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Impairment in heart functions and prognostic role of N-terminal pro-brain natriuretic peptide in patients with chronic obstructive pulmonary disease exacerbation

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Abstract:

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) with comorbidities and cardiovascular disease is the most frequent one. The role of natriuretic peptides in determining prognosis of COPD exacerbations is not yet clear. The frequency of pathologic findings of transthoracic echocardiography (TTE) during COPD exacerbation showed wide variability. This study aims to evaluate the predictive role of N-terminal pro-brain natriuretic peptide (NT-proBNP) in determining the short-term prognosis of patients hospitalized with COPD exacerbation. As a secondary outcome, we aimed to investigate the frequency of TTE findings in these patients.

MATERIALS AND METHODS: Eighty-six consecutive patients with COPD exacerbation were included. NT-proBNP levels were measured and TTE was carried out to whole of the participants at administration. The primary outcome was development of "event" (readmission or rehospitalization or mortality) within 30 days. The predictive role of NT-proBNP level for the development of "event" was evaluated. As a secondary outcome of the study, the frequency of TTE findings was recorded.

RESULTS: NT-proBNP level of the patients who developed event within 30 days had significantly higher than who did not (2343.16 ± 4107.17 pg/mL vs. 843.22 ± 2349.96 pg/mL, $P = 0.001$). A high negative correlation was found between NT-proBNP level and "time to event" ($r = -0.992$, $P < 0.001$). Multivariable logistic regression analysis showed that NT-proBNP level was an independent predictor for the development of "event" ($P < 0.001$) and the cutoff point of it was found to be 303.5 pg/mL (0.639 sensitivity and 0.720 specificity). The most frequent echocardiographic findings were pulmonary hypertension (54.7%) and left ventricle diastolic dysfunction (39.5%).

CONCLUSION: NT-proBNP level is a strong predictor for short-term prognosis of patients hospitalized with COPD exacerbation. Further and larger studies are needed to determine exact role of NT-proBNP in long-term prognosis of these patients.

Keywords:

B-type natriuretic peptide, chronic obstructive pulmonary disease, prognosis

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Introduction

Cardiovascular disease (CVD) is the most frequent comorbidity of chronic obstructive pulmonary disease (COPD).[1] COPD patients have systemic inflammation, vascular dysfunction, and air trapping that may make contribution to the development of CVD in these patients.[2,3] COPD itself is one of the most important risk factors for CVD.[4] B-type natriuretic peptide (BNP), which is a hormone excreted from heart to bloodstream, has natriuretic and diuretic effects. The levels of natriuretic peptide are elevated when myocardial strain increased.[5] Natriuretic peptide levels may increase in COPD patients without congestive heart failure.[6] It has been proposed that increased natriuretic peptide level indicated poorer survival in stable COPD patients.[7,8] During acute exacerbation of COPD (AECOPD), natriuretic peptide levels are higher than in stable periods of the disease.[9,10] The importance of these peptides in the prediction of prognosis in COPD exacerbation is not yet clear. The common signs and symptoms of CVD such as dyspnea may be overlooked in COPD patients, especially in the exacerbation period. Cardiac dysfunction of COPD patients may become more prominent during exacerbations of the disease. The frequency of pathological findings on transthoracic echocardiography (TTE) during COPD exacerbation showed wide variability.[11] This study aims to evaluate the predictive role of NT-proBNP level in determining the short-term prognosis of patients hospitalized with COPD exacerbation. As a secondary outcome, we aimed to investigate the frequency of TTE findings in these patients.

Materials and Methods

Eighty-six consecutive patients who were hospitalized with the diagnosis of AECOPD between September 2016 and December 2018 were included. This was a prospective study. Approval for the study was taken from the local ethical committee; informed consent was given by all participants. Primary endpoint of the study was development of "event" (readmission or rehospitalization or mortality) within 30 days. Secondary endpoint was frequency of TTE findings. Excluded from the study were COPD patients who had renal failure; chronic lung disease other than COPD (by medical history, physical examination, spirometry, and chest X-ray); ischemic ST-T changes (by electrocardiogram) or chest pain; any systemic disease that can cause pulmonary hypertension such as collagen vascular diseases (by medical history, physical examination, and serum level of connective tissue markers in patients who had clinical suspicion); and moderate and high clinical probability for acute pulmonary embolism (by modified Wells score[12]). The study design is summarized in Figure 1.

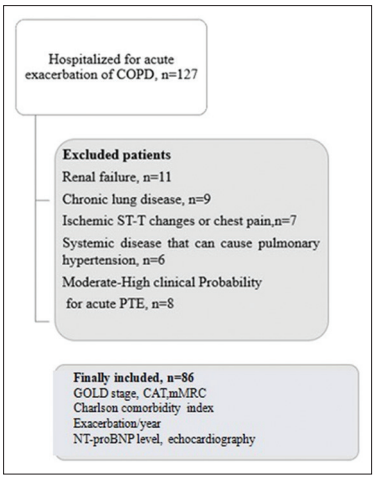

Figure 1: The design of the study

The diagnosis of COPD was approved through medical history and recorded results of spirometry. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria was used to determine the grouping of COPD. The development of respiratory symptoms that led to a change in medication of a patient with COPD is described as exacerbation.[13] Severity of exacerbation was classified based on the GOLD guideline as mild: treated with short-acting bronchodilators (SABAs) only; moderate: treated with SABAs plus antibiotics and/or oral corticosteroids; and severe: patients required hospitalization or visits the emergency room or with acute respiratory failure.[13]

Venous blood samples were taken within 4 h for the evaluation of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. NT-ProBNP levels were evaluated by the ROCHE Elecsys-ProBNP assay. It uses two polyclonal antibodies. One of them is labeled with ruthenium complex and evaluates the inactive cleavage product of BNP, NT-proBNP. The electrochemiluminescent test is applied on the automated Elecsys immunoassay analyzer and takes 18 min for the first results. Two cutoffs are used, one at 125 pg/mL for patients younger than 75 years old and a second at 450 pg/mL for patients older than 75 years of age.[14]

TTE was performed at the administration. In this study, a Vingmed System echocardiography unit (Vivid 7 Pro, General Electric, Horten, Norway) was used. Echocardiography was applied by two cardiologists who did not know the medical condition of the patients. B-mode, M-mode, continuous pulse-wave Doppler, and color Doppler examinations were performed. Systolic pulmonary arterial pressure >35 mmHg was accepted as pulmonary hypertension.[15] Left ventricle (LV) systolic dysfunction was described as an ejection fraction <50%.[16] In case of discrepancy between the

results, a third cardiologist performed the TTE, and a decision was made based on majority voting.

The history of patients' symptoms during the stable phase was evaluated by the COPD assessment test[17] and the modified British Medical Research Council dyspnea scale.[18] Charlson comorbidity score is an automatized method designed to determine for analytic purposes. In this method, the patients were classified in such a way as to take 1, 2, 3, and 6 points and the total score of the patients' comorbidities in this scale was categorized. With increased level of the comorbidity index, there were stepwise increases in the cumulative mortality attributable to comorbid disease.[19] Charlson comorbidity score of the participants were calculated. Exacerbations per year, 30-day mortality, rehospitalization, and readmission to the emergency department within 30 days for each patient were recorded. The readmission or rehospitalization or mortality within 30 days was described as "event." NT-proBNP levels of patients who developed event and who did not were compared. NT-proBNP levels of COPD patients were compared according to severity of exacerbation. The correlation between NT-proBNP level and time to event and also between NT-proBNP level and number of exacerbation over the last year was evaluated.

Statistical analysis

To test whether the data are normally distributed, the Kolmogorov–Smirnov and Shapiro–Wilk tests were used. Homogeneities of variances were tested by Levene test. Student's *t*-test or Mann–Whitney U-test for continuous variables and Chi-square test for categorical variables were used to evaluate differences between groups. We used one-way ANOVA test to evaluate NT-proBNP levels according to exacerbation severity from mild to severe. Degree of association between variables was calculated by point biserial, Spearman, Cramer's V, and phi correlation coefficients where appropriate. A Cox model provides an estimate of the treatment effect on survival after adjustment for other explanatory variables and allows us to estimate the hazard with standard errors and 95% confidence intervals (CIs). Hence, we ran univariate and multivariate Cox proportional hazard model analyses to determine independent predictors of event. Receiver operating characteristic (ROC) curves were constructed to illustrate the sensitivity and specificity performance characteristics of pro-BNP and a cutoff value was estimated using the index of Youden. Frequencies (percentages), mean ± standard deviation, and median (minimum–maximum) were given as descriptive statistics. Statistical analyses were performed using SPSS 23.0 (IBM©, United states) and $P < 0.05$ was considered statistically significant.

Results

Eighty-six patients were enrolled in the study. The mean age of thepatients was 71.8 ± 9.56 years. Forty-eight of the patients (55.8%) were male, and the rest of them were female (44.2%). Table 1 shows demographic properties and clinical properties of patients.

The 30-day mortality rate of the study group was 2.3%. No participants were in Stage A and B and only two patients were in Stage C, so these groups were not evaluated for comparison of NT-proBNP level. The mean NT-proBNP levels according to exacerbation severity from mild to severe were as follows 371.97 ± 937.66, 942.16 ± 1333.11, and 2649.57 ± 4412.59 pg/ml, respectively. The difference between the patients in respect to exacerbation severity was not statistically significant ($P = 0.202$). NT-proBNP level was positively correlated with the annual number of COPD exacerbation ($r = 0.296$, $P = 0.006$) [Figure 2].

NT-proBNP level of the patients who developed event within 30 days was significantly higher than who did not ($P = 0.001$). The comparison of NT-proBNP level of patients who developed event and who did not is shown in Table 2. The significant negative correlation was found between NT-proBNP level and time to event ($r = –0.992$, $P < 0.001$). Figure 3 shows the correlation between NT-proBNP level and time to event.

Univariable cox regression analysis showed that NT-proBNP level, having ejection fraction <50%, and presence of LV diastolic dysfunction on TTE were the variables that can be affective on development of event ($P < 0.001$, $P = 0.001$, and $P = 0.022$, respectively) [Table 3]. Multivariable

Table 1: Demographic and general clinical properties of patients

Age (years)	71.8±9.56
Gender, *n* (%)	
Male	48 (55.8)
Female	38 (44.2)
mMRC	3.59±7.5
CAT	25.16±9.34
Charlson comorbidity index	2.15±1.03
Exacerbation/year	1.97±0.98
GOLD, *n* (%)	
I	2 (2.3)
II	28 (32.6)
III	29 (33.7)
IV	27 (31.4)
A	0
B	0
C	2 (2.3)
D	84 (97.7)

mMRC: Medical Research Council Dyspnea Score, CAT: COPD assessment test score, GOLD: Global Initiative for Chronic Obstructive Lung Disease, COPD: Chronic obstructive pulmonary disease

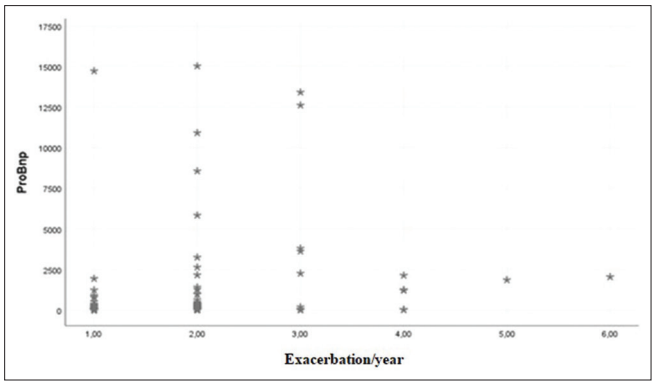

Figure 2: The correlation (evaluated by Spearman Rho) between N-terminal pro-brain natriuretic peptide (pg/mL) level and number exacerbation/year

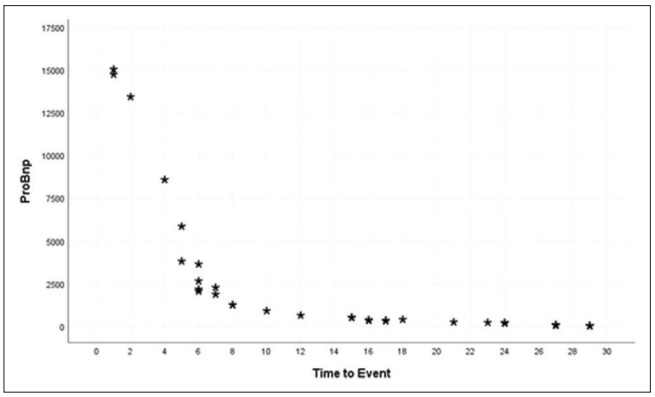

Figure 3: The correlation (evaluated by Spearman Rho) between N-terminal pro-brain natriuretic peptide (pg/mL) level and time to event (day)

Table 2: Comparison of N-terminal pro-brain natriuretic peptide level of patients who developed event and who did not (evaluated by Mann-Whitney U-test)

Event	NT-proBNP (pg/ml)		*P*
	Median (minimum-maximum)	Mean±SD	
Absent (*n*=50)	123.50 (1.00-12,616.00)	843.22±2349.96	0.001
Present (*n*=36)	451.00 (27.00-15,024.00)	2343.16±4107.17	

Event: Readmission or rehospitalization or mortality within 30 days, NT-proBNP: N-terminal pro-brain natriuretic peptide, SD: Standard deviation

Cox regression analysis by backward elimination showed that NT-proBNP level was the only variable that was significantly affective on development of event ($P < 0.001$) [Table 4]. The cutoff level of NT-proBNP predicting development of event within 30 days following an AECOPD was 303.5 pg/mL (sensitivity 63.9% and specificity 72%). The area under the ROC curve was 0.711 (95% CI: 0.602–0.820, $P = 0.001$) [Figure 4].

At least one pathological finding on echocardiogram was noted in 82.55% of the patients. The most frequent pathology on TTE was pulmonary hypertension (54.7%). Other findings on TTE were as follows: LV diastolic dysfunction, 39.5%; left atria dilatation, 38.4%; right atria dilatation, 26.7%; right ventricle (RV) dilatation, 22.1%; LV systolic dysfunction, 17.4%. Pulmonary arterial pressure, presence of LV diastolic dysfunction, ejection fraction, and presence of RV dilatation were not different between the GOLD stages ($P > 0.05$, for all).

Discussion

The main results of the study were as follows: NT-proBNP level is an independent predictor for short-term prognosis of AECOPD. The cutoff level of NT-proBNP for development of event was found to be 303.50 pg/ml. Most of the patients with COPD exacerbation (82.55%) had at least one pathological finding on echocardiogram. The most common echocardiographic finding was pulmonary hypertension (54.7%) in patients with AECOPD.

NT-proBNP is released from the myocytes into circulation in cases of myocardial strain. In addition, hypoxia stimulates the release of natriuretic peptides. These two mechanisms, myocardial strain and hypoxia, may be present in COPD patients, and their effects may become more pronounced during exacerbation periods of the disease.[20]

In a large cohort with stable COPD, Labaki *et al*. found that a higher NT-proBNP level was associated with an increased risk of COPD exacerbations within 1 year of follow-up, regardless of the presence of underlying CVD.[21] Our study population contained COPD patients who were in exacerbation period and this is consistent with the results of Labaki *et al*. NT-proBNP levels were positively correlated with annual exacerbation frequency of COPD patients. NT-proBNP was higher in Stages C and D compared to Stages A and B; it was also significantly higher in Stage D compared to Stage B in Labaki *et al*.'s study,[21] whereas we cannot compare GOLD stages because of the uneven distribution of participants among the GOLD stages in our study population. In addition, in the present study, although the difference was not statistically significant, NT-proBNP levels increased with increasing exacerbation severity. Myocardial strain and hypoxia due to COPD exacerbation may increase related to severity of exacerbation.

Previous studies evaluating prognostic role of natriuretic peptides after AECOPD had conflicting results. In a meta-analysis, it was reported that high NT-proBNP levels are significantly related to mortality in COPD patients, independently from cardiovascular history.[22] Høiseth *et al*. also showed that the higher levels of NT-proBNP during AECOPD were associated with increased long-term mortality.[23] Medina *et al*. showed increased 1-year mortality in AECOPD patients with NT-proBNP level >459.9 pg/mL.[6] Chang *et al*.

Table 3: Univariable cox regression analysis of variables that may affect the development of event

Variable	β	SE	HR	95% CI		*P*
				Lower	Upper	
NT-proBNP (pg/ml)	0.002	0.001	1.002	1.001	1.0013	<0.001
Smoking history (pack/year)	−0.015	0.013	0.985	0.961	1.010	0.236
FEV1	0.391	0.464	1.479	0.595	3.672	0.399
Charlson comorbidity index	0.115	0.138	1.121	0.856	1.468	0.405
Severity of exacerbation						
Mild						0.134
Moderate	−0.212	0.641	0.809	0.230	2.841	0.740
Severe	0.650	0.364	1.916	0.939	3.911	0.074
Ejection fraction <50%	1.438	0.451	4.213	1.742	10.189	0.001
RV dilatation	0.064	0.368	1.066	0.518	2.193	0.863
LV diastolic dysfunction	0.857	0.375	2.356	1.130	4.912	0.022
Pulmonary arterial pressure	0.005	0.024	1.005	0.959	1.053	0.835
Annual exacerbation rate	0.016	0.161	1.016	0.742	1.393	0.920

NT-proBNP: N-Terminal pro-brain natriuretic peptide, SE: Standard error, HR: Hazard ratio CI: Confidence interval, FEV1: Forced expiratory volume in 1 s, LV: Left ventricle, RV: Right ventricle

Table 4: Multivariable cox regression analysis by backward elimination

Variable	β	SE	HR	95% CI		*P*
				Lower	Upper	
NT-proBNP	0.002	0.001	1.002	1.001	1.0013	<0.001

SE: Standard error, HR: Hazard ratio, CI: Confidence interval, NT-proBNP: N-Terminal pro-brain natriuretic peptide

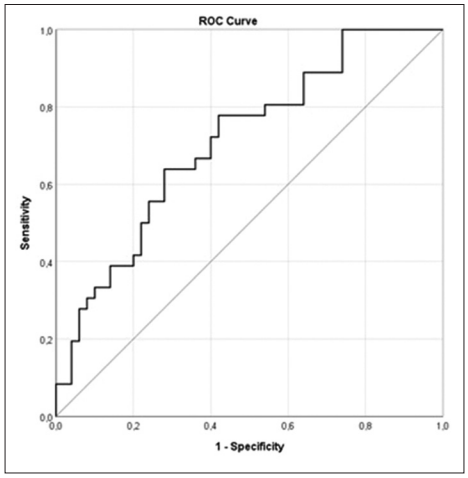

Figure 4: The receiver operating characteristic curve constructed from N-terminal pro-brain natriuretic peptide measurements as a predictor of development of event within 30 days following acute exacerbation of chronic obstructive pulmonary disease. The area under the receiver operating characteristic curve is as follows: 0.711 (standard error: 0.056 95% confidence interval: 0.602–0.820, *P* = 0.001)

proposed that mortality increased in patients with COPD exacerbation who had high NT-proBNP level (>220 pmol/L).[24] Consistent with these results, we found that high NT-proBNP level was independently strong predictor for poor outcomes of AECOPD. In the present study, the cutoff point of NT-proBNP for poor outcomes was similar to these studies.[6,23,24] However, Stolz *et al*. showed that BNP levels failed to adequately predict short-term and long-term mortality rates in AECOPD patients.[9] Pervez *et al*. reported that midregional pro-atrial natriuretic peptide concentrations, but not NT-proBNP concentrations, were associated with increased mortality risk in patients with AECOPD.[20]

Vallabhajosyul *et al*. showed that high BNP levels were correlated with worse hospital outcomes such as higher mechanical ventilation (MV) use, noninvasive ventilation failure, MV duration, and intensive care unit and total length of stay.[25] Supporting this result, we found that higher NT-proBNP levels predictive for worse short-term prognosis.

Recently, Ebrahimzadeh *et al*. showed that the mean serum level of NT-proBNP was higher in patients with more than two exacerbations over the last year in comparison to the other patients.[26] Our study also showed a positive relationship between NT-proBNP levels and frequency of COPD exacerbation over the last year.

Frequency of pulmonary hypertension in COPD patients was variable in different studies. Freixa *et al*. reported that 19% of COPD patients had pulmonary hypertension.[27] Otherwise, Gupta *et al*. reported high prevalence 63% of pulmonary hypertension in COPD patients.[28] Pulmonary hypertension was the most frequent pathology in our study population (54.7%). Its frequency did not differ according to the severity of disease. In contrast to our study, Freixa *et al*. and Gupta *et al*. reported that pulmonary hypertension was more frequent in COPD patients who had severe disease than in patients with mild disease.[27,28] The distribution of COPD patients in each stage of the disease was not uniform in the above-mentioned studies. This might have had an effect on the conflicting results of the studies.

More than half of the COPD patients had LV dysfunction in the study performed by Flu *et al*. They showed that the combination of these two clinical conditions increased risk of mortality.[29] The prevalence of LV dysfunction (systolic and diastolic) was similar in our study population (56.9%).

Variable frequencies of LV diastolic dysfunction in COPD patients were reported. The frequency of LV diastolic dysfunction in COPD patients was lower in our study than in the study by Caram *et al*. (39.5% vs. 88%). In contrast to our results, they found that LV dysfunction was accompanied to

increased severity of COPD.[30] Gupta *et al*. found a prevalence higher than in our study (47.5%).[28] However, a recent study reported a lower frequency (12%) of LV dysfunction in COPD patients upon their first hospital admission.[27] The variation in the frequency of LV diastolic dysfunction in these studies may have been resulted from sample characteristics and differences in study design.

The limitations of the study were as follows: First, this was a unicentric study that contained a limited number of patients. Second, the follow-up period for the patients was short to evaluate the real role of NT-proBNP level in predicting the long-term prognosis of AECOPD. Third, because Charlson comorbidity index contains renal failure and collagen vascular diseases which were in exclusion criteria, the results might have been influenced.

Conclusion

NT-proBNP level is an independent predictor for short-term prognosis of AECOPD; the cutoff point of NT-proBNP level for poor outcome of AECOPD was found to be 303.5 pg/mL (0.639 sensitivity and 0.720 specificity). Most of the AECOPD patients had symptomatically silent cardiac dysfunction. The most frequent pathology on TTE was pulmonary hypertension (54.7%). Further and larger studies are necessary to investigate the exact role of NT-proBNP level in determining the long-term prognosis of the AECOPD.

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Conflicts of interest
There are no conflicts of interest.

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