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# A Study on the Correlation of Chronic Obstructive Pulmonary Disease with Metabolic Syndrome and Its Components

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## Abstract

**Introduction:** COPD and metabolic syndrome are both widely prevalent and significant contributors to mortality and morbidity across the world. COPD is the fourth leading cause of death in the world. There is limited epidemiological and clinical evidence is there to support a higher frequency of metabolic syndrome among COPD patients suggesting a possible link between metabolic syndrome and lung function impairment. In our study we aimed to study the correlation of COPD severity with the components of metabolic syndrome and also to find the correlation of CRP as a marker of systemic inflammation with COPD severity.

**Materials and Methods:** The study was conducted on patients attending medicine and chest medicine OPDs of IPGME and R, Kolkata from February 2018 to August 2019. Anthropometric measurements were taken, spirometry was conducted, mMRC scale was used for dyspnea severity assessment, metabolic syndrome was defined as per revised NCEP criteria and relevant blood investigations were done. 94 men and 6 women enrolled for the study.

**Results:** In the study population of 100 COPD patients, 48 had metabolic syndrome. The mean FBS of COPD patients in GOLD stage III was significantly higher than those in stage I and II ($p<0.001$). Patients in GOLD stage III was found to have significantly higher mean SBP than those in GOLD stage II ($p<0.005$). A significant negative correlation was also found between CRP and FEV1 ($\rho$ -0.0698, $p<0.001$). A significant negative correlation was found between fasting blood sugar levels with FEV1. No statistically significant difference in waist circumference BMI or triglyceride levels was found among COPD patients across all GOLD stages.

**Conclusion:** This study highlights the urgent need to assess, control and adequately manage metabolic syndrome and its parameters in patients of COPD. It also demonstrates a possible role of systemic inflammation and its adverse effect on lung function among patients with metabolic syndrome coexistent with COPD.

**Keywords:** Metabolic syndrome; Systemic inflammation; Population; Assessment; Investigations

**Abbreviation:** COPD: Chronic Obstructive Pulmonary Disease; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBS: Fasting Blood Sugar; WC: Waist Circumference; BMI: Body Mass Index; MetS: Metabolic Syndrome; GOLD: Global Initiative for Obstructive Lung Disease; FEV1: Forced Expiratory Volume in the 1$^{st}$ second after start of expiration; FVC: Forced Vital Capacity.

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [1]. Cigarette smoking is the major risk factor of COPD while other risk factors include: Childhood respiratory infections, air pollution, and occupational exposures [2]. Genetic associations include alpha 1 antitrypsin deficiency, slower metabolizing variant microsomal epoxide hydrolase (EPHX1) and polymorphisms in genes for glutathione S-transferase, heme oxygenase, TNF alpha and matrix metalloproteinases [3-6]. Patients with COPD experience an augmented inflammatory response that result in tissue destruction and impairment of repair and defence mechanisms.

COPD has been recognized as a disorder associated with systemic inflammation possibly resulting from spillage of inflammation from the lungs into the bloodstream.

**Role of CRP in COPD:** C-reactive protein is a marker of inflammation and tissue damage. It was found to be highly sensitive for predicting and also determining the severity of an exacerbation [7]. It also activates the classical complement pathway thus participating in the inflammatory process associated with COPD [8-10].

**Adiposity and COPD:** Adipose tissue secretes several hormones and protein factors called "adipokines" namely leptin and adiponectin

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amongst others. Leptin stimulates neutrophils and macrophage chemotaxis, activates T lymphocytes and promotes Th1 cell differentiation [11]. Adiponectin on the other hand reduces the production of TNF-α and IL-6 induces anti-inflammatory cytokine IL-10 and has IL-1 receptor antagonist action [12-14]. However, unlike leptin, it does not increase in obesity. Thus an adverse adipokine profile seen in obesity may contribute to the systemic manifestations of COPD.

**COPD and metabolic syndrome:** Metabolic syndrome is found to be twice as more common in COPD when compared to the general population. Several studies from different parts of the world have shown a prevalence of 25.6%-60.9% [15,16].

Relationship of COPD and individual components of metabolic syndrome.

The effects of obesity, particularly abdominal obesity on lung functions include:

- Abnormal ventilation/perfusion ratio.
- Decreased chest wall and pulmonary compliance.
- Increased work of breathing.
- Reduction of ventilatory muscle strength and endurance.
- Small airway dysfunction and expiratory flow limitation.

**COPD and the obesity paradox:** In patients with COPD, obesity has an unusual impact referred to as the "reverse epidemiology of obesity". A meta-analysis by Cao, et al., analyzed data on 22 studies which included about 21,150 subjects. It was found that patients with a lower BMI had a higher mortality rate than those who were overweight or obese [17]. It indicates that both cachexia and obesity represent the two extremes of the spectrum of metabolic abnormalities seen in patients with COPD leading to adverse clinical outcomes.

**COPD and hypertension:** The incidence of hypertension can vary from 6%-50% and depends upon the severity of airflow of obstruction. A recent study (INDACO study) demonstrated a 53% incidence of hypertension [18,19]. Mechanisms responsible for hypertension in COPD are hypoxia related vasoconstriction, free radical injury and endothelial dysfunction [20]. COPD patients experience recurrent hypoxemia, hypercapnia and increased intrathoracic pressure because of airway obstruction that could lead to persistent sympathetic overactivation and subsequent decrease in baroreceptor sensitivity. This may explain the common co-occurrence of hypertension in patients with COPD.

The important risk factors linking similar pathogenic mechanisms between COPD and MetS are smoking, genetics, obesity, physical inactivity and airflow limitation.

Low grade inflammation has been described as the common pathway responsible for MetS and comorbidities in COPD.

**COPD and hyperglycemia:** In a retrospective study using data collected from the Italian college of general practitioners health search database it was reported that compared to the non-COPD individuals, patients with COPD had a higher prevalence of DM. Systemic inflammation is probably an important contributory factor responsible for both COPD and diabetes mellitus. A study by Engstrom, et al., described that reduced lung function is an important risk factor for the development of diabetes in COPD. In a prospective Australian study, the fremantle diabetes study, blood glucose was found to be a strong negative predictor of lung function. The association between impaired lung function and diabetes is thought to be the result of systemic inflammation, oxidative stress, hypoxemia or direct damage caused by chronic hyperglycemia. The Rho-kinase pathway activation in diabetes leads to glucose induced bronchial hyperresponsiveness. Moreover T2DM also seems to be associated with impaired alveolar microvascular function which correlates with level of glycemic control and extrapulmonary microangiopathy.

**COPD and dyslipidaemia:** Previous conclusions of numerous studies on the relationship between COPD and blood lipid profiles remain conflicting. Systemic inflammation, physical inactivity and steroid use could lead to dyslipidemia in COPD patients.

COPD is complex disease with multiple systemic comorbidities and complications. COPD patients with the MetS have a more severe form of disease, more dyspnea, a lower FEV1 and require more inhalational glucocorticoids to control the disease. The prevalence of MetS and its comorbidities increases with advancing age. COPD patients with MetS have higher leptin levels, low adiponectin and greater insulin resistance. Thus this group of COPD patients with metabolic syndrome can considered as a high risk group which may require a close follow up.

### Aims and Objectives

- To find the correlation of COPD severity and FEV1 with various components of metabolic syndrome that is: Systolic blood pressure, diastolic blood pressure, fasting blood sugar, HDL, triglyceride level and waist circumference.
- To find the correlation of C-reactive protein (as a marker of systemic inflammation) with COPD severity and components of metabolic syndrome.

## Materials and Methods

**Study population:** Data was collected prospectively from 100 clinically stable COPD patients attending general medicine and chest medicine OPDs in IPGME and R, Kolkata during a period from February 2018 to August 2019.

**Study type:** Hospital based cross sectional observational study.

**Inclusion criteria:** COPD patients visiting chest medicine and general medicine OPDs.

- Not having an acute exacerbation.
- No history of exacerbation for at least 6 weeks prior to the study.
- Not on oral steroids for >3 weeks.
- Not having any other systemic inflammatory disease like SLE/RA/vasculitis.
- Not on antidiabetics/antihypertensives/statins.
- No known ischemic heart disease.

**Exclusion criteria:**

- COPD patients with acute exacerbation.
- Hospital admitted COPD patients.
- COPD with bronchiectasis/ILD/other pulmonary disease.
- Known systemic inflammatory disease.
- On antihypertensive, antidiabetic, immunosuppressives, statin.
- Known ischemic heart disease patient.

## Definition

**Metabolic syndrome:** The revised NCEP criteria were used for defining metabolic syndrome in the study population. It requires at least three of the following components:

- Abdominal obesity (waist circumference ≥ 90 cm for Asian men or ≥ 80 cm for Asian women.
- Triglycerides ≥ 150 mg/Dl.
- HDL cholesterol ≤ 40 mg/dL for men or 50 mg/dL for women.
- Systolic/diastolic blood pressure ≥ 130/85 mmHg or receiving drug treatment.
- Fasting plasma glucose ≥ 100 mg/dL.

Dysglycemia is defined as impaired fasting glucose and/or impaired glucose tolerance.

- FPG 100 mg/dL-125 mg/dL (5.6 mmol/L-6.9 mmol/L).
- 2 h PG 140 mg/dL-199 mg/dL (7.8 mmol/L-11.0 mmol/L).
- HbA1C 5.7%-6.4% (39 mmol/L-47 mmol/mol) or 10% or more increase in A1C.

  Diabetes was defined as in accordance with ADA guidelines. FPG ≥ 126 mg/dL (7.0 mmol/L) or 2 h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT or A1C ≥ 6.5% (48 mmol/mol) or classic symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

**Sample size:** The study was done on a sample of 100 stable COPD patients.

**Study variables and protocols:** The study was done on a sample of 100 COPD patients attending medicine and chest OPDs who met the inclusion criteria after informed consent.

Relevant history was obtained regarding smoking (in terms of pack years) and occupation. Symptom severity was assessed by mMRC scale.

Blood pressure was measured by auscultatory method after 5 mins of rest in both arms and the recording with the higher value was considered. 2 readings were taken (in accordance with ACC/AHA guidelines).

Waist circumference was measured half way between the costal margin and highest point of iliac crest with a measuring tape. Height and weight were also measured and BMI calculated. The patients were classified as underweight, normal range, overweight or obese (classes I, II, III) according to the WHO cut offs.

A chest X-ray was done to rule out other pleural and/or parenchymal disease. Lipid profile, FBS and CRP were measured in each patient.

Each participant underwent spirometry to characterize the severity of airflow limitation. Only participants with a post bronchodilator FEV1/FVC<0.7 and no/mild evidence of restriction with <12% variation between pre and post bronchodilator FEV1 values were selected. The patients were staged according to GOLD criteria depending on their post bronchodilator FEV1 levels as mild, moderate, severe or very severe COPD.

## Statistical analysis

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS ver. 26.0. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two sample t-tests for a difference in mean involved independent samples or unpaired samples and the variance between two groups whether significant or not is done by Levine's test for equality of variances. One-way Analysis of Variance (one-way ANOVA) was a technique used to compare means of three or more samples for numerical data. Correlation was calculated by Spearman correlation analysis.

If the calculated p-value was below the threshold chosen for statistical significance, then the null hypothesis is rejected in favour of the alternative hypothesis. P-value ≤ 0.05 was considered as statistically significant.

## Results

Among 100 patients, 94 were men and 6 women. Out of the study population, minimum age was 46, maximum age was 80 and the mean age was 64.2 ± 7.55, the mean post bronchodilator FEV1 in the study population was 57.45 ± 7.96%. The maximum pack years was 36 and mean pack years in the study population was 21.78 ± 7.38. In our study, 2% belonged GOLD stage I (FEV1 ≥ 80%), 77% belonged to GOLD stage II (FEV1 ≥ 50 to <80%) and 21% to GOLD stage III (FEV1 ≥ 30 to <50). None of the patients belonged to GOLD stage IV.

The mean triglyceride level in GOLD stage I was 112 mg/dl, in GOLD stage II was 149 mg/dl ± 30.25 mg/dl and in GOLD stage III was 156 mg/dl ± 24.32 mg/dl. ANOVA study did not reveal any statistically significant difference between mean triglyceride levels of patients across GOLD stages (p>0.05) I, II and III.

The minimum BMI in the study population was 17.5 and maximum 29.5 with a mean BMI of 24.23 ± 3.29. 10% were underweight (BMI<18.5), 15% had a normal range BMI (18.5-22.9), 25% were overweight/pre obese (BMI: 23-24.9) and 50% were obese class I (BMI of 25-29.9). Mean BMI in GOLD stage I patients was 22.5, that of GOLD stage II was 24.05 ± 3.13 and GOLD stage III was 24.92 ± 3.85. No significant statistical difference (p=0.41) was found in mean BMI across GOLD stages.

Among males, 24 (26%) had waist circumference between 70 cm-79 cm, 37 (39%) had waist circumference between 80 cm-89 cm and 33 (35%) had waist circumference between 90 cm-99 cm. 4 out of 6 female patients had waist circumference ≥ 80 cm. The mean waist circumference of male patients belonging to GOLD stage I was 84 cm, GOLD stage II was 83.6 cm ± 7.06 cm and GOLD stage III was 84.3 cm ± 7.21 cm. ANOVA study revealed no statistically significant difference in mean waist circumference among males in the study population in the GOLD stages I to III (p=0.227) (Table 1).

| GOLD stage | Mean triglyceride (mg/dl) p>0.05 | Mean SBP (mmHg) p<01 | Mean waist circumference (cm) P>0.22 | Mean FBS (mg/dl) P<0.01 | Mean BMI p>0.41 |
|---|---|---|---|---|---|
| I | 112 | 115 ± 7.07 | 84 | 88 | 22.5 |

| | | | | | |
|---|---|---|---|---|---|
| II | 149 ± 30.25 | 127.7 ± 13.61 | 83.6 ± 7.06 | 109.14 ± 16.52 | 24.05 ± 3.13 |
| III | 156 ± 24.32 | 138.25 ± 12.95 | 84.3 ± 7.21 | 124.91 ± 14.60 | 24.92 ± 3.85 |

**Table 1:** Comparison of metabolic syndrome parameters among GOLD stages.

The minimum systolic blood pressure was 100 mmHg; maximum was 160 mmHg with a mean value of 129.98 ± 14.18. The minimum diastolic blood pressure was 70 mmHg, maximum of 100 mmHg with a mean value of 79.88 mmHg ± 7.90 mmHg. 6% had a systolic blood pressure between 100 mmHg-109 mmHg, 13% between 110 mmHg-119 mmHg, 24% between 120 mmHg-129 mmHg, 22% between 130 mmHg-139 mmHg, 23% between 140 mmHg-149 mmHg and 11% between 150 mmHg-159 mmHg and 1% ≥ 160 mmHg.

The mean SBP in GOLD stage I was 115 mmHg ± 7.07 mmHg, in stage II was 127.7 mmHg ± 13.61 mmHg and in stage III was 138.25 mmHg ± 12.95 mmHg. ANOVA study with post hoc Tamhane test revealed that there was a statistically significant difference of mean SBP between GOLD stages II and III with patients in GOLD stage III having significantly higher mean SBP than those in GOLD stage II ($p<0.005$). 31% of study population had diastolic blood pressure between 70 mmHg-79 mmHg, 48% had diastolic blood pressure between 80 mmHg-89 mmHg, 17% between 90 mmHg-99 mmHg and 4% with diastolic blood pressure ≥ 100 mmHg. The mean diastolic blood pressure in GOLD stage I was 70 mmHg, in stage II was 79.21 mmHg ± 7.38 mmHg and in stage III was 82.75 mmHg ± 8.80 mmHg, 35% of the study population was normotensive, 19% had elevated blood pressure with SBP between 120 mmHg-129 mmHg and DBP <80, 18% had stage I hypertension and 28% had stage II hypertension.

In the study population, 40% had FBS<100 mg/dl, 25% had FBS between 100 mg/dl-125 mg/dl and 34% had FBS ≥ 126 mg/dl.

The mean FBS in GOLD stage I was 88 mg/dl, in stage II was 109.14 mg/dl ± 16.52 mg/dl and in stage III was 124.91 mg/dl ± 14.60 mg/dl. ANOVA study revealed there is statistically significant difference in mean FBS across GOLD stages I, II and III. Post hoc Tamhane test shows the mean FBS in GOLD stage III was significantly higher than those in stage I and II ($p<0.001$).

48% of the study population had metabolic syndrome in accordance with NCEP ATP III criteria. The mean age in the group with metabolic syndrome was 62.67 ± 6.83 years and the mean age in those without metabolic syndrome was 65 ± 7.95 years. The mean age in the group with metabolic syndrome was significantly lower compared to those without metabolic syndrome ($p<0.05$). The mean FEV1 in the patient group with metabolic syndrome was 53.91% ± 6.57% and the mean FEV1 in the patient group without metabolic syndrome was 60.7% ± 7.79%. There is significant statistical difference between mean FEV1 of groups with and without metabolic syndrome ($p<0.001$) with the mean FEV1 of those with metabolic syndrome being significantly lower than those without metabolic syndrome (Table 2).

| Parameters | Group | N | Mean | Std. deviation | p value |
|---|---|---|---|---|---|
| FEV1 | 1 | 48 | 53.92 | 6.575 | |
| | 2 | 52 | 60.71 | 7.795 | <0.001 |
| SBP | 1 | 48 | 140.79 | 8.493 | |
| | 2 | 52 | 120.00 | 10.598 | <0.001 |
| Pack years | 1 | 48 | 23.60 | 7.756 | |
| | 2 | 52 | 20.10 | 6.664 | <0.001 |
| DBP | 1 | 48 | 84.04 | 6.983 | |
| | 2 | 52 | 76.04 | 6.715 | <0.001 |
| FBS | 1 | 48 | 123.48 | 12.470 | |
| | 2 | 52 | 102.38 | 15.433 | <0.001 |
| HDL | 1 | 48 | 43.02 | 3.091 | |
| | 2 | 52 | 43.94 | 4.968 | 0.138 |
| LDL | 1 | 48 | 111.71 | 14.870 | |
| | 2 | 52 | 100.92 | 10.177 | <0.001 |
| TG | 1 | 48 | 173.13 | 21.581 | |
| | 2 | 52 | 129.92 | 17.583 | <0.001 |
| WC | 1 | 48 | 89.42 | 4.099 | |
| | 2 | 52 | 79.19 | 6.322 | <0.001 |
| BMI | 1 | 48 | 26.69 | 1.847 | |
| | 2 | 52 | 21.96 | 2.655 | <0.001 |
| CRP | 1 | 48 | 4.95 | 0.773 | |

| | | | | | |
|---|---|---|---|---|---|
| | 2 | 52 | 2.70 | 1.189 | <0.001 |

**Note:** SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBS: Fasting Blood Sugar; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; TG: Triglyceride; WC: Waist Circumference; BMI: Body Mass Index; N: Number of patients.

**Group 1:** Patients with metabolic syndrome.

**Group 2:** Patients without metabolic syndrome.

**Table 2:** Comparison of metabolic syndrome parameters, FEV1 and CRP between those with and without metabolic syndrome.

In the study population of 100 COPD patients a significant negative correlation was found between SBP and FEV1 (ρ=-0.56, p<0.001) and a significant negative correlation was found between DBP and FEV1 (ρ=-0.34, p<0.001). In the study population of 100 COPD patients a significant negative correlation was found between FBS and FEV1 (ρ=-0.649 p<0.001). A weak positive correlation was found between HDL and FEV1 (ρ= 0.148 p=0.138), but it was not significant. Also a weak negative correlation was found between LDL and FEV1 (ρ=-0.151 p=0.134) but was not significant. In the study, a significant negative correlation was found between BMI and FEV1 (ρ=-0.358, p<0.001) and a significant negative correlation was found between waist circumference and FEV1 (ρ=-0.287, p<0.001) (Table 3).

| Correlation of FEV1 with | Spearman Correlation coefficient (ρ) | p value | Type of correlation |
|---|---|---|---|
| CRP | -0.69 | <0.001 | Negative |
| FBS | -0.65 | <0.001 | Negative |
| SBP | -0.56 | <0.001 | Negative |
| DBP | -0.34 | <0.001 | Negative |
| HDL | 0.15 | <0.14 (not significant) | Positive |
| TG | -0.41 | <0.001 | Negative |
| WC | -0.28 | <0.001 | Negative |
| BMI | -0.36 | <0.001 | Negative |

**Note:** SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBS: Fasting Blood Sugar; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; TG: Triglyceride, WC: Waist Circumference; BMI: Body Mass Index.

**Table 3:** Correlation of various metabolic syndrome components with FEV1.

## Discussion

In our study, out of 100 patients in the study population, 94 (94%) were males and 6 (6%) were females. The minimum age was 46, maximum age was 80 and the mean age was 64.2 ± 7.55 years. The mean age was 60.46 ± 11.56 years in a study on 100 stable COPD patients by Bhupendra Kumar Jain, et al. 2% of the study population belonged to the age group 40-49 years, 25% to the age group 50-59 years, 46% to the age group 60-69 years, 25% to the age group 70-79 years and 2% to the age group 80-89 years.

In our study 48% of the study population had metabolic syndrome in accordance with NCEP ATPIII criteria similar to a study by Gherald Bermudez, et al. of 157 patients with COPD in which 40.3% was found to have metabolic syndrome using the NCEP/ATPIII criteria. However the frequency of metabolic syndrome in our study was lower than that of Breyer, et al.,q with a frequency of 57%. The mean age in the group with metabolic syndrome was 62.67 ± 6.83 years and the mean age in those without metabolic syndrome was 65 ± 7.95 years. The mean age in the group with metabolic syndrome was significantly lower compared to those without metabolic syndrome (p<0.05). Out of 100 COPD patients, 46 had SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg. 15 patients had low HDL (HDL ≤ 40 (males) and ≤ 50 (females). 49 patients had triglyceride level ≥ 150 mg/dl. 33 patients had high waist circumference (≥ 90 cm for males and ≥ 80 cm for females). 65 patients had FBS ≥ 100 mg/dl.

The minimum post bronchodilator FEV1 was 36%, maximum 82% and the mean post bronchodilator FEV1 in the study population was 57.45% ± 7.96%. 2% belonged GOLD stage I (FEV1 ≥ 80%), 77% belonged to GOLD stage II (FEV1 ≥ 50 to <80%) and 21% to GOLD stage III (FEV1 ≥ 30 to <50). The Mean post bronchodilator FEV1 in age group 40-49 years was 47% ± 1.4%, 50-59 years was 55.56% ± 7.2%, 60-69 years was 59.17% ± 8.6%, 70-79 years was 57.52% ± 6.8% and ≥ 80 years was 51% ± 7.07%. Out of 48 patients of COPD with metabolic syndrome 14 (29%) belonged to GOLD stage III (FEV1 30-<50%) and 34 (71%) belonged to GOLD stage II (FEV1 50-<80%). In the study of Wats, et al. the frequencies of MetS in GOLD stages I-IV were 50%, 53%, 37% and 44% respectively. Akpinar, et al., reported the distribution of the prevalence of MetS between GOLD stages as follows: 38.5%, 52.8%, 30% and 33.3%. In the study of Diez-Manglano, all patients were in GOLD II, III, IV stages and the frequencies of MetS were 51.2%, 41.2% and 25.5%, respectively found significantly different MetS prevalence in COPD patients in different GOLD stages: The highest prevalence was observed in stage II (59%) and the lowest one in stage IV (4.5%), thus MetS was more frequent in the early stages of the disease.

Among patients without metabolic syndrome 7 (13%) belonged to GOLD stage III (FEV1 30-<50%), 43 (83%) belonged to GOLD stage II (FEV1 50-<80%) and 2 (4%) belonged to GOLD stage I (FEV1 ≥ 80%). The minimum FEV1 value in patients with metabolic syndrome was 36% and in those without metabolic syndrome was 46%. The maximum FEV1 value in patients with metabolic syndrome was 67% and in those without metabolic syndrome was 82%. The mean FEV1 in the patient group with metabolic syndrome was 53.91% ± 6.57%and the mean FEV1 in the patient group without metabolic syndrome was 60.7% ± 7.79%. There was significant statistical difference between mean FEV1 of groups with and without metabolic syndrome ($p<0.001$) with the mean FEV1 of those with metabolic syndrome being significantly lower than those without metabolic syndrome. This is in contrast to the study result by Diez-Manglano, et al, which showed that metabolic syndrome in COPD was associated with higher FEV1.

The maximum pack years was 36 and mean pack years in the study population was 21.78% ± 7.38.6% had a smoking history of 0-10 pack years, 37% a had a smoking history of 11-20 pack years, 45% had a smoking history of 21-30 pack years, 12% had a smoking history of 31-40 years. No patient in the study population had a smoking history of more than 40 pack years. Mean pack years of patients in GOLD stage I (FEV1 ≥ 80%) was 17.5 ± 0.7, GOLD stage II (FEV1 ≥ 50% to <80%) was 20-62 ± 5.39, GOLD stage III (FEV1 ≥ 30% to <50%) was 26.42 ± 11.29. The maximum Pack years in the patient group with metabolic syndrome was 32 and in the patient group without metabolic syndrome was 36. The mean pack years in the group with metabolic syndrome was 20.02 ± 6.71 and in the group without metabolic syndrome was 23.6 ± 7.76. The difference in pack years was found to be statistically significant ($p<0.05$) with the group without metabolic syndrome having higher mean pack years.

The minimum systolic blood pressure was 100 mmHg; maximum was 160 mmHg with a mean value of 129.98 ± 14.18. The minimum diastolic blood pressure was 70 mmHg, maximum of 100 mmHg with a mean value of 79.88 mmHg ± 7.90 mmHg. 6% had a systolic blood pressure between 100 mmHg-109 mmHg, 13% between 110 mmHg-119 mmHg, 24% between 120 mmHg-129 mmHg, 22% between 130 mmHg-139 mmHg, 23% between 140 mmHg-149 mmHg and 11% between 150 mmHg-159 mmHg and 1% ≥ 160 mmHg. The mean SBP in GOLD stage I was 115 mmHg ± 7.07 mmHg, in stage II was 127.7 mmHg ± 13.61 mmHg and in stage III was 138.25 mmHg ± 12.95 mmHg. ANOVA study reveals that there is statistically significant difference of mean SBP across 3 groups GOLD stage I, II and III. Post hoc analysis using Tamhane test shows a statistically significant difference of mean SBP between GOLD stage II and III with patients in GOLD stage III having significantly higher mean SBP than those in GOLD stage II ($p<0.005$). The mean SBP in the groups with and without metabolic syndrome were 140.79 mmHg and 120 mmHg respectively and the difference was statistically significant ($p<0.001$). Those with metabolic syndrome had significantly higher mean SBP. In the study population of 100 COPD patients a significant negative correlation was found between SBP and FEV1 ($\rho=-0.56$ $p<0.001$). Similar results were obtained in the study by N Logvinenko, et al., which showed a significant negative correlation between SBP, DBP and FEV1 ($p<0.001$).

31% of study population had diastolic blood pressure between 70 mmHg-79 mmHg, 48% had diastolic blood pressure between 80 mmHg-89 mmHg, 17% between 90 mmHg-99 mmHg and 4% with diastolic blood pressure ≥ 100 mmHg. 35% of the study population was normotensive, 19% had elevated blood pressure with SBP between 120 mmHg-129 mmHg and DBP<80, 18% had stage I hypertension and 28% had stage II hypertension as per AHA classification, 2017. The mean diastolic blood pressure in GOLD stage I was 70 mmHg, in stage II was 79.21 mmHg ± 7.38 mmHg and in stage III was 82.75 mmHg ± 8.80 mmHg. ANOVA study of mean DBP among 3 groups patients in GOLD stages I, II and III revealed statistically significant difference between groups. Post hoc Tamhane test shows no statistically significant difference in mean DBP of patients between patients in GOLD stages II and III ($p>0.09$). However significant statistical difference was found was between mean DBP of stage I with those of stages II and III, the mean value of DBP was significantly lower in COPD stage I compared to stages II and III ($p<001$). The mean DBP in the groups with and without metabolic syndrome were 84 mmHg and 76 mmHg respectively and the difference was statistically significant ($p<0.001$). Those with metabolic syndrome had significantly higher mean DBP. In the study by Ghatas T, et al., Abdominal obesity, hypertension and hyperglycemia were significantly more in COPD patients with metabolic syndrome similar to what we had found in our study.

In the study population of 100 COPD patients a significant negative correlation was found between DBP and FEV1 ($\rho=-0.34$, $p<0.001$).

Among males, 24 (26%) had waist circumference between 70 cm-79 cm, 37 (39%) had waist circumference between 80 cm-89 cm and 33 (35%) had waist circumference between 90 cm-99 cm. out of 6 female patients had waist circumference ≥ 80 cm. The mean waist circumference in male patients belonging to GOLD stage I was 84 cm, GOLD stage II was 83.6 cm ± 7.06 cm and GOLD stage III was 84.3 cm ± 7.21 cm. ANOVA study revealed no statistically significant difference in mean waist circumference in the study population in the GOLD stages I to III ($p=0.227$). In the study by Popovic-GrleS et al. Waist circumference did not reveal significant variations between GOLD 2 and GOLD 3 stages ($p>0.5$) similar to our observation. The mean waist circumference in the groups with and without metabolic syndrome were 89 cm and 79 cm respectively and the difference was statistically significant ($p<0.001$). Those with metabolic syndrome had significantly higher mean waist circumference. In the study population of 100 COPD patients a significant negative correlation was found between waist circumference and FEV1 ($\rho=-0.287$ $p<0.001$), but the correlation was found to be weak. In the study but Foumani AA, et al., waist circumference was not observed to have an impact on lung function but it was a predictive factor for COPD severity in patients. The mean FEV1/FVC in both normal weight and overweight patients did not statistically significantly correlate with WC.

6% of the study population had triglyceride level between 90 mg/dl-109 mg/dl, 12% between 110 mg/dl-129 mg/dl, 33% between 133 mg/dl-149 mg/dl, 21% between 150 mg/dl-169 mg/dl, 21% between 170 mg/dl-189 mg/dl, 3% between 190 mg/dl-209 mg/dl and 4% ≥ 210 mg/dl. 49% had a triglyceride level ≥ 150 mg/dl. Elevated triglyceride levels in 51.4% of COPD patients in the study population in the study by Neveen Mahmoud Ameen, et al. The mean Triglyceride level in GOLD stage I was 112 mg/dl, in GOLD stage II was 149 mg/dl ± 30.25 mg/dl and in GOLD stage III was 156 mg/dl ± 24.32 mg/dl. ANOVA study did not reveal any statistically significant difference between mean triglyceride levels of patients across GOLD stages ($p>0.05$) I, II and III. The mean triglyceride levels in the groups with and without metabolic syndrome were 173 mg/dl and 129.9 mg/dl respectively and the difference was statistically significant ($p<0.001$). Those with metabolic syndrome had significantly higher

mean triglyceride. In the study population of 100 COPD patients a significant negative correlation was found between triglyceride level and FEV1 (ρ=-0.409 p<0.001) which is supported by a study by Neveen Mahmoud Ameen, et al., a negative correlation of triglyceride level was found with FEV1. (r =-0.3, p value 0.047)

The minimum value of HDL was 30 mg/dl, maximum of 56 mg/dl with mean value of 43.5 mg/dl ± 4.17 mg/dl. The minimum value of LDL was 86 mg/dl, maximum value of 150 mg/dl and mean value of 106.1 mg/dl ± 13.69 mg/dl. The minimum triglyceride level was 99 mg/dl, maximum of 240 mg/dl and mean value of 150.66 mg/dl ± 29.17 mg/dl. 17% females had HDL levels between 30 mg/dl-40 mg/dl, 50% between 41 mg/dl-50 mg/dl and 33% between 51 mg/dl-59 mg/dl. 4% males had HDL levels between 51 mg/dl-59 mg/dl, 84% males had HDL levels between 41 mg/dl-50 mg/dl and 12% had HDL between 30 mg/dl-40 mg/dl. None had HDL below 30 mg/dl. The mean HDL in the groups with and without metabolic syndrome were 43.02 mg/dl and 43.94 mg/dl respectively and the difference was not statistically significant (p>0.05). According to the study by Bhupendra Kumar Jain, et al. The severity of COPD had no significant correlation with the triglycerides, LDL, HDL and LDL/HDL risk ratio. Similar results were found in the study by Modini Venkata Rao, et al. The study population of 100 COPD patients a weak positive correlation was found between HDL and FEV1 (ρ=0.148, p=0.138), but it was not significant.

The minimum BMI in the study population was 17.5 and maximum 29.5 with a mean BMI of 24.23 ± 3.29. 10% were underweight (BMI<18.5), 15% had a normal range BMI (18.5-22.9), 25% were overweight/pre obese (BMI: 18.5- 22.9) and 50% were obese class I (BMI of 25-29.9). The mean FEV1 of those with BMI<18.5 was 56.1% ± 7.49%, those with BMI between 18.5-22.9 (normal range) was 63.13 ± 9.28, those with BMI 23-24.9 (overweight/pre-obese) was 61.04 ± 6.15 and those with BMI between 25-29.9 (obese class I) was 54.22 ± 6.87. Mean BMI in GOLD stage I patients was 22.5, that of GOLD stage II was 24.05 ± 3.13 and GOLD stage III was 24.92 ± 3.85. None of the patients belonged to GOLD stage IV. No significant statistical difference (p=0.41) was found in mean BMI across GOLD stages. But in the study by Mitra M, et al. BMI of the patients were decreasing with increasing severity of the disease (GOLD) and it was statistically significant (P<0.05).

Our study found a negative correlation between FEV1 and BMI in contrast to the study by Zhenchao Wu, et al., in which BMI was moderately correlated with pulmonary function positively and exacerbations negatively. The mean BMI in the groups with and without metabolic syndrome were 26.69 and 21.96 respectively and the difference was statistically significant (p<0.001). Those with metabolic syndrome had significantly higher BMI.

40% had FBS<100 mg/dl, 25% had FBS between 100 mg/dl-125 mg/dl and 34% had FBS ≥ 126 mg/dl. In the study by Vinay Mahishale, et al. Prevalence of DM in COPD patients was found to be 25.63% compared to 34% in our study population. The mean FBS in GOLD stage I was 88 mg/dl, in stage II was 109.14 mg/dl ± 16.52 mg/dl and in stage III was 124.91 mg/dl ± 14.60 mg/dl. ANOVA study revealed there is statistically significant difference in mean FBS across GOLD stages I, II and III. Post hoc Tamhane test shows the mean FBS in GOLD Stage III was significantly higher than those in stage I and II (p<0.001). The mean FBS in the groups with and without metabolic syndrome were 123 mg/dl and 102 mg/dl respectively and the difference was statistically significant (p<0.001). Those with metabolic syndrome had significantly higher mean FBS. A significant negative correlation was found between FBS and FEV1 (ρ=-0.649 p<0.001). According to a study by Dharwadkar AR, et al., lung functions were found to be negatively correlated with glycemic status. (r=-0.390, -0.342).

There is significant positive correlation between CRP and SBP with a ρ value of 0.75 and p value of <0.001. There is significant positive correlation between CRP and DBP with a ρ value of 0.49 and p value of <0.001 in accordance with a study by Susan G. Lakoski, et al. It showed that the geometric mean CRP in hypertensive participants was 2.3 mg/l ± 0.07 mg/l compared with 1.6 mg/l ± 0.07 mg/l among normotensive participants (p<0.0001). There is significant positive correlation between CRP and triglyceride levels with a ρ value of 0.68 and p value of <0.001.There is significant but weak negative correlation between CRP and HDL with a ρ value of -0.21 and p value of <0.05. There is significant positive correlation between CRP and waist circumference with a ρ value of 0.52 and p value of <0.001. There is significant positive correlation between CRP and FBS with a ρ value of 0.74 and p value of <0.001. The study by Bhavita Patel DT, et al., showed hs-CRP levels correlated positively with BMI (r=0.26, p<0.001) and waist circumference (r=0.45, p<0.001) in obese non-diabetic subjects. As the number of components of MetS increased, mean hs-CRP levels also increased.

## Conclusion

COPD is one of the major causes of mortality and morbidity in India. COPD has been found to be associated with metabolic syndrome and various previous studies had shown increased prevalence of metabolic syndrome in COPD patients. We had aimed to study the prevalence of metabolic syndrome among cases of stable COPD and also to determine if there was any correlation with COPD severity and C-reactive protein with metabolic syndrome components *i.e.* SBP, DBP, FBS, waist circumference, HDL and triglyceride levels. We did our study on 100 COPD patients who met the inclusion criteria. We found that:

Majority (94%) were males with a mean pack year of 21.78. The mean age was 64.2 years.

77% of the study population belonged to GOLD stage II and 21%to GOLD stage III. The mean post bronchodilator FEV1 was 57.45%.

48% of the study population had metabolic syndrome. The mean age of the group of COPD patients with metabolic syndrome lower (62.6 years) compared to those without metabolic syndrome (65.6 years).

In the study population, the mean SBP was 129 mmHg and mean DBP was 79 mmHg, 46% had hypertension. The mean SBP was significantly higher in GOLD stage III compare to stage II. Higher SBP was correlated with lower FEV1 in our study population.

35% males had a waist circumference ≥ 90 cm. 66% females had waist circumference ≥ 80 cm. No statistically significant difference was found in the mean waist circumference across GOLD stages.

Almost half the patients (49%) had triglyceride level ≥ 150 mg/dl. We found a negative correlation between triglyceride levels and FEV1. But there was no statistically significant difference in mean triglyceride levels across GOLD stages.

12% males and 67% females had HDL ≤ 40 mg/dl and ≤ 50 mg/dl respectively stages. No significant correlation was found between HDL with FEV1.

The mean BMI was 24. 23.50% were obese class I. There was no significant statistical difference in mean BMI across GOLD stages.

59% had FBS ≥ 100. The mean FBS in stage III COPD was significantly higher compared to stages I and II. Higher FBS was correlated with lower FEV1 in our study population.

The group of COPD patients with metabolic syndrome had significantly lower mean FEV1 compared to the group without metabolic syndrome.

The CRP concentration in the group with metabolic syndrome was found to be significantly higher compared to the group without metabolic syndrome.

The present study shows that metabolic syndrome is an important systemic manifestation of COPD present in 48% of subjects and is significantly correlated with both post bronchodilator FEV1 (marker of COPD severity) and C-reactive protein (marker of systemic inflammation). So management of COPD should focus not only on treatment of airflow limitation but also on management of systemic co morbidities of metabolic syndrome to improve morbidity, mortality and quality of life of COPD patients.

## Limitations

- The sample size for this study was small as compared to the prevalence of COPD in the population.
- The patients in COPD groups I and IV were underrepresented in the study.
- A single standardized spirometer could not be used in all patients for measurement of lung function parameters.
- In the absence of a control group, we could not compare the prevalence of metabolic syndrome between normal individuals and COPD patients.
- COPD comorbidities like obstructive sleep apnea/ischemic heart disease and other manifestations of systemic inflammation were not assessed.

## Ethics Statement

The study was granted ethical committee approval by institutional ethics committee of IPGME and R.

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