Original Article

Chronic obstructive pulmonary disease: Does gender really matter?

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ABSTRACT

Background: Limited data is available on the clinical expression of chronic obstructive pulmonary disease (COPD) from India. The impact of gender on expression of COPD has received even less attention. Apart from tobacco smoke, indoor air pollution, especially from biomass fuel may play an important role in development of COPD in women. **Materials and Methods:** Seven hundred and two patients of COPD were studied regarding the etiological and risk factors leading to COPD, gender-related differences in clinical presentation, radiological expression of COPD and the co-morbidities in COPD. **Results:** Tobacco smoke in the form of *beedi* smoking was the predominant smoke exposure in males, whereas smoke from biofuel burning was the predominant exposure in females. As compared to males, females were younger, reported more dyspnea, more severe bronchial obstruction, more exacerbations, and exhibited higher prevalence of systemic features. Also, females smoked less and had lesser incidence of productive cough, lower body mass index, lesser co-morbidities and less number of hospital admissions as compared to males. Males were more likely than females to have an emphysema-predominant phenotype, while airway-predominant disease was more common among females. **Conclusion:** The current study shows that gender-related differences do exist in COPD patients. Understanding these differences in etiological agent and clinical picture will help early diagnosis of COPD in females.

KEY WORDS: Biomass fuel, chronic obstructive pulmonary disease, gender, indoor pollution, smoking

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INTRODUCTION

By 2030, chronic obstructive pulmonary disease (COPD) will be the third most frequent cause of death in the world.[1] The influence of gender on the expression of COPD has received limited attention.

Silverman *et al* [2] indicated that women may be more susceptible to tobacco smoke than men and more likely to develop early-onset COPD. Also, the prevalence of women smokers in developing countries is predicted to rise to 20% by 2025.[3]

Indoor air pollution due to the use of unprocessed solid fuels such as coal and biomass (dung, crop residues, and wood) for cooking and space heating has been implicated as an important risk factor for the development of COPD. [4,5] About >71% of households in India use such fuels, and studies on characteristics of women with COPD exposed to biomass smoke and the degree to which they differ from COPD in men (mainly due to tobacco smoking) from Indian context are missing.

The prevailing notion that COPD primarily affects men may put women at particular risk of under-diagnosis.[6] In the general population, it has been reported that females report dyspnoea and cough more frequently and phlegm less often than males.[7]

Although airflow obstruction is the hallmark of COPD, this can develop on the basis of airways disease, emphysema, or both. Dransfield *et al* (2007) [8] had reported variability in obstruction/ emphysema in very severe cases of COPD and gender-related changes in lung parenchyma on high-resolution computed tomography (HRCT).

Women have been under-represented in many clinical

trials, which may result in inadequate diagnosis and suboptimal management.

Also, the impact of gender on the development of comorbidities (such as cardiac disease, diabetes mellitus, hypertension, osteoporosis, etc) in relation to COPD is not known.

Thus, despite multiple investigations it is difficult to draw final conclusion on the impact of gender on COPD. Also, there is paucity of these data from Indian scenario.

AIMS AND OBJECTIVES

To study the etiological and risk factors leading to COPD, gender-related differences in clinical presentation, radiological expression of COPD, and the co-morbidities in COPD.

MATERIALS AND METHODS

The study was carried out during 2008-2009 period on 702 patients of COPD, diagnosed by global initiative against obstructive lung diseases (GOLD) guidelines.[9]

Patients with COPD symptoms, i.e., dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease and, forced expiratory volume in 1st second/forced vital capacity (FEV$_1$/FVC) ≤ 70% on spirometry, FEV$_1$ ≤80% predicted normal, an increase of less than 12% or 200 ml of FEV$_1$ after bronchodilator reversibility testing on spirometry, were included.

Patients with history of asthma or FEV$_1$ increased more than 12% and 200 ml after bronchodilatation, patients not willing to be evaluated, patients with active pulmonary tuberculosis (due to the effect of active tuberculosis on the symptoms and signs of the patients), and other significant extra pulmonary diseases that can influence the results of the study, were excluded.

Patients were interviewed regarding symptoms, patient's exposure to risk factors, occupation, past medical history, family history of COPD or other chronic respiratory disease, history of exacerbations or previous hospitalizations for respiratory disorder, and presence of complications and co-morbidities.

All the patients were subjected to spirometric evaluation and measurements were evaluated by comparison with reference values based on age, height, sex, and race. Bronchodilator reversibility testing was done using drug protocols given in GOLD (2007)[9] guidelines.

Chest X-ray posteroanterior view was done in all patients to see for radiological changes associated with COPD, i.e., signs of hyperinflation, hyperlucency of the lungs, and rapid tapering of the vascular markings.[9] Chest X-ray

was also used to evaluate the severity and for detecting co-morbidities and complications present.

Based on clinical suspicion and chest radiograph findings, patients were subjected to computed tomography (CT) of the chest, if required, to evaluate the presence of complications and/or co-morbidities such as bronchiectasis, carcinoma lung, pneumonia, pneumothorax, and pulmonary embolism.

Arterial blood gas analysis was done in patients with severe disease or if clinical suspicion of respiratory failure was noted.

Appropriate standard tests were performed to look for or exclude the presence of co-morbidities/complications like diabetes mellitus, anemia, osteoporosis, rheumatoid arthritis, obstructive sleep apnea etc.

The data collected were analyzed by using GraphPad InStat computer software. Chi Square and Student *t* test and proportion tests were applied for statistical significance.

OBSERVATIONS

The study included 702 patients of COPD of which 493 (70.2%) were males and 209 (29.8%) females. Table 1 shows the general characteristics of the patients. The mean age of the patients was 60.61 ± 10.36 years. All the patients complained of dyspnea of varying grades. About 49.1% patients presented at grade 2 dyspnea. Other common symptoms reported by patients were cough (96%), fever (35.3%), edema feet (12.8%), chest pain (7.7%), anorexia (5.3%), abdominal pain (4.8%), body ache (4.1%), and hemoptysis (2.7%).

Average body mass index (BMI) of the patients was 18.36 ± 3.02. Females had lower BMI than males (17.53 ± 2.8 v/s 18.68 ± 3.05, $P < 0.001$). Also low BMI was found to be associated with more exacerbations, especially in females and statistically significant lower FEV$_1$ values on spirometry ($P < 0.001$).

About 66.1% patients (313 males and 151 females) had exacerbations, which did not lead to admission. Out of the 313 males, 65.8% males had 0-1 such exacerbations. Out of 151 females, 53.6% had 0-1 such exacerbations. About 33.9% patients had history of hospitalization, with majority 53.8% had history of one such episode. Average duration of hospital stay was 6.6 ± 2.9 days. Among the males, heart failure was noted in 25%, pneumonia in 12.8%, pneumothorax in 5.6%, and pulmonary embolism in 1.1% at the time of hospitalization. In females, 17.2% had heart failure, 12.2% had pneumonia and 1.7% had pneumothorax at the time of hospitalization.

As shown in Table 2, about 84.8% males smoked *beedi*, 11.8% smoked cigarette, and 1.8% smoked tobacco in

Table 1: General characteristics and symptoms

Characteristics	Male (*n*=493)	Female (*n*=209)	*P* value
Mean age (years)	61.57 ± 10.37	58.34 ± 9.99	$P < 0.001$
Mean BMI	18.68 ± 3.05	17.53 ± 2.8	$P < 0.001$
MMRC dyspnea grade (percentage)			
0-2	72.8	47.4	$P < 0.001$
3-4	27.2	52.6	
Other symptoms (percentage)			
Cough	96.6	94.7	ns
Expectoration	80.7	71.3	$P = 0.016$
Fever	34.3	37.8	ns
Edema feet	12.8	12.9	ns
Systemic features of COPD (percentage)			
Cachexia	44.8	70.3	$P = 0.0006$
Skeletal muscle wasting	10.1	19.1	$P = 0.002$

ns: Not signficant

Table 2: FEV_1, type of smoke exposure and radiological findings

Characteristics	Male (*n*=493)	Female (*n*=209)	*P* value
FEV_1 % of predicted	48.42 ± 14.52	43.39 ± 13.28	$P < 0.001$
Pack-years smoking	36.7 ± 15.5	13.5 ± 7.4	$P < 0.001$
Type of smoke exposure (percentage)			
Beedi	84.8	51.2	$P < 0.0001$
Cigarette	11.8	0.5	$P = 0.0050$
Biomass smoke (chula)	0.2	89	$P < 0.0001$
Non smoker	6.3	48.3	$P < 0.0001$
Radiology (percentage)			
Hyperinflation	89.5	71.3	$P < 0.001$
Increased bronchovascular markings (BVM)	32	62.7	$P < 0.001$
Tubular heart	31	18.2	$P < 0.001$
Low Placed diaphragm	81.7	60.3	$P < 0.001$
Presence of bullae	61.9	35.9	$P < 0.001$

Table 3: Co-morbidities and Complications

Characteristics	Male (*n*= 493)	Female (*n*= 209)	*P* value
Co-morbidities (percentage)			
Presence of atleast one co-morbidity (%)	62.9	49.8	$P = 0.0014$
Past History of PTB	28.4	29.7	ns
Carcinoma lung	12	4.3	$P = 0.003$
Cardiovascular disease	19.3	11	$P = 0.010$
Acid peptic disease, Gastro-esophageal reflux disease	18.1	7.2	$P = 0.0001$
Diabetes mellitus	3	3.3	ns
Others – hemorrhoids, hernia, rheumatoid arthritis, other cancers etc	4.9	3.3	ns
Complications			
PaO2 (mmHg)	55.71 ± 15.98	49.95 ± 14.31	ns
PaCO2 (mmHg)	51.68 ± 13.08	53.59 ± 12.55	ns
Right heart failure	18.7	16.6	ns
Pneumonia	10.8	8.6	ns
Bronchiectasis	9.8	6.2	ns
Pneumothorax	4.1	1.4	ns
Pulmonary embolism	0.4	0	ns

ns: Not signficant

form of hookah and/or chillum. Also 89% of females had exposure to chula (biomass smoke). Most (68%) of these female patients used wood, rest 32% also used dung (kanda), grass, leaves, etc. Wood was used for cooking purposes and rest of the material for other purposes like heating water. Significant proportion, i.e., 42.1% females had exposure to both chula and tobacco smoke.

On chest X-ray, males had more prevalence of hyperinflation (89.5% v/s 71.3%, respectively, $P<0.001$). Typical tubular heart was seen in 31% males as compared to 18.2% females. Presence of bullae was noted more frequently in males (61.9%) than females (35.9%). Basal bullae were observed more frequently than apical bullae (56.2% v/s 28.2% in males and 29.2% v/s 11.5% in females).

Mean FEV_1 of the patients was 46.93 ± 14.32 of the predicted. Females had considerably lower FEV_1 values as compared to males (mean FEV_1 of 43.39 ± 13.28 in females v/s 48.42 ± 14.52 in males). Among the non-smoking population, females showed more severe obstruction as compared to males (mean FEV_1 of 45 ± 13.3 v/s 48.5 ± 17.1, respectively). Among the smokers, the mean FEV_1 of

females was even lower, i.e., 41.9 ± 13.2 as compared to males (48.4 ± 14.3).

Table 3 shows the prevalence of co-morbidities and complications. The most common co-morbid conditions observed were acid peptic disease/ gastro-esophageal reflux disease, carcinoma lung, and cardiovascular diseases like ischemic heart disease, systemic hypertension, pulmonary arterial hypertension, arrhythmias, etc. Males had higher prevalence of carcinoma lung ($P = 0.003$), cardiovascular diseases ($P = 0.01$), and acid peptic disease/gastro-esophageal reflux disease ($P = 0.0002$) as compared to females. Presence of diabetes was noted in 3.1% patients. About 4.4% patients had other associated diseases like silicosis, carcinoma esophagus, carcinoma breast, oral cancer, alcoholic liver disease, hyperthyroidism, obstructive sleep apnea, hernia, etc. Around 28.8% patients had history of pulmonary tuberculosis in past. These patients had pulmonary tuberculosis 29.1 ± 8.8 years earlier.

Right heart failure, pneumonia, bronchiectasis and pneumothorax were most common complications noted.

DISCUSSION

Females were found to be younger as compared to males (mean age 58.34 ± 9.99 years v/s 61.57 ± 10.37 years, $P < 0.001$). This could be because biomass smoke exposure begins early in females who start cooking using wood stoves at a very early age and also, sleep and eat in the same room where they cook.

Males smoked more than females (mean pack year smoking of 36.7 ± 15.5 v/s 13.5 ± 7.4, $P < 0.001$) and majority male smokers (93.7%), smoked *beedi*. Jindal *et al* (2006)[10]

indicated a higher prevalence of COPD among *beedi* smokers than cigarette smokers (8.2% v/s 5.9%).

Some 186 (89%) females were exposed to smoke from biomass burning. This biomass smoke has been proposed to produce pathologic changes of COPD similar to those observed in cigarette smokers by Rivera *et al* (2008).[11] Also, several researchers have reported prevalence of COPD/chronic bronchitis in people exposed to biomass smoke especially from wood and cow dung.[12-16]

Patients exposed to both biomass smoke and tobacco smoke had the worst FEV_1 scores of 42.39 ± 12.43. This combined exposure is suspected to have an additive effect,[15] probably leading to increased severity of the obstructive airway disease.

The average duration of exposure to biomass smoke in the female patients was around 29 ± 8 years. The average daily time spent in the kitchen was around 8-10 hours. Studies have shown that the risk of airflow obstruction increases with increasing hour-years exposure of biomass smoke.[17,18] The exact hour-year exposure was not calculated, but a similar trend was noted in the current study.

In comparison to males, females reported more dyspnea at presentation (grade 3 v/s grade 2, $P < 0.001$). This could be due to females displaying more bronchial obstruction than males (mean FEV_1 of 43.39 ± 13.28 v/s 48.42 ± 14.52, respectively, $P < 0.001$). This could also be related to the increased susceptibility of Indian females to etiological agents (tobacco and biomass smoke) or delay in the diagnosis of COPD in females at primary health care level and/or late referral to a tertiary care hospital (which may be due to knowledge gap regarding COPD in females and/or less use of spirometry to diagnose or grade COPD severity).

The lower mean FEV_1 values of the patients as compared to their western counterparts,[8,19] could be due to increased susceptibility of the Indian patients to tobacco smoke or increased toxic effects of *beedi* smoking. A recent study has demonstrated this fact that pulmonary functions are more affected in *beedi* smokers than in cigarette smokers.[20]

FEV_1 values in female patients who smoked were considerably lower than those observed in nonsmoker females (mean FEV_1 of 41.9 ± 13.2 and 45 ± 13.3, respectively). This difference in males was not significant. This may imply that smoking disproportionately affects females than males.[21]

Females had more exacerbations than males, but had relatively lesser number of hospital admissions in the preceding year. This may imply that even though females have more symptomatic exacerbations of the disease that requires medical attention; they receive fewer specialist referrals than males due to ignorance or gender bias that exists in availing the hospital facilities or simply these exacerbations were not severe enough to require hospital admission.

Males had more prevalence of emphysema seen on chest radiograph as compared to females. Females were more likely to have "increased markings" pattern (that resembles the "dirty chest" appearance seen in chronic bronchitis) than males (62% v/s 32% respectively, $P < 0.001$). These findings are similar to that reported by various researchers that male smokers with COPD have more extensive emphysema than women.[8,22,23] Also, about 90% of the females in the current study had exposure to biomass smoke, which has been described as the predisposing factor for development of chronic bronchitis.[15,16,24,25]

Contrary to the previous data, no association was found in the occurrence of pneumonia and type of inhaled corticosteroid used (budesonide v/s fluticasone). No significant difference was observed between males and females with regard to presence of complications such as pneumonia, right heart failure, pneumothorax, pulmonary embolism, etc.

Presence of atleast one co-morbid conditions was noted in 310 (62.9%) males and 104 (49.8%) females ($P = 0.0014$). More than 55% patients had 1-2 co-morbid conditions, and 3% had 3-4 co-morbid conditions. The lesser number of co-morbidities than reported by Van Manen and colleagues[26] could be due to the fact that we studied only a limited number of such conditions.

Anemia (associated with higher morbidity and mortality in COPD) was seen more commonly in females as compared to males (23.4% and 10.1%, respectively, $P < 0.0001$). Potential explanations could be malnutrition, particularly poor dietary intake of iron, increased blood loss during menstruation/child birth, or due use of oral steroids.

Higher prevalence of carcinoma lung and cardiovascular diseases in males could be attributed to the fact that smoking is a common risk factor for them and there were more number of male who smoked with heavier smoking history than females. Also, alcohol consumption and smoking are associated with increased incidence of acid peptic disease, both of which were more common in males.

Cachexia, skeletal muscle wasting and depression were noted more in females as compared to males, probably displaying a severe expression of COPD in females. This also stresses on the fact to look for these systemic features, more so in females so as to offer the patient a less morbid life.

Chronic airway obstruction occurs following tuberculosis[27-29] and is reported to be functionally comparable to COPD patients.[27] In the current study, past history of pulmonary tuberculosis (TB) was noted in 28.8% of the cases (similar to a recent study from India,[30] which reported the prevalence to be 28.4% in the COPD patients). These patients with COPD post-TB were younger as compared to COPD patients with no past history of TB (mean age of 59 ± 9 years and 61 ± 10 years, respectively,

$P = 0.01$). On spirometry, patients with COPD post-TB had FEV_1 values better than the other group (mean FEV_1 of 48 ± 14 and 46 ± 14, respectively, $P = 0.02$).

Since women tend to have untreated or delayed treatment of TB due to prevailing socio-cultural systems,[5] cases due to COPD post-tuberculosis may see a rise in future specially in females. Larger field based studies are needed to further define this fact.

Thus, in comparison to males, females were younger, reported more dyspnea, more severe bronchial obstruction, more exacerbations and higher prevalence of systemic features. Also, females smoked less and had lesser incidence of productive cough, lower BMI, lesser co-morbidities and less number of hospital admissions as compared to males. Tobacco smoke in the form of *beedi* smoking was the predominant smoke exposure in males, whereas smoke from biofuel burning was the predominant exposure in females. Males were more likely than females to have an emphysema-predominant phenotype, while airway-predominant disease was more common among females.

To conclude, there are several gaps in the current knowledge regarding COPD in women. There is an urgent need for larger cohort or population studies with a significant number of women exclusively designed to evaluate the effect of gender on the clinical manifestations of COPD and the response to treatment.

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