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## Original Research Article

# Predictors of co-morbidities in chronic obstructive pulmonary disease patients at a tertiary care centre in north India

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## ABSTRACT

**Background:** Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation. COPD is characterised by an intense inflammatory process in the airways, parenchyma, and pulmonary vasculature. It is possible in some cases that the inflammatory process may overflow into the systemic circulation, promoting a generalised inflammatory reaction. Patient with COPD often have concomitant chronic illness (co-morbidities). The aim of this study is to know the pattern of co-morbidities in COPD patients.
**Methods:** This study was a cross sectional observational study conducted on 172 COPD patients (IPD and OPD) diagnosed on the basis of GOLD guideline 2017. Co morbidities were diagnosed as per standard defined criteria laid down in the respective guidelines.
**Results:** 55.3% of the patients with COPD had co morbidities. 18/88(20.5%) patients presented with multiple co-morbidities. 49/88, 55.7% COPD patients were affected with cardiac (either only cardiac or had multiple organs affected besides cardiac), the commonest co-morbidity. Amongst cardiac, hypertension and congestive heart failure (CHF) was the commonest (n=19/49, 38.8% each) followed by CAD/CSA/IWMI/IHD/AF. Others were metabolic (n=14/88, 15.9%), GERD (n=13/88, 14.8%), Depression (n=11/88, 12.5%). Less prevalent co-morbidities were Osteoporosis (n=8/88, 9.1%), Lung cancer (n=6/88, 6.8%), Bronchiectasis (n=5/88, 5.6%) and OSA (n=3/88, 3.4%).
**Conclusions:** Urban indwelling, advancing age and duration of illness, presentation with low mood, loss of pleasure/ interest, appetite disturbances and heart burn with relief on taking proton pump inhibitor can be predictors of co-morbidities in COPD patients. Chance of finding co-morbidities may be multifactorial. Thus, it is important to look out for co morbidities in each and every COPD patients.

**Keywords:** Co-morbidity, Chronic obstructive pulmonary disease, Predictors of co-morbidities

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation.[1] COPD is characterized by an intense inflammatory process in the airways, parenchyma, and pulmonary vasculature. It is possible in some cases that the inflammatory process may overflow into the systemic circulation, promoting a generalized inflammatory reaction. Furthermore, while authors believe that COPD is responsible for the systemic inflammation, there exists the possibility of reverse causation; the possibility that systemic inflammation causes injuries to the airways leading to COPD changes cannot be fully denied.[2]

Patient with COPD often have concomitant chronic illness (co-morbidities) at time of diagnosis, including cardiovascular disease, metabolic syndrome, skeletal muscle dysfunction, osteoporosis, depression/anxiety, gastroesophageal disease, bronchiectasis, obstructive sleep apnoea, lung cancer etc.[3]

## METHODS

A cross sectional observational study was conducted in Department of Respiratory Medicine, King George's Medical University, Lucknow. Indoor and outdoor patients were recruited from August 2017 to September 2018. 172 patients who gave the written informed consent were recruited. 13 patients were lost to follow up. Thereafter, assessment of 159 patients was done. Diagnosis of COPD was made on the basis of GOLD guideline 2017.[1] Patients of COPD with coexisting diagnosis of HIV, chronic renal failure, metastatic lung malignancy, patients on long term systemic steroid or cytotoxic drugs, post tubercular COPD and pregnant women were excluded from the study. After taking thorough history and clinical examination the patients were investigated for various comorbidities.

Co-morbidities were diagnosed as per standard defined criteria laid down in respective guidelines. Patients were diagnosed with systemic hypertension if, mean systolic pressure was ≥140 mm Hg and/or diastolic BP ≥90 mm Hg or current consumption of anti-hypertensive medication.[4] Diagnosis of other cardiac co-morbidities were based on sign/symptoms like palpitation, fainting, light headedness associated with or without shortness of breath, chest pain and significant findings on investigations like Pro BNP, serial Trop-T, electrocardiogram and 2D echocardiography. Diagnosis of metabolic syndrome was made by hyperglycemia (fasting glucose ≥110 mg/dl) in addition to at least two of following: waist circumference ≥ 94 cm in males or ≥80 in females; dyslipidemia (triglycerides ≥150 mg/dl or HDL cholesterol <40 mg/dl in males and <50 mg/dl in females and systemic hypertension.[5] Diagnosis of diabetes mellitus was made if fasting blood sugar was >126 mg/dl and HbA1c ≥6.5 or patient was currently on insulin or oral hypoglycemic drugs.[6] Diagnosis of bronchiectasis was as per HRCT thorax criteria.[7] Osteoporosis was diagnosed based on clinical sign and symptoms and investigation like Bone x-ray and confirmed by BMD (bone mineral density) by dual energy x-ray absorptiometry.[8] Diagnosis of depression was made if there were more than four symptoms (with at least one major symptom).[9] Major symptoms like persistent sadness or low mood and /or, loss of interest or pleasure, fatigue or low energy (at least one of these for two weeks and associated symptoms) and minor symptoms like disturbed sleep, poor concentration, low self-confidence, poor/increased appetite ,suicidal thought/act, guilt or self-blame, agitation or slowing of movement . Depression in a COPD patient has poor prognosis. Screening criteria for gastroesophageal reflex disease (GERD) was based on questionnaires, like Do patient have heart burn for three weeks? Improvement in symptoms after taking short term proton pump inhibitors.[10] Diagnosis of lung cancer was made with histopathology and or cyto histopathology reports of transthoracic biopsy & FNAC and/or bronchoscopic guided biopsy and /or thoracoscopic guided biopsy and/ or pleural fluid /sputum for malignant cell.[11] Screening for obstructive sleep apnoea (OSA) was done by STOP BANG criteria for OSA (S - snoring, T - tiredness, O - observed sleep apnoea, P - blood pressure, B - BMI, A-age, N - neck circumference, G - gender) BMI >35 Kg/m$^2$, age >50 year, neck circumference >16 inches (40.6 cm) in women and >17 inches (43.2 cm) in men. Score suggesting high risk of OSA: 5-8, Intermediate risk: 3-4, low risk OSA: 0-2. Patients with score of ≥3 on 'STOP BANG' criteria were subjected to polysomnography (PSG).[12] Final diagnosis was based on PSG criteria.

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 24.0 statistical analysis software. The values were represented in number (%) and mean±SD.

## RESULTS

Among 172 patients were recruited during the study. 13 patients were lost to follow up. Thereafter, assessment of 159 patients was done. Diagnosis of COPD was made on the basis of GOLD guideline 2017. Study population was categorized into two groups. Group I and II on the basis of presence or absence of co-morbidities respectively (Figure 1).

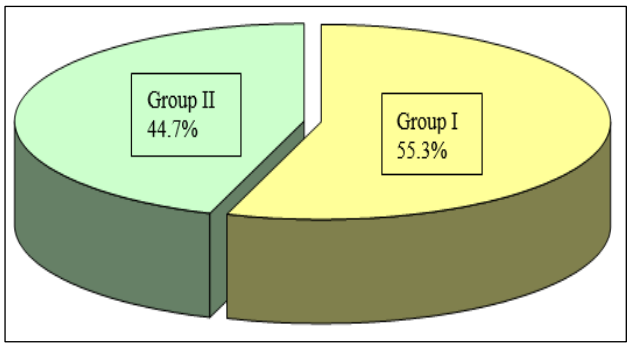


**Figure 1: Groupwise distribution of study population (n=159)**

Group I (co morbidity group n=88; 55.3%).
Group II (non co morbid group 71; 44.7%).

Out of 159 COPD patients, majority had co-morbidities (n=88; 55.3%), rest (n=71 44.7%) patients were without any co-morbidity. In both the groups predominantly, patients were from rural background (61/88, 69.3% Vs 56/71, 78.9% respectively) while rest were from urban population (27/88, 30.7% Vs 15/71, 21.1%). Thus, chance of finding co-morbidities is 1.65 (95% CI:

0.7979-3.4221, p=0.1763) times in urban patients in comparison to rural patients which was statistically insignificant. Farming profession was the major representation in both groups (55.7% in Group I and 54.9% in Group II) (Table 1).

**Table 1: Group wise Comparison of Demographic Variables (n=159).**

| Sn | Demographic variables | | Group I (n=88) | | Group II (n=71) | | Total (n=159) | |
|---|---|---|---|---|---|---|---|---|
| 1 | Mean Age±sd | | 61.14±9.65 | | 58.30±8.69 | | 59.87±9.31 | |
| | | | 'T'=1.929; p=0.056 | | | | | |
| | | | NO. | % | NO. | % | NO. | % |
| 2 | Gender | Female | 9 | 10.2 | 12 | 16.9 | 21 | 13.2 |
| | | Male | 79 | 89.8 | 59 | 83.1 | 138 | 86.8 |
| | | | $\chi^2$=1.527; P=0.217 | | | | | |
| 3 | Habitat | Rural | 61 | 69.3 | 56 | 78.9 | 117 | 73.6 |
| | | Urban | 27 | 30.7 | 15 | 21.1 | 42 | 26.4 |
| | | | $\chi^2$=1.846; p=0.174 | | | | | |
| 4 | Occupation | Farmer | 49 | 55.7 | 39 | 54.9 | 88 | 55.3 |
| | | Housewife | 9 | 10.2 | 12 | 16.9 | 21 | 13.2 |
| | | Retired/none | 10 | 11.4 | 3 | 4.2 | 13 | 8.2 |
| | | Business* | 8 | 9.1 | 7 | 9.9 | 15 | 9.4 |
| | | Professional | 2 | 2.3 | 1 | 1.4 | 3 | 1.9 |
| | | Teacher/Accountant** | 5 | 5.7 | 0 | 0.0 | 5 | 3.1 |
| | | Labourer*** | 5 | 5.7 | 9 | 12.7 | 14 | 8.8 |
| | | | $\chi^2$=10.176; p=0.117 | | | | | |

*Shopkeeper/Business, **incl. Supervisor, ***Skilled/Unskilled labour

All patients were subjected to spirometry. On comparing the spirometry findings of patients of above two groups, differences in none of the above parameters were found to be statistically significant (Table 2).

Authors further categorized these patients into exposed and nonexposed group to see its effect on co morbidities. By exposure authors mean either smoker or ex-smoker and/ or biomass fuel exposure. Out of 159 patients, 142 (83.3%) were in exposure group. In comparison to 76 (53.52%) patients amongst all exposed, 12 patients (70.59%) out of 17 unexposed had one or more co-morbidities. Authors report odds of developing co morbidities in COPD patients to be 0.48 (95% CI: 0.1606 to 1.4330, p=0.1883) amongst exposed group which is statistically insignificant (Figure 2). This might be explained by the small population data. There might be other risk factors for co morbidities too. Duration of COPD among study population ranged from 4 months to 25 years. Mean duration of COPD was significantly higher among group I (7.66±5.48 years) as compared to group II patients (5.59±4.39%).

All the patients enrolled in the study were examined clinically and necessary investigations were done to find the existence of co-morbidities among the patients. Proportion of Group I and Group II patients presenting with Low mood (14.8% vs. 1.4%), loss of interest/pleasure (14.8% vs. 1.4%), appetite disturbance (71.6% vs. 47.9%), heart burn (14.8% vs. 1.4%), relief in heartburn on proton pump inhibitor (PPI) uptake (13.6% vs. 1.4%), and fracture/joint pain (10.2% vs. 0.0%) respectively was statistically significant (Table 3).

In both the groups (group I vs. group II), Stage III (40.9% & 50.7%) was the most common GOLD stage followed by Stage II (36.4% vs. 31.0%), Stage IV (19.3% vs. 16.0%) while least common GOLD stage was Stage I (3.4% vs. 1.4%). Distribution of patients of both the groups according to GOLD Stage was not found to be statistically significant (Figure 3).

Majority of the patients with COPD had co morbidities n=88/159 (55.3%). Out of 88 patients n=18/88(20.5%) patients presented with multiple co morbidities and rest (n=70/88; 79.5%) had single co-morbidity. 49/88; 55.7% COPD patients were affected with cardiac (either only cardiac or had multiple organs affected besides cardiac) co-morbidity. 14 of these patients (14/49) had other co morbidities too.

Thus, most prevalent co-morbidity with single organ affection was cardiac; n=35/88 (39.8%). Amongst cardiac, hypertension and congestive heart failure (CHF) was the commonest (n=19/49; 38.8% each) followed by coronary artery disease (CAD) / chronic stable angina (CSA) / inferior wall myocardial infarction (IWMI) / Ischemic heart disease (IHD) / atrial fibrillation (AF)

(n=11/49; 22.4%). Others were metabolic (n=14/88; 15.9%), GERD (n=13/88; 14.8%), Depression (n=11/88; 12.5%). Less prevalent co-morbidities were Osteoporosis (n=8/88, 9.1%), Lung cancer (n=6/88; 6.8%), Bronchiectasis (n=5/88; 5.6%) and OSA (n=3/88; 3.4%). Out of 18 (20.5%) patients with multiple co-morbidities, 15 patients presented with two co-morbidities and rest 3 presented with triple co-morbidities. Out of 14 COPD patients diagnosed to be affected with metabolic co morbidity, 10 patients had metabolic syndrome and rest 4 patients were suffering from Type 2 diabetes mellitus. Amongst 6 co morbid lung cancer patients, 5 (83.3%) had squamous cell carcinoma and 1 (16.7%) had adenocarcinoma (Table 4). In both the groups most common GOLD stage was Stage III (40.9% & 50.7%) followed by Stage II (36.4% vs. 31.0%), Stage IV (19.3% vs. 16.0%) while least common GOLD stage was Stage I (3.4% vs. 1.4%). Distribution of patients of both the groups according to GOLD Stage was not found to be statistically significant.

**Table 2: Group wise comparison of Spirometrics findings.**

| Sn | Spirometry parameters | Group I - co-morbid (n=88) | | Group II - non co-morbid (n=71) | | Total (n=159) | |
|---|---|---|---|---|---|---|---|
| | | MEAN | SD | MEAN | SD | 'T' | 'P' |
| 1 | FVC (PRE) | 1.90 | 0.69 | 1.80 | 0.66 | 0.925 | 0.356 |
| 2 | FVC (POST) | 2.07 | 0.75 | 1.93 | 0.61 | 1.245 | 0.215 |
| 3 | FVC (% PRED.) | 59.48 | 28.47 | 56.85 | 17.42 | 0.682 | 0.496 |
| 4 | FEV1 (PRE) | 2.29 | 9.05 | 0.99 | 0.47 | 1.204 | 0.230 |
| 5 | FEV1 (POST) | 1.19 | 0.48 | 1.62 | 4.64 | -0.871 | 0.385 |
| 6 | FEV1 (% PRED.) | 46.19 | 19.63 | 40.94 | 12.80 | 1.934 | 0.055 |
| 7 | FEV1/FVC (PRE) | 55.23 | 10.67 | 53.93 | 12.06 | 0.720 | 0.472 |
| 8 | FEV1/FVC (POST) | 55.74 | 11.83 | 54.72 | 9.26 | 0.597 | 0.551 |
| 9 | FEV1/FVC (%PRED.) | 65.45 | 19.53 | 66.55 | 12.98 | -0.409 | 0.683 |

**Table 3: Group wise comparison of presenting symptoms.**

| Sn | Presenting symptoms | Total(n=159) | Group I – co-morbid(n=88) | | Group II – non co-morbid(n=71) | | Significance of differences | |
|---|---|---|---|---|---|---|---|---|
| | | | No. | % | No. | % | $\chi^2$ | 'p' |
| 1 | Dyspnea | 159 | 88 | 100.0 | 71 | 100.0 | – | – |
| 2 | Expectoration | 62 | 32 | 36.4 | 30 | 42.3 | 0.573 | 0.449 |
| 3 | Low mood | 14 | 13 | 14.8 | 1 | 1.4 | 8.740 | 0.003 |
| 4 | Loss of Interest/Pleasure | 14 | 13 | 14.8 | 1 | 1.4 | 8.740 | 0.003 |
| 5 | Low energy | 45 | 31 | 35.2 | 14 | 19.7 | 4.658 | 0.031 |
| 6 | Disturbed sleep | 52 | 33 | 37.5 | 19 | 26.8 | 2.059 | 0.151 |
| 7 | Poor concentration | 3 | 3 | 3.4 | 0 | 0.0 | 2.467 | 0.116 |
| 8 | Low confidence | 3 | 2 | 2.3 | 1 | 1.4 | 0.159 | 0.690 |
| 9 | Appetite disturb.* | 97 | 63 | 71.6 | 34 | 47.9 | 9.281 | 0.002 |
| 10 | Suicidal thought | 1 | 1 | 1.1 | 0 | 0.0 | 0.812 | 0.368 |
| 11 | Guilt/self-blame | 0 | 0 | 0.0 | 0 | 0.0 | – | – |
| 12 | Agitation | 1 | 1 | 1.1 | 0 | 0.0 | 0.812 | 0.368 |
| 13 | Heart burn | 14 | 13 | 14.8 | 1 | 1.4 | 8.740 | 0.003 |
| 14 | Relief in heartburn on ppi | 13 | 12 | 13.6 | 1 | 1.4 | 7.826 | 0.005 |
| 15 | Stroke/tia | 2 | 2 | 2.3 | 0 | 0.0 | 1.634 | 0.201 |
| 16 | Paralysis | 2 | 2 | 2.3 | 0 | 0.0 | 1.634 | 0.201 |
| 17 | Back pain | 24 | 17 | 19.3 | 7 | 9.9 | 2.743 | 0.098 |
| 18 | Fracture/joint pain | 9 | 9 | 10.2 | 0 | 0.0 | 7.697 | 0.006 |
| 19 | Snoring | 3 | 3 | 3.4 | 0 | 0.0 | 2.467 | 0.116 |
| 20 | Sleep apnoea | 4 | 3 | 3.4 | 1 | 1.4 | 0.641 | 0.423 |

*Increased/Decrease

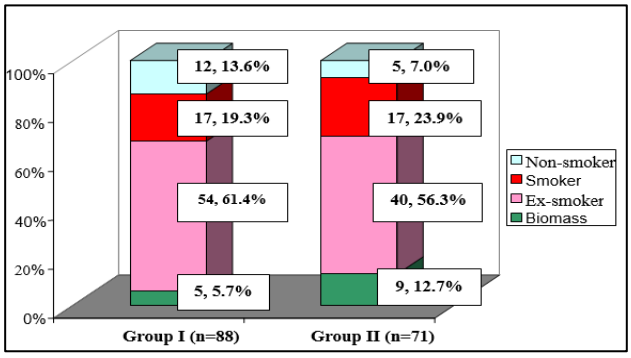


**Figure 2: Group wise comparison of exposure to smoke (n=159).**

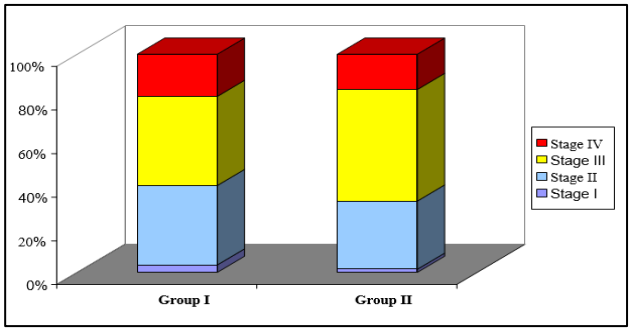


**Figure 3: Group wise comparison of GOLD stage (n=159).**

**Table 4: Prevalence of different co-morbidities among group I COPD patients (n=88).**

| Sn | Co-morbidities | No. of patients | Percentage |
|---|---|---|---|
| | Single co-morbidity | | |
| 1 | Cardiac | 35 | 39.8 |
| 2 | Metabolic | 3 | 3.4 |
| 3 | Bronchiectasis | 3 | 3.4 |
| 4 | Osteoporosis | 7 | 8.0 |
| 5 | Anxiety/Depression | 6 | 6.8 |
| 6 | GERD | 9 | 10.2 |
| 7 | Lung cancer | 6 | 6.8 |
| 8 | OSA | 1 | 1.1 |
| | Multiple co-morbidities | | |
| 9 | Cardiac + Metabolic | 8 | 9.1 |
| 10 | Cardiac + GERD | 1 | 1.1 |
| 11 | Cardiac + Depression | 1 | 1.1 |
| 12 | Cardiac + OSA | 1 | 1.1 |
| 13 | Cardiac+ Metabolic + Depression | 1 | 1.1 |
| 14 | Cardiac + Metabolic + Bronchiectasis | 2 | 2.3 |
| 15 | GERD + Depression | 2 | 2.3 |
| 16 | GERD + OSA | 1 | 1.1 |
| 17 | Osteoporosis + Depression | 1 | 1.1 |
| | TOTAL | 88 | 100.0 |

## DISCUSSION

Co morbidities often coexist with COPD that may have a significant impact on disease course. Co-morbidities like cardiovascular diseases are common in COPD.[1] In our study majority of the patients with COPD had co morbidities n=88/159 (55.3%). Most prevalent co-morbidity with single organ affection was cardiac {n=35/88 (39.8%)}. Amongst cardiac, hypertension and congestive heart failure (CHF) was the commonest (n=19/49; 38.8% each) followed by CAD/CSA/IWMI/IHD/AF (n=11/49; 22.4%). Similar were the findings of R.W. Dal Negro et al. (2015), where the predominant co-morbidity in the whole sample (n=3,198) were cardio-vascular 39%.[13] Another study done by Vinay Mahi shale et al. (2015) was hospital based cross sectional study, showed that the prevalence of HTN, DM and CVD in the 2432 COPD subjects was 37.25%, 25.94%, and 13.93%, respectively.[14]

Metabolic co-morbidity (n=14/159; 8.81%) was the next most common co morbidity in our study, while R.W. Dal Negro et al. (2015) reported 10.4% metabolic co-morbidity.[13] The prevalence of bronchiectasis in our study was (n=5; 3.15%). These patients were in GOLD stage III & IV. While in the study done by Gunaseelan.G.et al (May 2017) the prevalence reported was 34.7 % more commonly in GOLD Stage IV.[15] Authors found less number of patients of bronchiectasis may be because authors excluded more severe patients who could not perform spirometry which was essential criteria to make a COPD diagnosis.

This is also one of the limitations of the study. Authors found lesser number of osteoporosis (n=8/159, 5.03%) patients in comparison to the other studies such as Jorgensen NR et al. (2006), Hatthiholi J et al (2014), Bhat SA et al. (2017), where the prevalence was 44.8%, 66.6 % and (27% to 65%, as per site specific data) respectively.[16-18] Amongst 8 osteoporotic patients, n=2/21, 9.52% were female, while male was n=6/138, 4.34%. This finding was similar to other abovementioned studies where osteoporosis was more common amongst females in comparison to male COPD patients.

In our study co morbid depression was (n=11, 6.92%) which was lesser in comparison to study done by Chaudhary SC et al. 19 (28.4%) and Tian Xiao et al 20 (13.8%). Authors diagnosed depression on the basis of questionnaire/symptoms, while other studies done by Chaudhary SC et al., Tian Xiao et al were based on the Hospital Anxiety and Depression Scale (HAD) and EQ-5D visual analogue (EQ-5Dvas) to evaluate their mental health and quality of life.[19,20] GERD in our study was (n=13/159, 8.18%) comparable to 8.6% reported by R.W. Dal Negro et al. (2015), while Serhat Bor et al (2007) reported 16.3 % amongst COPD patients.[13,21] This difference in numbers may be due to different definitions used, where Serhat Bor et al defined 'Frequent symptoms', defined as GERD, as a major symptom

(heartburn and/or regurgitation), which occurred at least once a week or commonly, while in our study the mean duration of heart burn taken was minimum three weeks and improvement of symptoms after taking oral proton pump inhibitors were considered.

Obstructive sleep apnoea (OSA) was reported in n=3 COPD patients. This was based on screening the patients with STOP BANG criteria 12 and thereafter if the score was more than 3, these patients were subjected to polysomnography (PSG). Authors could not perform PSG in all COPD patients. Whereas Greenberg-Dotan S et al showed 7.6% prevalence of OSA with COPD based on PSG (AHI index >5), Soler X et al. (2015) reported 66.9%. 6 (3.8 %) patients of lung cancer were diagnosed in our study.[22,23] Majority were n=5/159 (3.14%) squamous cell carcinoma and 1 (0.62%) was adenocarcinoma. So, our study showed that squamous cell carcinoma is more common in COPD and in advanced age, which was also showed by previous study.[24]

Overall in our study the spectrum of different co-morbidities is less in number than the previous studies. The reasons may be small sample size and indoor patients who were critically ill, who could not perform the spirometry, were excluded.

## CONCLUSION

Urban indwelling, advancing age and duration of illness, presentation with low mood, loss of pleasure/interest, appetite disturbances and heart burn with relief on taking proton pump inhibitor (PPI) can be predictors of co-morbidities in COPD patients. Chance of finding co-morbidities may be multifactorial. Most common co-morbidity is cardiovascular specially CHF and HTN and least prevalent co-morbidity is OSA. Larger scale studies are required to decode many more unanswered facts about co-morbidities amongst COPD patients.

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