

## Nt-probnp as a Prognostic Marker in Different Gold Classes in Patients with Chronic Obstructive Pulmonary Disease (COPD)

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### Abstract

#### Background:

Chronic obstructive pulmonary disease (COPD) was the fifth leading cause for early death and disability in 2020 with approximately 2.75 million deaths per year, which was 4.8% in total from the general mortality. Right ventricular hypertrophy with preserved systolic function is the most common finding in patients with COPD. The development of pulmonary hypertension leads to DV (right ventricle) dilatation and DV heart failure during the course of the disease.

#### Material and methods:

The design of the research was a prospective-clinical cross-sectional study as we analyzed 94 patients with COPD. All patients were divided in groups according to the degree of obstruction and classified by the GOLD classification system into four groups from GOLD 1 – GOLD4. All of our patients were analyzed thoroughly on admission and during hospital stay. ECG was made, Nt-proBNP analysis and basic and advanced echocardiography evaluation. Natriuretic peptides were measured and processed by commercially available assays with excellent precision where cut-off value was 125pg/ml. Echo analysis was done by Vivid 7 echo machine with a special feature to right heart chamber characteristics.

#### Results:

In terms of risk factors, hypertension, diabetes mellitus and hyperlipidemia were examined in all 94 patients in our study. Arterial hypertension was present in half of the patients, 51.06%. Diabetes mellitus was present in 19.15% of analyzed patients. The analysis of Nt-proBNP level in our study showed that the average value of this natriuretic peptide was above reference range and it was 236.27pg/ml. The highest average values of NT-proBNP were registered in GOLD class 3, while the lowest average and maximum value of NT-proBNP was found in GOLD class 2. According to the results of the Tukey post-hoc test, there was a statistically significant difference in Nt-proBNP levels between GOLD class 2 and GOLD class 3. The average values

of Nt-proBNP in the group of patients with acute exacerbation was far higher than in the group of chronically stable patients. The difference between the two groups was 3.5 times in GOLD class 3 and approximately 2 times in GOLD class 4.

**Conclusion:**

BNP and NT-proBNP are natriuretic peptides that are secreted under conditions of cardiac stress and weakness. They are established biomarkers and are listed in the guidelines for chronic heart failure as they are quantitative markers used for diagnosis and risk stratification. Still, more studies with a larger number of patients are needed to confirm the role of Nt-proBNP in patients with COPD in different stages of GOLD and progression of the disease.

**Keywords:** Nt-proBNP, right heart, echo parameters

**Introduction:**

Chronic obstructive pulmonary disease (COPD) according to World Health Organization was the fifth leading cause of early death and disability in 2020 with approximately 2.75 million deaths per year, which was 4.8% in total from the general mortality. In conditions with acute exacerbation, in-hospital mortality increases from 2.5-10 %. Mortality from COPD is higher in men, it increases with age, and the severity and the duration of the disease also increases.<sup>1)2)</sup>

COPD is manifested with typical presentation of progressive shortness of breath, chronic cough, recurrent wheezing and sputum production. According to spirometry and Tiffeneau index, COPD patients are divided by GOLD classification system into 4 class: from GOLD 1 class (FEV1 >80%) to GOLD 4 where patients have severely reduced lung capacity, (FEV1 <30%).

As the disease progresses, more cardiovascular complications appear. Right ventricular hypertrophy with preserved systolic function is the most common finding in patients with COPD. COPD results in a relatively slow process of elevation of pulmonary artery pressure creating the opportunity for adequate adaptation of the right ventricle. Increased pulmonary vascular resistance (PVR) is not so rare in COPD patients. The development of pulmonary hypertension leads to DV (right ventricle) dilatation and DV heart failure during the course of the disease.

Patients with more severe form of COPD have more complications and have a more pronounced degree of right heart failure. Hypoxemia, right ventricular overload due to secondary pulmonary hypertension are important stimuli for BNP and NT-proBNP release from the right side of the heart. The mechanism in fact increases the pulmonary pressure which induces right ventricular wall stretching and hence promotes NT-proBNP release.<sup>3)4)</sup>

Increased Nt-proBNP levels are found in COPD patients with no signs of heart failure, most likely due to right ventricular load. COPD causes the wall of the right ventricle to stretch and dilate, while on the other hand, increased vascular pressure promotes secretion of NT-proBNP. BNP is released in case of hypoxemia in patients with COPD with no signs of heart failure.<sup>3)4)</sup>

**Material and methods:**

The design of our research was a prospective-clinical cross-sectional study. We analyzed 94 patients with COPD. All patients were divided in groups according to the degree of obstruction and classified by the GOLD classification system into four groups. Tiffeneau index (FEV1/FVC <70%) defines GOLD groups into 4 stages of the disease according to the degree of obstruction.

GOLD 1-patients with mild form of COPD (FEV/FVC >80%)

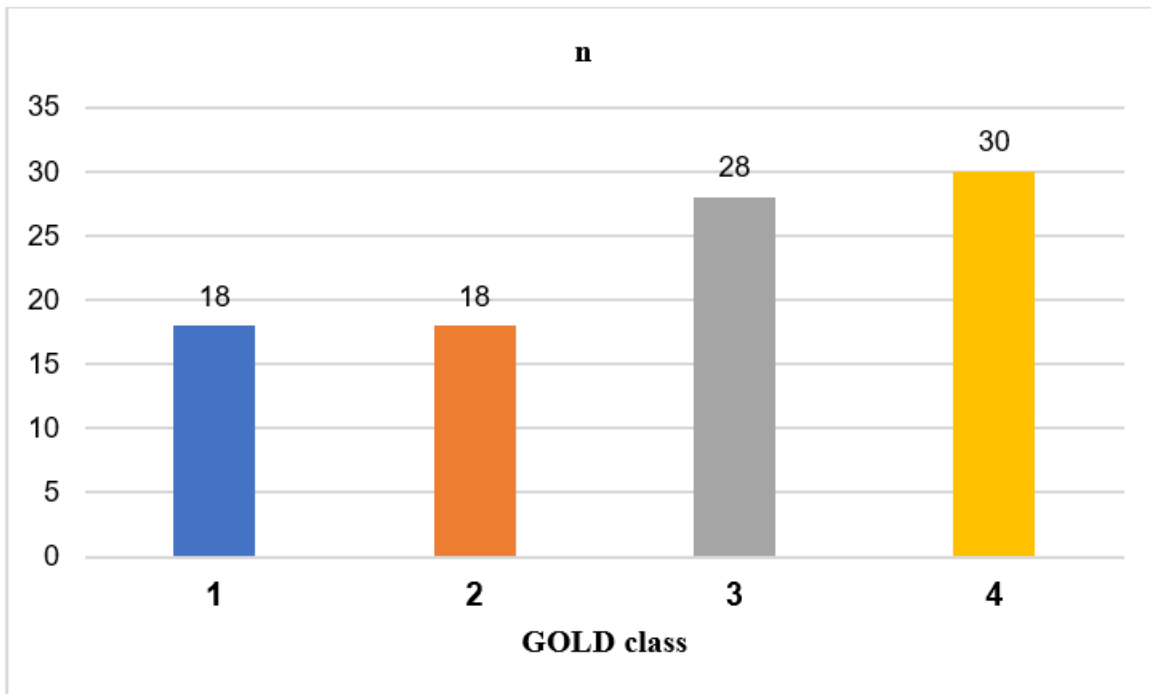
GOLD 2-patients with moderate form of COPD (FEV1/FVC 50-80%)

GOLD 3- patients with severe form of COPD (FEV1/FVC 30-50%)

GOLD 4-patients with very severe form of COPD (FEV1/FVC <30%)

**Results:**

Figure1.Distribution of patients in GOLD classification



GOLD I and GOLD II class included 18 patients each, GOLD III comprised 28 and GOLD IV consisted of 30 patients.

In our study all patients were analyzed thoroughly on admission and during hospital stay, which included ECG, Nt-proBNP analysis and basic and advanced echocardiography evaluation. In all patients, venous blood was taken in a serum tube (5 ml) for analysis of NT-proBNP. Natriuretic peptides were measured and processed by commercially available assays with excellent precision. Their value was expressed in pg/ml, pmol/L. In our study the hormone Nt-proBNP could be analyzed due to its availability and possibility of quantification at the University Clinic

for Biochemistry. Cut-off value for Nt-proBNP above 125 pg/ml was considered to be pathological.

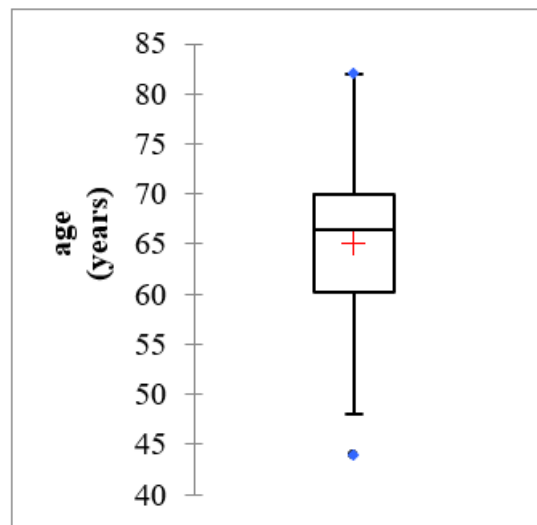
**Table 1.** (male/female)

gender	N	%
male	64	68,09
female	30	31,91
total	<b>94</b>	<b>100,00</b>

In our study of 94 patients, male gender was predominant with 64 patients *versus* 30 female patients (tab 1). Additional subcategorization by GOLD classes confirmed male predilection.

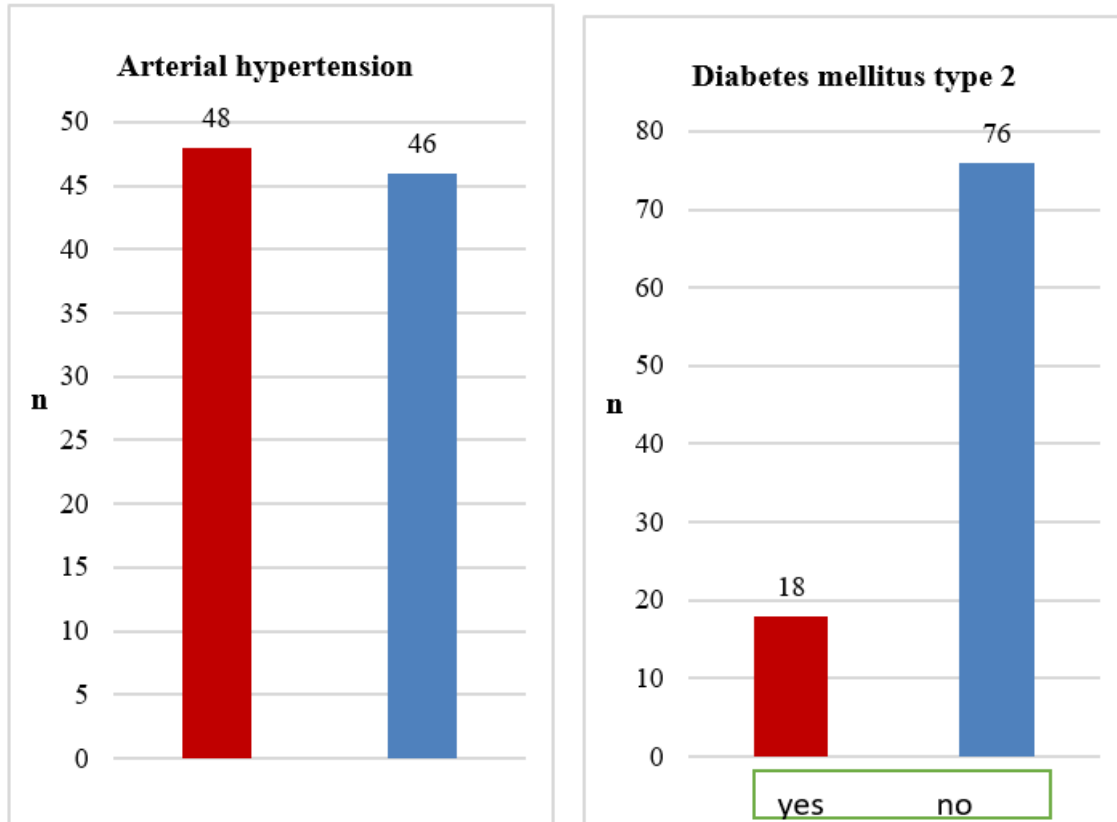
Our study included all patients over 18 years old. The average age of patients in this study was 65 years with standard deviation (SD)+/- 15.04, while the minimum and maximum age was 44 and 82, respectively(tbl2).

**Table 2.** Distribution of patients with COPD by age



In terms of risk factors, hypertension, diabetes mellitus and hyperlipidemia were examined in all 94 patients in our study. Arterial hypertension was present in half of the patients, 51.06% (tbl 3). Arterial hypertension was lowest in GOLD class 1, with presence of 12.5% and significantly higher in GOLD class 3 (35.42%) and in GOLD class 4 (33.33%).

**Table 3.** Arterial hypertension and diabetes mellitus type 2 in patients with COPD



Diabetes mellitus was present in 19.15% of analyzed patients (tbl 3). It is an interesting fact that the number of patients with diabetes mellitus type 2 was smallest in GOLD class 4 (11.11%) compared to GOLD classes 1 and 2 (33.33%).

The prevalence of hyperlipidemia was relatively low in all patients (5.32%).

The analysis of Nt-proBNP in our study showed that the average value of this natriuretic peptide was above the reference range and it was 236.27+/- 284.96pg/ml (tbl 4).

**Table4.**NT-proBNP level in all 94 patients

NT-proBNP(pg/ml)	Value
<b>N</b>	94
<b>Average</b>	236.27
<b>Standard deviation</b>	284.96
<b>Minimum</b>	14.96
<b>Maximum</b>	1881.00

**Table 5.**Nt-proBNP levels according to GOLD classes

NT-proBNP(pg/ml)	GOLD class				Kruskal-Wallis-test
	1	2	3	4	
<b>N</b>	18	18	28	30	
<b>average</b>	159,62	118,93	357,02	239,97	
<b>Standard deviation</b>	165,67	74,84	444,03	176,58	0,031
<b>Minimum</b>	62,20	18,07	14,96	24,82	
<b>maximum</b>	605,80	249,10	1881,00	683,00	

The highest average values of NT-proBNP and at the same time the most extensive maximum and minimum levels were registered in GOLD 3 class, while the lowest average and maximum NT-proBNP level was found in GOLD class 2 (table 5). Non-parametric Kruskal-Wallis test showed that the total differences in the distribution of the values of Nt-proBNP in all 4 GOLD groups were statistically significant.

**Table 6.**Analysis of the differences in Nt-proBNP levels between GOLD classes with the Tukey post-hoc test

Comparison between classes	GOLD	Difference (pg/ml)	Standard deviation	Tukey (HSD) Post-hoc test
2 versus 3		238.086	2.869	0.026
2 versus 4		121.043	1.478	0.455
2 versus 1		40.690	0.444	0.971
1 versus 3		197.396	2.379	0.089
1 versus 4		80.353	0.981	0.760
4 versus 3		117.044	1.622	0.372

Using the Tukey post-hoc test, a comparison of Nt-proBNP was performed for all 6 combinations of the four GOLD classes. According to the results of the Tukey post-hoc test, there was a statistically significant difference in Nt-proBNP levels between GOLD class 2 and GOLD class 3. The average Nt-proBNP level in GOLD class 2 was 238,086 pg/ml, and it was lower than in GOLD class 3 (table 5). Therefore, the Nt-proBNP level in this study was a marker of the risk of progression of pulmonary worsening only from GOLD class 2 to GOLD class 3.

There was a statistically significant difference in distribution of the of Nt-proBNP levels in GOLD class 2 and 3. (Table 6).

**Table 7.** Comparison of Nt-proBNP levels between acutely and chronically ill patients

Nt-proBNP(pg/ml)	Acute patients	Chronically stable	Mann-Whitney test
<b>N</b>	63	31	
<b>Average</b>	281.74	143.86	
<b>St deviation</b>	332.15	102.771	0.057
<b>Minimum</b>	14.961	16.80	
<b>Maximum</b>	1881.00	514.50	

In our study, a correlation of the Nt-proBNP levels in the group of patients with acute and chronic form of the disease was made. All our results are shown in Table 7.

Out of the entire group of 94 patients, 63 were patients with acute exacerbation while 31 were classified as chronically stable patients. As it can be seen from Table 7, the average Nt-proBNP levels in the group of patients with acute exacerbation were much higher than in the group of chronically stable patients (table 7).

**Table 8.** Comparison of Nt-proBNP levels between the GOLD classes in relation to acute and chronic patients

NT-proBNP(pg/ml)	GOLD 1		GOLD 2		GOLD 3		GOLD4	
	acute	chronic	acute	chronic	acute	chronic	acute	chronic
<b>n</b>	18	0	11	7	17	11	17	13
<b>average</b>	159,62	0	116,00	123,53	492,60	147,48	307,44	151,74
<b>SD</b>	165,67	0	66,41	92,08	527,99	82,23	182,20	127,32
<b>minimum</b>	62,20	0	58,15	18,07	14,96	16,80	24,82	33,11
<b>maximum</b>	605,80	0	225,00	249,10	1881,00	264,00	683,00	514,50
<b>Mann-Whitney test</b>	/	/	0,717	0,717	0,048	0,048	0,033	0,033

The difference between the two groups was 3.5 times in GOLD class 3 and approximately 2 times in GOLD class 4 (Table 9). With reference to the remaining groups with GOLD 2, 3 and 4, the Mann Whitney test showed a statistical significance of Nt-proBNP levels between the group of acute and the group of chronically stable patients (p<0.05).

**Table 9.** Analysis of Nt-proBNP levels in relation to acute and chronic patients in GOLD class 3 and 4 using Tukey (HSD) post-hoc test

Correlation	difference	Standard deviation	Tukey (HSD) Post-hoc test
Acute/chronically stable patient	245. 772	2.945	0.005

According to the results, there was a clear and highly statistical significance of NT-proBNP levels in relation to acute and chronic patients in GOLD class 3 and 4 ( $p < 0.01$ ).

**Discussion:**

Nt-proBNP is a noninvasive biomarker for diagnosis and monitoring of heart failure. Plasma concentration of BNP and Nt-proBNP are recommended as initial diagnostic tests in patients with symptoms suggestive of heart failure to rule out the diagnosis. The upper limits of normal setting are 35 pg/ml for BNP, and 125 pg/ml for Nt-proBNP.<sup>5)</sup>

Right ventricular end-diastolic wall stress and stiffness may be the predominant risk factor for Nt-proBNP release. They play a major role in patients with COPD due to existing pulmonary hypertension and right ventricular dysfunction and are a result of pulmonary ‘‘pressure overload’’. COPD itself causes stretching of the right ventricular wall and its dilatation, increased vascular pressure which in terms promotes secretion of Nt-proBNP.

Increased levels of Nt-proBNP are an independent risk factor for death in patients with COPD, hence some studies emphasize the importance of Nt-proBNP in COPD progression and the possibility of secondary pulmonary hypertension development.

In a recent study, published by a group of authors from Egypt, Nt-proBNP was pointed out to be a significant marker for acute exacerbation of COPD. **6)**The study evaluated the significance of NT-proBNP as a marker in acutely aggravated forms of COPD, which we have also done in our study. Nt-proBNP levels are much higher in more advanced GOLD classes, especially in terms of acute exacerbation. Our study demonstrated that Nt-proBNP as a natriuretic peptide can be a significant marker of the risk of progression of pulmonary damage, but only from GOLD 2 to GOLD3 class. In terms of deterioration of the lung function when serious changes occur at the level of the right ventricle and pulmonary circulation, this marker will have its own meaning.

In a paper published few years ago as a systematic review, analysis of 51 studies was done, where Nt-proBNP was evaluated in patients with COPD. The analysis showed that Nt-proBNP levels were significantly higher in more advanced GOLD classes, especially in forms of acute exacerbation.<sup>5)</sup> In our study of 94 patients, most of the patients(53) had a significantly higher level of Nt-proBNP above the reference range of 125 pg/ml.

In another recent study, analysis of Nt-proBNP was made in two groups- a group of acute exacerbation and a control group. The results showed that patients with acute exacerbation had



much higher levels of Nt-proBNP and longer hospital stay. All of the results listed above are in agreement with our study results.<sup>7)</sup>

The increased Nt-proBNP levels were seen in a group of acute exacerbated patients with COPD in hospital terms, in a study published a couple of years ago.<sup>8)</sup> These results were similar to the results obtained in our study. Thirty-seven patients out of 94 patients in our study (with acute worsening) had increased Nt-proBNP levels. In regards to the results obtained for Nt-proBNP as a marker of heart failure, the highest average levels for Nt-proBNP were found in GOLD class 3. The analysis showed that patients with acute worsening and patients in chronically stable condition had average Nt-proBNP levels much higher in the group of acute exacerbation of COPD in each of the GOLD classes. This difference was 3.5 times in GOLD class 3 and 2 times in GOLD class 4.

Similar, if not identical to our results are those published in another study. They showed that the difference between the two groups regarding Nt-proBNP was significant.<sup>9)</sup>

Stolz *et al.* made an analysis of the level of Nt-proBNP in terms of COPD exacerbation, where after recovery they observed decreased BNP level after the improvement of hypoxemia. Our study showed that Nt-proBNP can be used in assessing the severity of the disease in patients with COPD as well as predictors of disease worsening. Our study demonstrated the particular role of Nt-proBNP in more advanced stages of COPD (GOLD 3 and 4), especially in terms of acute exacerbation.<sup>10)</sup>

Several years ago, another study revealed results from 61 patient showing higher levels of Nt-proBNP in terms of more severe form of the disease and in terms of more advanced GOLD class. Nt-proBNP levels were much higher in GOLD class 3 and 4 compared to GOLD class 1 and 2. They identified natriuretic peptide as an important marker for disease progression as well as identification of secondary pulmonary hypertension. Our results were consistent to their results.<sup>11)</sup>

**Conclusion:**

BNP and NT-proBNP are natriuretic peptides that are secreted under conditions of cardiac stress and weakness. They are established biomarkers and are listed in the guidelines for chronic heart failure as they are quantitative markers used for diagnosis and risk stratification.

In acute exacerbation of COPD, levels of Nt-proBNP are much higher. This is due to the rich inflammatory process and deterioration of the lung function which is replicated on the right heart cavities resulting in high release of Nt-proBNP. Deterioration of the lung function leads to right heart strain and weakness and increased excretion of Nt-proBNP.

Still, more studies with larger number of patients are needed to confirm the role of Nt-proBNP in patients with COPD in different stages of GOLD and a progression of the disease.

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