ORIGINAL RESEARCH PAPER

Pulmonology

KEY WORDS: Chronic obstructive pulmonary disease, Spirometry, BODE index, C-Reactive protein

STUDY OF INFLAMMATORY MARKERS (CRP) AND BODE INDEX IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Dr. C. Siddhuraj* Assistant Professor, Department of Tuberculosis & Respiratory Medicine, Vinayaka Mission Kirupananda Variyar Medical College, Salem. *Corresponding Author

Dr. M. Punitha Senior Resident, Department of Tuberculosis & Respiratory Medicine, Vinayaka Mission Kirupananda Variyar Medical College & Hospital, Salem.

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality in adults and currently represents the third leading cause of death in world and it is recently recognized as a multicomponent disorder, associated with systemic inflammation and extra pulmonary manifestation. Current study aimed to assess the correlation of BODE index severity and CRP levels (systemic inflammatory biomarker) in COPD. Study is designed as prospective, cross sectional study design and 60 subjects fulfilling criteria were recruited. Spirometry was performed to note FVC, FEV1, FEV1/FVC, FEF25-75% and PEFR. The BODE index was calculated for each patient using the body mass index, FEV1%, the distance walked in 6 min and modified Medical Research Council (MMRC) dyspnoea scale score. The systemic inflammatory marker C Reactive Protein (CRP) was found to be positive in 21 patients (35%) out of 60. 13 patients (72.2%) out of 18 in Severe COPD had CRP positive, while only 7 (28%) out of 25 in Moderate and 1 (6.25%) out of 17 in Mild COPD showed CRP positive. BODE index severity directly correlates with the CRP which implies that underlying systemic inflammation is present in COPD.

INTRODUCTION:

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality in adults and currently represents the third leading cause of death in world (1). It has become a major and growing health problem with a mortality rate that continues to increase (2-5). COPD is not only restricted to pulmonary inflammation and structural remodelling, COPD is also recognized as a multicomponent disorder, associated with systemic inflammation and extra pulmonary manifestation. The severity of COPD is often graded with use of single physiological variable – forced expiratory volume in one second (FEV1) (6). However, the patients with COPD have systemic manifestations that are not reflected by the FEV1 alone. Hence BODE index, a multidimensional grading system that assessed the respiratory and systemic expressions of COPD was designed to predict outcome in these patients(7).

The four factors that predicted the severity were, the body-mass index (B), the degree of airflow obstruction (O), dyspnoea (D), and exercise capacity (E) measured by the six-minute–walk test. These variables were used to construct the BODE index, a multidimensional 10-point scale in which higher scores indicate a higher risk of death. Since systemic inflammation has been recognized as an indisputable component of COPD, the role of inflammatory cytokines has also been widely investigated in the natural history of COPD [8]. It has been shown that C-reactive protein (CRP) levels are elevated in the serum of COPD patients even in stable disease [9]. Hence, we aim to assess the correlation of BODE index severity and CRP levels (systemic inflammatory biomarker) in COPD.

METHODOLOGY:

This is Prospective, Cross sectional study design done in Vinayaka Missions Kirupananda Variyar Medical College and Hospital in Salem which is a 750 bedded tertiary care centre. Study was carried out during the period of June 2019 to December 2019. 60 stable COPD patients diagnosed according to GOLD guidelines in our pulmonary outpatient clinic were included in the study. Institutional human-research Ethical Review approval was obtained and written informed consent was obtained from all patients. Inclusion criteria were: COPD patients in stable conditions (no exacerbations due to any reason in the last 6 weeks). COPD was defined as a history of smoking of more than 20 pack-years and a FEV1/forced vital capacity (FVC) ratio of less than 70% after 20 minutes after salbutamol administration [10]. Exclusion criteria were: patients with other inflammatory diseases (inflammatory bowel disease, rheumatologic diseases, vasculitis), interstitial lung diseases, active pulmonary tuberculosis, presence of atopy, history of myocardial infarction in the last 6 months, decompensated cardiovascular disease and walking disability.

Demographic details, history, detailed history of smoking, personal and family medical histories were obtained. MMRC dyspnoea scale was used to score the patients dyspnoea. Patient details were collected regarding how many times he is presenting to OPD in view of exacerbation over a period of 1 year from his outpatient card. Six-minute walk test was performed as per standard guidelines. Patients were asked to walk on a level ground for maximum possible distance within duration of 6 minutes. Periods of rest taken, was also included in the 6 minutes test period. Body mass index (BMI) was calculated by the formula. BMI = Weight in Kgs / (Height in Mts)^2

Spirometry was performed with equipment that met the American Thoracic Society performance criteria and 20 minutes following the administration of salbutamol (2.5mg) nebulisation for reversibility. The following parameters were noted FVC, FEV1, FEV1/FVC, FEF25-75% and PEFR. The procedure was repeated on 3 occasions and the average value was taken.

The BODE index was calculated for each patient using the body mass index, FEV1%, the distance walked in 6 min and modified Medical Research Council (MMRC) dyspnoea scale score. The patients received points ranging from 0 (lowest value) to 3 (maximal value). For body mass index the values were 0 for (>21) and1 for (<21). The scores for FEV1 were 0 (more than or equal to 65%), 1 (50 – 64%), 2 (36 – 49%) and3 (less than or equal to 35%).

The 6-minute walk test scores were 0 (> 350 mts), 1 (250 – 350 mts), 2 (150 – 249 mts) and3 (< 150 mts). The MMRC dyspnoea 0 for grade 0 and I, 1 for grade II, 2 for grade III and 3 for grade IV.

The points for each variable were added, so that the BODE index ranged from 0 to 10 points in each patient. The BODE score of 0 – 2 was taken as mild COPD. Scores between 3– 5 was considered as moderate disease and those more than or

equal to 6 was considered as severe COPD.

BODE INDEX:

BODE score	0	1	2	3
FEV1	≥65%	50 – 64 %	36 – 49 %	≤35%
6 min walk test	>350 mts	250- 349 mts	150 – 249 mts	<149 mts
MMRC scale	0-1	2	3	4
BMI Kg/M2	>21	≤ 21		

(Mild COPD – 0-2, Moderate COPD – 3-5 and Severe COPD - ≥6)

CRP was estimated using the latex agglutination method. Positive result was expressed when the agglutination occurred. The statistical analysis was carried out using windows Excel and SPSS software.

RESULTS:

Table 1: Severity Of BODE Index

Severity of BODE Index	Total No. of Patients	Average
Mild (0-2)	17	28.3%
Moderate (3-5)	25	41.6%
Severe (>6)	18	30%
Total	60	

Table 2: Age Wise Distribution Of BODE Index Severity

Age group	Mild (0-2)	Moderate (3-5)	Severe (>6)	Total	Average
40-50	4	3	0	7	11.6%
51-60	6	9	3	18	26.6%
61 and above	7	13	15	35	58.33%
Total	17	25	18	60	

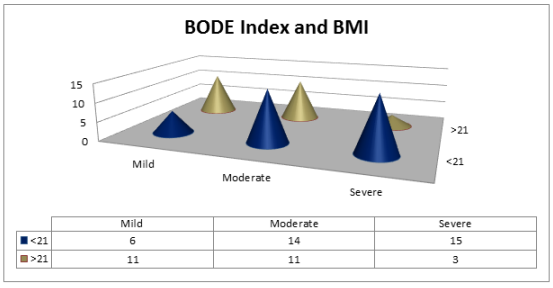

Table 3: BODE Severity And Number Of Exacerbations In One Year

No. of Exacerbations	BODE Severity			p value Pearson Chi Square test
	Mild	Moderate	Severe	
Less than 3	15	8	3	$X^2 = 20.479$
More than 3	2	17	15	
Average exacerbations/ year	1.9	4.04	4.72	P = < 0.0001

Table 4: Severity Of BODE Index With CRP Status

CRP	BODE Severity			Total	p value Pearson Chi Square test
	Mild	Moderate	Severe		
Negative	16	18	5	39	$X^2 = 17.83$
Positive	1	7	13	21	p = 0.0001
% of positivity	6.25%	28%	72.2%	35%	

DISCUSSION:

COPD is the only leading cause of death showing increase in prevalence worldwide. COPD is the third leading cause of death in adults according to a study published by the World Health Organization (2). Although the BODE index is a predictor of the risk of death, we hypothesized its correlating it with systemic inflammation. CRP is systemic biomarker that has been widely used for inflammatory diseases like COPD. Many of extrapulmonary effects of COPD are thought to be mediated by systemic inflammation. It is widely accepted that lung inflammation plays a prominent role in COPD pathogenesis and the systemic inflammation exist (8). Many studies demonstrate that there is an increase in inflammatory cytokines like TNF- α, IL-6, IL- 8(11) not only in the lung, but systemically.

Our study observations are among 60 cases of COPD patients enrolled into the study; total exacerbation rate is having a positive correlation between BODE index (P < 0.0001). The systemic inflammatory marker C Reactive Protein (CRP) was found to be positive in 21 patients (35%) out of 60. 13 patients (72.2%) out of 18 in Severe COPD had CRP positive, while only 7 (28%) out of 25 in Moderate and 1 (6.25%) out of 17 in Mild COPD showed CRP positive. CRP was showing a positive correlation between BODE index (P< 0.0001). We took C Reactive Protein (CRP) a marker of systemic inflammation, since it has been shown to up regulate the production of proinflammatory cytokines and tissue factors by monocytes, increase the uptake of LDL by macrophages and directly induce expression of adhesion molecules by the human endothelial cells. Additionally CRP may deposit directly into the arterial wall during atherogenesis, interacting with other inflammatory mediators to create foam cells, which serve as building blocks to atherosclerotic plaques (12). Karadag F (13) and Cirillo et al (14) showed an increasing CRP value with worsening airflow obstruction.

Furthermore, in a study by Karadag *et al*. [13] inflammatory markers such as CRP, IL-6, and TNF-α were raised in patients with stable COPD. de Torres *et al*. [9] found that CRP levels were significantly raised and were an important factor in the outcome of stable COPD patients. This was also confirmed by a study conducted by Bhandohal *et al*. [15] who evaluated serum biomarkers of oxidative stress and airway inflammation in COPD. Various studies have attempted to find the association of biomarkers of inflammation with BODE index. In a study conducted by Garcia-Rio *et al*.,[16] IL-6 and CRP had a significant association with BODE index. It showed that as the values of BODE index increased, the levels of IL-6 and CRP also increased. In another study carried out by Agustí *et al*.,[17] levels of CRP, IL-6, and TNF-α increased with the severity of airflow limitation and BODE index. Thus, the study corroborates with most of the Western studies which show a correlation between inflammatory markers (CRP), and BODE index.

CONCLUSION:

To conclude BODE index severity directly correlates with the CRP. Which implies that there is underlying systemic inflammation is present in COPD which has to be given importance for prevention of exacerbations and treatment.

Limitations:

As the population of patients in this study is small, the finding of this study needs to be confirmed on larger multicentric study on common protocol population. The association needs to be further confirmed with a follow-up study.

REFERENCES:

1. Murray C.J.L., Lopez A.D. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;349:1269–1276.
2. World Health Organization. Global initiative for chronic obstructive lung disease. Geneva, Switzerland: World Health Organization, 2002.
3. Pauwels R.A., Buist A.S., Calverley P.M. et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am. J. Respir. Crit. Care Med. 2001;163:1256–1276.
4. Mannino D.M., Homa D.M., Akinbami L.J. et al. Chronic obstructive pulmonary disease surveillance — United States, 1971–2000. MMWR Surveill. Summ. 2002;51:1–16.
5. Pauwels R. Global initiative for chronic obstructive lung diseases (GOLD): time to act. Eur. Respir. J. 2001;18:901–902.
6. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive

Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med2001; 163:1256-76.
7. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnoea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005–12
8. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 2004;59:574-580.
9. De Torres JP, Cordoba-Lanus E, López-Aguilar C, Muros de Fuentes M, Montejo de Garcini A, Aguirre-Jaime A, Celli BR, Casanova C. C-reactive protein levels and clinically important predictive outcomes in stable COPD patients. Eur Respir J 2006; 27:902-907.
10. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Rev Respir Dis 1991; 144:1202-1218.
11. Pinto – Plata VM, Livnat G, Girish M et al. Systemic cytokines, clinical and physiological changes in patients hospitalized for exacerbation of COPD. Chest. 2007; 131(1):37-43
12. Hannsson GK. Inflammation, artherosclerosis, and coronary artery disease. N Engl J Med. 2005; 352(16):1685- 95
13. Karadag F, kirdar S, Karul AB. The value of C- reactive protein as a marker of systemic inflammation in stable chronic obstructive pulmonary disease. Eur J Int Med. 2008; 19(2):104-8
14. 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
15. Bhandohal JS, Tandon R, Khanna HD. Evaluation of serum biomarkers of oxidative stress and airway inflammation in chronic obstructive pulmonary disease. Am J Pharm Health Res. 2014;2
16. Garcia-Rio F, Miravitlles M, Soriano JB, Muñoz L, Duran-Tauleria E, Sánchez G, et al. Systemic inflammation in chronic obstructive pulmonary disease: A population-based study. Respir Res. 2010; 11:63. [PMCID: PMC2891677] [PubMed: 20500811]
17. Agustí A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: A novel phenotype. PLoS One. 2012;7: e37483. [PMCID: PMC3356313] [PubMed: 22624038]