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Chronic Obstructive Pulmonary Disease: Should there be difference in therapeutic approach in smoker and non-smoker COPD? A prospective study.

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Abstract:

Introduction: COPD is a leading contributor of morbidity and mortality worldwide. Smoking and inhaling harmful chemicals and particles from indoor and outdoor air pollution are the main environmental exposures that cause COPD. Non-smoking related COPD affects more people in developing countries than it does in developed countries. This study was initiated primarily to assess the response of standard treatment in COPD among smokers and non-smokers. The proportion of COPD patients whose condition was not caused by tobacco smoking was also assessed. Non-smoking related chronic obstructive pulmonary disease (COPD) is a neglected entity.

Material and Methods: This was an observational, prospective, case-control study. All patients were diagnosed for COPD, aged 18 years or above, were included in this study. Patients were divided into case (non-smoker COPD) and control (smoker COPD). Standard treatment for COPD would be given to both groups according to latest GOLD guidelines for COPD. Treatment response was evaluated in both groups.

Results and Discussion: In this study 49.1% patients were smokers while 50.9% patients were non-smokers, which is in accordance with the worldwide trend of half of the patients of COPD being due to risk factors other than smoking. It was found that smoking COPD occurs at an older age. There was no significant difference in pulmonary function test values, 6-minute walk distance (6MWT), COPD Assessment Test (CAT) score and Modified British Medical Research Council (mMRC) grading between the two groups.

Among serological tests it was found that Total Leucocyte Count (TLC), Neutrophil-Lymphocyte Ratio (NLR) and Packed Cell Volume (PCV) were statistically higher in the smoker COPD group than the non-smoker group.

Both the groups were taken up for follow up, and it was found that Forced Expiratory Volume in 1st second (FEV_1) and 6 Minute Walk Test decreased more in non-smoking COPD patients than the smoker COPD over the months. After 2 months there was only 1 patient and after 3 months there were 3 patients among 193 smoker COPD patients who had exacerbation. Among non-smoker COPD patients 2 patients had exacerbations within 2 months, while 7 patients had exacerbation within 3 months. Clinical assessment done by CAT score also demonstrated lower scores in non-smoker COPD patients. Hence, non-smoker COPD patients are having more exacerbations and clinical deterioration than their smoking counterparts on treatment according to same treatment guidelines

Introduction: The term Chronic Obstructive Pulmonary Disease (COPD) refers to a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, cough, sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, frequently progressive, airflow obstruction.[1] With a significant and growing economic and social burden, COPD is a leading contributor of morbidity and mortality worldwide.[2,3] A combination of ongoing exposure to COPD risk factors and population ageing around the world is expected to result in a rise in COPD prevalence and burden during the ensuing decades.[4] COPD is an outcome of gene (G)- environment (E) interactions that occur over the lifetime (T) of the individual (GETomics) and may harm the lungs and/or alter their normal development/aging processes.[5] Smoking and inhaling harmful chemicals and particles from indoor and outdoor air pollution are the main environmental exposures that cause COPD, although other environmental and host variables (such as aberrant lung development and accelerated lung ageing) can also cause the disease.[5,6] Other pathogenic factors must be taken into account because it is estimated that tobacco use accounts for only half of all COPD cases worldwide.[6] Non-smoking related chronic obstructive pulmonary disease (COPD) is a neglected entity. Although, many studies have been conducted to assess the treatment response in COPD patients, in general, but no study has been conducted to compare treatment response in smoker related and non-smoking related COPD.[7] Non-smoking related COPD affects more people in developing countries than it does in developed countries.[8] These group of individuals that are not associated with tobacco smoking (Non-smoker COPD or NSCOPD), are given the same treatment as those associated with tobacco smoking although having difference in etiopathogenesis.[9] Hence, this study was initiated primarily to assess the response of standard treatment in COPD among smokers and non-smokers. Secondary objectives were to assess the proportion of COPD patients whose condition was not caused due to active smoking, and to study the clinic-demographic profile difference between smoker (SCOPD) and non-smoking COPD (NSCOPD) patients.

Material and Methods:

This was an observational, prospective, case-control study. The study was conducted after obtaining approval from the Institutional Ethical Committee, latter No. MC/IEC/2021-43. It was conducted in a time period of 11 months (15th October 2021 to 14th September 2022) in a tertiary care institute of Garhwal region in Uttarakhand. All patients diagnosed with COPD, aged 18 years or above, were included in this study. Patients were divided into case (non-smoker COPD) and control (smoker COPD). Patients who had fulfilled the criteria of nicotine dependence by International statistical classification of diseases (ICD-10) and among them who were having a score above 5 in Fagerstrom test for nicotine smoking dependence were considered as smokers. Patients who did not fulfill the criteria of nicotine use or dependence and those who had a low score of 1-4 in Fagerstrom test were considered non-smoker.[10,11] Patient's requiring hospital admission and those who were hemodynamically unstable, were excluded from the study. Standard treatment for COPD would be given to both groups according to latest GOLD guidelines for COPD.[9] Treatment response was evaluated

through spirometry, 6-minute walk test9(6-MWT), Frequency of exacerbations and COPD assessment test(CAT) score.[12, 13]

These tests were done monthly till 3 months to assess the response of treatment. Active tobacco smokers were counselled for smoking cessation in tobacco cessation clinic as outlined in the GOLD 2022 guidelines.[9]

Results: In our study, a total no of patients 438 were enrolled for the study, out of which 416 patients gave their consent for the study. Among these 416 patients, 23 patients were lost to follow-up. Hence, a total no of patients of 393 has been considered for the final results.

Smoking was implicated in 193 patients out of 416, while 200 patients were nonsmokers. Out of 193 smoker COPD, 68 (35.2%) were female and 125 (64.8%) were male whereas among 200 non-smoker COPD patients, 143 (71.5%) were female and 57 (28.5%) were male. The difference in clinic-demographic profile and the lung function between both groups is elaborated in Table No. 1.

Table No. 1: - Subject demographics, lung function and clinical assessment

Variables	**S-COPD**	**NS-COPD**	**P-value *significant <0.05**
No. of Subjects (N)	193	200	_
Sex (M: F)	1.83	0.39	_
Age (Years)	67.5+8.2	65.9+9.4	0.035*
BMI (Kg/m^2)	19.5+3.6	20.1+4.1	0.063
FEV_1 Pre (Percentage Predicted)	44.2+16.4	42.3+14.1	0.083
FVC Pre (Percentage Predicted)	64.8+19.3	63.3+17.8	0.259
Reversibility FEV_1 (ml)	162+96	178+124	0.095
Reversibility FEV_1 (Percentage)	14.8+5.4	15.6+9.4	0.254
6MWT (metres)	382+137	398+152	0.165
CAT score	23.6+7.4	23.1+6.8	0.32
mMRC grade	2.4+1.6	2.2+1.4	0.068

Serological tests done in smoker and non-smoker COPD are compared in Figure 2

Figure 2: Subject serological tests			
Variables	**S-COPD**	**NS-COPD**	**P-value**
ESR ($mm/1^{st}$ hour)	18.6+6.4	17.8+5.3	0.056
AEC ($cells/mm^3$)	402+158	386+182	0.239
TLC (10^3 $cells/mm^3$)	9.1+1.3	8.8+1.5	0.016*
NLR (Percentage)	3.08+0.81	2.83+0.76	0.0007*
Hemoglobin (mg/dL)	13.9+3.1	13.4+3.4	0.062
PCV (Percentage)	41.1+7.7	39.8+6.9	0.022*

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Follow up variables are shown separately for S-COPD and NS-COPD patients in Figure 3. The general condition of NS-COPD patients was much worse than those of S-COPD patients.

Figure 3. Monthly follow up findings of patients of S-COPD and NS-COPD

Variables	Start of treatment	Follow up after 1 month	Follow up after 2 months	Follow up after 3 months
FEV1 (S-COPD) percentage predicted	44.2	45.8	45.2	44.6
FEV1 (NS-COPD) percentage predicted	42.3	42.9	42.6	42.3
6MWT (S-COPD)	382	389	388	388
6MWT (NS-COPD)	398	403	401	396
No. of exacerbations (S-COPD)	0	0	1	3
No. of exacerbations (NS-COPD)	0	0	2	7
CAT score S-COPD	23.6	24.2	23.8	23.6
CAT score NS-COPD	23.1	23.5	23.5	22.7

Discussion: In this study 193 (49.1%) patients were smokers while 200 (50.9%) patients were non-smokers, which is in accordance with the worldwide trend of half of the patients of COPD being due to risk factors other than smoking [6]. The male to female ratio in smoker COPD group is much greater than that to non-smoker group as in India, majority of males are tobacco smokers compared to females [14]. Among non-smoker COPD, 143 (71.5%) were female and 57 (28.5%) were male. This in contrast to a study done in central India, where 54% were female and 46% were male [15]. Out of 193 smoker COPD, 68 (35.2%) were female and 125 (64.8%) were male.

Among demographic variables, it was found that smoking COPD occurs at an older age. There was no significant difference in pulmonary function test values, 6-minute walk distance (6MWT), COPD Assessment Test (CAT) score and Modified British Medical Research Council (mMRC) grading between the two groups. In a study done in Pune, India, Pulmonary function test values and CAT score between the smoking and non-smoking groups were not significant, while mMRC grade and 6MWT were not recorded [16]

Among serological tests it was found that Total Leucocyte Count (TLC), Neutrophil-Lymphocyte Ratio (NLR) and Packed Cell Volume (PCV) were statistically higher in the smoker COPD group than the non-smoker group. Erythrocytic Sedimentation Rate (ESR), Absolute Eosinophil Count (AEC) and Hemoglobin (Hb) were similar in both groups. In a study from India, PCV, Hb and AEC was similar in both groups while NLR, TLC and ESR were not measured [16]. Although, it is already known that NLR is increased in COPD patients, especially during exacerbations [17]. Even ESR and CRP are increased in patients of COPD, but there was no previous documentation of difference in PCV, NLR and TLC between smoker and non-smoker groups of COPD patients [18].

Both the groups were taken up for follow up, and it was found that Forced Expiratory Volume in 1st second (FEV_1) and 6MWT decreased more in non-smoking COPD patients than the smoker COPD over the months. After 2 months there was only 1 patient and after 3

months there were 3 patients among 193 smoker COPD patients who had exacerbation. Among non-smoker COPD patients 2 patients had exacerbations within 2 months, while 7 patients had exacerbation within 3 months. Clinical assessment done by CAT score also demonstrated lower scores in non-smoker COPD patients. Hence, non-smoker COPD patients are having more exacerbations and clinical deterioration than their smoking counterparts on treatment according to same treatment guidelines [9].

Conclusion: There is an increase in TLC, PCV and NLR in smoker group of COPD patients and the improvement in symptoms is also not long lasting or as effective in non-smoker group of patients. Hence it is clear, that non-smoker COPD patients may require a difference in treatment strategy and further research in this regard is warranted. Non-smoker COPD entity would remain neglected if it is not seen as a different group from smoker COPD. This was a pilot study. The shortcomings of this study were that the duration of follow up was restricted to 3 months and patients were not further divided into treatment groups according to GOLD guidelines, Hence further research is warranted into this topic for better understanding.

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