e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(10); 201-207

Original Research Article

Correlation of BODE Index with Extra-Pulmonary Effects of Chronic Obstructive Pulmonary Disease among Patients Attending Tertiary Care Centre

Vimal Raj R.[1], Dhamgaye T. M.[2], Pujari V.V.[3], Sundrani R. M.[4]

[1]Associate Professor, Department of Respiratory Medicine, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth (Deemed-to-be University), Puducherry, India

[2]Professor, Department of Respiratory Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Sawangi, Wardha, Maharashtra., India

[3]Professor, Department of Respiratory Medicine, Govt. Medical College, Jalgaon, Maharashtra, India

[4] Former Professor and Head, Department of Pulmonary Medicine, Grant Medical College & Sir JJ Group of Hospitals, Mumbai, India, Currently practicing Pulmonologist in the city of Mumbai

Received: 25-07-2024 / Revised: 23-08-2024 / Accepted: 25-09-2024
Corresponding Author: Dr. Vimal Raj R
Conflict of interest: Nil

Abstract:

Background: The extrapulmonary effects of COPD (Chronic Obstructive Pulmonary Disease) need to be searched meticulously in every patient for timely intervention. In any case, the components of this systemic inflammation may account for the systemic manifestations of COPD and may worsen comorbid diseases.

Aims and Objectives: To study the correlation between BODE (Body mass index, airflow Obstruction, Dyspnoea, and Exercise capacity) index score and the extrapulmonary effects in COPD patients, to assess the prognosis of the disease based on the BODE index score, and to analyze the change in severity of the disease process based on the BODE index score.

Materials and Methods: 104 COPD patients diagnosed based on GOLD spirometry criteria were enrolled and the BODE index score for the patients was calculated at the baseline and then actively screened for the presence of underlying extrapulmonary effects. Patients were reviewed again by calculating their BODE index score and the presence of extrapulmonary effects at 1 year.

Results: The change in the BODE score was also statistically highly significant ($p<0.001$) with the change in the number of extrapulmonary effects. The increase in the BODE score was statistically significant ($p<0.004$) with the risk of mortality at the end of one year.

Conclusion: COPD patients should be thoroughly evaluated beyond the lungs, and the BODE index scoring system is a simple, easy-to-use, and effective tool, the use of which should be encouraged more for the optimal management of this dreadful disease.

Keywords: COPD, BODE Index, Spirometry, Extrapulmonary Effects.

Introduction

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. [1] It is currently the fourth-leading cause of death worldwide, [2] but as per the WHO (World Health Organization) projections, it will become the third-leading cause by 2030. [3] Tobacco (Cigarette / Bidi / other forms) smoking is an established risk factor for the development of COPD. Likewise, emerging evidence suggests that approximately 25-45% of patients with COPD have never smoked thus highlighting the burden of COPD due to other causes like biomass fuel exposure. About half the global population (3 billion) is exposed to smoke from biomass fuel as compared to 1.01 billion people to tobacco smoke, suggesting that exposure to biomass smoke might be the biggest global risk factor for developing COPD. [4] The best-recognized manifestations include the presence of concomitant cardiovascular compromise, malnutrition involving the loss and dysfunction of skeletal muscles, osteoporosis, anemia, diabetes, pulmonary hypertension, increased gastroesophageal reflux, clinical depression, and anxiety primarily. [5] In any case, the components of this systemic inflammation may account for the systemic manifestations of COPD and may worsen comorbid diseases. Hence, the need for a comprehensive tool became imminent for identifying the extrapulmonary effects rather

than the standard FEV1, which can only track the decline in lung function.

BODE index includes body mass index (B), the degree of airflow obstruction (O), functional dyspnea (D), and exercise capacity (E) as assessed by the six-minute walk test. This multidimensional index was first described in 2004 by Celli et al. [6] It is a 10-point scale in which higher scores indicate a higher risk of mortality. Our study tried to find out whether this multidimensional scoring system reflects the severity of the extrapulmonary effects present in a COPD patient; to find out if there is any correlation between the BODE index and the number of extrapulmonary effects in a COPD patient. To assess if regular treatment of the pulmonary component of the disease has any bearing on the extrapulmonary effects.

Aims and Objectives

To study the correlation between BODE index score and the extrapulmonary effects in COPD patients, to assess the prognosis of the disease based on the BODE index score, to analyse the change in severity of the disease process based on the BODE index score when more than one extrapulmonary component is present in COPD patients, to study the prevalence of coexistent systemic diseases with COPD at the time of presentation and to study the effects of treatment on BODE index and extrapulmonary effects.

Material and Methods

The present study was conducted at B.J. Government Medical College, Pune – a tertiary care teaching centre in Western India, over a period of 24 months (from 1 November 2010 to 30 November 2012) on 104 patients complaining of difficulty in breathing, chronic cough or sputum production, and/or history of exposure to tobacco smoke, indoor, outdoor pollutants, attending chest OPD, or patients referred for evaluation from other departments. Spirometry was done, and the diagnosis of COPD was confirmed based on GOLD criteria. Prior approval from the Institutional Human Ethics Committee was obtained before the start of the study.

Inclusion Criteria and Exclusion Criteria: The COPD patients diagnosed based on GOLD staging I–IV and COPD with cor pulmonale were included. The subjects under 18 years, HIV patients, unwilling or uncooperative patients, acute left heart failure, lung malignancy patients, post-TB COPD patients, acute exacerbations of COPD, and pulmonary infections were excluded from the study.

Study Procedure: All patients attending the chest OPD with breathlessness, cough, or sputum production and/or a history of exposure to risk factors or those referred to chest OPD from other departments for the evaluation were chosen. After written informed consent, all were subjected to sputum examination and HIV-ELISA. Those who turned sputum-positive or HIV-reactive were excluded from the study. Spirometry was done in the remaining, and those who were found to have obstructive airway disease based on GOLD spirometry criteria were selected. They were classified as per the severity of the disease based on GOLD criteria. The BODE score was calculated by analyzing all four variables in the following way: (1) Height and weight were measured using body mass index. (2) Airflow obstruction (O) was obtained from the spirometry reading—post-bronchodilator FEV1. (3) Dyspnoea (D) was calculated by questioning the patient about the severity of breathlessness based on the Modified Medical Research Council grading. (4) Exercise tolerance (E) was measured by the 6-minute walk test. The scoring for every patient was done by analyzing all the four parameters, and the final BODE score (out of a maximum of 10) was obtained.

Then the patients were screened for the presence of all seven extrapulmonary effects—anemia, diabetes mellitus, pulmonary hypertension, glaucoma, musculoskeletal dysfunction, depression, and osteoporosis-in the following way: anemia was diagnosed based on WHO criteria by hemoglobin level < 13 g/dl in males and < 12 g/dl in females. [7] Diabetes mellitus was diagnosed based on the current WHO diagnostic criteria for diabetes mellitus: fasting plasma glucose ≥ 7.0 mmol/ l (126mg/dl) or 2-hour plasma glucose ≥ 11.1 mmol/l (200mg/dl). [8]

Pulmonary hypertension was diagnosed based on the transthoracic 2D-ECHO by the TR jet method; the presence of mPAP greater than 25 mmHg was considered as the criteria for defining pulmonary hypertension. (25–35 mmHg: mild; 35–45 mmHg: moderate; > 45 mmHg: severe pulmonary hypertension). Glaucoma screening was done by non-contraction tonometry; a value of 21 mmHg was considered a cut-off. All the patients were advised to follow-up after 6 months, and more frequent follow-up was advised for a few patients depending upon the values. Depression was screened based on the ICD-10 criteria,[9] which includes 10 questions, and the patient was classified as having mild, moderate, or severe depression based on his or her reply to the questions. Osteoporosis was screened based on the DEXA (Dual Energy X-Ray Absorptiometry) scan. A T-score of more than (-2.5) was diagnostic of osteoporosis. Values between (-1) and (-2.5) signify that the patient was osteopenic; values < -1.0 were considered normal. After screening for all the extrapulmonary effects, patients were started on treatment for the underlying diseases. After 1 year,

all the previous investigations were repeated, and the new BODE score was again calculated. The change with regard to the extrapulmonary effects in the patients was noted.

Statistical Analysis: Statistical analysis was performed using a statistical software package. All categorical variables were summarized and expressed as percentages. A 'p–value' of < 0.05 was considered to be statistically significant.

Results

Out of all the patients who presented with difficulty breathing, chronic cough or sputum production, and/or history of exposure to tobacco smoke or indoor or outdoor pollution, 104 patients met the inclusion criteria and were enrolled in the study and taken up for analysis.

The study comprised 104 patients, of which 85 were male (81.7%) and 19 were female (18.3%). Patients were in the age group range of 40–69, with the mean ± SD found to be (60.19 ± 7.6). The mean ± SD for the height was 160.96 ± 7.57. Similarly, the enrolled patients were in the weight range of 31 kg to 78 kg, with a mean ± SD of 52.52 ± 11.6 kg at baseline. There was a highly significant ($p < 0.001$) fall in the weight of the patients at the end of one year. There was a fall in all the individual BODE parameters i.e., BMI, FEV_1, 6MWD, and MMRC grades; more than 10 meters fall in 6MWD; and a 5% increase in the number of patients in MMRC grade III.

There was an increase in the severity of dyspnoea at the end of 1 year, reflected by the fall in 6MWD. 30.1% of the patients had BODE scores of either 8 or 9 after 1 year. More than one-third (34.9%) of the patients had a rise of at least 1 BODE index score; one-third (30.1%) had no change in the BODE index score after 1 year, while only 14.4% showed a fall in the BODE index score at the end of 1 year. All the extrapulmonary effects showed an increasing trend at the end of 1 year, maximum among those who had anemia (13% rise). The only patient who had glaucoma succumbed before follow-up. 54% of the patients showed an increase in the number of extrapulmonary features at the end of 1 year, of which 1.2% had 3 more extrapulmonary effects. When the BODE score increased, the number of extrapulmonary effects increased (Table 1)-both at baseline ($r = 0.665$) and at the end of one year ($r = 0.657$)-both were statistically highly significant ($p < 0.001$). The change in the BODE score with the change in the number of extrapulmonary effects was also highly significant ($r = 0.456$; $p < 0.001$).

Higher BODE index score, more extrapulmonary effects, less distance covered in 6 minutes and lower BMI were significant risk factors for mortality at the end of 1 year (Table 2). There was a statistically significant (p-value = 0.004) increase in the mortality of the patients as the BODE score increased. 15 patients (35.71%) with BODE score ≥ 7 died at the end of one year (Table 3). Patients who took irregular treatment had 3 times more risk of dying within 1 year when compared to those who took regular treatment (Table 4). Patients who took regular treatment covered more distance than those who took irregular treatment (Table 5). There was a positive correlation between (Table 6) deterioration in the BODE score and irregular treatment but it was not statistically significant ($p = 0.064$).

Though not statistically significant ($p = 0.903$), it is found that a smaller number of people (19 people) had an increase in the number of extrapulmonary effects if they had taken treatment regularly rather than irregularly. The incidence of anemia was the highest (37.5%), followed by pulmonary hypertension (28.6%) and osteoporosis (22.2%). No new case of glaucoma was diagnosed at the end of 1 year. The percentage of patients who were at stage III of GOLD (severe COPD) had increased (15.6%), while there was a drop in the stage IV patients (very severe COPD) due to death during the follow-up period. More than 2/3rd (69.9%) of the patients did not have any change in the GOLD stage at the end of 1 year, while 18.1% had deteriorated. There was a moderate positive correlation (Pearson correlation coefficient, $r = 0.58$ and 0.61) between the GOLD staging and the BODE index scores at the baseline and at 1 year, and it was statistically highly significant ($p < 0.001$). However the change in the BODE score had a weak positive correlation (Pearson correlation coefficient, $r = 0.264$; $p = 0.016$) with the change in GOLD stage (Table 6).

There was a weak positive correlation between the GOLD staging and the number of extrapulmonary effects, both at the baseline (Pearson correlation coefficient, $r = 0.22$; $p = 0.025$) and at 1 year (Pearson correlation coefficient, $r = 0.372$; $p = 0.001$) (Table 7). There was no significant ($p = 0.341$) correlation between mortality and the GOLD staging. Though not statistically significant ($p = 0.903$), it was found that an increase in the number of extrapulmonary effects after 1 year was less in people who had taken treatment regularly than irregularly. Bidi smoking (64.4%) was found to be the most common risk factor, followed by indoor biomass exposure (18.3%).

Table 1: BODE Parameters at Baseline and After 1 Year

BODE Parameter	Baseline	After 1 Year
	No. of Patients [N = 104]	No. of Patients (N = 83)
BMI (Mean ± SD)	20.35 ± 4.41	20.06 ± 4.05
FEV1 (Mean ± SD)	41.37 ± 11.35	41.06 ± 9.38
6MWD (Mean ± SD)	241.83 ± 84.71	231.69 ± 77.02
MMRC, n (%)		
I	2 (1.9)	0 (0)
II	50 (48.1)	37 (44.6)
III	52 (50)	46 (55.4)

Table 2: Comparison of Baseline Features between Alive and Deceased

At Baseline	Alive (N = 83)	Deceased (N = 21)	P-Value*
BODE	5.35 ±1.94	7.33 ± 1.88	<0.001
6MWD	260.36 ±75.92	168.57 ± 79.13	<0.001
FEV1	42.72 ±11.54	36 ± 8.88	0.006
BMI	20.77 ± 4.61	18.71 ± 3.017	0.017
No. of Extra Pulmonary Features	2.39 ± 1.36	3.81 ± 1.07	<0.001

Table 3: Association between BODE Score at Baseline and Mortality [N = 83]

BODE Score at Baseline	Alive	Deceased	% of Mortality
<5	29	2	6.45
5 & 6	27	4	12.90
≥ 7	27	15	35.71
Chi square p-value = 0.004			

Table 4: Association between Treatment and Mortality [N = 83]

Treatment	Deceased	Alive	% of Mortality
Regular	17	49	25.76
Irregular	4	34	10.53
Fischer Exact test p-value = 0.078 Odds ratio = 2.949, 95% CI - 0.9116 - 9.540			

Table 5: Difference between 6MWD in Those Who had Regular or Irregular Treatment (Baseline – 1 Year.)

Treatment	Regular (49)	Irregular (34)
Mean ± SEM	32.24 ± 6.29	23.52 ± 7.76
t test p value = 0.383		

Table 6:

Change in BODE Score at 1 Year	Treatment (N)	
	Irregular	Regular
-2	0	3
-1	4	5
0	15	10
1	18	11
2	7	4
3	3	1
4	2	0
Effect of Treatment on Change in BODE Score [N = 83] after 1 Year. Mann-Whitney U test, p-value = 0.064.		
Correlations	**Pearson Correlation Coefficient, r**	**P-Value**
At baseline (N = 104)	0.58	<0.001
At 1 year (N = 83)	0.61	<0.001
Change in BODE score with change in GOLD stage (N = 83)	0.264	0.016
Correlation between BODE Score and GOLD Stage		

Table 7: Correlation between GOLD Stage and No. of Extra Pulmonary Features

Correlations	Pearson Correlation Coefficient, r	P-Value
At baseline (N = 104)	0.22	0.025
At 1 year (N=83)	0.372	0.001
Change in GOLD stage with change in no. of extrapulmonary features (N=83)	-0.114	0.304

Discussion

BODE index was proved by Celli et al., [6] in 2004 to be a better prognostic tool for COPD than FEV_1. Peak oxygen uptake, which is the gold standard of exercise capacity, replaced 6MWD in the modified BODE index. The measurement of peak oxygen uptake requires ergometry, which, though can be present in teaching institutions and state-of-the-art pulmonology clinics, because of its cost and its complexity, is not available in many of the centres. Hence, as of now, its use as a routine diagnostic modality for the study of COPD patients is far from reality. It was found to be as good as conventional BODE in predicting mortality among COPD patients, and the authors suggest a simpler modality—the conventional BODE for the comprehensive evaluation of COPD patients. [10]

Our study comprised an age group with a mean±SD of 60.19±7.6. The study group is younger when compared to that of Celli et al., [6] in which the mean age was 66±9 and 70±7 for those who survived and for those who died, respectively. The FEV1 percent predicted was less than in the Celli [6] study group (41.37±11.35 vs. 43±19) though the FEV_1 values were lower in the group that died (28±12). BMI in our study group is also less when compared to Celli's study group (20.35±4.41 vs. 26±5). The 6 MWD in our study group at baseline was 241.83±84.71 as compared to 264±113' in the Celli group. Regarding the risk factors for COPD, the most common risk factor among the patients in our study group was bidi smoking. It was found in 67 patients (64.4%), followed by indoor biomass exposure found in 19 patients (18.3%). Cigarette smoking was found as the risk factor in 17 patients only (16.3%). One patient was a ganja smoker. Gupta et al., [11] in their study on tobacco consumption in the Indian population noted that bidi was the predominant form of tobacco consumption in India (53%). 19% of consumption was in the form of cigarettes. The rest was a smokeless form of tobacco. In our study, all the persons who smoked were males, while indoor biomass exposure was found exclusively in females.

Two-thirds of our patients were in GOLD III (61.5% at baseline and 77.1% at 1 year), as against an almost even distribution of the patients in the Celli group (GOLD I: 30%, GOLD II: 33%, GOLD III: 38%). This shows that our patients' COPD is worse at the baseline itself than in the compared study, and the severity of the lung condition deteriorated over 1 year. With regard to the BODE scores, Celli's [6] patients had a BODE score across the spectrum, of which the maximum concentration was a BODE score of 3 (15%). This is in contrast to our study, in which approximately 20% (17.3% at baseline and 20.5% at 1 year) had a BODE score of 8.

Thus, Celli's study had patients equally from all the BODE scores, whereas our group had a significant number of severe and very severe COPD patients, and hence the prognosis of the patients was also found to be grave, compared to the study by Celli [5]. Among the extrapulmonary effects, the prevalence of anemia is strikingly different when compared to other studies. It was 17% in a study by Cote et al. [12] which investigated the prevalence of anemia among USA Veterans COPD outpatients. Our study had a prevalence of 50.96% and 63.9% at the baseline and at 1 year, whereas 18 (37.5%) new patients became anemic during the study period. This prevalence of anemia is reflective of the prevalence of anemia in India (50%), as per the WHO criteria [7] for the same. Thus, the protein-calorie malnutrition and the poor socioeconomic status of the Indian population may have a reflection on this gross variation in the prevalence of anemia in the study groups.

Chambellan et al. [13] in their study noted that, for every 5% increase in the hematocrit, the risk of death decreased by 14%. They also noted that hematocrit was found to be the strongest predictor of mortality, next only to age. In our study, we found that anemic patients had 8 times more risk of dying from COPD than the non-anemic population, and the data is statistically highly significant ($p<0.001$). The prevalence of diabetes mellitus in our study was found to be 15.4% and 24.1% at the baseline and at 1 year, respectively, with 6 (8.7%) new cases of diabetes mellitus developing over the 1-year study period. In the study by Yeh et al., [14] it was found that lung functions also decrease in patients with type II diabetes mellitus. They noted that the predominant type of lung dysfunction in their study group was restrictive.

However, in our study, restrictive lung disease or a mixed pattern was not found among the diabetes mellitus patients, though all the patients diagnosed with diabetes mellitus were type II. Pulmonary hypertension, considered to be a late event in the course of COPD, was found in 49.03% of the

patients at the baseline. 14 new patients (28.6%) developed pulmonary hypertension in the study period. This prevalence is similar to that of the study by Thabut and his colleagues [15] where the prevalence was 50% but the cut-off value was 20 mmHg. The cut-off value in our study was 25 mmHg. Higham et al., [16] noted that 55% of the patients in his study had pulmonary hypertension. The sensitivity of 2D echo in diagnosing pulmonary hypertension is approximately 50%. Right heart catheterization is considered to be the gold standard for diagnosing pulmonary hypertension. Our study had a 20.2% (21 patients) mortality rate at the end of 1 year. Celli et al.,[6] in their study found that one-year mortality in the fourth quartile (BODE index score 7–10) was 5%, in the second year it was 31%, and at 52 months it was 80%. In our study, at the end of one year, there was a 35.71% mortality among those in the fourth quartile. This is a significant finding since patients in our study die a year earlier than their contemporaries of a different nation.

This can also be attributed to the severity of COPD since our patients had a more severe form of COPD as compared to that of the compared group. About the contrast in the features of the deceased group with the patients who survived, in our study, it is evident that the patients had a higher BODE score (statistically highly significant, $p < 0.001$), lower FEV_1, lower BMI (statistically significant, $p = 0.017$), covered less distance in 6 minutes (statistically highly significant, $p < 0.001$), and had more extrapulmonary features (statistically highly significant, $p < 0.001$). In our study, patients who had regular therapy had a better outcome at the end of one year. Those who had irregular treatment were three times more at risk of dying at the end of one year than those who took treatment regularly.

In this era of personalized medicine, a personalized and effective diagnosis and tailor-made treatment strategies for every patient inculcating their extrapulmonary diseases are needed to optimize their clinical outcomes. [17] This can be augmented by a comprehensive Pulmonary Rehabilitation program encompassing all the relevant disciplines. [18] Patient education and increased awareness about the disease will help in better compliance among the group that defaults on the treatment, not owing to the monetary reason. In our study, regular treatment was found in only one-third of the patients. In those who took treatment regularly, the 6MWD improved at the end of 1 year, along with the mortality benefit, as mentioned earlier. Thus, concerning the extrapulmonary effects, the number of patients within the regular treatment group rose at the end of one year. But it was not statistically significant ($p = 0.903$). The BODE index score also improved in the regular treatment group as compared to the irregular treatment group. Thus, it can be concluded that regular treatment of the pulmonary component had some effect in controlling the extrapulmonary components of the disease.

Conclusion

The extrapulmonary effects need to be searched meticulously in every COPD patient for timely intervention. The BODE index is a simple, quick, effective, and valid scoring system for the better assessment of COPD patients. BODE index score increases as more extrapulmonary effects are present in a patient. The risk of mortality increases as the BODE index score increases. Anemia, pulmonary hypertension, and musculoskeletal dysfunction had a prevalence of more than 50% among COPD patients. BODE index rather than GOLD staging better reflected the severity of the extrapulmonary effects in a COPD patient. Overall, every COPD patient should be thoroughly evaluated beyond the lungs, and the BODE index scoring system is a simple, easy-to-use, effective, and point-of-care clinical tool, the use of which should be encouraged more for the optimal management of this dreadful disease.

Acknowledgements: This study was a Postgraduate Dissertation done by the first/corresponding author under the guidance of the co-authors (former faculty) at Byramjee Jeejeebhoy Government Medical College (B.J.G.M.C.), Pune, Maharashtra during the period mentioned earlier.

This work was presented at the National Conference on Pulmonary Diseases (NAPCON) 2013, Chennai, and the abstract was published in the conference souvenir.

References

1. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006;27(2):397–412.
2. World Health Organization. The Global Health Observatory, Global Health Estimates: Life expectancy and leading causes of death and disability [accessed Sep 2024]. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates.
3. World Health Organization. The Global Health Observatory, Global Health Estimates: Life expectancy and leading causes of death and disability [accessed Sep 2024]. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death
4. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009 Aug 29;374(9691):733-43. doi:

10.1016/S014 0-6736(09)61303-9. PMID: 19716966.
5. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet 2007;370(9589):765-73.
6. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004; 350(10):1005–12.
7. Hemoglobin concentrations for the diagnosis of anemia and assessment of severity, Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization 2011: p. 3. (WHO/NMH/NHD/MNM/11.1)
8. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia : report of a WHO / IDF consultation. World Health Organization 2006: p. 12.
9. The lCD-10 Classification of Mental and Behavioural Disorders. Clinical Descriptions and diagnostic guidelines. Geneva: World Health Organization 1992:119-24.
10. Warwick H, Doig A. Smoke the killer in the kitchen: Indoor air pollution in developing countries. ITDG Publishing, Southamptom Row, London WC1B HLD, UK 2004:103-105. URL: http://itdgpublishing.org.uk.
11. Gupta PC, Asma S. Bidi Smoking and Public Health, New Delhi: Ministry of Health and Family Welfare, Government of India 2008.
12. Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B. Hemoglobin level and its clinical impact in a cohort of patients with COPD. Eur Respir J 2007;29(5):923-9.
13. Chambellan A, Chailleux E, Similowski T. Prognostic value of the hematocrit in patients with severe COPD receiving long-term oxygen therapy. Chest 2005;128(3):1201-8.
14. Yeh HC, Punjabi NM, Wang N-, Pankow JS, Duncan BB, Cox CE, et al. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 2008;31(4):741-6.
15. Thabut G, Dauriat G, Stern JB, Logeart D, Lévy A, Marrash-Chahla R, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest 2005;127(5):1531-6.
16. Higham MA, Dawson D, Joshi J, Nihoyannopoulos P, Morrell NW. Utility of echocardiography in assessment of pulmonary hypertension secondary to COPD. Eur Respir J 2001;17 (3):350-5.
17. Xiang Y, Luo X. Extrapulmonary comorbidities associated with chronic obstructive pulmonary disease: a review. Int J Chron Obstruct Pulmon Dis 2024;19:567-578.
18. Machado A, Marques A, Burtin C. Extra-pulmonary manifestations of COPD and the role of pulmonary rehabilitation: a symptom-centered approach. Expert Rev Respir Med 20 21;15(1):131-142.