The Relationship between Some Pro-inflammatory Markers and BODE Index in Patients with Chronic Obstructive Pulmonary Disease

Yesar MH Al-Shamma[1], Najah R Hadi[2*], Abdullah Elttayef Jasim[3], Ahmed Abdullah Ajrash Al-Khafaji[4], Ali M Janabi[5]

[1]College of Dentistry, Islamic University, Najaf, Iraq
E mail: yesarmh47@iunajaf.edu.iq
[*2]Department of Pharmacology and Therapeutic, Faculty of Medicine, University of Kufa, Najaf, Iraq
E mail: dr_alher@yahoo.com, drnajahiraq@gmail.com
[3]College of Medicine, Iraqi University, Baghdad, Iraq
E mail: Drabdul1@yahoo.com
[4]AL-Merjan Hospital, Babylon Health Directorate, Babel, Iraq
E mail: aa0107279@gmail.com
[5]Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Kufa, Najaf, Iraq
E mail: alimhjanabi@gmail.com

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a common clinical pathological disease characterized by rapid deterioration of lung function. Lack of effective treatment and complete understanding of mechanism of this disease lead to increased incidence of mortality and morbidity rate globally. The aim of this study is to determine the association of proinflammatory mediators with BODE index in patients with COPD. This study is a case control study including 87 COPD patients and 100 healthy individuals (as a control). FEV1 was assessed using spirometry to investigate pulmonary function. ELIZA technique was applied to examine the serum levels of IL-1B, IL-6 and TNF-a. There was significant increase in bothinterleukin-1 (IL-1) and interleukin-6 (IL-6) in COPD patients when compared to healthy individuals. However, the levels of tumor necrosis factor alpha (TNF-a) in COPD patients were not significantly different when compared to healthy individuals. FEV1/FVC ratio in COPD patients was significantly decreased when compared to healthy group. The pro inflammatory markers, IL-1 and IL-6, are more likely to be applicable in diagnosis and assessment of COPD. Additionally, BODE index is a suitable tool for assessment of severity of the disease.

Keywords: COPD, IL-1B, IL-6, TNF-a, BODE index.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) refers to a group of lung diseases characterized by air way inflammation and tissue destruction with irreversible air flow limitation. Air flow limitation is generally progressive and associated with abnormal response of the lungs to noxious particles or gases such as cigarette smoke, coal mining dust, diesel exhaust, and fumes from burning biomass fuels for cooking or heating that leads to chronic air way inflammation [1-3]. COPD is one of the dead lies diseases globally and is estimated as the third highest cause of mortality worldwide [4]. Treatments that effectively halt progression or reverse the disease or reduce the occurrence and/or severity of exacerbation are urgently required [5]. The lack of efficient treatment results mainly from the inadequate understanding of pathogenesis of COPD. The pathogenesis of this disease is driven by chronic inhalation of noxious particles, often cigarette smoke that persistently stimulates innate and inflammatory response [6]. Pulmonary function test (PFT) permits an accurate measurement of the respiratory function and severity level of COPD when compared to healthy person that can be estimated according to the basis of the height, age and race of the patient [7-8]. The recognition that assessment of COPD disease severity requires a multi-dimensional approach, has led to development of multi-dimensional indices including BODE index [Body mass index, Obstruction, Dyspnea, Exercise]. The BODE index assesses disease severity by measuring body mass index, degree of airflow obstruction (FEV1% predicted), dyspnoea (Medical Research Council Dyspnoea Scale MRC) and exercise limitation (as measured by the 6-minute walking test [6MWT]).BODE index score is divided into 4 quartiles, a higher BODE index score indicates a greater mortality among COPD patients [9-11]. The aim of this study was to determine the effect of pro inflammatory markers with BODE index in COPD.

MATERIALS AND METHODS

Study design, settings and duration

This study is a case control study conducted in respiratory consultancy clinic of Al-Sadar Teaching Hospital / Al-Najaf governorate and Merjan Teaching Hospital / Babylon governorate during the period from 1st of January to 31st of December 2018. The ethical approval was taken from Ethical Committee of Faculty of Medicine / University of Kufa. Individuals in this study were subjected to inclusion and exclusion criteria as following:

Inclusion Criteria	Exclusion Criteria
Adults (age>35 years)	Atopic Diseases
Smokers or ex-smokers	Asthma
Exertion Dyspnea	Cystic fibrosis
Chronic Cough	Acute infection
Wheezy chest	Inflammatory Diseases
Regular Sputum production	Cardiovascular diseases
Frequent winter bronchitis	Renal impairment
	pregnancy
	Active Cancer

Sample

After applying the equation, a convenient sample of 87 COPD patients was selected after eligibility to inclusion and exclusion criteria. As a control group, a convenient sample of 100 adult healthy individuals was selected or presented for consultancy clinics for simple conditions, figure (1). The control individuals must be non-smokers and without history of ex-smoking. The healthy controls were having FEV1 more than 80% of predicted value and without any other respiratory disease.
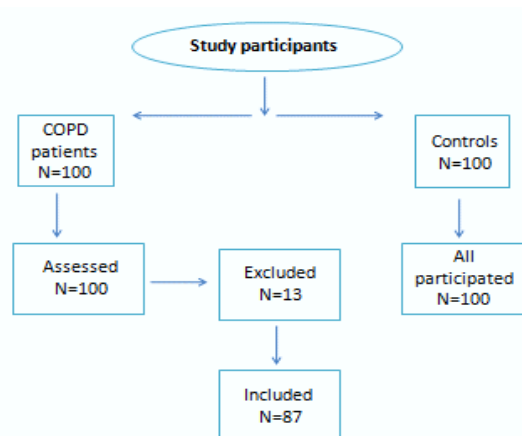

Figure (1): Inclusion of study participants

METHODS

Data Collection

The data were collected from patients and questionnaires were filled. The questionnaire was designed with the consideration of different aspects including demographic characteristics of study participants (age and gender), body mass index of study participants, spirometry findings of study participants (forced expiratory ratios), proinflammatory markers of study participants (IL-1B, IL-6 and TNF-a) and BODE index.

Assessment of patients

Proper history and examination for all patients were performed. The included COPD patients were diagnosed according to the guidelines of Global Initiative for Chronic Obstructive Lung Disease [3]. All study participants were also referred to radiology department of consultancy clinic for chest x-ray to assess their status. The weight and height of study participant was measured in consultancy clinic. The body mass index was classified according to WHO definition of BMI as following: normal (<25 Kg/m^2), overweight (25-29.9 Kg/m^2) and obese ($\geq$30Kg/m^2) (WHO, 1995).

Pulmonary function test

Using spirometry device (Spiro lab III, Italy), the pulmonary function test was measured in respiratory unit of Al-Sadar and Marjan hospitals. The accuracy and reproducibility of this device was evaluated [12]. After three consecutive testes, the best test was chosen according to the American thoracic society guidelines FEV1, FVC. The FEV1/FVC ratio was measured and COPD was diagnosed according to the guidelines of Global Initiative for Chronic Obstructive Lung Disease. All the measurements were made in sitting position after a period of steady state.

Examination of pro-inflammatory markers

IL-1B, IL-6 and TNF-a, were determined using ELISA assay by applying Elabscinse Human kits according to the manufacturer's instructions. It is an in vitro enzyme – linked immunosorbent assay for the quantitative measurement of human TNF-alpha, IL-1B, and IL-6 in serum and / or plasma. This assay employs an antibody specific for human cytokine which is coated on a well plate.

BODE index

The BODE index of study participants was measured by measurement of BMI, airways obstruction (FEV1), scaling Dyspnea and exercise test according to American Thoracic Society (ATS) guidelines [13]. For Dyspnea scale, concentrations of expired oxygen and carbon dioxide were analyzed breath by breath. The present study used 30 sec averages of minute ventilation, tidal volume, respiratory rate, oxygen uptake, and carbon dioxide output and gas exchange ratio. For exercise, 6 minute-walking test was used for study participants and finished after patients being exhausted. After calculating BODE indices, the BODE score was calculated in range between 0-10.

Statistical analysis

All data are either mean $\pm$ SD orfrequencies (as percentages) using SPSS, version 24. Multiple contingency tables were conducted, and appropriate statistical tests performed. Chi-square test was used for categorical variables (Fishers exact test was used when total expected variables were less than 20%). Independent sample t-test was used to compare between two means. Statistical significance was considered for P <0.05.

Results

Demographic distribution of age, gender and BMI of study participants

There was no significant difference in mean age between COPD patients and healthy people. Males represented the highest proportions in both COPD and healthy individuals. There was no significant difference in mean BMI between COPD patients and healthy individuals (Table 1)

Table (1): Demographic distribution of age, gender and BMI of study participants

Variable	COPD	Controls	P value	OR	95% CI
	Mean ± SD*	Mean ± SD*			
Age (years)	46.5±9.48	45.1±11.4	0.38	1.6	{-1.74-4.5}
BMI (Kg/m^2)	28.1±4.5	26.7±5.1	0.07	1.3	{-0.1-2.7}
Gender					
Male	75(96.2) 96.2%)**	95(95%)**	0.7	1.3	{0.3 -5.6}
Female	3 (3.8%)**	5 (5 %)**			

OR=Odds Ratio, CI=Confidence Interval.
* Independent sample t-test,
** Fishers exact test

Spirometry findings of study participants
There was a significant decrease of FEV1/FVC ratio in COPD patients when compared to control people (p<0.001; OR=-33.4), table (2).

Table (2): FEV1/FVC ratio of study groups

Variable	COPD	Controls	P value *	OR	95% CI
	Mean ± SD	Mean ± SD			
FEV1/FVC	48.7±3.6	82.4±3.04	<0.001	-33.4	{-6.4_ -4.4}

FEV1=First Second of Forced Expiration, FVC=Forced Vital Capacity, OR=Odds Ratio, CI=Confidence Interval.
* Independent sample t-test

Pro-inflammatory markers of study participants
1. Interleukin-1B
There was a significant increase of mean IL-1B in COPD patients when compared to control people (p=0.03; OR=1.7), table (3).

Table (3): IL-1Bof study groups

Variable	COPD	Controls	P value *	OR	95% CI
	Mean ± SD	Mean ± SD			
IL-1(IU)	29.1±7.2	27.3±3.5	0.03	1.7	{0.09_ 3.3}

* Independent sample t-test

2. Interleukin-6
There was a significant increase of IL-6 level in COPD patients when compared to people control (p < 0.001; OR=16.9), table (4).

Table (4): IL-6levels of study groups

Variable	COPD	Controls	P value *	OR	95% CI
	Mean ± SD	Mean ± SD			
IL6 (IU)	44.5±28.5	27.6±10.7	<0.001	16.9	{10.7_ 23}

* Independent sample t-test

3. Tumor necrosis factor alpha
No significant difference in TNF-a levels was observed between COPD patients and control group (p=0.2), table (5).

Table (5): TNF-a levels of study groups

Variable	COPD	Controls	P value *	OR	95% CI
	Mean ± SD	Mean ± SD			
TNF-a	34.7±8.1	35.9±4.9	0.2	-1.2	{-3.1_ 0.7}

* Independent sample t-test

BODE index

There was a significant increase of BODE index scores among COPD patients in comparison to controls (p<0.001; OR=4.5), table (6).

Table (6): BODE index of study groups

Variable	COPD	Controls	P value *	OR	95% CI
	Mean ± SD	Mean ± SD			
BODE	5.3±1.8	0.8±0.2	<0.001^S	4.5	{4.1_ 4.8}

Independent sample t-test

BODE index score

The BODE index score of COPD patients was classified into four quartiles. There was a highly significant association between higher BODE index score and COPD patients (p<0.001), table (7). Table (7): BODE index score of study groups

BODE index score	COPD		Controls		P value *	OR	95% CI
	No.	%	No.	%			
Quartile 1 (0-2)	48	55.2	100	100.0			
Quartile 2 (3-4)	21	24.1	0	-			
Quartile 3 (5-6)	11	12.6	0	-			
Quartile 4 (7-10)	7	8.1	0	-			

* *Fishers exact test*

DISCUSSION

The chronic obstructive pulmonary disease (COPD) is likely to be in the top list of deadliest diseases all over the world at 2030 [14]. COPD is associated with a gradual limitation of airflow as well as stimulated chronic airways inflammation [15].The inflammatory markers and classifications of severity for patients with COPD are all aimed to help physicians to predict the patients at risk for early treatment in an attempt to decrease the morbidity and mortality rates [16]. In terms of COPD incidence, the mean age of COPD patients in this study was 56.5 years which is similar to findings conducted in a study in Iraq which found that age of COPD patients was more than 55 years [17]. However, the mean age of COPD patients in this study was lower than results of another study which revealed that the age of COPD patients was 65.3 years [18]. This lower age of COPD patients might be attributed to the increase in the prevalence of COPD among younger adult population in Iraqi society in the last few years due to increased smoking behavior among population. A previous study showed that two out of ten students in Karbala University / Iraq were smokers in addition to the fact that about half of smokers were starting smoking below age of 18 years [19]. Present study showed that the gender of majority of COPD patients was male. This proportion is higher than a proportion found in a study in Iraq (71.1%of COPD patients were males) [20]. Current study findings are also inconsistent with results of study in USA which stated that COPD and smoking prevalence is increased in women and in some countries the smoking prevalence was equal for both men and women [21]. Another study found that prevalence of emphysema and COPD among smoker men is higher than women, but the women with less packs/year smoking has higher risk of emphysema and COPD [22]. In present study, mean BMI of COPD patients was 28.1 Kg/m². This finding is consistent with results stated by Wu and coworkers who documented that mean BMI of majority of COPD patients was 27.9 Kg/m² and the development of COPD was positively related to BMI while COPD exacerbations were negatively related to BMI [23]. A study in Iraq found that

weight loss is common in COPD and BMI could be used to assess the relationship between smoking and COPD [24]. Furthermore, mortality risk of COPD was significantly lower among overweight COPD patients in comparison to underweight ones and the mortality risk increases with an increase of BMI [25]. Current study showed that first second of forced expiration to the full forced vital capacity (FEV1/FVC) ratio of COPD patients was 48.7. This finding is consistent with results of study which reported that FEV1/FVC ratio is an important spirometry assessment tool for diagnosis of COPD when it becomes less than 70%. The FEV1/FVC ratio is useful in diagnosis and prediction of small cell lung carcinoma. The lambda-mu-sigma method is regarded as a new technique clarifying the lower limit of normal ratio of FEV_1/FVC. Current study showed a significant decrease of FEV1/FVC ratio among COPD patients. This finding is consistent with results of many studies which showed that FEV1/FVC ratio was significantly lower among COPD patients in comparison to controls [26-27]. The spirometry is currently represented the first choice in diagnosis and assessment of airflow obstruction and for classification of COPD severity depending on specific threshold for forced expiratory ratio (FEV1/FVC <0.7 after bronchodilator) and first second of forced expiration to the full forced vital capacity (mild ≥80%, moderate 50-80%, severe 30-49% and very severe<30%). The FEV1 is expected to decrease with age and the rate of this decrease is used to detect the course of COPD and its severity. The inflammatory response is commonly accompanying COPD especially in small airways and lung parenchyma which represented by elevated levels of macrophages, Neutrophils, and T lymphocytes. Unlike asthma, COPD is not clearly associated with inflammatory mediators, however, lipid mediators, reactive oxygen species, inflammatory peptides, nitrogen cytokines and growth factors are observed in inflammations that lead to fibrosis of small airways and destroyed alveoli [28]. Present study showed an increase in IL-1 level in COPD patients which is close to results of a study done in Egypt [29], where they also revealed that IL-1B has an interesting role in diagnosis and

classification of COPD. Likewise, this finding is in line with results revealed a significantly higher level of IL-1 among COPD patients indicating its great role in diagnosis of COPD [30]. Although, the IL-6 level of COPD patients in this study is lower than IL-6 level reported in a published study [31], the IL-6 levels in both studies were higher than that of healthy population. This difference in IL-6 level between two studies might be due to alterations in risk factors like smoking between patients and differences in other pro-inflammatory factors in addition to differences in study designs. Similarly, a systematic review and meta-analysis study showed that IL-6 level is elevated in COPD patients when compared to healthy population [32]. Although IL-1B and IL-6 levels were elevated significantly, present study showed that no significant difference in TNF-a level was observed between COPD patients and control people. However, some people stated that TNF-a level is increased with increasing severity of COPD concluding that TNF-a, is important for diagnosis of COPD and severity classification of patients with COPD [33-34]. Current study showed a significant increase of BODE index scores among COPD patients. This finding is in line with results revealed by Powrie (2004) in the UK which confirmed the role of BODE index in predicting the mortality of COPD [35]. BODE index is a simple prognostic readout for measuring the physical and respiratory functions in elderly people, where BODE index is increased in COPD patients in comparison to normal population [36-37]. BODE index is originated from BMI, airways obstruction assessed by spirometry (FEV1), Dyspnea (Dyspnea scale) and exercise capacity [38]. In spite of different elements of BODE index, only BMI and Dyspnea findings are simply recorded while other elements need conflicted preparations [39]. Many studies confirmed the role of BODE index as an appropriate tool for health and outcome of debilitated patients [40].

CONCLUSIONS

The pro-inflammatory markers, IL-1B and IL-6, are more likely to be applicable in diagnosis and assessment of COPD. The BODE index is considered as suitable readout for severity assessment and mortality prediction of COPD. Furthermore, pulmonary function test measurements of forced expiratory ratio are still a convenient method for screening and diagnosis of chronic obstructive pulmonary disease.

REFERENCES

1. Celli, B.R. and MacNee, W.(2004). Standards for the diagnosis and treatment of patients with COPD: a summary of ATS/ERS position paper. Eur. Respire J., 23: 932 – 946.
2. Sarkar SK, Basuthakur S, Das SK, Das A, Das S, Choudhury S, et al. (2015). Evaluation of correlation of BODE index with health-related quality of life among patients with stable COPD attending a tertiary care hospital. Lung India: official organ of Indian Chest Society, 32(1): 24-28.
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention chronic obstructive pulmonary disease. Updated [2013] [cited 2013 March Available from http://www.csrd.org.cn/uploadfiles/img/file/20130305/2013030 511I459575957.pdf.
4. National institute for health and care excellence (NICE 2010), chronic pulmonary disease; management of COPD in adult in primary and secondary (partial up date). London: National clinical Guideline center, 2010).
5. Fricker M, Deane A, Hansbro PM. Animal models of chronic obstructive pulmonary disease, Expert opines Drug Disc 2014; 9: 629-645.
6. Keely S, Talley NJ, Hanspro PM. Pulmonary-intestinal cross-talk in mucosal inflammatory disease. Mucosal Immunol [2012]; 5: 7-18.
7. Marion, M.S.; Leonardson, G.R.; Rhades, E.R.; Welty, T.K; Paul, L. and Enright, P.L., (2001). Spirometry Reference values for American Indian Adults. Chest, 120:489-495.
8. Fulambarker, A.; Coper, A.S.; Javeri, A.; Jeres, S. and Cohen, M.E., (2004). Reference values for pulmonary function in Asian Indians living in the United States. Chest, 126:1225 - 1233.
9. Celli BR, Cote CG, Marin JM. (2004), the body-mass index, airflow obstruction, Dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med, 350(10):1005–1012.
10. NurhanSarioglu, Aylin Ozgen Alpaydin, Aysinsakercoskun, pinarcelik, Beyhancengizozyurt, ArzuYorgancioglu, Multidisciplinary respiratory Medicine 2010; 5(2): 84 – 91.
11. Simona E. Busulac, Hmarike Boezen, Pieter S., Hiemstra, theresslapperre, JUDI m, vonk , wimtimens , DIRK JE S.POSTMA .(2012) ; 7(8) : e431 24.
12. Yesar M.H. AL – Shamma, Hussain M. Hussain, Zainab. Yesar Mohammed (2009), Kufa Med. J. 12 (2): 126 – 131.
13. Crapo RO, Casaburi R, Coates AL. (2002). ATS statement: guidelines for the six-minute walk test, Am J Respire Crit Care Med, 166(1):111–117.
14. Mathers CD, Loncar D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med, 3(11):e442.
15. Qaseem A, Wilt TJ, Weinberger SE. (2011). Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med, 155:179–191.
16. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, et al. (2013). Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA, 309(22):2353-2361.
17. Al-Lami F, Salim Z. (2017). Prevalence and determinants of chronic obstructive pulmonary disease among a sample of adult smokers in Baghdad, Iraq, 2014. East Mediterr Health J, 23(2):67-72.
18. Al-Obaidy MW. (2012). Chronic obstructive pulmonary disease; an epidemiological prospective

study. The Iraqi Postgraduate Medical Journal, 11 (Suppl 2012): 600-607.

19. Al-Mousawi A. (2014). The Prevalence of smoking among Karbala/Iraq University students in Iraq in 2005.Tobacco Use Insights, 7: 9–14.

20. Rasheed ZH, WtwtMA, Farhood HF. (2016).Risk of malnutrition in adult patients with chronic obstructive pulmonary disease. Iraqi J Comm Med (2): 10-19.

21. Han MK, Postma D, Mannino DM, Giardino ND, Buist S, Curtis JL, et al. (2007). Gender and chronic obstructive pulmonary disease: why it matters. American journal of respiratory and critical care medicine, 176(12): 1179-1184.

22. Hardin M, Foreman M, Dransfield MT, Hansel N, Han MK, Cho MH, et al. (2015). Sex-specific features of emphysema among current and former smokers with COPD. The European respiratory journal, 47(1): 104-112.

23. Wu Z, Yang D, Ge Z, Yan M, Wu N, Liu Y. (2018). Body mass index of patients with chronic obstructive pulmonary disease is associated with pulmonary function and exacerbations: a retrospective real world research. Journal of thoracic disease, 10(8): 5086-5099.

24. Sultan KM, AlObaidy MW, Hussein AI. (2009). The Prevalence of Weight Loss Assessed by Body Mass Index in Patients with Stable Chronic Obstructive Pulmonary Disease. The Iraqi Postgraduate Medical Journal, 8 (4): 327-331.

25. Guo Y, Zhang T, Wang Z, Yu F, Xu Q, Guo W, et al. (2016). Body mass index and mortality in chronic obstructive pulmonary disease: A dose-response meta-analysis. Medicine, 95(28): e4225.

26. Johns DP, Walters JA, Walters EH. (2014). Diagnosis and early detection of COPD using spirometry. Journal of thoracic disease, 6(11): 1557-69.

27. Abd El Aziz AA, Elwahsh RA, Abdelaal GA, Abdullah MS, Saad RA. (2017). Diaphragmatic assessment in COPD patients by different modalities. Egyptian Journal of Chest Diseases and Tuberculosis, 66 (2): 247-250.

28. Barnes PJ. (2004). Mediators of chronic obstructive pulmonary disease. Pharmacol Rev, 56 (4): 515-548.

29. Hammad DR, Elgazzar AG, Essawy TS, Abd El Sameie SA. (2015). Evaluation of serum interleukin-1 beta as an inflammatory marker in COPD patients. Egyptian Journal of Chest Diseases and Tuberculosis, 64 (2): 347-352.

30. Zou Y, Chen X, Liu J, Zhou DB, Kuang X, Xiao J, et al. (2017). Serum IL-1β and IL-17 levels in patients with COPD: associations with clinical parameters. International journal of chronic obstructive pulmonary disease, 12: 1247-1254.

31. EmamiArdestani M, Zaerin O. (2015). Role of Serum Interleukin 6, Albumin and C-Reactive Protein in COPD Patients. Tanaffos, 14 (2): 134-140.

32. Wei J, Xiong XF, Lin YH, Zheng BX, Cheng DY. (2015). Association between serum interleukin-6 concentrations and chronic obstructive pulmonary disease: a systematic review and meta-analysis. PeerJ, 3: e1199.

33. Mathanraj S, Kumar V, Yuvarajan S, Reddy V. (2017). Correlation of serum TNF alpha level with severity of chronic obstructive pulmonary disease. Int J Res Med Sci, 5:3309- 3316.

34. Deveci Y, Deveci F, Ilhan N, Karaca I, Turgut T, Muz MH. (2010). Serum ghrelin, IL-6 and TNF-α levels in patients with chronic obstructive pulmonary disease.TuberkToraks, 58(2):162-172.

35. El-Shimy WS, El-Dib AS, Nagy HM, Sabry W.(2014). A study of IL-6, IL-8, and TNF-α as inflammatory markers inCOPD patients. Egyptian Journal of Bronchology, 8:91–99.

36. Roberts MH, Mapel DW, Bruse S, Petersen H, Nyunoya T. (2013). Development of a modified BODE index as a mortality risk measure among older adults with and without chronic obstructive pulmonary disease. American journal of epidemiology, 178(7): 1150-60.

37. Khan NA, Daga MK, Ahmad I, Mawari G, Kumar S, Kumar N, et al. (2016). Evaluation of BODE index and its relationship with systemic inflammation mediated by proinflammatory biomarkers in patients with COPD. Journal of inflammation research, 9: 187-198.

38. Celli BR, Cote CG, Marin JM. (2004). The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med, 350(10):1005–1012.

39. Crapo RO, Casaburi R, Coates AL. (2002). ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med, 166(1):111–117.

40. Ko FW, Tam W, Tung AH. (2011). A longitudinal study of serial BODE indices in predicting mortality and readmissions for COPD. Respir Med, 105(2):266–273.