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Study of Metabolic Syndrome in Chronic Obstructive Pulmonary Disease and its Clinical Implications

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is not only a disease of lungs but is also associated with significant extra-pulmonary effects. Metabolic syndrome (MS) and associated cardiovascular morbidity and mortality are more frequent in COPD.

Objective: To study the prevalence of MS in hospitalised COPD patients. To compare their clinical characteristics with presence of MS. To correlate the presence of MS with GOLD spirometric severity and ABCD groups.

Methods: With a cross-sectional design, 100 hospitalised COPD patients were studied. They were asked about history, subjected to clinical examination and investigations to screen for MS and comorbidities. MS was identified using modified NCEP-ATPIII criteria and COPD was diagnosed based on GOLD guidelines 2017. They were classified based on spirometric grading and combined ABCD assessment. Being hospitalised patients, all subjects were either in group B or group D.

Results: MS was found in 40% of COPD patients. Patients with coexisting MS had more number of exacerbations (mean 2.50 *vs*. 2.03), prior history of hospitalisation (37.5% *vs*. 30%), longer duration of hospitalisation (7.25 *vs*. 4.73 days) and higher prevalence of comorbidities like diabetes and hypertension, as compared to those with COPD alone. The prevalence of MS decreased with increasing spirometric severity, with highest prevalence in mild obstruction (66.7%). Prevalence of MS was higher in group D patients as compared to group B (48.4% *vs*. 25%).

Conclusion: The presence of MS is frequent in hospitalised COPD patients and is associated with adverse clinical parameters. It is more common in earlier spirometric grades and Group D patients. Hence, this population should be considered for screening for MS.

Keywords: COPD; GOLD; Metabolic syndrome

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; GOLD: Global Initiative for Obstructive Lung Diseases; HDL: High Density Lipoprotein; MS: Metabolic Syndrome; NCEP-ATPIII: National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adults Treatment Panel III) (ATP III).

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and is projected to be the 3rd leading cause of death worldwide by 2020 [1]. It is considered as a systemic disease. The 2016 GOLD guidelines highlighted the importance of the extra-pulmonary effects in contributing towards the disease severity [2]. Metabolic syndrome (MS) is characterized by a group of risk factors that increase the risk of development of several diseases such as coronary artery disease, diabetes mellitus. It was first described in 1988 by Reaven and is also known as Insulin Resistance Syndrome or Syndome X [3]. Recently, the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adults Treatment Panel III) (ATP III) have highlighted the importance of metabolic syndrome and provided guidelines for the screening of this syndrome [4].

MS is found to be almost twice more common in COPD as compared to the general population. Different studies have reported a varied prevalence of 25.6% to 60.9% [5-8]. The comorbidities such as diabetes, hypertension, coronary artery disease, heart failure, and osteoporosis are more frequent when both COPD and MS co-exists. They also have a more severe form of disease [9].

There are very few studies on the prevalence of MS in hospitalised COPD patients and its clinical impact. Jesus Diez-Manglano et al. have found a prevalence of 42.9% in hospitalised COPD patients [7]. The prevalence of MS in such patients is hard to predict because metabolic syndrome tends to be more prevalent in early stages of obstruction while patients experiencing severe exacerbation, requiring hospitalisation often have advanced disease. On the other side, MS may impact the natural course of COPD and predispose to exacerbations leading to hospitalisations. This might lead to increased prevalence of MS in hospitalised patients.

In the present study we evaluated the prevalence of MS in COPD patients with comparing the clinical profile with presence of MS. We have also correlated the presence of MS with recent GOLD stages of COPD. Though various studies have shown that the prevalence of MS decreases with increasing spirometric severity, there are no studies on correlation with the ABCD groups as per the revised combined ABCD assessment tool advocated by 2017 GOLD guidelines. We did this study to find out whether the recent clinical staging (ABCD groups) correlates with presence of MS.

Aims and Objectives

- To study the prevalence of MS in hospitalised COPD patients.

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- To compare the clinical characteristics like exacerbation rate, hospitalisation rate, duration of hospitalisation and presence of co-morbidities with presence of MS.
- To correlate the presence of MS with spirometric severity and ABCD groups as per GOLD 2017 criteria.

Materials and Methods

Study design

The study was a hospital based cross-sectional study.

Inclusion criteria

The study was carried out on all COPD patients admitted to Department of Pulmonary Medicine, SCB MCH, Cuttack during the period from July 2015 to March 2017.

Exclusion criteria

Following patients were excluded from the study.

- Presence of asthma or other chronic respiratory diseases.
- Presence of malignancy or serious comorbidities that would prevent the study completion.
- Patients with active pulmonary tuberculosis
- Use of systemic corticosteroid in the preceding 3 months.

Sample size

The study included 100 hospitalised COPD patients.

Study method

All the patients were analyzed for clinical and laboratory findings, including full history taking, clinical examination. They were asked about the m MRC dyspnoea grade, history of exacerbations and hospitalisation in the previous year. Anthropometric measures including body weight, height, and waist circumference were obtained in all participants. Waist circumference was measured using an inelastic tape at the midpoint between the lowest rib and the iliac crest. Blood pressure was taken from both arms and the higher measurement was used for analysis. Participants were asked to fast for 12 hours before blood sampling. Fasting blood glucose and lipid profile were measured in the biochemistry laboratory of the hospital. Chest X-ray and Standard Pulmonary Function Tests, in the form of spirometry, was done for all participants. Spirometry was done in stable condition or those with spirometry done in last 6 weeks were also considered. Other laboratory investigations including complete blood picture with differential white cell count, complete liver and kidney functions, electrocardiogram and 2D Echocardiography were done in all patients to find out associated comorbidities.

Case definitions

COPD was diagnosed based on Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines for diagnosing COPD (post-bronchodilator FEV1/FVC <0.7). Patient's obstruction was classified according to the severity of airflow limitation based on post-bronchodilator FEV1 as follows:

GOLD1: mild (FEV1≥ 80% predicted)

GOLD2: moderate (50% ≤ FEV1<80% predicted)

GOLD3: severe (30% ≤ FEV1< 50% predicted)

GOLD4: very severe (FEV1<30% predicted)

They were also classified based on GOLD 2017 revised combined ABCD assessment. All being hospitalised patients, had higher grades of dyspnoea thereby coming in either group B or group D (Figure 1).

MS was diagnosed based on Modified National Cholesterol Education Program (NCEP): Adults Treatment Panel III (ATPIII). According to Modified NCEP: ATP III criteria, three or more of the following must be present.

Central obesity

Waist circumference >102 cm in Males, >88 cm Females

Hypertriglyceridemia

Triglycerides ≥ 150 mg/dL or specific medication

Low High density lipoprotein (HDL) cholesterol

HDL Cholesterol<40 mg/dL for men and <50 mg/dL, for women respectively or specific medication

Hypertension

Blood pressure ≥ 130 mm systolic or ≥ 85 mm diastolic or specific medication

Hyperglycemia

Fasting plasma glucose ≥ 100 mg/dL or specific medication or previously diagnosed Type 2 diabetes.

Statistical analysis

Data were entered into Microsoft excel and analysed using SPSS software version 21.0. Results were displayed using appropriate graphs/tables. Appropriate tests for statistical significance were used. p-value <0.05 was taken as the level of significance.

Ethical considerations

Informed written consent was taken from all patients. Confidentiality of data was maintained. The study was approved by the Institutional Ethics Committee of the coordinating center, S.C.B. Medical College, Cuttack, Odisha (398/18.2.17).

Results

Sample characteristics

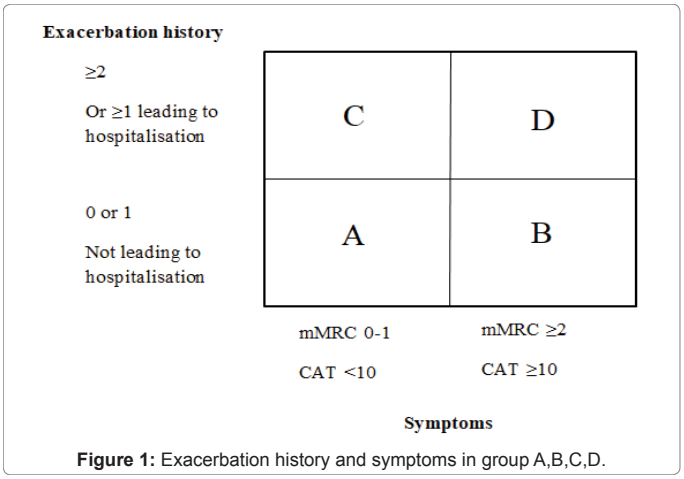

Figure 1: Exacerbation history and symptoms in group A,B,C,D.

The study finally included a total of 100 cases of COPD patients. The mean age was 66.15 ± 10.4 years. 77% of cases were males and 23% were females with male: female ratio of 3.3:1. Out of total, 63% of patients were smokers whereas 81.8% of males were smokers. All the females were non-smokers.

MS and its components

The prevalence of MS in COPD patients was 40%. Among the components of MS, hypertension was the most prevalent component followed by low HDL and hyper-glycemia with a prevalence of 58% and 39% respectively. MS was found to be more prevalent in younger patients with age ≤ 70 years as compared to those above 70 years. Our study also revealed a higher prevalence of MS in females as compared to males (65.2% *vs*. 32.5%) which was statistically significant(p value=0.005). The prevalence of MS increased with increasing body mass index (BMI) with maximum prevalence in obese patients with BMI ≥ 30 kg/m^2 (Tables 1-3).

Clinical differences in patients of COPD with MS and without MS

Those COPD patients with coexisting MS had more number of exacerbations in last year in as compared to those with COPD alone (2.50 *vs*. 2.03), but the difference was not statistically significant (p value=0.311). Out of total 40 patients with coexisting MS, 37.5% patients had history of hospitalisation for an exacerbation in last year as compared to 30% of patients with COPD alone (p value=0.435). Also they had a significantly longer duration of current hospitalisation (7.25 days *vs*. 4.73 days) (p value<0.005 using unpaired t-test) (Table 4).

The prevalence of comorbidities like hypertension, diabetes mellitus and chronic kidney disease was higher in those with MS but it was statistically significant only for diabetes mellitus (77.5% *vs*. 21.6%) and hypertension (75% *vs*. 53.3%). But the prevalence of dilated cardiomyopathy was higher in those without MS. The prevalence of corpulmonale (27.5% in patients with MS *vs*. 31.6% in patients without MS) and valvular heart disease (25% *vs*. 33.3%) was almost similar in both the groups (Table 4).

Comparison of MS with GOLD stages of COPD in study group

In our study, as per spirometric severity grading, maximum numbers of patients were having moderate and severe obstruction with 37% of cases in each grade followed by very severe obstruction seen in 20% of cases. As per the revised combined COPD assessment (ABCD scheme) by GOLD guidelines 2017, 64% were in group D whereas 36% were in group B (Figure 2).

There was an inverse association of MS with greater GOLD spirometric severity, the prevalence of MS being highest in grade 1 (66.7%) followed by grade 2 (56.7%). 25% of patients of group B had coexisting MS whereas 48.4% of patients of group D had MS i.e., prevalence of MS was higher in group D as compared to group B (Figure 3 and Tables 5, 6).

Age group	40-55 Years N=16 (n%)	56-70 Years N=51 (n%)	71-85 Years N=30 (n%)	>85 Years N=3 (n%)
With MS	7 (43.7%)	26 (51%)	7 (23.3%)	0 (0%)
Without MS	9 (56.3%)	25 (49%)	23 (76.7%)	3 (100%)

Table 1: Prevalence of MS in comparison with age.

Sex	Male N=77 (n%)	Female N=23 (n%)
With MS	25 (32.5%)	15 (65.2%)
Without MS	52 (67.5%)	8 (34.8%)

Table 2: Prevalence of MS in comparison with sex

BMI (KG/M^2)	<18.5 N= 30 (n%)	18.5-24.9 N=53 (n%)	25-29.9 N= 10 (n%)	≥ 30 N=7 (n%)	≥ 40 N=2 (n%)
With MS	3 (10%)	23 (43.4%)	8 (80%)	6 (85.7%)	2 (100%)
Without MS	27 (90%)	30 (56.6%)	2 (20%)	1 (14.3%)	0 (0%)

Table 3: Prevalence of metabolic syndrome in comparison with BMI

	With MS N=40	Without MS N=60	p-value
Previous Exacerbations (Mean No.)	2.5	2.03	0.311
Previous Hospitalisation	15 (37.5%)	18 (30%)	0.435
Duration Of Current Hospitalisation (Days)	7.23	4.73	0
Comorbidities			
CorPulmonale	11 (27.5%)	19 (31.6%)	0.26
Dilated cardiomyopathy	0 (0%)	2 (100%)	0.24
Hypertension	30 (75%)	32 (53.3%)	0.03
Valvular Heart disease	1 (25%)	2 (33.3%)	0.81
Diabetes mellitus	31 (77.5%)	13 (21.6%)	0.01
Chronic kidney disease	2 (5%)	1 (1.7%)	0.74

Table 4: Clinical differences in patients of COPD with metabolic syndrome and without metabolic syndrome.

Discussion

Our study which used the modified NCEP-ATP III criteria, found the prevalence of MS in COPD patients to be 40%, which is more or less similar to earlier studies. Marquis et al. [10] observed a prevalence of MS in 47% of patients compared with 21% of controls using the NCEP-ATP III criteria; and Breyer et al. [11] which showed MS was present in 57% of the COPD patients using criteria of the International Diabetes Federation (IDF). Other studies have also found similar results: Watz et al. [8] has shown the prevalence of MS in COPD patients to be 47.5%. Another study by Acharyya et al. [12] in an Indian population found that among the COPD subjects, 44%, 46%, and 31% had coexisting MS as defined by NCEP ATP III, modified NCEP ATP III, and IDF criteria, respectively. In contrast, studies by Lam et al. [13] have shown lower prevalence of MS in COPD patients (22.6%). and 25% respectively). Diez-Manglano et al. [7] found the overall prevalence of MS in hospitalised COPD patients was 42.9% whereas Mekov et al. found a prevalence of only 25% in hospitalised patients [14].

In our study, among the components of MS, hypertension was the most prevalent component with a prevalence of 62% followed by low HDL and hyperglycemia. This is similar to the previous studies by Watz et al. [8] which showed hypertension to be highly prevalent in COPD patients (70%) and Mannino et al. [15] found that frequency of hypertension in COPD patients was 55%. Fumagalli et al. [16] also demonstrated a 53% incidence of hypertension. In our study central obesity had comparatively lower prevalence (24%) which may be due to low socioeconomic status and under nutrition seen in this locality [17].

The variability among different studies might be due to different criteria used for the diagnosis of MS in different studies, the study inclusion criteria and differences between the populations (physical activity, diet, lifestyle, ethnicity etc.). Also our study has taken hospitalised patients which mean they might be having advanced stage of COPD and so COPD associated muscle wasting and cachexia thereby having a lower mean waist circumference in COPD patients as

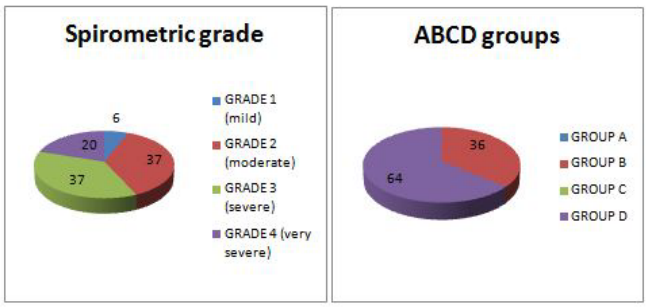

Figure 2 : Classification of COPD according to GOLD spirometric severity and ABCD assessment.

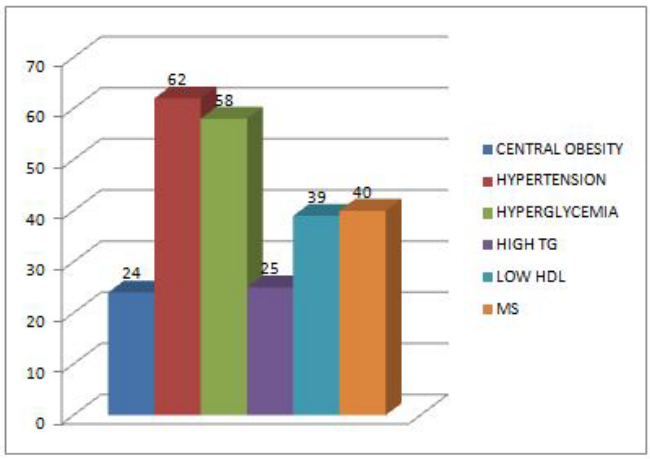

Figure 3: Prevalence of MS and its components.

	Gold1 N=6 (n%)	Gold2 N=37 (n%)	Gold3 N=37 (n%)	Gold4 N=20 (n%)	Total N=100 (n%)
With MS	4 (66.7%)	21 (56.7%)	11 (29.7%)	4 (20%)	40 (40%)
Without MS	2 (33.3%)	16 (43.3%)	26 (70.3%)	16 (80%)	60 (60%)

Table 5: Comparison of MS with spirometric severity.

	Group B N=36 (n%)	Group D N=64 (n%)	Total N=100 (n%)
With MS	9 (25%)	31 (48.4%)	40 (40%)
Without MS	27 (75%)	33 (51.6%)	60 (60%)

Table 6: Comparison of MS with ABCD groups.

compared to healthy subjects [18].

Also MS was more prevalent in females as compared to males (65.2% *vs*. 32.5%). This is more or less similar to study by Diez-Manglano et al. [7] which found MS to be more frequent in women (59.5%) than men (40.8%), p=0.02. Park et al. [6] also found the prevalence of MS to be more frequent in women. In our study MS was found to be more prevalent in younger patients and prevalence increased with increasing BMI with a maximum prevalence in obese patients with BMI ≥ 30 kg/m^2 consistent with the study by Mekov et al. [14] and Breyer et al. [11].

Another observation in our study that supported the worse clinical outcome in those with MS was their higher no of exacerbations, hospitalisations, longer duration of hospitalisation and more comorbidity, though few parameters did not reach clinical significance. The study by Mekov et al. [14] found a significant difference between the number of total exacerbations according to the presence of MS (2.4 *vs*. 0.7; p=0.015). On the contrary, Diez-Manglano et al. [7] in their study found that patients with MS had neither more exacerbations in the previous year nor more admissions for COPD, although they were hospitalized more frequently for any cause. Breyer et al. [11] found that the presence of MS in COPD patients had no functional consequences, but it coincided with more cardiovascular co-morbidity and type II diabetes. The association of MS with comorbidities (except for diabetes and hypertension) is difficult to confirm from our study due to exclusion of severe comorbidities from the study.

Our study found that there was an inverse association of MS with increasing spirometric severity, the frequencies of MS being 66.7%, 56.7%, 29.7% and 20% in patients with GOLD spirometric grades 1, 2, 3 and 4 respectively. This finding is in line with other reports by Watz et al. [8], Marquis et al. [10] and Akpinar et al. [19]. The weight loss that frequently occurs in patients who are in the more severe stages of COPD may be the cause of these observations [20].

Based on the revised combined ABCD assessment scheme advocated by GOLD 2017, in this study, maximum no. of patients i.e., 64% were in group D followed by 36% of cases in group B. No patients were found in group A and group C. As we had included only hospitalised patients in our study, majority of patients were having higher dyspnoea grades of mMRC3 and mMRC4 and more no. of exacerbations, especially one leading to hospitalisation, so being included in either group B or group D. Our study also found a greater prevalence of MS in group D as compared to group B (48.4% and 25% respectively). To our knowledge there is no study in literature using the recent ABCD assessment. Group D suggests patients having more severe grade of dyspnoea, more COPD Assessment Test score, more no. of previous exacerbations, increased hospitalisations and so poor clinical outcome. The worse prognosis associated with group D might be related to underlying comorbidities such as diabetes, hypertension and MS.

This study is the only study till date which has used the recent revised GOLD guidelines, 2017 in assessing the relation with MS which has a significant impact on predicting the clinical outcome.

Our study has some limitations:

- The number of patients included in the study was limited
- The COPD patients recruited had an acute exacerbation. It is possible that patients with MS have more or less frequent acute exacerbations, and this element could produce some bias in the data.

Future longitudinal studies with larger sample sizes are required to further investigate the causal relationship between COPD and MS.

Conclusion

Our findings suggest that the features of the MS are frequent in patients with COPD with hypertension being the most prevalent component, it is also more common in females and the prevalence increases with increasing BMI. Among the COPD patients, those with coexisting MS had a significantly longer duration of hospital stay and higher prevalence of comorbidities like diabetes and hypertension as compared to those with COPD alone. MS is more prevalent in the early stages of spirometric obstruction and decreases with COPD progression and also more common in GOLD ABCD group D suggesting poor clinical outcome.

So, it is recommended to screen all the COPD patients for associated MS and more attention should be paid to subjects with mild and moderate obstruction, GOLD group B and group D and

overweight and obese COPD patients for the potential coexistence of MS, so that patients can be advised for lifestyle modifications as a result of which the natural course of the disease may be modified. However more research in this field is required to prove such association.

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