Non-smoker COPD represents a clinically Distinct Phenotype: A Prospective Observational Study

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Abstract

Background: Chronic obstructive lung disease (COPD) has been characterized as a smoker’s disease, which has resulted in the usual exclusion of never-smokers from COPD studies. It is now recognized that never-smokers account for nearly one-fourth of all COPD cases, and thus airflow limitation in never-smokers needs further evaluation. Our study aims to elucidate the clinical and physiological aspects of COPD in nonsmokers and to compare smokers and nonsmokers with COPD.

Materials and methods: A total of 200 naïve sequential patients with COPD were recruited. The severity of airflow limitation in COPD patients was defined as per Global Initiative for COPD (GOLD) 2019 criteria, and the severity of breathlessness was assessed by the modified Medical Research Council (MRC) dyspnea scale. Data was collected using a patient pro forma, including risk factors for COPD and detailed clinical history. Phenotypic differences along with biomass exposure between never-smokers and smokers were analyzed.

Results: Compared to smokers, never-smokers presented at a younger age (55.69 ± 11.5 years; p < 0.001), with a longer duration of dyspnea (5.05 ± 4.96 vs 7.35 ± 6.98 years, p < 0.01). Chest radiographs revealed hyperinflation in a higher number of smokers as compared to never-smokers (82.9 vs 64.6%, p < 0.05). On spirometry evaluation, smokers were found to have significantly poorer lung function [forced expiratory volume in first second (FEV1) 40.36 ± 17.76%; forced vital capacity (FVC): 58.16 ± 17.02%] as compared to never-smokers (FEV1: 47.1 ± 16.47%; FVC: 67.38 ± 17.02%) with p < 0.05. With respect to severity at presentation, most (45.8%) never-smokers presented with stage 2 COPD as compared to the majority of smokers (46.7%) who presented with stage 3 COPD (p-value of <0.05). Absolute eosinophil count (AEC) and eosinophil count in total leucocyte count (TLC) was significantly higher in never-smokers as compared to the smokers (232 ± 82 vs 204.2 vs 309 ± 238.8, p < 0.05). Risk factor analysis showed mean biomass exposure index was significantly higher in never-smokers as compared to smokers (56.02 vs 6.28; p-value of <0.001).

Conclusion: Compared to smokers, COPD in never-smokers presents at a younger age, with a longer duration of dyspnea and higher eosinophil count. Biomass exposure is one of the major contributors to etiologies for COPD in nonsmokers.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of disability, adjusted life years, and deaths worldwide.1 As per the 2001 report of the GOLD, COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways following exposure to noxious particles or gases.2 Due to progressive loss of lung parenchyma in COPD, patients tend to have an adverse impact on the health-related quality of life.3

Historically COPD has been considered a smokers’ disease, which has resulted in the usual exclusion of nonsmokers from the studies pertaining to COPD,4–7 but it’s now recognized that never-smokers account for nearly one-fourth of all COPD cases5–10 and thus the airflow limitation in nonsmokers needs further evaluation.11 Data on the pathogenesis of COPD in nonsmokers is limited compared to that in smokers. Some studies have explored risk factors other than smoking that play a role in the development of COPD among nonsmokers, like air pollution, occupational exposure, asthma, and antiprotease deficiency.12–18 A study on phenotypic comparison by Salvi et al. showed that compared to COPD in smokers, nonsmokers present with the obstructive pulmonary disease at a younger age with a predominant small airway disease with less emphysema, preserved lung diffusion, and a slower rate of decline in lung functions.19 A study on COPD among nonsmokers done by Jindal et al. further demonstrated the higher rate of exacerbations and healthcare resource utilization among the subgroup with no smoking history.20

Despite this, there is a dearth of evidence, both prospective and cross-sectional which delves into the subject of nonsmokers’ COPD and associated risk factors. The evidence from India is further scarce.

The present study is an attempt to elucidate the clinical and physiological aspects of COPD in nonsmokers and to compare the smoker’s COPD phenotype with that of a nonsmoker, with a particular interest in the risk factors associated with the development of the disease.

Materials and Methods

Study design and setting: The present study is a prospective cross-sectional observational study conducted in the Medicine, Pulmonary, and Critical Care Department at a tertiary care teaching hospital in Northern India. The study was conducted over a period of 1 year and 6 months (July 2019–December 2020). Prior Ethical and Institutional Review Board clearance was taken vide letter number BREC/293/Ins/HR/2013/RR-19 dated 1st February 2020.

Sample size and study participants: The study sequentially recruited 200 naïve patients with COPD from the outpatient department. Inclusion criteria included >40 years of age, history of cough, expectoration, and/or breathlessness for over 3 months in 1 year for 2 or more years, and spirometry showing postbronchodilator forced expiratory volume in first second (FEV1)/forced vital capacity (FVC) ratio of <0.70 in past 2 months and having insignificant bronchodilator reversibility. Patients with a history of tuberculosis were excluded from the study. Additional exclusion criteria used were the presence of alternate causes of chronic dyspnea or pulmonary symptoms, such as obstructive sleep apnea, neuromuscular...
disorders (diaphragmatic paralysis and myasthenia gravis), thoracic wall disease (such as flail chest and kyphoscoliosis), congestive heart failure, pleural effusion, pneumothorax, pulmonary embolism, pulmonary edema, interstitial lung diseases, or pulmonary artery hypertension. Patients suffering from any active malignancy or history of hospitalization in the recent 1 month or prior thoracic surgery were also excluded. Bronchial asthma was considered in all cases, and the presence of atopy with the variability of clinical symptoms was used as a criterion of exclusion.

Diagnostic criteria for COPD: Spirometry was performed for diagnosis and classification of the severity of COPD by GOLD 2019 criteria. The severity of airflow limitation in COPD patients was defined by GOLD criteria, and the severity of breathlessness was assessed by a modified Medical Research Council (MRC) dyspnea scale. Bronchodilator reversibility was used to rule out the diagnosis or overlap of bronchial asthma.

Data collection and statistical analysis: A patient pro forma including detailed clinical history, risk factors for COPD, health status, and comorbidities was administered. Patients also underwent routine laboratory investigations, including baseline biochemical investigations along with Absolute eosinophil count (AEC). The data was initially collected in paper format and later entered in a coded format in Microsoft excel® version 2019, and the final analysis was done using IBM® Statistical Package for the Social Sciences version 26.0. Descriptive statistics were used to summarize demographic characteristics, and an unpaired t-test was used for quantitative data comparison of all clinical indicators between two independent groups. The Chi-squared test and Fisher exact test were used for qualitative data. For multivariate analysis, the Pearson correlation test was done. The level of significance was set at p ≤ 0.05.

Ethical considerations: The study was approved by the Institutional Review Board and Ethics Committee. Confidentiality of the data was maintained, and no personal identifier was used or shared in the study analysis.

Results
Over the period of study duration, 450 subjects were screened, of which 200 patients were included in the study (Fig. 1). The mean age of recruited subjects was 60 ± 9.9 years, with 41 females and 159 males. There were 48 nonsmokers and 152 smokers among the participants. The mean age of nonsmokers was 55.69 ± 11.5 years, and of smokers was 60.65 ± 9.10 years (p-value of <0.001). Most patients belonged to the age group between 60 and 69, both smokers 38.1% (58/152) and nonsmokers 35.4% (17/48) (Table 1). The majority of the study participants were from rural areas and constituted nearly 61% of the total study subjects.

Table 2 summarizes the phenotypic differences among smokers and nonsmokers with their associated p-values. Nonsmokers were found to have a longer duration of shortness of breath at presentation as compared to smokers, with a mean difference of 2.30 years (5.05 ± 4.96 vs 7.35 ± 6.98 years, a p-value of <0.01). Duration of other respiratory symptoms in the nonsmoker COPD population was also higher when compared to the smokers COPD subgroup, albeit the difference was not found to be statistically significant.

Upon evaluation of chest radiographs, 82.9% (126 out of 152) of smokers showed hyperinflation, in contrast to nonsmokers, where only 64.6% (31 out of 48) showed features of hyperinflation (p < 0.05). High-
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The present study sequentially enrolled 200 naïve cases of COPD after objectively confirming the diagnosis and found that there were significant phenotypic differences among smokers and nonsmokers with COPD. Smoking has been considered the single most important risk factor for COPD, but there is mounting evidence that the disease also affects people who have never smoked.10 In addition to biomass exposure, other risk factors have also been associated with COPD among nonsmokers like outdoor pollution, occupational exposure to dust and fumes, history of repeated lower respiratory tract infections, and occupational exposure to coal and charcoal.


discussion

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Table 2: Phenotypic characteristics of the COPD patients

<table>
<thead>
<tr>
<th>Phenotypic characteristics</th>
<th>Smoker</th>
<th>Nonsmoker</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms (in years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Cough</td>
<td>4.79 (6.002)</td>
<td>5.35 (6.15)</td>
<td>0.57</td>
</tr>
<tr>
<td>Wheezing</td>
<td>1.92 (3.102)</td>
<td>2.58 (3.712)</td>
<td>0.22</td>
</tr>
<tr>
<td>Sputum production</td>
<td>4.92 (6.706)</td>
<td>4.96 (5.87)</td>
<td>0.97</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5.05 (4.96)</td>
<td>7.35 (6.98)</td>
<td>0.01</td>
</tr>
<tr>
<td>Radiological findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperinflation on chest radiography</td>
<td>82.9% (126/152)</td>
<td>64.6% (31/48)</td>
<td>0.03</td>
</tr>
<tr>
<td>Bronchial wall thickening on HRCT chest</td>
<td>(21/42)</td>
<td>(6/10)</td>
<td>0.56</td>
</tr>
<tr>
<td>Bullae on HRCT chest</td>
<td>(12/42)</td>
<td>(2/10)</td>
<td>0.26</td>
</tr>
<tr>
<td>Emphysema on HRCT chest</td>
<td>(26/42)</td>
<td>(6/10)</td>
<td>0.64</td>
</tr>
<tr>
<td>Spirometry findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (in L)</td>
<td>2.24 (0.75)</td>
<td>2.17 (0.93)</td>
<td>0.56</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>58.16 (17.02)</td>
<td>67.38 (17.02)</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV1 (in L)</td>
<td>1.28 (0.63)</td>
<td>1.38 (0.64)</td>
<td>0.34</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>40.36 (17.76)</td>
<td>47.1 (16.47)</td>
<td>0.02</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>51.25 (10.007)</td>
<td>51.25 (9.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>COPD severity (GOLD staging)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>8</td>
<td>2</td>
<td>0.03</td>
</tr>
<tr>
<td>Stage 2</td>
<td>36</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>71</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Stage 4</td>
<td>37</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Blood picture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>2.23 (2.02)</td>
<td>3.06 (2.81)</td>
<td>0.06</td>
</tr>
<tr>
<td>AEC</td>
<td>232.49 (204.15)</td>
<td>309.63 (238.76)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total leukocyte count (TLC)</td>
<td>4347.37 (3473.85)</td>
<td>4051.67 (3510.32)</td>
<td>0.6</td>
</tr>
<tr>
<td>% Granulocytes</td>
<td>4.99 (2.52)</td>
<td>4.42 (2.58)</td>
<td>0.17</td>
</tr>
<tr>
<td>% Lymphocytes</td>
<td>2.16 (1.701)</td>
<td>2.06 (1.52)</td>
<td>0.71</td>
</tr>
<tr>
<td>% Monocytes</td>
<td>2.53 (2.38)</td>
<td>2.77 (2.66)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

HRCT, high-resolution computed tomography; FVC, forced vital capacity; FEV1, forced expiratory volume in first second; GOLD, Global Initiative for COPD; The bold values highlight observations.
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Infections during childhood, pulmonary tuberculosis, asthma, preterm birth, and intrauterine growth retardation, as well as exposure to incense stick combustion,18,22,23 But the physiological difference between COPD caused by smoking and nonsmoking risk factors is poorly studied.

In the index study, nonsmokers constituted 24% of the total cases. These proportions coincide with findings from previous studies from the United States of America (25%),10 the United Kingdom (22.9%),24 and Spain (23.4%),25 where a similar prevalence of nonsmokers amongst COPD patients has been reported.

Additionally, Hagstad et al., in their study from China, reported that around 20% of the participants from a random sample of 2,470 COPD patients were nonsmokers.26 Gender-related finding of our study is also consistent with studies performed in Spain, Austria, South Africa, Iceland, Poland, and Australia.22,28 The majority of nonsmoker patients were females (62.5%), which may be attributed to relatively higher exposure of females to biomass fuel and indoor air pollution in developing countries.29 In the population-based Burden of Chronic Obstructive Lung Disease study,28 similar findings were encountered, with nonsmokers constituting 27.7% of all COPD cases, with females making up nearly 71%.

Another interesting finding of the index analysis was that the mean age of nonsmokers was significantly less than the mean age of smokers (55.6 vs 60.6 years, p < 0.05). This observation contrasts with the Western (Lee et al.) studies where the mean age was more in nonsmokers at (65.7 vs 62.8 years), however, results from an Indian study by Salvi et al. corroborate our findings.10,19 The likely reason might be the early initiation of exposure to noxious gases in the form of biomass fuel exposure and indoor air pollution amongst the nonsmoker group, especially amongst females. Additionally, the genetic predisposition towards the development of chronic airway inflammation may also contribute to the early onset of COPD among these subjects.

Biomass exposure has been a major cause of COPD in nonsmokers, especially in developing countries, in particular the rural population where it is used as a cooking fuel.31 Since our study populations constituted mostly rural participants, this risk factor was particularly prominent. Out of a total of 200 COPD cases, 26.5% gave a history of biomass fuel exposure, and 50% of nonsmokers had a history of biomass fuel exposure. In contrast, a case-control study from Turkey by Ekici et al. reported that only22 23% of nonsmokers have a history of biomass exposure, which reflects upon the geographical heterogeneity of the use of biomass fuel. The present study also demonstrated a linear correlation between the severity of COPD and increasing exposure to biomass fuel combustion, which is in coherence with the findings demonstrated by Mahmood et al.33 in their cross-sectional study from Allahabad, India.

The relationship between smoking and a decline in FEV1 has been well-established in the general population.34 In our study, the percent predicted FVC and FEV1 were significantly higher in nonsmokers as compared to smokers. This contrasts with the study published by Salvi et al., where it was shown that the degree of airflow obstruction measured by FEV1% predicted was higher in nonsmokers (smokers COPD: 43.1% vs nonsmoker COPD: 40.7%).10 This contradiction can be attributed to the delay in the diagnosis of COPD amongst nonsmokers as well as the lack of awareness about the entity of nonsmoker COPD. This is further reflected in the finding of the duration of dyspnea which was higher in nonsmokers (7.35 vs 5.05 years).

Investigations like laboratory and radiological findings in our study also corroborate with earlier studies. In the present study, radiological abnormalities like emphysema and hyperinflation were significantly more prevalent in smokers than nonsmokers (83.3 vs 63.6%), which was anticipated in view of the casual association of smoking with the destruction of alveolar walls.

Among the analysis of hematological investigations, the overall TLC count was found to be higher in smokers as compared to the never smokers’ group, albeit it was not statistically significant. However, the AEC and eosinophil percentage in DLC were significantly higher among nonsmokers as compared to smokers. The result was supported by previous studies by Bajpai et al.35 and Salvi et al.19

One of the major strengths of our study was that we sequentially recruited only naive cases of COPD, which decreases bias and provides a clear picture of the proportion of never-smokers amongst naive cases of COPD. Never smokers have a longer duration of illness, with relatively preserved lung functions and hematological features suggestive of eosinophilic inflammation. Despite the methodology, there are some lacunae in our study, like selection bias as our center is a tertiary care hospital which may result in referral bias, a relatively small number of cases given the high prevalence of COPD, and the inability to account for other risk factors like air pollution. Also, the sputum examination could have added further value to the study. Due to financial constraints, inflammatory cytokine levels were not done, which would have been a better marker of eosinophil inflammation.

**Conclusion and Recommendations**

There is an increasing burden of COPD among nonsmokers with various associated risk factors like biomass exposure, air pollution, and tuberculosis, among others. The present study shed some light on the presentation of COPD in nonsmokers, which can be atypical with a longer duration of dyspnea and earlier age of presentation with higher eosinophil count. Also, there is a higher proportion of females among nonsmokers presenting with COPD, mostly from rural backgrounds reflecting upon the menace of biomass fuel exposure. Nonsmoker COPD remains a heterogenous, common, and neglected phenotype, which requires bigger and more prospective studies to further elucidate its pathogenesis.

**Site Where Study Was Conducted**

Pt BD Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India.

**Author Credit Statement**

- Conceptualization: DC and TG
- Methodology: PKS, MBG, and RR
- Ethical and review board approvals: RR
- Data collection: RR and PKS
- Data entry and curations: RR, MBG, and PKS
- Formal Analysis: P, PKS, and DC
- Writing-original draft: P, RR, and MBG
- Review and editing: DC and TG
- Overall supervision: DC

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**References**

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