was found between patients with successful and failed noninvasive mechanical ventilatory. Invasive mechanical ventilation was applied to 63 patients (41 due to noninvasive mechanical ventilation failure).

Cardiovascular diseases are the most common comorbidity in patients with COPD and affect up to 30% of the patients. These diseases are related to increased mortality and are consequently considered as important prognostic factors. Cardiovascular examination, particularly echocardiography, is essential for diagnosis, follow-up, and treatment of cardiac failures. Although echocardiographic evaluation is an important diagnostic tool for cardiac failure, it has various restrictions, such as imaging difficulty and user dependency during mechanical ventilatory in ICU. Natriuretic peptides, namely, brain natriuretic peptide (BNP) and amino terminal pro BNP (NT-pro BNP), are biomarkers released from ventricles in response to myocardial wall stress in case of impaired myocardial function. These peptides may be used as valid biomarkers for diagnosis of cardiac failure (**19**).

Increased BNP levels are associated with several conditions, such as primary pulmonary hypertension, myocarditis, cardiac allograft rejection, right ventricle failure, renal failure, advancing age, and sepsis. The right ventricle is mostly affected in COPD, whereas both ventricles may be affected in AECOPD. Hence, high levels of BNP and NT-pro BNP have a prognostic value and are related to increased mortality in AECOPD (**10).**

The present study showed that as regard comparison between levels of NT-Pro PNP in patients who needed invasive mechanical ventilation and those who didn’t need invasive mechanical ventilation and it show highly statistically significant difference between them. As regard relation between NT-Pro PNP and mortality and it show highly statistically significant difference between them. As regard Correlation between levels of NT-Pro BNP and different patients parameters show highly positive significant correlation between levels of NT-Pro PNP and each of PH (r=0.321, P=0.004), PaO2/FiO2 (r=0.309, P=0.005) and ICU stay (r=0.374, P=0.001) and negative significant correlation between levels of NT-Pro BNP and PaCO2 (r=-0.252 , P=0.024). Using ROC curve, NT-Pro BNP levels was a best predictor of need for invasive mechanical ventilation and mortality at cut off point of >991.9 and >1099.6 respectively with high sensitivity and specificity 100% for each.

Our results were supported by study of **(6)** as they reported that the mean amino terminal pro-brain natriuretic peptide level was found to be lower in cases with noninvasive mechanical ventilation success than those with noninvasive mechanical ventilation failure (p=0.053). In addition, the mean amino terminal pro-brain natriuretic peptide level was significantly higher (4740 pg/mL vs. 3004 pg/mL, p=0.001) in patients who needed invasive mechanical ventilation support than in patients who did not. The mortality rate was significantly higher in patients who had an increasing trend of amino terminal pro-brain natriuretic peptide levels during hospitalization than in patients who had decreasing levels (59% vs. 23%, p=0.015). Based on the receiver operating characteristic analysis, the increasing trend of amino terminal pro-brain natriuretic peptide levels during intensive care unit stay predicted mortality with area under curve of 0.84 (p<0.0001, 95% CI: 0.75-0.93) and predicted invasive mechanical ventilation need with area under curve of 0.68.

In the study of **(22)** BNP levels were significantly elevated during the acute exacerbation compared to recovery (65 pg/mL; interquartile range [IQR], 34 to 189 pg/mL; vs 45 pg/mL; IQR, 25 to 85 pg/mL; p < 0.001), particularly in those patients requiring ICU treatment (105 pg/mL; IQR, 66 to 553 pg/mL; vs 60 pg/mL; IQR, 31 to 169 pg/mL; p = 0.007). In multivariate Cox regression analysis, BNP accurately predicted the need for ICU care (hazard ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.24 for an increase in BNP of 100 pg/mL; p = 0.008). In a receiver operating characteristic analysis to evaluate the potential of BNP levels to predict short-term and long-term mortality rates, areas under the curve were 0.55 (SD, 0.71; 95% CI, 0.41 to 0.68) and 0.56 (SD, 0.53; 95% CI, 0.45 to 0.66, respectively).

**Marcun et al., 2012 (15)** demonstrated that NT-pro BNP and troponin T were elevated on admission in 60% and 36%, and at discharge in 28% and 19% of patients. During follow-up, 53 (42%) patients were hospitalized and 17 (13%) patients died. In Kaplan Meier analysis of survival curves, NT-pro BNP on admission distinguished between deceased and surviving patients (p=0.011) whilst troponin T at discharge separated hospitalized and non-hospitalized patients (p=0.017). The adjusted Cox proportional hazard model confirmed these findings: discharge troponin T predicted hospitalisation (hazard ratio 2.89, 95% confidence interval 1.13–7.36) and admission NT-pro BNP predicted mortality (hazard ratio 4.20, 95% confidence interval 1.07–14.01).

Also, **(16)** revealed that in the hospitalized subjects, the median plasma BNP level (interquartile range) was 55.4 (26.9–129.3) pg/mL and was higher than that of patients with stable COPD: 18.3 (10.0–45.3) for Global Initiative for Chronic Obstructive Lung Disease grade I; 25.8 (11.0–53.7) for grade II; 22.1 (9.1–52.6) for grade III; and 17.2 (9.6–22.9) pg/mL for grade IV, all P<0.001. In 15 subjects studied prospectively, the median plasma BNP level was 19.4 (9.8–32.2) pg/mL before AECOPD, 72.7 (27.7–146.3) pg/mL during AECOPD, and 14.6 (12.9–39.0) pg/mL after AECOPD (P<0.0033 and P<0.0013, respectively). Median plasma BNP levels during AECOPD were significantly higher in ten unsuccessfully discharged subjects 260.5 (59.4–555.0) than in 48 successfully discharged subjects 48.5 (24.2–104.0) pg/mL (P=0.0066). Only 5.6% of AECOPD subjects were associated with systolic dysfunction defined as a left ventricular ejection fraction (LVEF) <50%; a further 7.4% were considered to have impaired relaxation defined as an E/A wave velocity ratio <0.8 and a deceleration time of E >240 ms. BNP levels were weakly correlated with the E/peak early diastolic velocity of the mitral annulus (Ea) ratio (Spearman's rank correlation coefficient =0.353, P=0.018), but they were not correlated with the LVEF (Spearman's rank correlation coefficient =-0.221, P=0.108).

**El Mallawany et al., 2014 (7)** revealed that NT-pro BNP showed a statistically significant inverse correlation with pH (p = 0.005), ejection fraction (p = 0.007) and a direct one with both left ventricular systolic (p = 0.008) and diastolic (p = 0.016) dimensions and E/A (p = 0.016). The NT-pro BNP significantly decreased after recovery from AECOPD (p = 0.030).

In the study of **(13)**, patients with raised NT- pro BNP levels on admission had lower levels on follow‐up (P = 0.04) but these remained higher than the group without raised NT- pro BNP levels on admission. Two of the eight patients with raised levels on admission had missing values (one had died and one declined).

Furthermore, **(9)** stated that elevated NT-pro BNP values were related to increased risk of all-cause mortality in COPD patients both with and without exacerbation (hazard ratio (HR): 2.87, p < 0.0001 and HR: 3.34, p = 0.04, respectively). The results were confirmed also after meta-regression analysis for confounding factors (previous cardiovascular history, hypertension, HF, forced expiratory volume at 1 second and mean age). NT-pro BNP may be considered a reliable predictive biomarker of poor prognosis in patients with COPD.

However, in the study of **(1)**, NT-pro-BNP levels were not associated with COPD severity and comorbid illnesses. Log-transformed NT-pro-BNP levels were positively associated with echo cardiographically estimated right ventricular systolic pressure (r=0.3658; 95% confidence interval [CI]: 0.2060–0.5067; P<0.0001). Patients with elevated NT-pro-BNP levels were more likely to require intensive care (63% vs 43%; P=0.0207) and had a longer hospital length of stay (P=0.0052). There were no differences in the need for noninvasive positive pressure ventilation (P=0.1245) or mechanical ventilation (P=0.9824) or in regard to in-hospital mortality (P=0.5273). The difference may be due to different inclusion criteria from our study.

**5.Conclusion**

In cases of acute exacerbation of chronic obstructive pulmonary disease requiring mechanical ventilation, amino terminal pro-brain natriuretic peptide measurement and monitoring of its trend may be a valuable asset in predicting mortality, noninvasive mechanical ventilation, weaning success, and need for invasive mechanical ventilation.

**Funding**

* This paper was not funded

**Author contributions**

* All authors were involved in the study design, analysis, interpretation of the data and revising its content. All authors agree to be accountable for all aspects of the work.

**Declaration of interest**

* The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

**Ethical approval**

* The Research Ethics Committee at the Faculty of Medicine, Benha University has approved the study. Informed consent was obtained from every single individual member incorporated into the study.

**6.References**

1. M.Adrish, V.B.Nannaka, E.J.Cano, B.Bajantri, G.Diaz-Fuentes, Significance of NT-pro-BNP in acute exacerbation of COPD patients without underlying left ventricular dysfunction. International journal of chronic obstructive pulmonary disease.vol.12,pp.1183,2017.
2. Bar SL, Swiggum E, Straatman L, Ignaszewski A. Nonheart failure- associated elevation of amino terminal pro-brain natriuretic peptide in the setting of sepsis. Can J Cardiol 2006; 22:263-6.
3. L.Brochard, A.Rauss, S.Benito, Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med.vol.150,pp.896,‏1994.
4. A.Buchan, R.Bennett, A.Coad, S.Barnes, R.Russell, AR.Manuel, The role of cardiac biomarkers for predicting left ventricular dysfunction and cardiovascular mortality in acute exacerbations of COPD. Open Heart.vol.2(1),pp.e000052,2015.
5. CL.Chang, SC.Robinson, GD.Mills, GD.Sullivan, NC.Karalus, JD.McLachlan, Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. Thorax.vol.66,pp.764-8,2011.
6. Ö.Ediboğlu, C.Kıraklı, Can NT-pro BNP Levels Predict Prognosis of Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease in the Intensive Care Unit?. Balkan medical journal.vol.35(6),pp.422,2018.
7. H.El Mallawany, M.I.Mahmoud, T.S.Morsi, R. M.EL-Shiekh, Role of N-terminal pro B-type natriuretic peptide in acute exacerbation of chronic obstructive pulmonary disease. Egyptian Journal of Chest Diseases and Tuberculosis.vol.63(1),pp.57-65,2014.
8. Garpestad E, Brennan J, Hill N. Noninvasive ventilation for critical care. Chest 2007;132: 711-720
9. Global Initiative for Chronic Obstructive Lung Diseases (GOLD 2020)
10. NM.Hawkins, A.Khosla, SA.Virani, JJ.McMurray, JM.FitzGerald, B-type natriuretic peptides in chronic obstructive pulmonary disease: a systematic review BMC Pulm Med.vol.17,pp.11,2017.
11. A.D.Høiseth, T.Omland, T.A.Hagve, P.H.Brekke, V.Søyseth, NT-proBNP independently predicts long term mortality after acute exacerbation of COPD–a prospective cohort study. Respiratory research.vol.13(1),pp.1-9,2012.‏
12. JR.Hurst, J.Vestbo, A.Anzueto, N.Locantore, H.Müllerova, R.Tal-Singer, B.Miller, DA.Lomas, A.Agusti, W.Macnee, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med.vol. 363,pp.1128–1138,2010.
13. M.H.S.Lee, C.L.Chang, A.R.Davies, M.Davis, R.J.Hancox, Cardiac dysfunction and N‐terminal pro‐B‐type natriuretic peptide in exacerbations of chronic obstructive pulmonary disease. Internal medicine journal.vol.43(5),pp.595-598,2013.
14. R.Lozano, M.Naghavi, K.Foreman, S.Lim, K.Shibuya, V.Aboyans, J.Abraham, T.Adair, R.Aggarwal, SY.Ahn, Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study. Lancet .vol.380,pp.2095–2128,2012.
15. R.Marcun, A.Sustic, PM.Brguljan, S.Kadivec, J.Farkas, M.Kosnik, Cardiac biomarkers predict outcome after hospitalisation for an acute exacerbation of chronic obstructive pulmonary disease. Int J Cardiol.vol.161,pp.156-9,2012.
16. K.Nishimura, T.Nishimura, K.Onishi, T.Oga, Y.Hasegawa, P.W.Jones, Changes in plasma levels of B-type natriuretic peptide with acute exacerbations of chronic obstructive pulmonary disease. International journal of chronic obstructive pulmonary disease.vol.9,pp.155,2014.
17. W.Pan, J.Yu, L.Zhang, H.Yang, Y.Yuan, Predictors of in-hospital mortality in patients with acute exacerbation of COPD requiring ventilation: a retrospective study. Int J Clin Exp Med.vol.9,pp.22093-22101,2016.
18. W.Pan, Yu J, Zhang L, Yang H, Yuan Y. Predictors of in-hospital mortality in patients with acute exacerbation of COPD requiring ventilation: a retrospective study. Int J Clin Exp Med 2016; 9:22093-22101.
19. R.Pavasini, G.Tavazzi, S.Biscaglia, F.Guerra, A.Pecoraro, F.Zaraket, Amino terminal pro brain natriuretic peptide predicts all-cause mortality in patients with chronic obstructive pulmonary disease: Systematic review and meta-analysis. Chron Respir Dis.vol.14,pp.117-26,2017.
20. ARC.Patel, GC.Donaldson, AJ.Mackay, JA.Wedzicha, JR.Hurst, The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. Chest .vol.141,pp.851–857,2012.
21. JG.Patel, SP.Nagar, AA.Dalal, Indirect costs in chronic obstructive pulmonary disease: a review of the economic burden on employers and individuals in the United States. Int J Chron Obstruct Pulmon Dis.vol.9,pp.289–300,2014.
22. D.Stolz, T.Breidthardt, M.Christ-Crain, R.Bingisser, D.Miedinger, J.Leuppi, C.Mueller, Use of B-type natriuretic peptide in the risk stratification of acute exacerbations of COPD. Chest.vol.133(5),pp.1088-1094,2008.
23. J.Vestbo, S.S.Hurd, A.G.Agustí, P.W.Jones, C.Vogelmeier, A.Anzueto, R.Rodriguez-Roisin, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. American journal of respiratory and critical care medicine.vol.187(4),pp.347-365,2013.‏
24. AG.Wheaton, TJ.Cunningham, ES.Ford, JB.Croft; Centers for Disease Control and Prevention.; Employment and activity limitations among adults with chronic obstructive pulmonary disease – United States, 2013. Morbidity and Mortality Weekly Report (MMWR) .vol.64(11),pp.289–295,2015.