Prevalence of Metabolic Syndrome in COPD Patients Attending a Tertiary Care Setting, at Kozhikode District in Kerala

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ABSTRACT

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterised by progressive dyspnoea on exertion and cough. COPD is associated with comorbidities that influence mortality and hospitalizations independently. Metabolic syndrome (MS) consists of central obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL), hyperglycaemia and hypertension. Presence of metabolic syndrome in patients with COPD increases the frequency of exacerbations and their duration. This study was done to find out prevalence of metabolic syndrome in COPD patients and its influence on exacerbations.

METHODS

This prospective observational study was conducted in a tertiary care teaching hospital in South India. 174 patients meeting the inclusion criteria were recruited for this prospective observational study, out of which 13 were excluded due to various reasons. Selected patients underwent detailed clinical examination and investigations including chest X-ray, spirometry, fasting blood sugar, fasting lipid profile, electrocardiogram (ECG) etc. Patients were further grouped in to those with metabolic syndrome and those without. They were followed up for one year with review on every two months for assessing exacerbation of COPD. Data was evaluated at the end of the study, statistical evaluation was done using Statistical Package for Social Sciences (SPSS software version18).

RESULTS

A total of 174 patients were recruited for the study, among which 13 were excluded. 161 patients were included in the final evaluation, out of which 157 patients were male (97.5 %). 44.7 % were belonging to global initiative for obstructive lung disease (GOLD stage III), 37.3 % stage IV and 18 % stage II. 70 (43.5 %) had metabolic syndrome. 51.6 % had normal body mass index (BMI), 23.6 % over weight and 3.7 % were obese. Mean number of exacerbations were 3.20 in those with metabolic syndrome, whereas 1.52 in those without, during the follow up period.

CONCLUSIONS

Prevalence of metabolic syndrome among COPD patients was 43.5 % in this study. COPD patients with metabolic syndrome had more mean number of exacerbations than those without metabolic syndrome.

KEYWORDS

COPD, Exacerbations, Metabolic Syndrome, Co-morbidities

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BACKGROUND

COPD is a common preventable and treatable disease, characterized by airflow limitation that is usually progressive and associated with chronic inflammatory response in airways and lungs to noxious particles and gases. Exacerbations and co morbidities contribute to the overall severity in patients. COPD is the 4th leading cause of death in the world.[1] Many patients with COPD have co morbidities that have major impact on quality of life and survival.

Clinical diagnosis of COPD should be considered in any patient who has dyspnoea, chronic cough or sputum production and a history of exposure to risk factors for the disease. An exacerbation of COPD is defined as an acute event characterized by worsening of the patient's respiratory symptoms that is beyond normal day to day variations and leads to change in medications.[3-5] Criteria for diagnosing COPD exacerbation are increased sputum volume, worsening of dyspnoea or sputum purulence according to COPD GOLD 2013 guidelines.

COPD also has significant extrapulmonary effects including weight loss, nutritional abnormalities and skeletal muscle dysfunction. Cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression and lung cancer are comorbidities that occur frequently in COPD. These can occur in patients with COPD, regardless of the severity of airflow obstruction. Comorbidities influence mortality and hospitalizations independently, hence, deserve specific treatment.[6,7] The guidelines for the diagnosis, assessment of severity and management of individual's co-morbidities in patients with COPD are the same as for all other patients. In COPD, co morbidities should be treated as if the patient does not have COPD and COPD should be treated as if he has no co morbidities. Metabolic syndrome and manifest diabetes are more frequent in COPD and the latter is likely to impact on prognosis.[7] Systemic inflammation shared with other diseases represents a link between COPD and some of its co morbidities.[8]

The metabolic syndrome (Syndrome X, insulin resistance syndrome) consists of a group of metabolic abnormalities that predisposes to increased risk of cardiovascular disease and diabetes mellitus. Prominent features of the metabolic syndrome include central obesity, hyper triglyceridaemia, low levels of high-density lipoprotein cholesterol hyperglycaemia and hypertension. According to National cholesterol education program adult treatment panel III report (NCEP ATP III) report.[9] Metabolic syndrome is diagnosed when three out of five clinically identifiable variables are present: hypertension, glucose intolerance, low serum high-density lipoprotein (HDL)-cholesterol, elevated serum triglyceride and abdominal obesity. Adipose tissue-derived macrophages may be the primary source of proinflammatory cytokines locally and in the systemic circulation.

Several aetio-pathogenic mechanisms have been proposed as a possible link between COPD and metabolic disorders, that include systemic inflammation, adipose tissue inflammation, physical inactivity, hypogonadism and effect of steroids.[10,11] Metabolic syndrome is found to be twice more common in COPD, compared to the general population. Studies from different parts of the world have shown a prevalence of 25.6 - 60.9 % of metabolic syndrome in COPD patients.[12-15] Both cachexia and obesity represent the two extremes of a spectrum of metabolic abnormalities that are seen in patients with COPD leading to adverse clinical outcomes. Certain studies have categorized this group (COPD with metabolic syndrome) into a definite COPD phenotype which requires special attention. Thus, it may warrant extensive research to elucidate the exact mechanisms to understand the relationship between MS and COPD.

Presence of MS in patients with COPD increases the frequency of exacerbations and their duration.[16] MS may also increase the risk of a COPD exacerbation with associated hyperglycaemia, hypertriglyceridemia, and C-reactive protein (CRP) elevation. Systemic inflammation and physical inactivity have been identified as relevant extrapulmonary markers of the severity of COPD, as both conditions are related to exacerbations, hospitalizations, and mortality in this patient population. More research is needed to determine whether prevention or prompt treatment of exacerbations can reduce insulin resistance and improve metabolic syndrome in COPD.

Aim

To estimate the prevalence of metabolic syndrome in COPD, and the difference in exacerbation frequency in COPD patients with and without metabolic syndrome

METHODS

This is a prospective observational study conducted at Institute of Chest Diseases, Govt. Medical College Kozhikode, Kerala from January 2015 to May 2016. Patients attending the out-patient department (OPD) with a suspected diagnosis of COPD were included.

Inclusion Criteria

Stable COPD patients attending Institute of chest diseases, diagnosed by clinical and spirometry criteria.

Exclusion Criteria

Patients with the following conditions:

- Asthma.
- Type 2 respiratory failure.
- Hypothyroidism or hyperthyroidism.
- Malignancies.
- Stroke.

Procedure

Consecutive stable COPD patients attending the OPD, at the Institute of chest diseases, who had consented to participate in the study, were evaluated with detailed clinical history, physical examination and spirometry. Spirometry standards were met as per the ATS/ERS Criteria.[17] Post bronchodilator

spirometry testing was performed 15 - 30 minutes after inhalation of 400 mcg Salbutamol. Pre- and post-bronchodilator spirometry values were obtained for: forced vital capacity (FVC), forced expiratory volume (FEV1), and FEV1/FVC. Those with post bronchodilator FEV1/FVC ratio < 0.7 were diagnosed as having COPD according to GOLD 2013 guidelines. Bronchodilator reversibility (that is an increase in FEV1 > 12 % and > 200 mL), if any were noted and such cases were diagnosed as having coexisting asthma and excluded from the study. Those with type 2 respiratory failure were also excluded from the study.

Thyroid dysfunctions and the metabolic syndrome are the two most common endocrine disorders with a substantial overlap.[18] Hence thyroid function test (TFT) was done. Those with hypothyroidism and hyperthyroidism were excluded. Those who were known case of malignancies and stroke were also excluded from the study.

Height and weight of each patients were measured, BMI was calculated and were classified according to WHO 2004, The international classification of adult underweight, overweight and obesity according to BMI.[19] Waist circumference was measured by following World Health Organization (WHO steps protocol) (WHO, 2008b). Chest X ray and ECG were taken. Fasting blood sugar, fasting lipid profile and other relevant routine investigations were done.

Finally, these stable COPD patients were categorized in to group with metabolic syndrome, and another group without metabolic syndrome according to NCEP ATP 3 guidelines. Based on these harmonizing criteria for metabolic syndrome, cut off value for waist circumference was taken as >/= 90 cm, >/= 80 cm respectively for men and women.

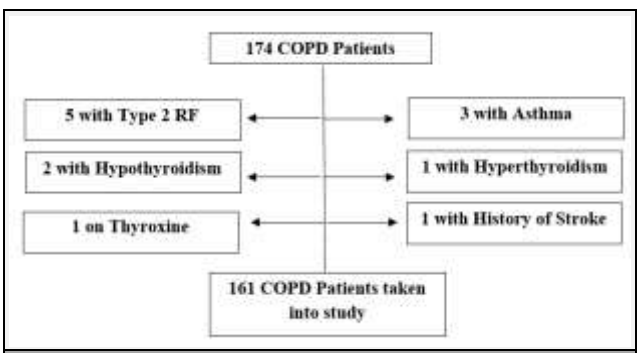
Patients were treated as per COPD GOLD 2013 guidelines and they were followed up for a period of 1 year. They were reviewed at every 2 months interval and were requested to inform in case of hospitalization. The hospital records of admission for COPD exacerbation if any, were verified. At review, they were enquired about number of exacerbations of COPD, development of new symptoms if any, and detailed physical examinations were done. Finally, number of COPD exacerbations in both groups (COPD patients with and without metabolic syndrome) in 1 year follow up period was assessed.

Statistical Analysis

Data obtained were analysed using SPSS software version 18. Student t test was used to test independent samples and analysis of variance (ANOVA) was used for comparing mean between groups followed by Bonferroni correction. Qualitative variables were compared using chi-square test. P value less than 0.05 was taken as significant.

RESULTS

A total of 174 COPD patients meeting inclusion criteria were screened. Three persons with a reversibility of > 12 % and 200 ml of FEV1 in the spirometry were diagnosed as asthma and excluded from the study. 5 had type 2 respiratory failure and excluded. Two patients were found to have hypothyroidism, 1 had hyperthyroidism, 1 was already on thyroxine and all these patients were excluded. One person with history of stroke was also excluded from the study. Thus, out of 174 COPD patients who met the inclusion criteria, 13 were excluded and 161 stable COPD patients were taken into the study and were followed up for a period of one year [Flow chart]. Number of COPD exacerbations during this follow up period was noted. Out of these 161, five persons expired; two, at the third month of follow up, one each at the 6th, 7th and 10th month of follow up.



Flow Chart. COPD-Chronic Obstructive Pulmonary Disease; RF- Respiratory Failure

Majority of the study population were males (97.5 %) and mean age was 63.79 (SD - 6.621). 95.7 % of the patients were smokers. Evaluation of dyspnoea showed 54.7 % were belonging to grade 2 mMRC, 37.3 % were in grade 1 and 8.1 % in grade 3. Among the 161 patients, 72 (44.7 %) were in GOLD class III, 60 (37.3 %) in class IV and 29 in class II. There was no one belonging to class I (Fig.1). When they were classified in to severity groups, 62.7 % were in group D and rest in group C and no patients were in group A or B.

Features associated with metabolic syndrome were evaluated in the population. 60 (37.3 %) had waist circumference more than the cut of value (i.e. >/= 90 cm in men; >/= 80 cm in women). 47.8 % of the cases had diabetes mellitus. Triglycerides >/150 mg % or on specific drugs for hypertriglyceridemia were detected in 23.0 %. HDL cholesterol was less than the cut off value (< 40 mg % in men; < 50 mg % in women) in 19.3 %. BMI classification showed 23.6 % having overweight and 3.7 % were obese [Table -2]. Metabolic syndrome was present in 70 (43.5 %) of this COPD population (Fig.2). Overall COPD exacerbation rate during the follow up period was 2.25 (SD - 1.285).

Comparing the two COPD cohorts, (i.e. Those with and without metabolic syndrome), data showed that they were matching in respect of age. Mean exacerbation rate of COPD was more in patients with metabolic syndrome, 3.209 (SD 1.098) versus 1.52 (SD - 0.874) in the other group. FEV1 % was lower in MS group, 38.61 (SD - 10.828) whereas it was 40.19 (SD - 14.073) in those without MS. Waist circumference, BMI, blood pressure, fasting blood sugar and triglycerides were more in COPD with MS group compared to COPD without MS. (Table -3)

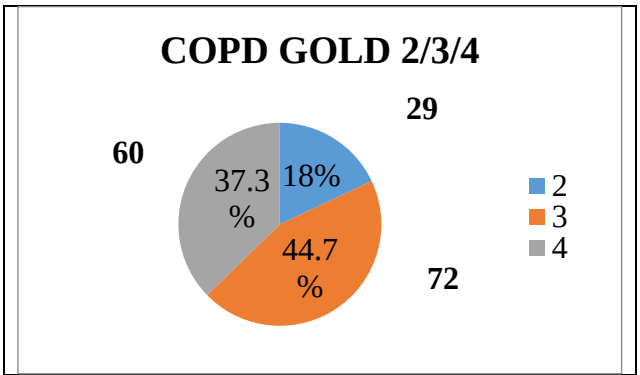


Figure 1. COPD Gold Stages

(COPD-Chronic Obstructive Pulmonary Disease; GOLD-Global Initiative for Obstructive Lung Diseases)

Data Analysis between Different COPD Stages

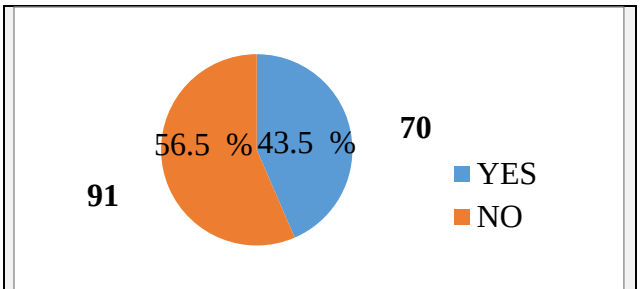


Figure 2. Metabolic Syndrome among COPD patients

(COPD-Chronic Obstructive Pulmonary Disease)

	COPD Stages	N	Mean	Std. Deviation	
FEV1	GOLD 2	29	60.28	8.916	P value 0.000
	GOLD 3	72	41.24	5.460	
	GOLD 4	60	27.38	1.462	
BMI	GOLD 2	29	24.366	4.3149	P value 0.000
	GOLD 3	72	22.917	4.1061	
	GOLD 4	60	20.492	3.8414	
No. of exacerbations of COPD in one year follow up	GOLD 2	29	2.17	1.167	P value is 0.904 (not significant)
	GOLD 3	72	2.24	1.369	
	GOLD 4	60	2.30	1.253	
Waist circumference in cm	GOLD 2	29	91.00	5.431	P value- 0.000
	GOLD 3	72	87.38	5.954	
	GOLD 4	60	82.82	5.595	
Systolic BP in mmHg	GOLD 2	29	138.83	13.560	P value- 0.030
	GOLD 3	72	132.39	13.592	
	GOLD 4	60	130.57	14.162	
FBS mg %	GOLD 2	29	116.17	17.682	P value - 0.011
	GOLD 3	72	103.33	20.397	
	GOLD 4	60	104.83	19.682	

Table 1. COPD-Chronic Obstructive Pulmonary Disease; GOLD-Global Initiative for Obstructive Lung Diseases

Mean compared between three stages of COPD using ANOVA, (P value less than 0.05 is significant)

	Frequency	Percent
Underweight	34	21.1
Normal	83	51.6
Overweight	38	23.6
Obese	6	3.7

Table 2. BMI Classification

(BMI-Body Mass Index)

Statistically significant difference in waist circumference was found between GOLD stages 2/3/4 (P value = 0.000) [Table-1]. In Post Hoc test, there was statistically significant difference between GOLD 2 & GOLD 3 (P = 0.014), GOLD 2 & GOLD 4 (P = 0.000), GOLD 3 & GOLD 4 (P = 0.000).

Following crosstab analysis, it was found that diabetes mellitus, waist circumference (> 80/90m), hypertension, triglycerides (> 150 mg) and HDL (< 40 mg) were more in COPD with MS group (P < 0.05) [Table-4].

		N	Mean	Standard Deviation	P Value
Age	With MS	70	64.29	7.365	0.405
	Without MS	91	63.41	6.002	
No. of exacerbations in one year follow up*	With MS	70	3.20	1.098	0.000
	Without MS	91	1.52	.874	
FEV1 %	With MS	70	38.61	10.828	0.440
	Without MS	91	40.19	14.073	
Waist circumference in cm*	With MS	70	91.66	4.501	0.000
	Without MS	91	82.23	4.382	
Systolic BP in mm of Hg*	With MS	70	140.51	11.429	0.000
	Without MS	91	126.99	13.000	
Diastolic BP in mm of Hg*	With MS	70	89.71	5.861	0.000
	Without MS	91	82.97	5.973	
FBS in mg %*	With MS	70	120.91	17.400	0.000
	Without MS	91	94.89	13.763	
Triglycerides in mg/dl*	With MS	70	153.03	22.165	0.000
	Without MS	91	137.68	12.925	
HDL in mg/dl*	With MS	70	44.64	6.690	0.042
	Without MS	91	46.45	4.483	
BMI in Kg/m2*	With MS	70	25.897	3.2854	0.000
	Without MS	91	19.487	2.5069	

Table 3. Statistics IN COPD Patients with/without Metabolic Syndrome

* Significant P value. (less than 0.05), (Mean compared between COPD patients with and without MS using t test)
MS-Metabolic syndrome, BMI-Body Mass Index, FEV1-Forced Expiratory Volume in 1 second, HDL-High Density Lipoproteins

		N	Chi-Square Value	df	Asymptotic Significance Value (2-sided)
DM/FBS >/= 100 mg %	With MS	58	60.907	1	.000
	Without MS	19			
Waist circumference >/90 cm (M); >/= 80 cm(W)	With MS	53	78.305	1	0.000
	Without MS	7			
HTN-SBP >/= 130/ =85 mmHg	With MS	70	36.522	1	0.000
	Without MS	91			
Triglycerides >/150 mg % mg/dl	With MS	31	31.758	1	0.000
	Without MS	6			
HDL < 40 mg/dl	With MS	27	29.723	1	.000
	Without MS	4			

Table 4. Correlation between Variables and COPD Cohorts

(MS-Metabolic syndrome, DM-Diabetes Mellitus, FBS-Fasting Blood Sugar, HTN-Hypertension, SBP-Systolic Blood Pressure, HDL-High Density Lipoproteins)
(P value less than 0.05, significant)

DISCUSSION

This was a study to find out the prevalence of metabolic syndrome in COPD and the number of COPD exacerbations in one year follow up period, in COPD patients with metabolic syndrome and without metabolic syndrome. Among 161 stable COPD patients, 70 (43.5 %) had metabolic syndrome. Studies from different parts of the world have shown a prevalence of 25.6 - 60.9 % for metabolic syndrome in COPD patients.[7-20] A study by Marquis K et al.[20] showed that 47 % of COPD patients and 21 % of control participants had metabolic syndrome. Another study in Indian population conducted by Acharya et al.[21] report that MS was found in 44 % of their COPD patients against 31 % among non-COPD controls. Prevalence of metabolic syndrome in our study was 43.5 %, which is comparable to these results. It should be noted that various studies show a trend of higher frequency of metabolic syndrome in COPD patients.

In our study, out of 161 COPD patients, 29 (18 %), 72 (44.7 %), 60 (37.3 %) were belonging to GOLD stage 2, 3,

4 respectively. Most of the COPD patients were belonging to GOLD stage 3 & 4. None of them were belonging to GOLD stage 1. Out of 161 COPD patients, 101 (62.7 %) belonged to COPD Group D and 60 (37.3 %) belonged to COPD Group C. None of them were belonging to COPD Group A or COPD Group B.

In a German study on 170 patients with COPD and 30 patients with chronic bronchitis, the prevalence of metabolic syndrome in chronic bronchitis, GOLD stage 1, 2, 3, 4 were 50 %, 53 %, 37 % and 44 % respectively (average = 47.5 %).[15] They had a slightly lower frequency of MS among patients with severe to very severe COPD. In our study, out of 70 COPD patients with MS, 19 (27.1 %), 32 (45.7 %), 19 (27.1 %) were belonging to COPD GOLD stage 2, 3, 4 respectively (P = 0.010); most of the COPD patients with metabolic syndrome were belonging to GOLD stage 3, due to the predominance of the stage 3 COPD (72 out of 161) in our study.

Average FEV1 % in 161 COPD patients was 39.50 ± 12.751. Mean FEV1 % in COPD GOLD 2, 3 & 4 were 60.28 ± 8.916, 41.24 ± 5.460, 27.38 ± 1.462 respectively (P value = 0.000.) Díez-Manglano J et al. found that COPD patients with the MS have a lower FEV1.[14] Evgeni Mekov found that there is no correlation between the presence of MS and the pulmonary function (FEV1 % in COPD with MS = 54.68, without MS = 55.56, (P value = 0.811).[22] In our study mean FEV1 % in COPD patients with metabolic syndrome was 38.61 +/- 10.828, in those without metabolic syndrome was 40.19 +/- 14.073 (P value = 0.440)

The presence of MS in patients with COPD increases the frequency of exacerbations and duration of exacerbations, according to Kupeli et al.[16] The mean frequency of exacerbation of COPD was 2.4 ± 0.8 in MS group versus 0.68 ± 0.6 in the control group (P < 0.001). Mean duration of each exacerbation was 7.5 ± 1.5 days in patients with MS versus 5 ± 2.4 days in patients without MS. According to Abdelghaffar et al. there is increased duration of COPD exacerbation in those with MS (8 days) than in those without (5.5 days).[23]

In our study, Average number of COPD exacerbations in one year follow up period was 2.25 ± 1.285. Mean number of COPD exacerbations in one year follow up period in those with and without metabolic syndrome were 3.20 ± 1.098 and 1.52 ± 0.874 respectively (P = 0.000). Number of exacerbations in COPD GOLD 2, 3, 4 stages were 2.17 ± 1.167, 2.24 ± 1.369, 2.30 ± 1.253 respectively (P = 0.904), i.e. There is no significant difference in number of COPD exacerbations between these groups. There is a significant difference in number of COPD exacerbation for one year in GROUP D COPD, with a mean of 2.43 ± 1.329 and GROUP C COPD, 1.95 ± 1.156 (P = 0.023). Our study showed increased mean number of exacerbations in COPD patients with metabolic syndrome than those without, as in previous studies. Possible reason for this could be that, unlike in other studies most of our patients were belonging to COPD GOLD stage 3 and 4. This group of COPD subjects can be further stratified in to a higher risk phenotype which requires a closer follow-up.

Average waist circumference in our study was 86.33 ± 6.443. In a study conducted by Marie Kathrin Breyer et al. average waist circumference was 98.5 ± 14.3.[24] Lower value in our study could be due to the racial difference in waist circumference in our population. Mean waist circumference in COPD patients with MS was 91.66 ± 4.501 and in those without MS was 82.23 ± 4.382 (P = 0.000). In another study by Biljana Lazovic, mean waist circumference for those with MS and those without MS were 102.62 ± 2.71, 93.86 ± 5.06 respectively (P = 0.80).[25] Our study showed an increased mean waist circumference in COPD patients with MS than those without, which is comparable to previous studies. In our study, out of 60 COPD patients with waist circumference >/= 90 cm (men) & >/= 80 cm (women) 53 (88.3 %) had MS and 7 (11.7 %) had no MS (P = 0.000). Evegeni Mekov et al. found that among COPD patients with increased waist circumference 86.8 % had MS.[22] Funakoshi Y et al. found that, among the various components of MS, waist circumference (OR, 1.76; 95 % CI, 1.24 - 2.50) showed a significant association with airflow obstruction of GOLD stage II - IV.[12]

In our study, 34 (21.1 %) patients were underweight, 83 (51.6 %) were having normal BMI, 38 (23.6 %) were having overweight and 6 (3.7 %) were obese. Overall, 38 % COPD patients were underweighted according to various study reports.[26] In a study by Steuten et al. overall prevalence of obesity in COPD was 18 % with the highest prevalence being in subjects with mild to moderate COPD (stages 1 and 2). Prevalence was 23.5 % in stage 2, 16.1 % in stage 1, and 5.9 % in stage 4.[27] Prevalence of obesity was highest among patients with milder forms of the disease (GOLD stages 1 and 2), and obesity was lowest in patients with most severe lung function impairment, in stage 4.[27-29] We have a prevalence of obesity of only 3.7 % in our patients, probably because most of our patients were belonging to stage 3 & 4. Prevalence of low body weight strongly increased in GOLD stage 4. Prevalence of obesity is highest in GOLD stages 1 and 2.[27] Average BMI in 161 COPD patients was 22.274 ± 4.2839. Mean BMI in those with MS was 25.897 ± 3.2854, and without MS 19.487 ± 2.5069 (P = 0.000). According to Cebron Lipovec N, compared to COPD patients without MS, those with MS had higher body mass index (BMI) (29.9 and 24.6 kg/m2, P < 0.001), which is comparable to our study result.[30]

CONCLUSIONS

Prevalence of metabolic syndrome among COPD patients was 43.5 % in our study. COPD patients with metabolic syndrome had more mean number of COPD exacerbations than those without metabolic syndrome.

Limitations of the Study

Sample size is not adequate for assessing the exacerbation frequency of COPD. Long term follow-up is necessary for assessing impact of metabolic syndrome on exacerbation of COPD.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

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