 doi:10.20944/preprints202206.0334.v1

Article

Environmental Exposures and Phenotype of Non-smoking COPD

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Abstract: Chronic obstructive pulmonary disease (COPD) is strongly associated with tobacco smoking and it is the increasing cause of morbidity and mortality worldwide. The prevalence of COPD among never smokers varies widely across regions, areas, and nations. COPD in smokers has been extensively explored worldwide, however, COPD in non-smokers is under-explored and there is limited data available on non-smoking COPD. We determined the role of environmental pollution and biomass fuel exposure in COPD patients who were non-smokers. We evaluated the clinical profile of non-smokers with COPD in a retrospective observational study. 180 non-smoker COPD patients were selected from the year 2016-to 2018. We found that many patients with COPD are non-smokers and the incidence is higher among the rural population, suggesting that non-smoking COPD is evolving rapidly due to biomass smoke and other environmental pollutant exposures.

Keywords: non-smoking COPD; phenotypes; air pollution; biomass; occupational exposure

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the major preventable chronic respiratory diseases. As described by Global Initiative for Obstructive Lung Disease (GOLD), COPD is a common preventable and treatable disease. The major characteristic of this disease is persistent airflow limitation that is usually progressive and noxious particles or gases leading to an enhanced chronic inflammatory response in the airways and the lungs [1].

A combination of emphysema (parenchymal destruction) and obstructive bronchiolitis (small airway diseases) leads to chronic airflow limitation and it relatively varies from person to person. About 210 million people are affected by COPD worldwide [2]. COPD was the globally fourth leading cause of death (5.1%), and by the year 2030, it is projected to occupy the third position (8.6%) [3]. Moreover, COPD was ranked 11th in 2002 as a major cause of chronic morbidity and is estimated to rise to seventh place in 2030 [4], and non-smoking COPD is emerging due to environmental pollution and exposures to airborne pollutants [5-13]. This includes, ozone, particulate matter (PM), ozone (O3), Nitrogen dioxide (NO2) and Sulphur dioxide (SO2), wildfire, biomass fuel burning/smoke, crop/paddy burning, and industrial gases and fumes.

Most of the studies reported earlier have only focused on smokers with COPD, but recent data has demonstrated that many patients with COPD are predominantly non-smokers between the age group of 50-80 yrs and that the risk of COPD in non-smokers is also higher than previously believed. Genetic factors, biomass smoke, long-standing asthma, environmental exposure, tuberculosis, outdoor air pollution, occupational exposure, and recurrent respiratory infection in early childhood. are the risk factors for COPD in non-smokers.

COPD occurs when permanent blockages from within the pulmonary system interfere with the transfer of vital gasses. The overall efficiency of the gas exchange process is

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reduced as this disease as it progresses, and leading to exacerbations of COPD. We determined the role of environmental pollution and biomass fuel exposure in the pathogenesis of COPD patients who were non-smokers in central rural India. We examined the clinical profile of non-smokers with COPD in a retrospective observational study. 180 non-smoker COPD patients were selected from the year 2016-to 2018 in the rural population.

2. Materials and Methods

It is a retrospective study of the population of central rural India, patients of the age group (50-80 yrs) coming to Ketki Research Institute of Medical Sciences (KRIMS) hospital from 2016 to 2018 with an approved IRB from KRIMS who were subsequently diagnosed with COPD were selected. History and clinical information with questionnaires was taken (**Suppl Tables 1,2**) and subsequent spirometry results were evaluated. Informed written consent was obtained with Study Approval #KRIMS2016COPD Phenotype Study. Various parameters, e.g. inclusion and exclusion criteria are given below.

2.1. Inclusion criteria

The following parameters were the inclusion/exclusion criteria to recruit subjects/patients:

- Patient willing to give informed consent.
- All patients of age group 50-80 yrs were recruited.
- A person who has never smoked tobacco
- Patients coming to Outpatients Department (OPD) in the period of 2016-2018
- Regular follow-up.

2.2. Exclusion criteria

- Pregnant female
- Patient lost in follow-up
- Patient not willing to give consent

2.3. Methods

A retrospective Non-Smoker COPD data was collected from the year 2016-to 2018. About 180 patients were found to be non-smokers who were diagnosed with COPD on their spirometry findings. According to GOLD Guidelines the patients were categorized into Mild, Moderate, Severe and Very Severe COPD **(Supp Table 3)**

2.4. COPD Diagnosis

COPD was diagnosed based on an obstructive pre-bronchodilator spirometry reading (FEV1/FVC<0.70) according to GOLD GUIDELINES [14-18]. Spirometry was performed by trained paramedical person according to the GOLD GUIDELINES, using a spirometer (COSMED SPIROMETER from ITALY) from 2016-2018. Spirometry results which did not meet GOLD GUIDELINES criteria for acceptability were classified as not interpretable. In KRIMS hospital study of 180 patients from (2016-2018) was taken who were diagnosed as COPD in non-smokers.

Statistical analyses: This is an observational and pilot clinical study, hence the exact numbers are given based on % rather than p values.

3. Results

The study consisted of 180 patients from the year (2016-2018) coming to the KRIMS hospital in the age group 50-80 years, out of which 83 were men and 97 were female. A physician examined and diagnosed COPD according to spirometry. A comparison between males and females showed that the percentage of females (53.88%) was observed

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to be more than males (46.11%) with 50-80 years of age as gender distribution of study population.

Patients were categorized according to Mild, Moderate, Severe and Very Severe by GOLD guidelines as shown in Table 1. Patients were also categorized according to occupation/profession and current ongoing exposure to environmental factors (Table 2). The patients were predominantly rural areas either farmers and/or pensioners. The number of patients in each category i.e. biomass (46.11%), chimney smoke (2.77%), toxic gases/fumes (26.66%), dust at construction site-(2.77%), vehicle smoke (2.22%).

Table 1. Distribution on the basis of severity according to the GOLD guidelines.

Categories of Non-Smoker Copd	Total Patient (Male & Female)
mild	26
moderate	53
severe	58
very severe	43

Table 2. Distribution according to occupation of the study population with one or more professions as listed.

Occupation	No of Patient
grocery shop	4
farmer	43
coal field worker	5
office job	8
agriculture officer	2
public transport driver	2
electricity department employee	4
public works department	2
caterer	2
dhaba /restaurant worker	2
it company	3
teacher	10
ordinance factory empolyee	1
manual labour	5
housewives/home maker	77
tailor	4
tea stall worker	2
clothing shop worker	2
utensil shop worker	2

Note: Some patients had one or more profession/occupation in the listed categories

The study found that dyspnea (32%), cough (26%), chest pain (19%), and wheezing (13%) were the predominant symptoms in total population using one or more symptoms (Table 3) indicating various associated clinical symptoms in these subjects. This shows that the total number of patients (male and female) having dyspnea, cough, chest pain, wheezing, and fever. Majority of the patients had cough and dyspnea.

 doi:10.20944/preprints202206.0334.v1

Table 3. Distribution according to symptoms of the study population alone or in combination of symptoms in recruited patients.

Clinical symptoms	Number of patient
Cough	132
Dyspnea	164
Wheezing	65
Fever	50
Chest Pain	96

Note: Patients have more than one symptoms which are given here.

The data further show that the patient population had diabetes mellitus, hypertension and allergic rhinitis as co-morbid conditions. The following distribution was characterized according co-morbid conditions of study population, i.e. 17.77% was diabetes mellitus, 34.44% hypertension, 13.88% allergic rhinitis, 10% kochs, 11.11% bronchiectasis, 6.11% hypothyroid. Various co-morbid conditions of patients and distributions according to region of residence were 61.11% subjects belonged to rural and 38.88% belonged to urban areas.

4. Discussion

In India and globally, COPD is an important public health problem. COPD may be caused due to non-smoking factors, especially in developing countries where biomass fuels are used as a source of domestic energy. Therefore, indoor biomass smoke and other forms of air pollution from these sources are important factors in the pathogenesis of COPD. The burden of non-smoking COPD is increasing day by day. Along with smoke from biomass fuel, major pollutants like particulate matter (PM), ozone (O3), Nitrogen dioxide (NO2) and Sulphur dioxide (SO2) is the strongest evidence-based cause of COPD. In the year 2012, it was reported that in India, due to outdoor pollution about 0.62 million premature excess deaths occurred and it has become the fifth leading cause of death. In this study, we investigated the evidence for the epidemiological interaction of COPD with biomass fuel, occupational exposure to dust and gases, pollutants from construction sites, outdoor air pollution and vehicle smoke.

The study performed at KRIMS hospital for Non-smoking COPD found that the middle age (50-80 yrs) group is highly affected by COPD. Age-associated changes and environmental effects on the structure and function of the lungs may increase a pathogenetic susceptibility to COPD. In old age, the lungs may directly develop COPD [18]. A similar study is observed by Fukuchi et al [17]. One more study reported by Peruzza et al states that elderly patients affected by COPD-related respiratory failure are frequently impaired in their social life, physical function and activities of daily living and therefore have greater chances of acquiring COPD [19]. The highest affected category was observed in the severe category. The co-morbid conditions increased with an increase in age and are more prevalent among rural populations. Similar findings are observed by other investigators [20,21].

We found a major complication in COPD is mild to moderate hypertension and such complications lead to an increased risk of exacerbations and decreased survival. During exacerbations, pulmonary hypertension usually worsens. About 38.8% of patients had hypertension from severe to very severe COPD but Chaouat et al's study has found that patients from Mild to Moderate are affected by COPD which does not comply totally with our study [20].

According to the evaluation, about 61.1% (male and female) belong to the rural area where men had farming as their occupation and females were housewives. Whereas, 38.9% (male and female) belong to the urban region where the maximum number of people were found to be working or had business as their occupation. This study shows that the rural population has the majority of COPD than the urban. Similar findings are seen in another study [18].

Considering the occupation of rural people as stated in the above discussion, farming is the major occupation observed in males and females are housewives. Farming involves a spectrum of activities that range from small-scale farms to large-scale farms used for the cultivation of crops. These farmers are exposed to various environmental ongoing exposures, like climatic conditions and toxic gases (i.e. pesticides, Insecticides, chemical fertilizer). All these toxic sprays used in fields are unfortunately inhaled by the farmers which directly contributes to the development of COPD in farmers. A study by Elliot et al has concentrated on the environmental exposure causing COPD whereas our study has observed that 26.66% of farmers acquired COPD due to ample use of toxic sprays in farms which are inhaled by farmers continuously [22].

Women of India residing in the rural region are mostly housewives who spend a lot of time in the cooking area. In such rural households, a chulha (a U- shaped construction made up of mud) pit is mostly used as a stove for household cooking. Also, these households lack proper vents/chimneys in the cooking area. Cooking under these conditions leads to a high level of exposure to smoke thus contributing to higher exposure to biomass. In our study, about 46.11% of women are exposed to biomass. Similar findings were reported in Kiraz and Arora et al studies [23,24].

5. Limitations

This pilot study was carried out in a single center in a regional center. The study population is limited to patients attending the hospital. We suggest the study needs to be multi-centered with larger study populations/cohorts including in other regions and countries. Further, we provided the number of subjects/patients used and were unable to provide the statistical values for this pilot study. We did not have post-bronchodilator testing performed

6. Conclusion

We have found that many COPD patients are non-smokers and among all rural populations is the higher exposed group. Patients who are non-smokers develop COPD caused by biomass fuel ongoing exposure and environmental pollution [25]. Even though COPD is a preventable disease, COPD will be the third leading cause of death by 2030. Therefore, there is a need to reduce the burden of COPD in India by adopting appropriate preventive strategies. Giving due attention to COPD by the medical community and policymakers will help reduce the morbidity and mortality rate caused by non-smoker COPD, i.e. non-smoking COPD caused by several environmental factors.

Author Contributions: SA and AA: Planned study, collection of data and wrote manuscripts; BA, PD, IR, SB, and PB manuscript organization and edited the text.

Acknowledgments: This study has not received any funding and the authors are thankful to the hospital for conducting this study.

Conflicts of Interest: The authors declare no conflict of interest.

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Supplemental Tables

Suppl Table 1: Questions asked to the study population during medical/clinical examination/investigation

Unique ID		
Age		
Sex		
Occupation		
Region		
QUESTIONS	**YES**	**NO**
Dyspnea		
Wheeze		
Chest tightness		
Fever		
Chest Pain		
Exposure to biomass		
Exposure to chimney		
Exposure to toxic gases		
Exposure to dust at construction site		
Exposure to vehicular smoke		
mMMRC scale		
CAT Test		

COPD ASSESSMENT TEST (CAT ™): The COPD assessment Test™ is an 8-item uni-dimensional measure of health status impairment in COPD [16]. It was developed to be applicable worldwide and validated translation available in wide range of languages [17].

Suppl. Table 2. Modified Medical Research Council Dyspnea Scale (mMRC).

Grade	Description of Breathlesness
mMRC 0	I only become breathless with strenuous exercise
mMRC 1	I become short of breath when hurrying on the level or walking up a slight hill
mMRC 2	I walk slower than most people the same age on the level because of breathlessness. Or I have to stop for breath when walking at my own pace on the level.
mMRC 3	I stop for breath after walking – 100m or after a few minutes on the level.
mMRC 4	I am too breathless to leave the house or breathless when dressing or undressing.

mMRC Scale: Modified Medical Research Council Dyspnea Scale (mMRC) is one of the important aspect considered in assessment of COPD [15]. In past

 doi:10.20944/preprints202206.0334.v1

COPD was viewed as a disease characterized by breathlessness. Therefore, a measure of breathlessness questionnaire given in mMRC is asked to patients.

Suppl Table 3. GOLD Criteria used in this study based on current guidelines

COPD	**Range**
Mild COPD	FEV1/FVC < 0.70 and FEV1 > 80% predicted
Moderate COPD	FEV1/FVC <0.70 and 50% < FEV1 < 80% predicted
Severe COPD	FEV1/FVC <0.70 and 30% < fev1< 50% predicted
Very Severe COPD	FEV1/FVC <0.70 and FEV1 < 30% predicted

Where, FEV1 = Forced expiratory volume in 1 second and FVC = Forced vital capacity.