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# Natriuretic peptides in elderly patients with chronic obstructive pulmonary disease

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## Abstract

**Background:** Natriuretic peptides (NPs) are considered a useful tool for diagnosing the cardiac or pulmonary origin of acute dyspnea in the emergency department. The aim of this study was to evaluate NP in elderly patients with chronic obstructive pulmonary disease (COPD).

**Materials and methods:** In the PubMed and Hinari databases, we identified 465 comprehensive articles in English, published in the years 1990–2021, which provided information on natriuretic peptides in elderly patients with COPD. The final bibliography contains 49 relevant sources.

**Results:** NP, specially BNP/NT-proBNP values are frequently elevated in patients with COPD, reflecting three complex aspects of the interrelated cardio-pulmonary continuum: (1) left ventricular systolic and diastolic dysfunction, (2) pulmonary vascular and right heart remodeling, (3) global cardiovascular risk and comorbidities. The additional increase in BNP/NT-proBNP values during acute exacerbation of COPD is probably a marker for both, acute estate of COPD and varying degrees of underlying cardiopulmonary disease.

The results of the studies suggest the role of natriuretic peptides as relevant prognostic biomarkers not only for patients with cardiovascular disease, but also for patients with chronic obstructive pulmonary disease, which has an important clinical implication. The determination of these biomarkers in patients with chronic obstructive pulmonary disease allows stratification for prognosis: it is able to select a subgroup of patients at higher risk, which requires increased attention and optimization of treatment.

**Conclusion:** NPs, especially BNP/NT-proBNP are relevant prognostic biomarkers not only for patients with cardiovascular disease, but also for patients with COPD, acute exacerbations and haemodynamic disorders like PH and cor pulmonale. Estimating BNP/NT-proBNP in COPD patients has an important clinical implication: it allows the selection of a subgroup of patients at higher risk, which requires increased attention and treatment optimization.

**Keywords:** Chronic obstructive pulmonary disease, The elderly, Dyspnea, Acute exacerbation, Natriuretic peptides

## Introduction

Natriuretic peptides (NP) are considered a useful tool for diagnosing or excluding left heart failure (HF), determining the severity and prognosis of chronic and acute HF [1–5], and for distinguishing in the emergency department the cardiac or pulmonary origin of acute dyspnea [1, 4, 5]. NPs are strong and independent predictors of death and adverse events in HF and even in asymptomatic subjects in the community. There are three types of NPs. Atrial natriuretic peptide (ANP) and B-type or brain natriuretic peptide (BNP) are secreted from the cardiac atria and ventricles, respectively, and are responsible for the activation of natriuretic peptide receptor-A (NPR-A) [6]. C-type natriuretic peptide (CNP) is known as a primary stimulator of long bone growth, but has other functions as well, like the activation of a related cyclase, natriuretic peptide receptor-B (NPR-B). Both, NPR-A

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and NPR-B, catalyze the synthesis of cGMP, which mediates most known effects of natriuretic peptides. ANP acts as an endocrine and paracrine signal to decrease the blood pressure and cardiac hypertrophy. BNP acts as a paracrine messenger to reduce ventricular fibrosis. The third natriuretic peptide receptor, natriuretic peptide receptor-C (NPR-C), clears natriuretic peptides from the circulation through receptor-mediated internalization and degradation [6].

Low levels of BNP are stored with ANP in atrial granules, but in greater concentrations BNP is found in cardiac ventricles. Here in the ventricles, BNP is transcribed as needed in response to cardiac stress states such as volume overload [7]. Compared to ANP, circulating BNP has a significantly longer half-life of around 20 min in humans. So, it is well argued the measurement of serum BNP levels in clinic practices as a diagnostic indicator for heart failure [8].

The ANP and BNP are activating the NPR-A, which decreases the blood pressure achieved through natriuresis and diuresis, vasorelaxation, increased endothelial permeability, and antagonism of the renin-angiotensin system. Moreover, the release of NPs suppress myocyte hypertrophy and interstitial fibrosis in the heart, arguing for an important autocrine-paracrine role of these peptides in controlling the cardiac response during hypertrophy. Therefore, the existing evidence supports a role for BNP as both a marker and a modulator of hypertrophy [6, 8].

In the case of an increased cardiovascular risk, intensive therapeutic management applied to the patients with an elevated BNP level, reduced the incidence of HF and LV dysfunction [9].

While ANP is secreted in his active form, BNP is secreted as precursor form- proBNP, that is split up in BNP, the biological active form, and NT-proBNP, an inactive fragment [6, 10]. Although NT-proBNP is widely considered a useful tool for diagnosing or excluding HF and for distinguishing acute dyspnea of cardiac or pulmonary origin, few such studies have been carried out in geriatrics [1]. The aim of this study was to evaluate the informativeness of natriuretic peptides in elderly patients with chronic obstructive pulmonary disease, and to purpose it as an important component of the diagnosis process, for ensuring early effective interventions and this way the correct allocation of health resources [11, 12].

## Materials and methods

In order to achieve the stated objective, the initial search of the specialized scientific literature, identified by the search engine Google Search and from the databases PubMed, Hinari, SpringerLink and Scopus (Elsevier) was performed. The publications were selected according to the following keywords: "chronic obstructive pulmonary disease," "natriuretic peptides," "dyspnea," "acute exacerbation," "elderly." After processing the information in the databases, we selected all publications in English starting with January 1990.

For the advanced selection of bibliographic sources, the following filters were applied: full text articles, articles in English, articles published during the years 1990–2021. After a preliminary analysis of the titles, original, editorial, narrative, systematic, and meta-analysis articles, were selected those articles that contained relevant information and contemporary concepts about the significance of natriuretic peptides in diagnostic algorithms of stable and complicated COPD in the intended geriatric population. Additionally, a search was performed in the bibliographic reference lists of the identified sources in order to highlight relevant additional publications, which were not found during the initial search in the databases. According to the search criteria, 465 full articles were identified. The final literature contains 47 relevant sources, which provided information on diagnostic relevance of natriuretic peptides in elderly patients with stable COPD, COPD in acute exacerbation, and COPD hemodynamic complications like heart failure and pulmonary hypertension.

## Results

After the analyzing and processing of the selected articles, were relieved several mechanisms that could explain the increase in BNP/NT-proBNP in patients with COPD:

1. Airway obstruction is decreasing the expiratory flow and causes pulmonary hyperinflation, which is associated with decreased cardiac function and may increase plasma BNP/NT-proBNP levels [4, 9, 13–15].
2. Chronic hypoxia causes NP secretion through two mechanisms: (1) hypoxia is the most important factor in the development of pulmonary hypertension (PH), by inducing pulmonary vasoconstriction, and RV wall distension with interventricular septum deviation, impaired filling and increased filling pressure in LV, (2) hypoxia causes the direct release of BNP/NT-proBNP from the myocardium [4, 13, 16].
3. The BNP/NT-proBNP level may be a marker of systemic or lung inflammation during acute exacerbation of COPD (AECOPD), which differs qualitatively or quantitatively from stable COPD. This change caused by inflammation syndrome may be related to LV preload due to systemic vasoconstriction, pulmonary hyperinflation, or inflammation process, that may increase BNP/NT-proBNP levels by increasing stress on the LV wall [17].

4. Exercise or respiratory disorders in sleep (overlap syndrome—the combination of obstructive sleep apnea and COPD) worsen the hypoxia, a fact that can cause additional increase of NPs [13–15, 18, 19].

Plasma BNP/NT-proBNP levels are elevated in patients with stable COPD, but due to lower myocardial mass, increases in BNP/NT-proBNP related to RV dysfunction, PH, and cor pulmonale in COPD patients are lower than those seen in patients with left heart dysfunction [2, 4, 16]. However, some scientists believe that BNP/NT-proBNP may play a role in the early detection of PH in COPD patients. In several conditions associated with PH, BNP/NT-proBNP levels correlate with the degree of functional lung damage [4, 16].

Also, according to age and other comorbidities, plasma BNP/NT-proBNP levels can suffer modifications. Fabio Fabbian et al. studied the influence of age, renal impairment, and COPD on BNP/NT-proBNP levels in patients aged 80 ± 6 years. The statistical analysis carried out, revealed that NT-proBNP was higher than the normal reference values in 68.7% of patients and its levels increased in the 5 different stages of chronic kidney disease. Subjects with high NT-proBNP had lower haemoglobin levels (11.6 ± 2.1 vs 12.8 ± 1.9 g/dl, $p = 0.003$), higher prevalence of atrial fibrillation (54.3 vs 25%, $p = 0.001$), and little lower prevalence of pulmonary diseases (29.7 vs 57.5%, $p = 0.005$). The study concluded that a disease different from cardiac heart failure appears to affect NT-proBNP plasma levels in elderly like chronic kidney disease, anemia, and cardiac rhythm alterations [20].

#### Stable chronic obstructive pulmonary disease

There are few studies that have examined the plasma levels of BNP/NT-proBNP in patients with stable COPD without PH or cor pulmonale [15, 21], and the clinical significance of BNP/NT-proBNP value in determining the severity of COPD and identifying the risk of secondary PH developing [18]. However, the usefulness of this parameter in patients with stable COPD and inpatients with AECOPD is still limited [15].

The test performed in elderly patients with stable COPD ruled out HF with reasonable accuracy (all negative predictive values were above 0.85 with positive predictive values of approximately 0.4). In patients with COPD, NT-proBNP/BNP showed high negative predictive values (0.80–0.98). However, in the population with stable COPD, the positive predictive values were relatively low [9, 22].

Plasma BNP/NT-proBNP levels are significantly higher in patients with stable COPD, including without HP and without a cor pulmonale, compared to healthy people, and higher at inpatients with AECOPD compared to patients with stable COPD [15, 21, 23, 24]. Plasma levels of NT-proBNP in patients with stable COPD increase significantly concomitantly with the severity of the disease according to the GOLD classification and correlate inversely proportional with the maximum expiratory volume in the first second [18, 21].

Plasma levels of BNP/NT-proBNP were significantly higher in men with stable COPD in stages II, III, and IV compared to control group subjects (healthy smoking men) [18], in patients with COPD in stage III and IV, had higher levels of BNP/NT-proBNP compared to patients with BPOC in stage II [13], and higher levels in patients with chronic respiratory failure associated with cor pulmonale compared to patients with chronic respiratory failure without cor pulmonale [25]

Thus, a significant increase in plasma BNP/NT-proBNP levels concomitantly with the severity of the disease, chronic respiratory failure progression and development of secondary PH and cor pulmonale in patients with previous stable COPD suggests that plasma BNP/NT-proBNP may be a useful prognostic marker to monitor COPD progress and identify cases of secondary PH in patients with stable COPD [13, 18, 26].

BNP/NT-proBNP levels, measured during the clinical stability of COPD patients, is an independent predictor of respiratory exacerbations, even in individuals without obvious CVD, is an indicator to stratify patients' risk for complications developing and can contribute to personalization of outpatient medical care [26].

#### Acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

Plasma levels of BNP/NT-proBNP were significantly higher in inpatients with AECOPD than in patients with stable COPD (during remission) [4, 14, 19, 21, 22]. Although BNP/NT-proBNP levels vary widely between subjects with stable COPD, they increase slightly but significantly during exacerbation in most subjects with COPD and decrease to baseline after recovery. The clinical significance of these changes is unclear, but evidence of cardiac dysfunction in the early stages of AECOPD is consistent with previous findings of arterial stiffness worsening a few days after the onset of exacerbation [22].

BNP/NT-proBNP level is a strong predictor of poor short-term (30 days) and long-term (5 years) prognosis among patients with AECOPD [17, 27]. Moreover, there was a strong association between the BNP/NT-proBNP levels and the need to admit patients to the intensive care unit, but there was no significant correlation between the BNP/NT-proBNP levels and mortality. Possibly a part of the BNP/NT-proBNP increase in these patients may be

due to inflammatory response observed in EABPOC, with unsuspected concomitant HF, or significant PH [4].

Nevertheless a retrospective cohort study and two prospective cohort studies confirmed that high BNP/NT-proBNP levels are a strong predictor for assessing the severity of COPD, predicting early (30 days) and late (12 months) mortality, early identification of developmental risk of clinical ventricular dysfunction in patients with AECOPD, with or without HF and independent of other known prognostic indicators. The pathophysiological basis for this finding is unknown, but acute cardiac involvement in AECOPD may be an important prognostic factor [28–30].

Elevated levels of NT-proBNP have also been observed in patients with AECOPD without primary CVD. Cor pulmonale, secondary PH and hypoxemia are important stimuli for the release of NT-proBNP from the right side of the heart [23, 24]. Patients with AECOPD with elevated NT-proBNP levels and no HF had a longer hospital stay and a higher likelihood of hospitalization in the intensive care unit. Thus, large-scale prospective studies are needed to validate these findings and to assess whether there is a direct correlation between the complications of AECOPD and right heart dysfunction [31].

Therefore, plasma NT-proBNP levels can be proposed as a potential useful biomarker for the differential diagnosis and prognosis of COPD and a good assessment tool of acute exacerbation [15]. Increased BNP/NT-proBNP values were found to be in 16–60% patients with AECOPD, even in the absence of PH, and persisted in about 50% of patients upon discharge [9]. BNP/NT-proBNP are mainly used to exclude HF at the threshold of < 125 pg/ml for NT-pro-BNP and < 35 pg/ml for BNP [32].

There are several possible explanations that may justify an increase in BNP/NT-proBNP in patients with AECOPD without clinical signs of HF. On the one hand, the pressure overload of RV, generated by hypoxic pulmonary vasoconstriction, acts as a stimulus for BNP/NT-proBNP synthesis and secretion. On the other hand, elevated NT-proBNP concentrations may be a consequence of subclinical LV dysfunction [33]. AECOPD has an independent impact on plasma levels of BNP/NT-proBNP that is not attributable to HF [22]. Elevated levels of BNP/NT-proBNP on discharge predict the outcome (death or survival) of hospitalized patients for AECOPD [34].

#### Chronic obstructive pulmonary disease and heart failure

NT-proBNP/BNP evaluation contributes to the detection of asymptomatic chronic HF, including diastolic LV dysfunction, in patients with COPD, which correlates with the severity and prognosis of COPD [35–37]. Some authors recommend a BNP level > 400 pg/mL or an NT-proBNP level > 2000 pg/mL for the diagnosis of HF [38, 39].

According to Rubinsztajn R et al. and Labaki W et al., the serum concentration of NT-proBNP was statistically significantly higher in the group of patients with COPD and HF, compared with patients with stable COPD with no comorbidities, this way predicting a poor short- or long-term prognosis. Using this modern tool for diagnosing the association of HF to COPD, will allow the necessary corrections in the therapeutic management [26, 40].

NT-proBNP/BNP have always been significantly elevated in patients with COPD and HF or COPD and concomitant LV systolic dysfunction compared to those without these comorbidities. In addition, there is no level of NT-proBNP/BNP that perfectly differentiates COPD in patients with or without HF [9, 22].

Although a prospective study found that NT-proBNP levels are a sensitive and specific method of distinguishing between acute cardiac and noncardiac dyspnea in patients aged 70 years or older (mean age 81 ± 7 years). The median value of the NT-proBNP concentration was 7906 pg/ml in patients with cardiac dyspnea, and 1066 pg/ml in patients with noncardiac dyspnea. At a cutoff of 2000 pg/mL, NT-proBNP had a sensitivity of 86%, a specificity of 71%, and an overall accuracy of 80% for cardiac dyspnea. The study concluded that NT-proBNP appears to be a sensitive and specific means of distinguishing pulmonary from cardiac causes of dyspnea in elderly patients. Also, it revealed that an optimal diagnostic strategy requires the use of 2 cutoffs and further investigations of patients with values in the gray area (with the 2 cutoffs < 1200 and > 4500 pg/mL [41].

Other study performed by Roderick H. Tung et al., evaluated the NT-proBNP values in dyspneic patients with previous chronic obstructive pulmonary disease or asthma associated with HF. The groups have been compared from the point of view of the presence of acute or chronic heart failure and the association of COPD or asthma to it. The study revealed that in patients who had both previous acute heart failure and chronic obstructive pulmonary disease or asthma ($n = 52$), median NT-proBNP levels were significantly higher in those with acute heart failure (4435 pg/mL) than patients with chronic obstructive pulmonary disease or asthma exacerbation (536 pg/mL), at cut off value of 450 pg/mL for patients younger than 50 years and 900 pg/mL for patients 50 years or older (sensitivity of 87% (95% confidence interval [CI] 72 to 93%) and a specificity of 84% (95% CI 76 to 88%)). They concluded that NT-proBNP may be a useful adjunct to standard clinical evaluation of dyspneic patients with previous obstructive airway disease [42].

### Chronic obstructive pulmonary disease and pulmonary hypertension (PH)

Serum BNP/NT-proBNP is elevated in patients with PH, including PH secondary to chronic lung disease, and may be a useful prognostic marker for monitoring the progression and severity of COPD complicated with PH [13, 18, 43]. However, its role in detecting PH associated with chronic lung disease is not well established [44].

According to the results of several studies, the serum concentration of NT-proBNP may be useful in the diagnosis of PH in patients with end-stage chronic lung disease and normal LV function. However, in patients with compensated disease or mild-to-moderate PH, the serum concentration of NT-proBNP may be within a normal range despite the presence of hemodynamically confirmed PH [43].

Two cohort studies have reported that NT-proBNP values < 95 ng/mL may be effective in excluding echocardiography-assessed PH in patients with chronic lung disease [45, 46]. Furthermore, studies have suggested that BNP/NT-proBNP concentrations are useful not only for identifying patients with RV dysfunction and hypoxic PH, but may also be a prognostic marker for monitoring the progression and severity of COPD, but also for diagnosing cor pulmonale in COPD patients [13].

### The prognosis' significance of natriuretic peptides in chronic obstructive pulmonary disease

A systematic literature review and meta-analysis and a more recent retrospective cohort study clearly illustrated that elevated BNP/NT-proBNP levels can be used as independent predictors of all-cause mortality, the need for intubation, and the application of invasive mechanical ventilation in patients with COPD with or without exacerbation [9, 23, 47]. The previous history of CVD, a common cause of increased BNP/NT-proBNP levels, did not influence the relationship between NT-proBNP and overall mortality in COPD patients. The predictive value of high NT-proBNP levels is maintained in both long-term and short-term follow-up [47]. Higher levels of NT-proBNP have been significantly associated with hospital rates, early and long-term mortality. Determination of BNP/NT-proBNP levels is helpful in diagnosing cardiac dysfunction in patients with COPD, especially during acute exacerbation [23].

A study of 192 consecutive patients aged 41 to 95 years (median 75 years) with AECOPD found an association of NT-proBNP > 587.9 pg/ml with a significant increase in mortality at 1 year and the value > 782.2 pg/ml with cardio-pulmonary deaths. This association persisted after adjustment for age, gender, creatinine levels, and heart rate. Negative predictive values for these cut-off points ranged from 89 to 97%. Therefore, NT-proBNP levels are significantly increased during acute exacerbations of chronic lung disease, in the absence of clinically apparent HF and could be particularly useful for stratifying the short-term risk of patients with chronic lung disease [48].

In geriatric patients with AECOPD, the determination and monitoring of average BNP/NT-proBNP dynamics is a valuable advantage in predicting mortality, the need for non-invasive mechanical ventilation, the need for invasive mechanical ventilation and transfer to stand-alone breathing [23, 49].

## Discussion

The studies mentioned above reveal that BNP/NT-proBNP evaluation contributes to the detection of asymptomatic chronic HF, including diastolic LV dysfunction, associated with COPD. Moreover, the BNP/NT-proBNP value correlates with the severity of the COPD disease and the development of hemodynamic complications such as PH and cor pulmonale. According to the studies available, the usefulness of the BNP/NT-proBNP in patients with stable COPD is still limited, but has a higher value at inpatients with AECOPD than stable COPD, and in stable COPD patients than in healthy subjects. Plasma levels of NT-proBNP in patients with COPD are increasing significantly concomitantly with the severity of the disease. So, we can conclude that, BNP/NT-proBNP level is a strong predictor of poor short-term (30 days) and long-term (5 years) prognosis among patients with AECOPD. Moreover, serum BNP/NT-proBNP is elevated in patients with PH, including PH secondary to chronic lung disease, and may be a useful prognostic marker for monitoring the progression, severity, and prognosis of stable COPD and PH.

## Conclusions

1. Natriuretic peptide values are frequently elevated in patients with chronic obstructive pulmonary disease, reflecting complex cardio-pulmonary interrelations by pulmonary vascular remodeling, followed by the cardiac reshaping with pulmonary hypertension, cor pulmonale, and diastolic dysfunction of LV. The additional increase in BNP/NT-proBNP values during acute exacerbation of chronic obstructive pulmonary disease is probably a marker for the assessment of acute estate of COPD and varying degrees of underlying cardiopulmonary disease.
2. Age and renal impairment may significantly affect circulating levels of BNP/ NT-proBNP, potentially undermining their diagnostic value. A limitation of the interpretation of natriuretic peptides in lung diseases is the confusing effect of concomitant diseases

- heart failure, hypoxia, sepsis and kidney failure. In patients over 65 years of age with many comorbidities, NT-proBNP should always be interpreted after a thorough and thorough examination of the entire clinical picture.
3. The results of the studies suggest the role of natriuretic peptides as relevant prognostic biomarkers not only for patients with cardiovascular disease, but also for patients with chronic obstructive pulmonary disease, which has an important clinical implication. The determination of these biomarkers in patients with chronic obstructive pulmonary disease allows stratification for prognosis: it is able to select a subgroup of patients at higher risk, which requires increased attention and optimization of treatment. Further studies are needed to determine the cut-off value of BNP/NT-proBNP that may predict the risk of exacerbation or death in patients with chronic obstructive pulmonary disease.

**Abbreviations**

COPD: Chronic obstructive pulmonary disease; NP: Natriuretic peptides; ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide; CNP: C-type natriuretic peptide; NPR-A: Natriuretic peptide receptor-A; NPR-B: Natriuretic peptide receptor-B; NPR-C: Natriuretic peptide receptor-C; proBNP: BNP precursor; NT-proBNP: Inactive terminal fragment of proBNP; HF: Left heart failure; LV: Left ventricle; RV: Right ventricle; PH: Pulmonary hypertension; AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; CVD: Cardiovascular disease.

**Authors' contributions**

All authors played an important role in producing the idea of the article and in writing the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

No datasets were performed or analyzed for the current study, so data sharing is not applicable to this article.

## Declarations

**Ethics approval and consent to participate**

All the studies included into the review had the ethics approval and consent to participate into the study.

**Consent for publication**

All the authors consented to the publication of the article.

**Competing interests**

The authors declare that they have no competing interests.

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**References**

1. Wang Q, Cao X, Wang X et al (2013) Utility of NT-proBNP for identifying LV failure in patients with acute exacerbation of chronic bronchitis. PLoS One 8(1):e52553.
2. André S, Conde B, Fragoso E et al (2019) COPD and cardiovascular disease. Pulmonology 25(3):168–176.
3. Blanco R, Ambrosio G, Belziti C et al (2020) Prognostic value of NT-proBNP, and echocardiographic indices of diastolic function, in hospitalized patients with acute heart failure and preserved left ventricular ejection fraction. Int J Cardiol 317:111–120.
4. Salerno D, Marik P (2011) Brain natriuretic peptide measurement in pulmonary medicine. Respir Med 105(12):1770–1775.
5. Wettersten N, Maisel A (2016) Biomarkers for heart failure: an update for practitioners of internal medicine. Am J Med 129(6):560–567.
6. Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM (2009) Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. Handb Exp Pharmacol 191:341–366. https://doi.org/10.1007/978-3-540-68964-5_15.
7. Thuerauf DJ, Hanford DS, Glembotski CC (1994) Regulation of rat brain natriuretic peptide transcription. A potential role for GATA-related transcription factors in myocardial cell gene expression. J Biol Chem 269(27):17772–17775.
8. Gardner DG (2003) Natriuretic peptides: markers or modulators of cardiac hypertrophy? Trends Endocrinol Metab 14(9):411–416.
9. Hawkins N, Khosla A, Virani S et al (2017) B-type natriuretic peptides in chronic obstructive pulmonary disease: a systematic review. BMC Pulm Med 17(1):11.
10. Luers C, Wachter R, Kleta S, Uhlir M, Koschack J, Scherer M, Binder L, Herrmann-Lingen C, Zapf A, Kulle B, Kochen MM, Pieske B (2010 Apr) Natriuretic peptides in the detection of preclinical diastolic or systolic dysfunction. Clin Res Cardiol 99(4):217–226.
11. Jarad N (2011) Chronic obstructive pulmonary disease (COPD) and old age? Chron Respir Dis 8(2):143–151.
12. Kobayashi S, Yanai M, Hanagama M, Yamanda S (2014) Burden of chronic obstructive pulmonary disease in the elderly population. Respir Investig 52(5):296–301.
13. Chi SY, Kim EY, Ban HJ et al (2012) Plasma N-terminal pro-brain natriuretic peptide: a prognostic marker in patients with chronic obstructive pulmonary disease. Lung 190(3):271–276.
14. Inoue Y, Kawayama T, Iwanaga T, Aizawa H (2009) High plasma brain natriuretic peptide levels in stable COPD without pulmonary hypertension or cor pulmonale. Intern Med 48(7):503–512.
15. Gupta N, Vanane J, Dubey G et al (2018) Plasma brain natriuretic peptide levels in chronic obstructive pulmonary disease patients without pulmonary hypertension. J. Evid. Based Med. Healthc 5(25):1926–1929.
16. Budweiser S, Luchner A, Jörres R et al (2007) NT-proBNP in chronic hypercapnic respiratory failure: a marker of disease severity, treatment effect and prognosis. Respir Med 101(9):2003–2010.
17. Shafuddin E, Fairweather S, Chang C, Tuffery C, Hancox R (2021) Cardiac biomarkers and long-term outcomes of exacerbations of COPD: a long-term follow-up of two cohorts. ERJ Open Res 7(1):00531–02020.
18. Mansour A, Abdelsamad A, El Arman M (2012) Prognostic value of plasma brain natriuretic peptide in patients withstable chronic obstructive pulmonary disease. Egypt J Chest Dis Tuberc 61:297–300.
19. Mallawany HE, Mahmoud MI, Morsi TS, EL-Shiekh RM. (2014) Role of N-terminal pro B-type natriuretic peptide in acute exacerbation of chronic obstructive pulmonary disease. Egypt J Chest Dis Tuberc 63:57–65.
20. Fabbian F, De Giorgi A, Pala M, Tiseo R, Portaluppi F (2011) Elevated NT-proBNP levels should be interpreted in elderly patients presenting with dyspnea. Eur J Intern Med 22(1):108–111. https://doi.org/10.1016/j.ejim.2010.07.013.
21. El Gazzar AG, Hibah NA, Gouda TM, Mansour AI, Sabry MY (2017) Plasma brain natriuretic peptide levels in COPD without pulmonary hypertension. Egypt J Chest Dis Tuberc 66:49–54.
22. Nishimura K, Nishimura T, Onishi K, Oga T, Hasegawa Y, Jones P (2014) Changes in plasma levels of B-type natriuretic peptide with acute exacerbations of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 9:155–162.
23. Ediboğlu Ö, Kıraklı C (2018) Can NT-proBNP levels predict prognosis of patients with acute exacerbations of chronic obstructive pulmonary disease in the intensive care unit? Balkan Med J 35(6):422–426.

24. Hoiseth A, Omland T, Hagve T, Brekke P, Soyseth V (2012) NT-proBNP independently predicts long term mortality after acute exacerbation of COPD - a prospective cohort study. Respir Res 13(1):97.
25. Bando M, Ishii Y, Sugiyama Y, Kitamura S (1999) Elevated plasma brain natriuretic peptide levels in chronic respiratory failure with cor pulmonale. Respir Med 93(7):507–514.
26. Labaki W, Xia M, Murray S et al (2018) NT-proBNP in stable COPD and future exacerbation risk: Analysis of the SPIROMICS cohort. Respir Med 140:87–93.
27. Akpinar E, Ateş C, Akpinar S, Hoşgün D (2020) Impairment in heart functions and prognostic role of N-terminal pro-brain natriuretic peptide in patients with chronic obstructive pulmonary disease exacerbation. Eurasian J Pulmonol 22:48–54.
28. Chang CL, Robinson SC, Mills GD et al (2011) Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. Thorax 66(9):764–768.
29. Yao C, Wang L, Shi F et al (2021) Optimized combination of circulating biomarkers as predictors of prognosis in AECOPD patients complicated with Heart Failure. Int J Med Sci 18(7):1592–1599.
30. Pérez-Calvo J, Sánchez-Marteles M, Ruiz-Ruiz F, Morales-Rull J, Nieto-Rodríguez J (2010) Differential prognostic utility of NTproBNP and Cystatin C in patients with acute exacerbation of chronic pulmonary disease. JRSM Short Rep. 1(5):44.
31. Adrish M, Nannaka V, Cano E, Bajantri B, Diaz-Fuentes G (2017) Significance of NT-pro-BNP in acute exacerbation of COPD patients without underlying left ventricular dysfunction. Int J Chron Obstruct Pulmon Dis 12:1183–1189.
32. Trinkmann F, Saur J, Borggrefe M, Akin I (2019) Cardiovascular comorbidities in chronic obstructive pulmonary disease (COPD) - current considerations for clinical practice. J Clin Med 8(1):69.
33. Sánchez-Marteles M, Cecilio-Irazola A, Vañó-Sanchis D, Nuviala-Mateo R, Serrano-Martínez S, Pérez-Calvo J (2009) NT-proBNP in chronic obstructive pulmonary disease patients. An Sist Sanit Navar 32(2):235–241.
34. Marcun R, Sustic A, Brguljan P et al (2012) Cardiac biomarkers predict outcome after hospitalisation for an acute exacerbation of chronic obstructive pulmonary disease. Int J Cardiol 161(3):156–159.
35. Le Jemtel T, Padeletti M, Jelic S (2007) Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. J Am Coll Cardiol 49(2):171–180.
36. AboEl-Magd G, Hassan T, Aly M, Mabrouk M (2017) Echocardiography and N-terminal-pro-brain natriuretic peptide in assessment of left ventricular diastolic dysfunction in stable COPD in relation to disease severity. Egypt J Chest Dis Tuberc 66:75–80.
37. Jelic S, Le Jemtel T (2006) Diagnostic usefulness of B-type natriuretic peptide and functional consequences of muscle alterations in COPD and chronic heart failure. Chest. 130(4):1220–1230.
38. Zeng Q, Jiang S (2012) Update in diagnosis and therapy of coexistent chronic obstructive pulmonary disease and chronic heart failure. J Thorac Dis 4(3):310–315.
39. de Miguel DJ, Chancafe Morgan J, Jiménez GR (2013) The association between COPD and heart failure risk: a review. Int J Chron Obstruct Pulmon Dis 8:305–312.
40. Rubinsztajn R, Nasiłowski J, Przybyłowski T, Karwat K, Chazan R (2013) Usefulness of NT-proBNP serum level in the diagnosis of dyspnea in COPD patients. Pneumonol Alergol Pol 81(1):24–29.
41. Berdagué P, Caffin P, Barazer I et al (2006) Use of N-terminal prohormone brain natriuretic peptide assay for etiologic diagnosis of acute dyspnea in elderly patients. Am Heart J 151(3):690–698.
42. Tung RH, Camargo CA Jr, Krauser D, Anwaruddin S, Baggish A, Chen A, Januzzi JL Jr. Amino-terminal pro-brain natriuretic peptide for the diagnosis of acute heart failure in patients with previous obstructive airway disease. Ann Emerg Med 2006 Jul;48(1):66-74. doi: https://doi.org/10.1016/j.annemergmed.2005.12.022. Epub 2006 Feb 17. PMID: 16781921.
43. Nowak J, Hudzik B, Niedziela J, Rozentryt P, Zembala M, Gąsior M (2018) Role of pro-brain natriuretic peptide serum concentration in the detection of pulmonary hypertension in patients with end-stage lung diseases referred for lung transplantation. Transplant Proc. 50(7):2044–2047.
44. Lewis R, Durrington C, Condliffe R, Kiely D (2020) BNP/NT-proBNP in pulmonary arterial hypertension: time for point-of-care testing? Eur Respir Rev 29(156):200009.
45. Andersen C, Mellemkjær S, Hilberg O, Bendstrup E (2016) NT-proBNP <95 ng/l can exclude pulmonary hypertension on echocardiography at diagnostic workup in patients with interstitial lung disease. Eur Clin Respir J 3:32027.
46. Bonderman D, Wexberg P, Martischnig A et al (2011) A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. Eur Respir J 37(5):1096–1103.
47. Pavasini R, Tavazzi G, Biscaglia S et al (2017) 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 14(2):117–126.
48. Medina AM, Marteles MS, Sáiz EB et al (2011) Prognostic utility of NT-proBNP in acute exacerbations of chronic pulmonary diseases. Eur J Intern Med 22(2):167–171.
49. Fabbian F, De Giorgi A, Pala M, Tiseo R, Portaluppi F (2011) Elevated NT-proBNP levels should be interpreted in elderly patients presenting with dyspnea. Eur J Intern Med 22(1):108–111.


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