

Original research article**A study on bode index as a predictor of severity and systemic involvement in patients with chronic obstructive pulmonary disease**

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Abstract

Aims and Objectives: To see if having a higher BODE index in chronic obstructive pulmonary disease correlates with having smoked for more years. To see if a higher BODE index is linked to more days spent in the hospital for patients. To see if a higher BODE is linked to more severe cardiac involvement. To see if a greater BODE index is linked to a patient's low nutritional status. To see if BODE index is linked to systemic inflammation.

Methods: This study was carried out at Department of Pulmonary Medicine and General Medicine, Government General Hospital Kakinada between August 2021 to February 2022. After obtaining institutional ethics committee approval. The BODE score was evaluated as a predictor of hospitalization and severity of systemic involvement in individuals with Chronic Obstructive Pulmonary Disease using a case control study design with sample size 60 (case: 40; controls: 20).

Results: As a result, our study suggests that the BODE index is reliable in determining the hospitalization and severity of systemic involvement in COPD patients and not only an indicator of mortality. The BODE index is extremely useful in evaluating COPD patients in any health-care setting. This will also organize the appropriate referral of COPD cases to the next level, resulting in the use of less resources.

Conclusion: The BODE index is a valid tool for determining the severity of COPD. The BODE index is directly connected to the length and intensity of smoking. It predicts hospitalization due to various causes of COPD. Systemic inflammation increases with increase in the severity of COPD. The changes in BMI and serum albumin can be attributed to reduction in nutritional status of COPD patients which is directly correlated by BODE index. An increase in cardiac effects with the severity of disease was seen when it was assessed by BODE index. Severe COPD is associated with Polycythemia.

Keywords: BODE index, inflammation, predictor, COPD

Introduction

The main cause of illness and mortality in the modern world is chronic obstructive pulmonary disease (COPD). About 3 million people globally die from COPD in 2012, making up 6% of all fatalities. Since its risk factors continue to contribute to rising mortality and morbidity, COPD is an urgent health issue worldwide. The symptoms of COPD are persistent respiratory symptoms and airflow restriction brought on by airway and/or alveolar abnormalities. These abnormalities are typically brought on by significant exposure to noxious particles and gases and are influenced by host factors such as abnormal lung development ^[1]. COPD is a common, treatable, and preventable disease.

Tobacco smoke, indoor and outdoor air pollution, occupational exposures such as chemicals and dusts, ageing and female sex, low birth weight and low socioeconomic status, and also past h/o asthma, recurring infections are some risk factors ^[2, 3]. The biochemical mediators for COPD are oxidative stress and increased circulating amounts of inflammatory mediators and acute-phase proteins. Malnutrition is visible in COPD patients because it promotes muscular wasting and weight loss. COPD patients experience selective fat-free mass loss, as well as changes in respiratory and skeletal muscle function and a lower exercise tolerance ^[4, 5]. Weight loss is also a poor predictor of future health ^[1]. Even while FEV1 can be used to determine the severity of COPD, cases of COPD include systemic implications that cannot

be determined only by FEV1. A multifactorial assessment tool was required to take these into account. The four variables that best predicted severity were the body mass index (B), the degree of dyspnea and airflow obstruction, both identified by the six-minute walk test, and exercise capacity (E). These data were used to build the BODE index, a multidimensional 10-point scale where higher scores are related to a greater chance of mortality^[6,7].

Because COPD affects such a wide population, extending the reach of healthcare facilities and ensuring COPD control is a monumental challenge. We need a logical and consistent scoring system that can identify people who need diagnostic or therapeutic assistance but can't afford it because of a health-care budget crunch. As a multidimensional scoring system, the BODE index completes or fulfils the purpose. The BODE index was investigated as a predictor of hospitalisation and the severity of systemic involvement in our study.

Materials and Methods

This study was carried out at Department of Pulmonary Medicine and General Medicine, Government General Hospital Kakinada between August 2021 to February 2022. After obtaining institutional ethics committee approval. The BODE score was evaluated as a predictor of hospitalisation and severity of systemic involvement in individuals with Chronic Obstructive Pulmonary Disease using a Case control study design with sample size 60 (Cases: 40; controls: 20).

Inclusion criteria

- Male patients with COPD-like symptoms were used as test subjects.
- Controls were male patients who came in for a master health checkup.

Exclusion criteria

- Spirometry was found to be accurate after administration of a bronchodilator (bronchial asthma is defined as an increase in FEV1 of more than 15% above the baseline value or 200 ml) i.e.; Bronchial asthma cases was excluded.
- Within the last four months, patient had a recent myocardial infarction (MI).
- Patients with uncontrollable angina.
- Patients with congestive heart failure (NYHA class III or IV).
- Spirometry or the six-minute walk test are not possible for this patient.
- Unrelated serious disease with a high risk of death.
- Hepatitis (disease of the liver).
- Patients suffering from an acute exacerbation.
- Sputum positive Tuberculosis patients.

Statistical analysis

After categorising the variables, statistical analysis was done on all 60 subjects (40 COPD patients and 20 controls). Data was gathered from these patients. Age, BMI, number of hospital days, mean haemoglobin concentration, QRS axis by electrocardiography, ejection fraction and pulmonary hypertension from 2D EHCO, serum albumin concentration, and CRP were the parameters that were examined.

The significance of the distinction in means from the study was assessed using the one-way ANOVA F-test amongst two groups, and the significance of the differences in proportions was assessed using the Chi square test. A P value of less than 0.05 was used to determine statistical significance. For the statistical analysis, the standard formula was utilised.

Results

The trial had 60 patients in total, with 20 healthy volunteers serving as controls and forty people with COPD serving as cases. The bulk of the cases and controls were male. Ten COPD patients (25%) had mild COPD with a BODE score between 0 and 2. There were 15 patients (37.5%) in each of the groups with mild (BODE score of 3-5) and serious. (BODE score above or equal to 6) COPD.

Table 1: Yearly distribution by age

Group	N	Mean (Years)	Standard. deviation	One-way ANOVA F test
Control	30	53.65	4.34	
Mild (0-2)	10	53.4	4.12	
				F=0.68
Moderate (3-5)	15	52.7	3.76	P=0.00010
Severe (>=6)	15	54.9	4.75	Significant
Total	60	53.7	4.21	

The study's participants were 53.7 years old on average. The BODE index was found to rise with age in

COPD patients, with an average age of 53.4 years for the mild group, 52.7 years for the intermediate group, and 54.9 years for the severe group. The control group likewise had comparable age distributions. The difference has a P value of 0.00010, which is statistically significant.

Table 2: Smoking status

Groups	Smoker				Total N	Pearson chi square test
	Yes		No			
	N	%	N	%		
Control	9	45	11	55	20	X ² -10.8578 P =0.01252 Significant
Mild	4	40	6	60	10	
Moderate	10	66.66	5	33.33	15	
Severe	14	93.3	1	6.6	15	
Total	37	61.6	23	38.3	60	

In comparison to the lower index group, the higher BODE index group had a larger percentage of smokers. The scores for the lower group and the control group did not significantly differ from one another. The BODE index is higher as a result of the positive risk connection that smoking status had (P = 0.01252).

Table 3: Pack years of smoking

Group	N	Mean (packyrs)	Standard deviation	One-way ANOVA F test
Control.	20	5.66	2.01	P = 0.01 Significant. F = 135.03
Mild	10	9.75	0.501	
Moderate	15	18.1	2.84	
Severe.	15	28.71	3.4	
Total	60	18.5	9.79	

According to the study, there is a significant correlation between the BODE score and the total number of pack years of smoking. 5.66 pack years were recorded for controls, 9.75 pack years for mild patients, 18.1 pack years for moderate cases, and 28.7 pack years for severe cases.

Table 4: B M I

Group	N	Mean (kg/m2)	Std. deviation	One-way ANOVA F Test	Multiple comparison (LSD)
Control	20	22.46	1.71	F = 12.54 P = 0.01 Significant	1 Vs 2,3,4
Mild	10	22.68	0.88		2vs 1,4
Moderate	15	21.51	2.52		3 vs 1,4
Severe	15	18.53	2.51		4 vs 1,2,3
Total	60	21.28	2.60		P=0.005

The average BMI of the individuals in our study was 21.28 kg/m². The BMI of the control group was 22.46 kg/m², having a standard deviation of 1.71. Patients with COPD were found to have significantly decreased BMIs. The mild group had a standard deviation of 0.88 and a weight of 22.68 kg/m², the moderate group had a standard deviation of 2.51 and a weight of 21.51 kg/m², and the severe group had a standard deviation of 2.51 kg/m².

After several comparisons, it was determined that there was no statistically significant difference among the mild & moderate groups. The other comparisons all showed a significant discrepancy.

Table 5: Number of days in the hospital in the last two years

Group.	N	Mean. (days)	Standard deviation	Oneway ANOVA F test	Multiple comparison (LSD)
Control.	20	0.5	1.62	F = 42.08 P = 0.001 Significant.	1Vs3,4
Mild	10	0.00	0.00		2Vs3,4
Moderate	15	5.80	1.30		3Vs1,2,4
Severe	15	25.13	5.33		4Vs1,2,3
Total	60	18.91	10.32		P. = 0.05

Over the past two years, a higher BODE score was linked to a higher likelihood of hospitalization for COPD-related reasons, according to the study's findings. The moderate COPD group had no significant hospital admissions in the previous two years, while the control group had an average stay of 0.5. According to the BODE score, the average length of stay in the moderate study group was 5.80 days, while it was 18.9 days in the severe COPD group. On several comparisons to different groups, each of these values were shown to be significant.

Table 6: Hemoglobin concentration in gm/dL

Group	N	Mean (gm/dL)	Std. deviation	One-way ANOVA F test	Multiple comparison (LSD)
Control	20	10.70	2.28	F = 5.57 P = 0.01 Significant	1Vs3,4
Mild	10	11.56	1.59		2Vs3,4
Moderate	15	9.36	2.30		3Vs1,2,4
Severe	15	10.70	2.28		4Vs1,2,3
Total	60	10.86	2.19		P = 0.05

When the haemoglobin readings from the different study groups were analysed, it was shown that patients with COPD had lower mean haemoglobin concentrations (10.54 gm/dL) than controls (10.70 gm/dL). However, in an experiment with multiple comparisons, this correlation was not determined to be significant. The values in the other two groups were much lower (moderate: 9.36 gm/dL and severe: 10.70 gm/dL). This was determined to be statistically significant with a P value of 0.05.

Table 7: QRS axis in ECG and BODE score

Group	ECG axis								Pearson chi square test
	Normal		RAD		LAD		Total		
	N	%	N	%	N	%	N	%	
Control	17	85%	1	5%	2	10%	20	100%	X ² =32.09 P = 0.01 Significant
Mild	9	90%	0	0%	1	10%	10	100%	
Moderate	10	66.7%	5	33.3%	0	0%	15	100%	
Severe	1	6.7%	12	80%	2	13.3%	15	100%	
Total	37	61.7%	18	30%	5	8.3%	60	100%	

It was discovered that the QRS axis varied between the several study groups. 17 patients in the control domain had normal axis, 2 had left axis, and 1 had Rad. 9 patients with regular axis and one individual with left axis variation were studied by the mild COPD group. In moderate, 5 had a right axis deviation, while 10 were normal. Twelve patients with severe copd had right axis deviations, one was normal, and two had left axis deviations.

Table 8: Ejection fraction Vs BODE score

Group	N	Mean (%)	Std. deviation	One-way ANOVA F test	Multiple comparison (LSD)
Control	20	69.55	4.39	F = 29.96 P = 0.01 Significant	1Vs3,4
Mild	10	68.10	10.37		2Vs1,3,4
Moderate	15	64.52	4.19		3Vs1,2,4
Severe	15	48.73	8.60		4Vs1,2,3
Total	60	62.84	10.75		P = 0.000

In the study, the Ejection % differed significantly between the groups. The mean EF for the control group was 69.55% (SD: 4.39). The mean fraction of ejection for all other groups was 64.52 (standard deviation: 4.19), 48.73 (standard deviation: 8.60), and 47.31 (standard deviation: 7.177) for severe COPD. With a P value of 0.000, the mean ejection fraction difference between every group was statistically significant.

Table 9: Pulmonary hypertension and BODE score

Group	Pulmonary hypertension								Pearson chi square test
	Normal		mild		Moderate		Severe		
	N	%	N	%	N	%	N	%	
Control	20	100%	0	0%	0	0%	0	0%	X ² =58.19 P = 0.01 Significant
Mild	10	100%	0	0%	0	0%	0	0%	
Moderate	9	65.5%	4	26.7%	2	13.3%	0	0%	
Severe	0	0%	2	13.3%	3	20%	10	66.7%	
Total	39	65%	6	10%	5	8.3%	10	16.7%	

According to the BODE scores, this study demonstrated that neither the group of controls nor the group with moderate COPD had any instances of pulmonary hypertension. In the group of patients with moderate COPD, 9 individuals had no pulmonary hypertension, whereas 2 patients had moderate PHT and 4 patients had mild PHT. However, all patients in the group with severe COPD developed PHT, with 2 having mild PHT, 3 having moderate PHT, and 10 having severe PHT.

Table 10: Albumin concentration vs BODE score

Group	N	Mean (gm/dL)	Std. deviation	One-way ANOVA F test	Multiple comparison (LSD)
Control	20	5.795	0.842	F = 26.26	1Vs3,4
Mild	10	5.580	1.266		2Vs3,4
Moderate	15	4.000	1.050		3Vs1,2,4

Severe	15	3.327	0.566	P = 0.001	4Vs1,2,3
Total	60	4.69	1.397	Significant	P = 0.05

With an increase in BODE score, it was discovered that albumin concentration gradually decreased. The average albumin levels were 4.69 gm/dL (SD 1.397) in the control group, 5.795 gm/dL (SD.842) in the mild group, 5.580 gm/dL (SD 1.266) in the moderate group, and .000 gm/dL (SD 1.050) in the group with severe COPD. There was no difference between the mild group and controls. But compared to other differences, the difference between the severe and moderate categories was more significant (P = 0.000).

Table 11: C reactive protein Vs BODE score

Group	N	Mean	Std. deviation	One-way ANOVA F Test	Multiple comparison (LSD)
Control	20	5.58	5.20		1 Vs3,4
Mild	10	27.06	21.68	F = 63.57	2Vs3,4
Moderate	15	51.45	18.11		3Vs1,2,4
Severe	15	70.46	13.62	P = 0.001	4Vs1,2,3
Total	60	36.85	29.85	Significant	P = 0.05

CRP was determined to be highest in the severe copd group in the BODE category with the highest scores of 70.46 (standard deviation: 13.62). A P value of 0.05 indicated statistical significance for the research, while a P value of 0.001 indicated statistical significance for the difference.

Table 12: Distribution of study population

Study group	Frequency	Percentage
Control	20	33.33%
Mild	10	25%
Moderate	15	25%
Severe	15	16.7%

Discussion

One of the main causes of death in the globe is COPD. Researchers looked for a more accurate tool to measure the severity of COPD and found that the BODE index would do. The index's usefulness resides in its capacity to foretell hospitalisation and death in COPD patients. Our study concentrated primarily on the extent of COPD in those patients as measured by hospitalisation, systemic inflammation, and systemic involvement. We have made a number of important discoveries that could affect how COPD patients are treated in the future. In order to make our study uniform, we only chose male patients. The discrepancies in the BODE index among the numerous patients tested would be eliminated by such a selection.

We divided COPD patients into three categories depending on their BODE scores: 0-2, 3-5, and 6 or more. Participants in our study were relatively evenly distributed among the different groups. In terms of hospitalisation and mortality, this classification closely correlates with severity. Because of this, we decided to classify the aforementioned groups as mild, moderate, and severe COPD. 20 people were also chosen to serve as controls.

	My study	Kian-Chung <i>et al.</i> ,	Celli <i>et al.</i> , Spain	Venezuela	USA
BODE	7.64±0.89	4.5 ±2.7	2.9± 2.2	4.9± 2.1	5.1 ±2.4
AGE	54.9 ±4.75	70.9 ±8.2	66 ±8	64 ±10	67± 9
Significance	0.0001	0.001			0.001

The BODE score increases with age, according to Celli *et al.*, [8] and Kian-chung *et al.*, [9]. This is brought on by COPD getting worse as people age. Even though our age range was narrower than that of Kian *et al.*, and Celli *et al.*, we saw a similar tendency. Some studies have shown no connection between the two. Contrary to our findings, this gap is mostly caused by the fact that duration of smoking and age weren't related to one another.

Bode Index	Smoking Index		
Bode	MY Study	Celli <i>et al.</i> ,	Kumar <i>et al.</i> ,
Mild	28.71	40 (80±48)	19.475
Severe	9.75	88 (80 ±48)	27.978
Significance	0.001	0.36	0.001

Like the majority of other studies, this one also discovered a connection amongst smoking and the BODE index. Research by Kumar *et al.*, [10] and Celli *et al.*, [8] have demonstrated a correlation between smoking for a longer duration and a higher BODE score. Despite the smoking index being in a higher domain in

Celli *et al.*, the significance was 0.36 as opposed to our study's and Kumar *et al.*'s., 0.001 in both investigations. According to the study, smoking for a longer duration was associated with a significant rise in the BODE index. The moderate COPD group and the control group showed few statistically significant variations between the study groups. This implies that if people give up smoking, the illness can still be treatable.

BODE	Kumar <i>et al.</i> , (mean days)	My study (mean days)
Mild	6.401±16.49	0
Moderate	12.46±14.32	5.80±1.30
Severe	19.45±18.97	25.13±5.33
Significance	0.000	0.001

The comparison between my work and that of Kumar *et al.*, is shown above, and there is importance in this comparison. With control groups, not much significance was discovered. The range in days can be attributed to institutional disparities in admission or to extreme values when determining the average number of days spent in the hospital.

A multicomponent staging system combining FEV1, 6-min walking distance, dyspnea scored on the MMRC scale, and PaO2 will better describe the use of healthcare resources among COPD patients in various geographic areas when compared to international COPD classifications like (ATS, British Thoracic Society and GOLD) [1]. As a gauge of the severity of COPD acute exacerbations, the BODE score fared better than FEV1. The same prediction was made in prospective research to validate the BODE index's accuracy in predicting hospital readmissions [11]. Also mentioned were regular physical activity and fewer hospital readmissions. These results are supported by a second study, which claims that a brief 6-minute walking test raises the risk of COPD hospitalisation (70). Therefore, it's probable that the many elements of the BODE scoring system's evaluation of physical performance status account for the BODE index's stronger power in predicting hospital readmissions for COPD patients than FEV1.

COPD	BMI (kg/m2)			
	My study	Schols <i>et al.</i> ,	Deoca <i>et al.</i> ,	Kumar <i>et al.</i> ,
Mild	22.68±0.88	>30	>30	26.153±3.52
Moderate	21.51±2.52	= 24	20- 24	24.42±3.42
Severe	18.53±2.51	> 12.9	<20	22.48±4.29
Significance	0.005	0.001	0.05	0.001

When used as a BMI criterion, the BODE Index considers a value of more than or less than 21 to be significant. We discovered a decline in BMI because COPD was more severe. According to Engelem *et al.*, and Schols *et al.*, [12, 13], who examined the systemic effects of COPD, Emil *et al.*'s (conclusion that BMI drops in COPD sufferers, as we discovered in our study, is supported. We compared these findings with those of Kumar *et al.*, [10] and Deocaetal, who reported similarly significant results. It is likely that the wasting syndrome observed in patients is a result of an imbalance in the ongoing process of protein destruction and replenishment. Our study's similar significance to that of Kumar *et al.*'s can be attributed to regional variations in the Built and corresponding BMI of the study population. In both cases, the BMI is in a wide range, ranging as low as 12 and this may be the result of superior clinical infrastructure that promotes longevity even in severely malnourished COPD cases.

The measures that were assessed in this regard included the body mass index, ECG axis, haemoglobin and albumin concentrations, the fraction of ejection, and pulmonary hypertension in ECHO and CRP for a systemic inflammation assessment.

Hypoxia in COPD patients causes the production of erythropoietin, which causes polycythemia. In accordance with BODE INDEX, individuals with mild COPD had lower haemoglobin levels compared controls, and as severity increases, the mean concentration of haemoglobin decreases, suggesting that these patients may not be receiving adequate nutrition.

Over 80% of patients with severe COPD and 33% of patients in the moderate COPD category in our study had a right axis deviation, which is consistent with the findings of Burch *et al.*, and Caird *et al.*, [14], who discovered that more than eighty percent of severe COPD patients have a right axis variation. This can be explained through the fact that the pulmonary functions and PAH of these individuals are declining more quickly. However, contrary to my research, it is only 29% in some studies as those by Chapell *et al.*, We can therefore draw the conclusion that those with a high BODE index are generally more likely to develop right heart disease.

similar to other research Echocardiographic alterations were comparable because the ejection fraction significantly decreased in our research groups. It's possible that smoking-related cardiomyopathy is to blame. Patients with COPD experience LV dysfunction because of Bernheim's effect, which is brought on by the interventricular septum's paradoxical movement.

According to Arcasoy *et al.*, [15], pulmonary hypertension occurred in over 16% of COPD patients. A

total incidence of 52.3% of PAH was found in our study. Stevens *et al.*, demonstrated that individuals with severe COPD, in whom the average PAH was 597 mmHg, had a greater percentage of patients with pulmonary hypertension. The severity group had a higher proportion, with 66.7% having severe PAH, 20% having moderate PAH and 13.3% having mild PAH. As a result of pulmonary vasoconstriction brought on by alveolar hypoxia, acidemia, and hypercarbia, as well as increased lung volume that compresses pulmonary vessels, the loss of small blood vessels brought on by emphysema, increased blood viscosity, and increased cardiac output, affected patients experience pulmonary hypertension.

Li *et al.*,^[16] showed direct effects of TNF and the time-and concentration-dependent decreases in total protein. In Wouters *et al.*,^[17], hypoalbuminemia in COPD patients was demonstrated. In our investigation, there was a substantial decrease in serum albumin levels and a commensurate rise in COPD severity as measured by the BODE score.

C-reactive protein (CRP) was chosen as the inflammatory marker in our study because it upregulates the production of tissue-specific factors and proinflammatory cytokines by monocytes, along with an increase in LDL uptake by macrophages and expression of molecule adhesion by human endothelial cells. This was shown by Cirillo *et al.*, who found that a decline in FEV1 was associated with an increase of one standard deviation in serum LDL levels. By reacting to inflammatory signals and transforming into foam cells, they cause atherosclerotic plaques to form on the walls of blood vessels. According to Cirillo *et al.*,^[18] increased CRP was observed to be associated with worsened airflow obstruction. Except for patients with mild COPD, moderate and severe instances were significantly correlated with low-grade systemic inflammation in our study.

Frequent visits, hospitalisations and active use of medical services are all linked to COPD. According to the results of this study, the BODE strategy may be helpful in allocating healthcare resources and directing therapy for patients after discharge. This multistage scoring system shouldn't be challenging to use or expensive to install on a regular basis because it can be quickly evaluated in any circumstance. The results of the present research support the use of the BODE index as a tool for evaluating COPD patients because it is a highly helpful prognostic information-giving tool, particularly for patients with COPD.

Conclusions

The BODE index can be used to assess the severity of COPD. The BODE index and smoking duration and intensity are directly related. It foretells hospitalisation as a result of numerous COPD causes. With an increase in COPD severity, systemic inflammation rises. The loss in nutritional status of COPD patients, which is directly associated with BODE index, can be blamed for the alterations in BMI and serum albumin. When the disease's severity was determined using the BODE index, a correlation between the cardiac consequences and it was observed. Having polycythemia is related to having severe COPD.

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References

1. Global Initiative for Chronic obstructive lung disease, 2021. (goldcopd.org).
2. WHO Global health estimates of (COPD), 2019.
3. Jindal SK, Gupta D, Aggarwal AN. Guidelines for management of chronic obstructive pulmonary disease in India: a guide for physicians. *Indian J Chest Dis Allied Sci.* 2003-2004;46:137-93.
4. Kohansal R, Martinez-Camblor P, Agusti A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit. Care Med.* 2009;180(1):3-10.
5. Raad D, Gaddam S, Schunemann HJ, *et al.*, Effects of water-pipe smoking on lung function: a systematic review and meta-analysis. *Chest.* 2011;139(4):764-74.
6. She J, Yang P, Wang Y, *et al.*, Chinese water-pipe smoking and the risk of COPD. *Chest.* 2014;146(4):924-31.
7. Gunen H, Tarraf H, Nemati A, Al-Ghobain M, Al-Mutairi S, Aoun Bacah Z. Waterpipe tobacco smoking. *Tuberk Toraks.* 2016;64(1):94-6.
8. Celli BR, Cote CG, Marin JM, *et al.*, The body-mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. *N Engl. J Med.* 2004;350:1005-12.
9. Kian Chung Ong FRCP, Arul Earnest M.Sc., Suat-Jin Lu MBBS. A multidimensional grading system (Bode Index) as a predictor of hospitalization for COPD. *Chest.* 2005;128:3810-3816.
10. Kumar, *et al.*, assessment of severity and systemic involvement in COPD by BODE index a cross sectional study; c2018.
11. Oroczo-Levi M, Garcia-Aymerich J, Villar J, Ramirez-Sarmiento A, Anto JM, Gea J. Wood smoke

- exposure and risk of chronic obstructive pulmonary disease. *Eur Respir J.* 2006;27:542-6.
12. Engelen MP, Schols AM, Baken WC, *et al.*, Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J.* 1994;7:1793-1797.
 13. Sin DD, Man SF. Why are patients with COPD at increased risk of cardiovascular diseases? The potential role of systemic inflammation on COPD; *circulation.* 2003;107:1514-9.
 14. Burrows B. Predictors of loss of lung function and mortality in obstructive lung diseases. *Eur Respir Rev.* 1991;1:340-5.
 15. Arcasoy SM, Christie DJ, *et al.*, Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease; *Am J Respir Crit. Care Med.* 2003;167:735.
 16. Pulmonary rehabilitation. *Am J Respir Crit. Care Med.* 1999;159:1666-1682.
 17. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit. Care Med.* 1998;157:1791-1797.
 18. Cirillo DJ, Agarwal Y, Cassano PA. lipids and pulmonary function in third national health and nutrition examination survey; *Am J Epidemiol.* 2002;155:842-848.