

# Clinical, demographic and radiological profile of smoker COPD versus nonsmoker COPD patients at a tertiary care center in North India

Jyoti Bajpai<sup>1</sup>, Surya Kant<sup>1</sup>, Darshan K. Bajaj<sup>1</sup>, Akshyaya Pradhan<sup>2</sup>,  
Kanchan Srivastava<sup>1</sup>, Akhilesh K. Pandey<sup>3</sup>

Departments of <sup>1</sup>Respiratory Medicine and <sup>2</sup>Cardiology, King George's Medical University, Lucknow, Uttar Pradesh,  
<sup>3</sup>Department of Community Medicine, Manipal University, Madhav Nagar, Manipal, Karnataka, India

## ABSTRACT

**Introduction:** Cigarette smoking is the most predominant risk factor for development of chronic obstructive pulmonary disease (COPD). However, a considerable amount of patients do develop COPD without exposure to cigarette smoking. We aimed to analyze the incidence, demographic and clinical profile of nonsmoker COPD subjects at a tertiary care center. **Methods:** In this prospective observational study, 410 patients were screened for dyspnea. On the basis of spirometry findings, 360 patients were diagnosed as COPD and enrolled into the study. Patients were categorized into 2 groups on the basis of smoking habits (smoker and nonsmoker COPD). Clinical and demographic attributes were compared in between these two groups. This study was conducted over a period of one year, from August 2014 to July 2015. All statistical analyses were performed using Statistical Package for the Social Sciences version 19.0 (SPSS Inc, Chicago, IL, USA). Values were considered to be statistically significant at  $P < 0.05$ . **Results:** Out of 360 COPD cases, about 2/3<sup>rd</sup> (60%) were smokers and the rest nonsmokers. Majority of the patients were in the age group of 51-70 years. The mean age of smokers with COPD was significantly higher than nonsmokers with COPD ( $59.29 \pm 10.28$  years vs.  $53.90 \pm 8.77$  years;  $P = 0.0001$ ). Overall, males were predominant (57.2%) but there were higher number of female patients in nonsmoker group (25% vs. 70%;  $P = 0.001$ ). At presentation, majority of nonsmoker with COPD were in GOLD severity grade II while in the smoking cohort majority were in GOLD severity Grade III. Among the 144 nonsmoker COPD patients, the most important and statistically significant risk factor was exposure to biomass smoke (68.06%). Other risk factors were long-standing asthma (37.50%), lower respiratory tract infection in childhood (32.60%), exposure to outdoor air pollution (17.92%). **Conclusion:** Nonsmoker COPD is emerging as a distinctive phenotype. They have less impairment in airflow limitation, and a lower prevalence of emphysema, chronic cough, and sputum compared with their smoking counterparts.

**Keywords:** Biomass fuel exposure, chronic obstructive pulmonary disease, nonsmoker, smoker, spirometry

## Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide.<sup>[1]</sup> Cigarette smoking is the most common risk factor to cause

COPD.<sup>[2]</sup> It is characterized by chronic inflammation and irreversible airflow obstruction, leading to structural changes in the lung.<sup>[3]</sup> Previously, most of the studies on COPD mainly focused on smoking as a risk factor but recent studies showed that nonsmokers also contribute a significant proportion of COPD. About 50% cases of COPD worldwide are related to smoking, and an estimated 10%-12% of individuals with COPD have never smoked.<sup>[4]</sup>

**Address for correspondence:** Prof. Surya Kant,  
Department of Respiratory Medicine, King George's Medical  
University, Lucknow, Uttar Pradesh, India.  
E-mail: skantpulmed@gmail.com

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The burden of COPD in nonsmoker is higher than previously believed in both developed and developing countries.<sup>[4]</sup> In addition to tobacco smoking, exposure to biomass and occupational dusts/gases/fumes, pulmonary problems in childhood, family history of respiratory disease, poor socioeconomic status, aging, lower body mass index (BMI), poor ventilation in the kitchen, age, and genetic susceptibility are other risk factors for COPD.<sup>[5]</sup>

The landmark study on COPD by Fletcher *et al.* excluded non-smokers, and thus no information was provided for subjects without a history of smoking but with chronic irreversible airflow obstruction.<sup>[6]</sup> Participants in clinical trials are also limited to smokers with COPD. Therefore, little is known about the clinical features of non-smokers with COPD or their differences and similarities compared with smokers who have COPD in Indian scenario.

The present study was conducted to find out the proportion of nonsmoker individuals among COPD patients and to determine various risk factors in nonsmoker COPD patients.

## Methods

The study was conducted in the Department of Pulmonary Medicine, over a period of 2 years, from August 2014 to July 2016. It was a prospective and observational cross-sectional study.

A consecutive of 410 patients aged >18 years and visiting outpatient setting with a clinical presentation suggestive of COPD, were screened for the study. Based on spirometry findings, 360 patient diagnosed to be COPD (as per GOLD guideline) were included in the study. An FEV1/FVC <0.70 was taken as the diagnostic criterion for COPD. All the patients qualifying inclusion criterion were explained in detail about the study and the procedures involved. Informed consent was duly taken. Patients with significant comorbidities like heart failure, prior myocardial infarction, chronic renal disease and hepatic failure were excluded.

## Methods

A detailed history was taken about symptoms such as a cough, expectoration, breathlessness, fever, and chest pain. Clinical examination and relevant investigations were done including chest radiograph in PA (postero-anterior) view, sputum acid-fast bacilli stain, and spirometry. Further, patients were subjected face to face interviewed for determining the history of exposure to various types of risk factors for COPD. The various risk factor of COPD taken into consideration were biomass fuel exposure, outdoor air pollution, history of childhood asthma and past history of treatment for tubercular infection. The duration (in years) and type of exposure (active or passive) was also noted.

## Sample size calculation

Prevalence formula was used to determine the sample size. We took 36% prevalence of nonsmokers among COPD. With 95%

significance level and 5% absolute precision, calculated sample size would be 354 COPD patients.

## Statistical analysis

The results are expressed as the mean  $\pm$  standard deviation and percentages. All statistical analyses were performed using Statistical Package for the Social Sciences version 19.0 (SPSS Inc, Chicago, IL, USA). Values were considered to be statistically significant at  $P < 0.05$ . The Chi-square test was used to compare the categorical variables. The unpaired *t*-test was used to compare two discrete variables. The one-way analysis of variance was used to compare more than two discrete variables.

## Results

A total of 360 COPD patients were included in the study, and they were classified into 2 groups – smoker (216) and nonsmoker (144), on the basis of history of smoking. The proportion of nonsmoker individuals (40%) among total COPD patients was found to be lower than smokers (60%).

## Demographic variables

Majority of the patients were in the age group of 51-70 years [Table 1]. However, there was a significant difference in age distribution between smoker and nonsmokers. The mean age of smokers with COPD was significantly higher than nonsmokers with COPD ( $59.29 \pm 10.28$  years vs.  $53.90 \pm 8.77$  years;  $P = 0.0001$ ). Overall, in our study males were predominant (57.2%) but there were higher number of female patients in nonsmoker group (25% vs. 70%;  $P = 0.001$ ; Figures 1 and 2). The mean pack years of smokers was  $17.56 \pm 13.83$  (median = 15). The majority of smokers (47.3%) had smoking index in between range of (100-500).

## Clinical symptoms

There was significant difference in symptom distribution between smoker and nonsmokers COPD [Table 2;  $P = 0.001$ ]. Chronic cough was the most common presenting symptom in nonsmokers with COPD, followed by breathlessness. This was in contrast to the smoker group where effort breathlessness was the predominant feature in COPD followed by cough and pedal edema.

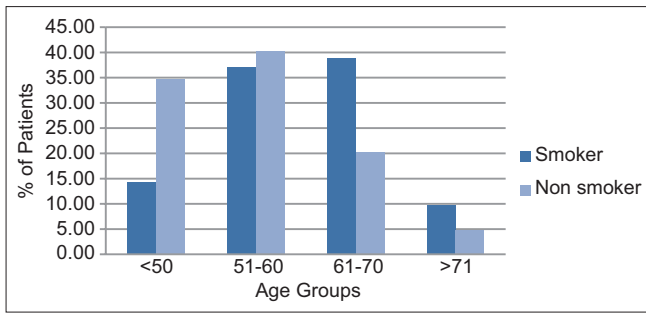
## Radiology and pulmonary function analysis

Radiological abnormalities such as Emphysema and hyperinflation were significantly more prevalent in Smokers vis-à-vis

**Table 1: Comparison of Age distribution between Study Groups**

	Smoker (n=216) no. (%)	Nonsmoker (n=144) no. (%)	P
<50	31 (14.35)	50 (34.72)	<0.00001*
51-60	80 (37.04)	58 (40.28)	
61-70	84 (38.89)	29 (20.14)	
>71	21 (9.72)	7 (4.86)	
Mean $\pm$ SD	59.29 $\pm$ 10.28	53.90 $\pm$ 8.77	0.0001

\*The Chi square statistic is 28.4729 the  $P=0.0001$ . The result is significant at  $P<0.005$



**Figure 1:** Distribution of age among smoker versus nonsmoker with COPD

nonsmokers (65.7% vs 49.3%;  $p=0.0015$ ). Normal chest radiology was observed slightly more frequently in nonsmokers (23% vs. 20%;  $P = 0.0015$ ). There was also a significant difference in spirometry parameters were significantly different. The mean FEV1 and FVC values were significantly higher in Nonsmoker versus smoker [Table 3]. As a corollary, the FEV1/FVC ratio was significantly higher in nonsmokers compared to active smokers ( $68.8 \pm 3.7$  vs.  $61.8 \pm 5.7$ ;  $P = 0.0001$ ).

### Biochemical parameters

Mean Hemoglobin values were significantly lower in nonsmokers with COPD as compared to the smoker group. Absolute eosinophil counts were higher in COPD patients who were nonsmoker versus those who were smokers ( $346 \pm 141.3$  cells per microliter vs.  $226 \pm 132.6$  cells per microliter;  $P = 0.0001$ ). On the other hand, total leucocyte counts were significantly higher in smokers with COPD as compared to nonsmokers afflicted with the disease.

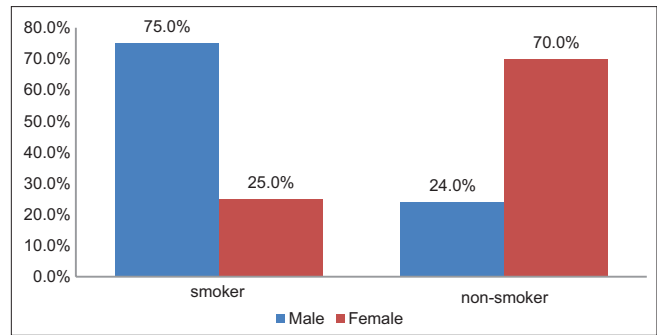
### Disease severity

Of note, majority (56.94%) of nonsmoker COPD patients had moderate disease (GOLD grade II), while among smokers majority (43.5%) were in severe disease (GOLD Grade III) [Table 4 and Figure 3]. Hence, almost 3/4<sup>th</sup> of smokers with COPD were in higher GOLD grades (III/IV) compared to only one-third of nonsmokers with COPD. Hence, more than three fourth (78.7%) of smoker COPD had advanced COPD (grade III/IV) as compared to nonsmoker, where only 33.3% had advanced disease.

### Risk factors

Among 144 nonsmoker COPD patients, the most important and statistically significant risk factor was exposure to biomass smoke (68.06%). Other significant risk factors were long-standing asthma (37.50%), lower respiratory tract infection in childhood (32.60%) and exposure to outdoor air pollution (17.92%). Nonsmokers COPD had higher exposure to biomass fuels, history of long standing asthma and lower respiratory infections while they had lesser risk of outdoor pollution.

History of pulmonary tuberculosis (TB) was found in 32.74% of nonsmoker COPD patients, which was found to be a statistically significant ( $P = 0.0001$ ) risk factor for development



**Figure 2:** Gender distribution of the smoker and nonsmoker. The Chi-square statistic is 62.1032. The  $P$  value is  $< 0.00001$

**Table 2: Comparison of predominant Symptoms between smoker and non Smoker with COPD**

Symptoms	Smoker (n=216) No. (%)	Non smoker (n=144) No (%)	P*
Cough	30 (14)	75 (52)	0.0001
Breathlessness	116 (54)	44 (31)	
Pedal edema	30 (14)	10 (7)	
Fever	20 (9)	10 (7)	
Chest tightness	20 (9)	5 (3)	

\*The Chi-square statistic is 62.1032

**Table 3: Comparison of Spirometry indices between smoker and non smoker with COPD**

Spirometry indices	Smoker COPD (n=216)	Non Smoker COPD (n=144)	P
FEV1 (L)	$1.64 \pm 0.533$	$1.79 \pm 0.642$	0.0165
FVC (L)	$2.12 \pm 0.422$	$2.90 \pm 0.764$	0.0001
FEV1/FVC	$61.8 \pm 5.7$	$68.8 \pm 3.7$	0.0001

**Table 4: Distribution of GOLD class among the smoker and non-smoker COPD**

GOLD class	Smoker COPD (n=216) no	%	Non Smoker COPD (n=144) no	%	P
I	22	10.19	14	9.72	$< 0.00001$
II	24	11.11	82	56.94	
III	94	43.52	33	22.92	
IV	76	35.19	15	10.42	
	216	100	144	100	

The Chi-square statistic is 93.0239. The  $P < 0.00001$

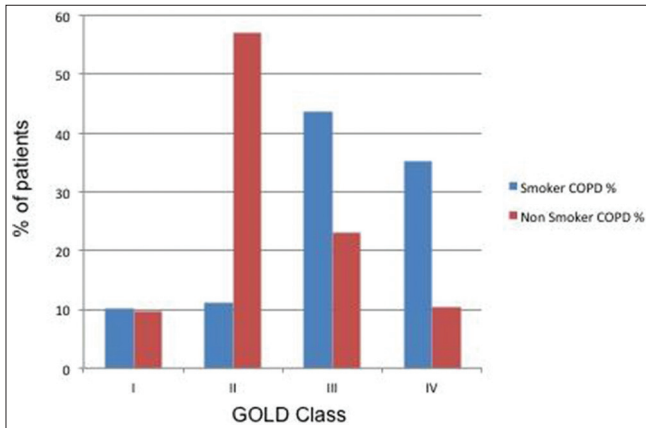
of COPD. Long standing asthma as a risk factor for COPD was found in 37.5% of patients of nonsmoker COPD group, which was statistically significant ( $P = 0.00001$ ) risk factor for the development of COPD [Table 5]. Although, the number of treated pulmonary TB patients were higher in nonsmokers, the values did not reach statistical significance. Similarly, the higher occupational exposure in smokers was not statistically important.

## Discussion

Nonsmoker COPD is an emerging sub group and has been gaining much attention of late. There is a wide variation

**Table 5: Distribution of risk factors in study population**

Risk Factors	No of Smoker COPD (n=216)	%	No of Non Smoker COPD (n=144)	%	Chi square	P
Exposure to biomass smoke	25	11.57	98	68.06	122.54	<0.00001
Exposure to outdoor air pollution	75	34.72	21	14.58	17.92	0.000023
Occupational exposure (factory worker)	20	9.26	10	6.94	0.61	0.436275
Treated pulmonary tuberculosis	45	20.83	40	27.78	2.31	0.128531
Long standing asthma >1 years	15	6.94	54	37.50	52.07	<0.00001
Lowerrespiratory tractinfection during childhood	10	4.63	47	32.64	50.86	<0.00001



**Figure 3:** Distribution of GOLD class among the smoker and nonsmoker patients with COPD

(9.4–68.6%) in proportion of nonsmokers among total COPD cohort in literature from India.<sup>[7]</sup> We found the proportion of nonsmoker COPD patients among total COPD patients cohort to be 40%. Ehrlich *et al.*<sup>[7]</sup> reported that nonsmokers made up 47.6% of patients with airway obstruction among 13826 adults in South Africa aged more than 18 years. A similar result was found by Brashier *et al.*<sup>[8]</sup> who stated that proportion of COPD patients who never smoked among 12055 participants above 45 years in India was 68.6%. However In these studies, a respiratory symptom questionnaire was used to define airway obstruction whereas we used spirometry to diagnose COPD. This must add strength to our study.

Nonsmokers with COPD patients had certain distinctive features as a class vis-à-vis the smoking group. Although, in the overall COPD cohort, the female representation was only 27.7%, there was a female preponderance (70%) in Non Smoker COPD subset. This suggests that the contribution of environmental exposures other than active smoking leading to COPD seems more substantial in females than in males. Indeed, our data confirm that one of these environmental exposures, namely biomass exposure, is higher in females than in males.<sup>[9,10]</sup> Likewise, more evidence is emerging on the increasing occurrence of COPD in nonsmoking individuals, especially in females.

Nonsmoker COPD patients also had significant higher prevalence of cough than the smoker COPD patients. In contrast, higher number of smokers with COPD had

breathlessness than nonsmokers. Biomass smoke exposure has been shown to be pro-inflammatory.<sup>[11]</sup> Majority of nonsmokers COPD patient have exposure to Biomass fuel which leads to Macrophage dysfunction, increased proteolytic activity of matrix metalloproteinases (MMP); greater gene expression of MMP, pulmonary surfactant deactivation, reduced bacterial clearance; and reduced mucociliary clearance.

Of the total 216 smoker COPD patients, almost 1/3<sup>rd</sup> (34.6%) patients were exposed to outdoor pollution compared to only 15% of nonsmoker COPD. Outdoor air pollution is the most important risk factor among total COPD patients, exposure to biomass smoke was most important (68.06%) and statistically significant ( $P = 0.0001$ ) risk factor for the development of COPD. A similar association has been found in another study from Finland and Sweden.

In India, where more than 70% of people use biomass fuel for cooking in comparison to smoking prevalence which is only 25%, it means exposure to biomass fuel may be a bigger risk factor for COPD in India.<sup>[12]</sup>

In a report from a longitudinal cohort of the Tuscon epidemiological study of airway obstructive disease, adults with asthma were found to have a twelve-fold higher risk of acquiring COPD over time than those without asthma, after adjusting for smoking. Another longitudinal study of people with asthma found that around 20% of subjects developed irreversible airflow limitation and reduced transfer coefficient. This calls for research to elucidate pathogenetic mechanisms of COPD other than smoking. Our study also provides an insight into spirometry data and disease severity among COPD patients who were smoker and who were not. Majority of nonsmoker COPD patients (56.94%) were in GOLD grade II followed by 22.92% in GOLD grade III severity whereas in Smoker COPD patients were in higher gold grade severity class III and IV (78%). These findings coincide with those reported by Zhou *et al.* who studied the prevalence of COPD in Chinese nonsmokers; they found that 38.6% of COPD patients were never smokers.<sup>[13]</sup>

There was also a significant difference in spirometry parameters in between smokers and nonsmokers COPD. The mean FEV1 and FVC values were significantly higher in Nonsmoker versus smoker. As a corollary, the FEV1/FVC ratio was significantly

higher in nonsmokers compared to active smokers ( $68.8 \pm 3.7$  vs.  $61.8 \pm 5.7$ ;  $P = 0.0001$ ). Non-smokers with COPD showed less air flow limitation than smokers with COPD. Tobacco smoking is the main cause of chronic inflammatory process in smokers COPD which induced thickening and narrowing of the small conducting airways, as well as destruction of the parenchyma and reduced alveolar-bronchiolar attachments.<sup>[14,15]</sup> These changes could contribute to more severe expiratory airflow obstruction in smokers with COPD.

Despite the emergence of various COPD phenotypes in literature viz. asthma-COPD overlap, frequent exacerbator, classic emphysema, and chronic bronchitis, the clinical relevance of such a categorization is unclear. Added to the misery, there is lack of consensus on what should be the ideal management approach based on these individual phenotypes.<sup>[16,17]</sup> The study adds to the growing data on distinct characteristics of nonsmoker COPD phenotypes and calls for further research into tailoring therapy for this subgroup.

### Implications for general practice

COPD is a disease which is widely prevalent in our country. Smoking has been the most common risk factor for COPD hitherto, but COPD in nonsmokers is also a reality now. COPD is an important differential diagnosis for patient presenting with dyspnea in primary care both in inpatient as well as outpatient setting alike. History of smoking or exposure to second hand smoke has remained a pivotal clue pointing towards COPD as an aetiology. The arrival of COPD in nonsmokers as a definite entity calls for an alert for the primary care physician to keep COPD in consideration when evaluating dyspnea in nonsmokers also. Our study adds to the growing body of evidence regarding high prevalence nonsmokers among COPD patients. The study calls to attention to importance of various vernacular factors like biomass fuel exposure, recurrent respiratory infection, long standing asthma, pulmonary tuberculosis and indoor air pollution contributing to airway disease in our country contrary to cigarette/bidi smoking. Absence of significant radiological abnormalities and milder severity may lead to a delay in diagnosis unless specifically sought for. Hence, physicians in primary care need to rely on spirometry when COPD is suspected rather than history of cigarette smoking.

### Conclusion

Among patients of COPD presenting to a tertiary care center, a considerable amount were nonsmokers. The nonsmokers with COPD presented earlier and more likely to be females. Exposure to biomass smoke was the most common risk factor in these nonsmokers with COPD. They have less radiological abnormalities and disease severity.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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