

ORIGINAL RESEARCH

Medicine Science 2019;8(4):847-51

Diagnostic biomarkers of acute exacerbation of chronic obstructive pulmonary disease at elderly patients

Yakup Arslan, Deniz Dogan

Health Science University, Gulhane Training and Research Hospital, Department of Chest Diseases, Ankara, Turkey

Received 10 April 2019; Accepted 16 May 2019

Available online 08.09.2019 with doi:10.5455/medscience.2019.08.9065

Copyright © 2019 by authors and Medicine Science Publishing Inc.

Abstract

Acute exacerbations of chronic obstructive pulmonary disease are caused by a variety of different etiologies. The aim of the current study was to determine the diagnostic biomarkers for verifying the diagnosis of acute exacerbations of chronic obstructive pulmonary disease and predicting the length of hospital stay at elderly patients. The files of 120 patients who had been hospitalized with the diagnosis of acute exacerbation of chronic obstructive pulmonary disease between January 2017 to December 2018 in the Chest Disease Department of Gulhane Education and Training Hospital were examined retrospectively. The numbers and the percentage of male and female patients were 83 (% 69) and 37 (% 31) respectively. Increases in the prohormone brain natriuretic peptide values of elderly patients were found as statistically significant ($p < 0.001$). Statistically significant positive correlation between the lengths of hospital stay with the prohormone brain natriuretic peptide values was found at elderly patients group ($r = 0.336$, $p = 0.001$). Also statistically significant positive correlation was found between high sensitive C-reactive protein values with procalcitonin and neutrophil/lymphocyte ratio ($r = 0.320$, $p = 0.001$ and $r = 0.257$, $p = 0.006$, respectively). Our study indicates significantly higher values of prohormone brain natriuretic peptide levels at elderly patients in accordance with length of hospital stay. These results would help us to consider the use of prohormone brain natriuretic peptide levels as a diagnostic biomarker for verifying the diagnosis of acute exacerbation of chronic obstructive pulmonary disease and predicting the length of hospital stay at elderly patients.

Keywords: COPD, proBNP, hs-CRP, exacerbation, elderly patients

Introduction

Chronic obstructive pulmonary disease (COPD), one the worldwide public health problem, is thought to affect 384 million people with a globally prevalence of 11.7 percent and it is also predicted to become the most fourth leading cause of human deaths by 2030 [1,2]. Acute exacerbation of COPD (AECOPD) is defined as the worsening period of the symptoms that reason the most of these patients enhancing their treatments [3]. The valid diagnostic test of AECOPD is not currently present, and only the health professionals' evaluation of patient symptoms and signs is used to diagnose of AECOPD [4-6]. COPD patients generally have a systemic inflammation that can be proofed with the high sensitive c-reactive protein (hs-CRP), interleukin (IL) and tumor necrosis factor alpha (TNF-alpha) [7]. However, the potential role of hs-CRP as a marker to reflect all aspects of pulmonary and extrapulmonary complications in COPD and its prognostic value in COPD need further investigation [8-11]. Some measuring methods have made it possible to define the hs-CRP even at lower

levels of inflammation [12]. B-type natriuretic peptide (BNP) and N-terminal fragment of prohormone-BNP (NT-pro-BNP) is derived from the pro-BNP. These are commonly used for diagnosis, risk stratification and management of hearth failure [13]. Since some receptor in various respiratory cells, such as type II alveolar cells and endothelial cells of pulmonary blood vessels is defined for BNP, the suggestion that BNP may modulate the respiratory system is becoming more acceptable. The exact mechanism is controversial but the experts claimed BNP/NTproBNP would be reliable biomarkers for the management of AECOPD patients [14]. COPD patients without hearth failure may have also high BNP [15-17]. Besides this, cytokines such as IL-1 β , TNF- α , and IL-6 would be responsible for BNP secretion [18]. The possible strong predictor of AECOPD diagnosed patients admitted to hospital may be an elevated NT-proBNP value [19]. This inflammatory aspect of AECOPD would be estimated to impact both the pulmonary and cardiac systems. Currently, the number of the studies that evaluating both hs-CRP and pro-BNP values at AECOPD patients requiring hospitalization is increasing [20,21].

Defining the possible role of hs-CRP and pro-BNP as the diagnostic biomarkers for verifying the diagnosis of AECOPD and predicting the length of hospital stay (LOHS) at elderly patients was the preliminary goal of this current study.

*Corresponding Author: Yakup Arslan, Dr. Health Science University, Gulhane Training and Research Hospital, Department of Chest Diseases, Ankara, Turkey
E-mail: yakuparslan75@yahoo.com

Material and Methods

This descriptive cross-sectional sort of study was conducted at the AECOPD diagnosed patients that have hospitalized between January 2017 to December 2018 in the Chest Disease Department of Gulhane Education and Training Hospital. Involvement of the patients into the study with the diagnose of AECOPD by the chest diseases doctors was completed with the interpretation of patient's anamnesis, symptoms, physical examination findings and the biochemical analysis. According to these, a total of 163 patient files were evaluated retrospectively; 43 of these patients were excluded from the study due to additional cardiac diseases like congestive hearth failure, acute coronary disease and valvular disease and non-pulmonary infectious diseases. And the total of 120 patients were included into the study. The files of 120 patients were analyzed according to the admission place, age, gender, body mass index, biochemical datas, preferentially hs-CRP, pro-BNP and the LOHS of the patients, retrospectively.

Statistical Analysis

Relationships of investigated parameters were evaluated statistically. SPSS for Mac 20.0 package program (SPSS Inc, Chicago, IL) was used for statistical evaluation. Data were summarized as the mean and standard deviation (SD) for the continuous variables, as absolute value and percentages for the categorical variables. The normality of the continuous variables was analyzed with the Kolmogorov-Smirnov test and Shapiro Wilks test. Chi-square test

for the categorical variables and Student's t-test or Mann-Whitney U statistical tests were used according to the suitability to the normal distribution for the continuous variables. In assessment of correlations, Spearman for data with non-parametric distribution was used. P-value less than 0.05 was considered as statistically significant with a 95% confidence interval.

Results

The fifty-five of one-hundred twenty patients included into the study had been diagnosed as AECOPD at the emergency service, and the rest sixty-five were at the polyclinic of Chest Diseases Department. The mean age of the patients was 68.9 ± 7.9 years and the body mass index (BMI) was 25.6 ± 3.9 . The numbers of male and female patients were respectively 83 (%69) and 37 (%31). Mean ages of males and females were respectively 68.4 ± 7.5 and 70.1 ± 8.9 years and no statistically significant difference was found between them. Mean BMI of male and female patients were respectively 24.8 ± 3.4 and 27.4 ± 4.3 , and there was a statistically significant difference between them ($p=0.002$). The values of hemoglobin (Hgb) and hematocrit (Hct) were found as lower at females ($p<0.001$) and the values of platelet (Plt) were found as lower at males ($p=0.017$), and all these were statistically significant. The statistically significant higher values of hs-CRP were found at male patients ($p=0.005$). A positive sided correlation between BMI with hgb ($r=0.256$, $p=0.019$) and BMI with htc ($r=0.304$, $p=0.005$) values were defined at male patients. All laboratory variables summarized in table-1.

Table 1. Demographic and clinical characteristics of the subjects

Variables	All patients (n=120)	Male (n=83)	Female (n=37)	p*
Age (year)	68.9 ± 7.9	68.4 ± 7.5	70.1 ± 8.9	NS
BMI (kg/m ²)	25.6 ± 3.9	24.8 ± 3.4	27.4 ± 4.3	0.002
Pack-year smoking history	41.8 ± 20.8	41.2 ± 19.8	42.3 ± 21.8	NS
WBC (10 ³ /μL)	11.5 ± 6.8	11.7 ± 8	11.1 ± 3	NS
Hemoglobin (g/dL)	13.8 ± 2.7	14.6 ± 2.4	11.9 ± 2.1	<0.001
Hematocrit (%)	43.4 ± 8.1	45.8 ± 7.7	38.1 ± 6.5	<0.001
Platelet count (10 ³ /μL)	255 ± 87.4	242.3 ± 68.3	283.5 ± 115.9	0.017
# neutrophil (%)	75.4 ± 11	75.1 ± 11.4	76.1 ± 10	NS
# lymphocyte (%)	15.2 ± 8.9	15.1 ± 9.4	15.6 ± 8	NS
# eosinophilia (%)	1.10 ± 1.36	1.17 ± 1.43	0.94 ± 1.21	NS
Albumin (g/dL)	3.49 ± 0.45	3.50 ± 0.43	3.47 ± 0.50	NS
LDH (U/L)	277.6 ± 103.3	283.4 ± 99.4	264.7 ± 111.5	NS
hs-CRP (mg/L)	71.08 ± 55.32	81.06 ± 58.89	49.74 ± 39.71	0.005
pro-BNP (pg/ml)	1154.3 ± 1376.8	1265.3 ± 1450.8	867.4 ± 1141.5	NS
Procalcitonin (ng/mL)	0.160 ± 0.323	0.18 ± 0.38	0.10 ± 0.09	NS
Neutrophil/lymphocyte ratio	8.19 ± 8.42	8.27 ± 8.53	8.01 ± 8.27	NS
pH	7.335 ± 0.37	7.322 ± 0.44	7.365 ± 0.07	NS
PaO ₂ (mmHg)	58.4 ± 13.1	56.9 ± 12.3	61.9 ± 14.3	NS
PaCO ₂ (mmHg)	51.1 ± 15.1	49.7 ± 15.1	54.32 ± 14.72	NS
SaO ₂ (%)	85.7 ± 8.8	85.2 ± 9.1	86.7 ± 8.3	NS
HCO ₃ (mEq/L)	28.1 ± 5.7	27.6 ± 5.7	29.2 ± 5.6	NS
Length of Hospital Stay (day)	5.7 ± 2.5	5.5 ± 2.6	6.1 ± 2.5	NS

BMI: body mass index, WBC: white blood cell, hs-CRP: high sensitivity c reactive protein, LDH: lactate dehydrogenase, BNP: brain natriuretic peptide, HCO₃: bicarbonate, NS: non-significant, * difference between male and female

According to the ages, two groups were identified; First group patients whose ages were <65 years were called as non-elderly, and the second group patients whose ages were ≥65 years were called as elderly. The statistically significant higher proBNP values were found at elderly patients ($p<0.001$). The values of hgb ($p=0.008$), htc ($p=0.015$) and albumin ($p=0.034$) were found lower as statistically significant at elderly patients. There were positive sided correlations between the values of albumin with hgb ($r=0.324$, $p=0.03$) and htc ($r=0.284$, $p=0.011$) at elderly patients. A statistically significant positive sided correlation between the values of pro-BNP with LOHS was found ($r=0.336$, $p=0.001$). However, no statistically significant correlation was found at LOHS between elderly with non-elderly patients, LOHS of elderly patients was found longer than non-elderly patients (Table 2). A statistically significant positive correlations between hs-CRP levels with procalcitonin (PCT) ($r=0.320$, $p=0.001$) and neutrophil/lymphocyte ratio (NLR) were announced ($r=0.257$, $p=0.006$).

Table 2. Demographic and clinical characteristics between non-elderly with elderly patients

Variables	All patients (n=33)	Male (n=87)	P
Male/Female (n)	25/8	58/29	NS
BMI (kg/m ²)	25.1±3.7	25.8±3.9	NS
Pack-year smoking history	42.9±20.6	40.6±21	NS
WBC (10 ³ /μL)	13.9±10.8	10.6±4.2	NS
Hemoglobin (g/dL)	14.8±2.8	13.4±2.5	0.008
Hematocrit (%)	46.3±8.8	42.3±7.6	0.015
Platelet count (10 ³ /μL)	248.3±77.1	257.5±91.3	NS
# neutrophil (%)	73.4±9.8	76.1±11.3	NS
# lymphocyte (x10 ³ / μL)	16.0±8.6	14.9±9.1	NS
# eosinophilia (%)	1.02±1.16	1.13±1.44	NS
Albumin (g/dL)	3.65±0.51	3.43±0.41	0.034
LDH (U/L)	273.6±106.2	279.0±102.7	NS
hs-CRP (mg/L)	71.00±57.43	71.11±54.87	NS
pro-BNP (pg/ml)	492.7±648.6	1453.7±1512.9	<0.001
Procalcitonin (ng/mL)	0.141±0.297	0.166±0.331	NS
Neutrophil/lymphocyte ratio	6.56±5.31	8.81±9.28	NS
pH	7.384±0.06	7.317±0.43	NS
PaO ₂ (mmHg)	57.9±12.5	58.6±13.3	NS
PaCO ₂ (mmHg)	49±14	51.8±15.4	NS
SaO ₂ (%)	86.2±8.4	85.5±9.1	NS
HCO ₃ (mEq/L)	28.7±5.8	27.9±5.7	NS
Length of Hospital Stay (day)	5.1±2.1	5.9±2.7	NS

BMI: body mass index, WBC: white blood cell, hs-CRP: high sensitivity c reactive protein, LDH: lactate dehydrogenase, BNP: brain natriuretic peptide, HCO₃: bicarbonate, NS: non-significant

Discussion

In the current study, the hs-CRP values were found as significantly higher at male patients. The consistent results from the studies by Alavi et al. [22], Breyer et al. [23] and Kony et al. [24] were analyzed. The mean hs-CRP level in the study of Ghobadi H. et al. [25] was not significantly different between males and females. Previous study conducted by Bridevaux et al. [26] exhibited the more frequent increase of hs-CRP level and decrease of Forced Expiratory Volume 1 (FEV1) at females compared to males. In this study, there was neither ability to measure FEV1 of patients,

and nor possibility to assess the relationship between exacerbation frequency with COPD stages.

Any correlation between BMI and COPD stages with hs-CRP levels was not found in the current study. At the study by Alavi et al. there was significantly correlation between hs-CRP with COPD patients stages, BMI, gender, tobacco habits and arterial carbondioxide pressure (PaCO₂) at exacerbation state. The severity of COPD stages at male patients may be the reason of these patients' higher CRP levels [22].

The positive sided correlation between BMI with hgb and htc values at male patients was detected in the current study. Some metabolic changes and muscle wasting at COPD patients would be responsible for higher inflammatory markers and hypermetabolic state. At the studies by Alavi et al., Bridevaux et al. and Pinto-Plata et al., the overweight and obese patients (measured by BMI) showed higher levels of CRP (as an inflammatory marker) than normal weighted patients [22,26,27]. The expectation that chronic inflammatory disease causes cachexia and weight loss is very common at COPD [28]. On the other hand, in a study in Ohio, Sahebhami and Sathianpitayakul discovered a correlation between dyspnea severity with lower weights. It can be argued that, as much as CRP level is correlated with the severity of COPD, the severe COPD (with higher levels of CRP) patients may become cachectic and thin [28].

Any statistically significant correlation between smoking history of the patients with hs-CRP values was not detected in the current study. In Alavi et al.'s study, the more percentage of smokers showed higher risk levels of hs-CRP ($p=0.043$), but no significant difference between pack/year history with hs-CRP levels was announced ($p=0.189$) [22]. The consistent results with this were claimed at the studies of De Torres et al. and Halvani et al. (2006) [29-31]. Some genetic differences may be responsible for variability of inflammatory reaction development [27].

The statistically significant higher pro-bnp values that are also consistent with published literatures were identified at elderly patients in our study [32,33]. Renal failed patients also had elevated BNP concentrations [34].

In Chen et al.'s study, the combined assesment of CRP and NT-proBNP in categorizing as outpatient or inpatient for AECOPD patients were evaluated. The combination approach was found more promising than the individual evaluation. This combination was also found significantly associated with mortality and LOHS. Although these results require more supportive clinical studies, the combination of biomarkers can potentially identify "severe" AECOPD patients and enable us to use more aggressive managements [33].

At the consideration of correlations; positive sided statistically significant correlation between LOHS with the values of Pro-BNP at all patients especially at elderly patients was detected. There was also positive sided correlation between lower albumin levels with lower hgb and htc values at elderly patients in the current study.

Elevated NT-proBNP leveled patients had lower BMI and albumin levels and elevated BUN levels, more intensive care unit (ICU)

requirement and LOHS [35,36].

AECOPD patients had different LOHS up to their illness severity and mechanical ventilation (MV) requirement [37].

At the study by Hoiseth et al. the association between NT-pro-BNP and long-term mortality were emphasized besides the lack of 12% of the patients spirometrically COPD confirmation [38].

The higher likelihood of ICU admission and longer LOHS were declared as associated with higher age-specific NT-pro-BNP at Adrish et al's study. [39].

The statistically significant positive correlation between hs-CRP with PCT and NLR was found in the current study. This result was consistent with Chen et al.'s study mentioning the correlation coefficient between CRP and NT-proBNP [33].

Notwithstanding to Chen et al.'s study, the concentrations of two biomarkers (CRP and in particular NT-proBNP) were related to key outcome measures including length of hospital stay and mortality rate [33].

Limitations

One of the important limitations of current study is absence of cardiological evaluation of patients before hospitalization, and the other one is the lack of the patients' control laboratory markers at discharge.

Conclusion

In the current study, the pro-BNP levels of the elderly patients were significantly higher than non-elderly patients'. And the higher proBNP level was found to be correlated positively with LOHS at all patients especially at elderly patients. On verifying the diagnose of AECOPD, the results are giving opinion that the increase of hs-CRP values must be evaluated with taking the patient's COPD stage, gender, anamnesis of exposure to air-pollution, BMI, smoking history, age, the exacerbation numbers of previous years, comorbidities and genetic features into the considerations.

As a conclusion, both hs-CRP and pro-BNP values were detected significantly increased at the patients having the diagnosis of AECOPD. A combinatorial measurement of these biomarkers could be helpful to categorize the patients to treat as outpatient or inpatient for optimal management of AECOPD patients.

Acknowledgements

The study was designed by YA. Data was collected and analyzed by YA and DD. Manuscript was written by YA and DD. There was no financial assistance in this project.

Conflict of interest

The authors declare that there are no conflicts of interest.

Financial Disclosure

All authors declare no financial support.

Ethical approval

Before the study, permissions were obtained from local ethical committee.

Yakup Arslan ORCID:0000-0002-9079-1701

Deniz Dogan ORCID:0000-0003-2596-3113

References

1. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of

COPD prevalence: systematic review and meta-analysis. J Glob Health. 2015;5:020415.

2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3:e442.
3. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187:347-65.
4. Quon BS, Gan WQ, Sin DD. Contemporary Management of Acute Exacerbations of COPD: A Systematic Review and Metaanalysis. Chest. 2008;133:756-66.
5. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: The reduce randomized clinical trial. JAMA. 2013;309:2223-31.
6. Aaron SD, Donaldson GC, Whitmore GA, et al. Time course and pattern of COPD exacerbation onset. Thorax. 2012;67:238-43.
7. Dahl M, Vestbo J, Lange P, et al. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;175:209-10.
8. Jones PW, Brusselle G, Dal Negro RW, et al. Properties of the COPD assessment test in a cross-sectional European study. Eur Respir J. 2011;38:29-35.
9. Jones PW, Harding G, Berry P, Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34:648-54.
10. Lee SD, Huang MS, Kang J, et al. The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients. Respir Med. 2014;108:600-8.
11. Jones PW, Adamek L, Nadeau G, et al. Comparisons of health status scores with MRC grades in COPD: implications for the GOLD 2011 classification. Eur Respir J. 2013;42:647-54.
12. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107:363-9.
13. Dickstein K, Cohen-Solal A, Filippatos G, et al; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29:2388-442.
14. Calzetta L, Orlandi A, Page C, et al. Brain natriuretic peptide: Much more than a biomarker. Int J Cardiol. 2016;221:1031-8.
15. Doyama K, Fukumoto M, Takemura G, et al. Expression and distribution of brain natriuretic peptide in human right atria. J Am Coll Cardiol. 1998;32:1832-8.
16. Hill NS, Klinger JR, Warburton RR, et al. Brain natriuretic peptide: possible role in the modulation of hypoxic pulmonary hypertension. Am J Physiol. 1994;266:308-15.
17. Cargill RI, Lipworth BJ. Atrial natriuretic peptide and brain natriuretic peptide in cor pulmonale. Hemodynamic and endocrine effects. Chest. 1996;110:1220-5.
18. Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. Eur J Heart Fail. 2004;63:261-8.
19. Chang CL, Robinson SC, Mills GD, et al. Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. Thorax. 2011;66:764-768.

20. Hoiseth AD, Omland T, Karlsson BD, et al. Standardized evaluation of lung congestion during COPD exacerbation better identifies patients at risk of dying. *Int J Chron Obstruct Pulmon Dis*. 2013;8:621-9.
21. Hopstaken RM, Witbraad T, van Engelshoven JM, et al. Interobserver variation in the interpretation of chest radiographs for pneumonia in community-acquired lower respiratory tract infections. *Clin Radiol*. 2004;59:743-52.
22. SA Alavi, F Soati, K Forghanparast, et al. HsCRP in patients with acute exacerbation of chronic obstructive pulmonary disease. *Iran Red Crescent Med J*. 2011;13:713-8.
23. Breyer MK, Spruit MA, Celis AP, et al. CIRO Network. Highly elevated C-reactive protein levels in obese patients with COPD: A fat chance. *Clin Nutr*. 2009;28:642-7.
24. Kony S, Zureik M, Driss F, et al. Association of bronchial hyperresponsiveness and lung function with C-reactive protein (CRP): a population based study. *Thorax*. 2004;59:892-6.
25. Ghobadi H, Fouladi N, Beukaghazadeh K, et al. Association of high sensitive CRP level and COPD assessment test scores with clinically important predictive outcomes in stable COPD patients. *Tanaffos*. 2015;14:34-41.
26. Bridevaux PO, Gerbase MW, Schindler C, et al. Sex-specific effect of body weight gain on systemic inflammation in subjects with COPD: results from the SAPALDIA cohort study 2. *Eur Respir J*. 2009;34:332-29.
27. Pinto-Plata VM, Mollerova H, Toso JF, et al. C-reactive protein in patients with COPD, control smokers and non-smokers. *Thorax*. 2006;61:23-8.
28. Sahebajami H, Sathianpitayakul E. Influence of body weight on the severity of dyspnea in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161:886-90.
29. de Torres JP, Pinto-Plata V, Casanova C, et al. C-reactive protein levels and survival in patients with moderate to very severe COPD. *Chest*. 2008;133:1336-43.
30. de Torres JP, Cordoba-Lanus E, Lopez-Aguilar C, et al. C-reactive protein levels and clinically important predictive outcomes in stable COPD patients. *Eur Respir J*. 2006;27:902-7.
31. Halvani A, Nadooshan HH, Shoraki FK, et al. Serum C-reactive protein level in COPD patients and normal population. *Tanaffos*. 2007;6:51-5.
32. El Mallawany H, Mahmoud MI, Morsi TS, et al. Role of N-terminal pro B-type natriuretic peptide in acute exacerbation of chronic obstructive pulmonary disease. *Egypt J Chest Dis Tuberc*. 2014;63:57-65.
33. Chen YR, Chen V, Hollander Z, et al. C-reactive protein and N-terminal prohormone brain natriuretic peptide as biomarkers in acute exacerbations of COPD leading to hospitalizations, *Plos one*. 2017;12:0174063.
34. McCullough PA, Duc P, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis*. 2003;41:571-9.
35. Souza R, Bogossian HB, Humbert M, et al. N-terminal-pro-brain natriuretic peptide as a haemodynamic marker in idiopathic pulmonary arterial hypertension. *Eur Respir J*. 2005;25:509-13.
36. Gale CP, White JE, Hunter A, et al. Predicting mortality and hospital admission in patients with COPD: significance of NT pro-BNP, clinical and echocardiographic assessment. *J Cardiovasc Med (Hagerstown)*. 2011;12:613-8.
37. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortalityrelated factors after hospitalization for acute exacerbation of COPD. *Chest*. 2003;124:459-67.
38. Hoiseth AD, Omland T, Hagve TA, NT-proBNP independently predicts long term mortality after acute exacerbation of COPD - a prospective cohort study. *Respir Res*. 2012;13:97.
39. Adrish M, Nannaka VB, Cano EJ, et al. Significance of NT-pro-BNP in acute exacerbation of COPD patients without underlying left ventricular dysfunction. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1183-9.