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Markers of Systemic Inflammation in Smoker and Non-Smoker Chronic Obstructive Pulmonary Diseases

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ABSTRACT

Non-smoker and tobacco smoker also have different inflammatory and proteolytic effects in the lung in experimental studies. **Objectives:** To compare the clinical, investigational profile and inflammatory markers e.g. ESR, CRP, Fibrinogen, IL-5 and IL-6 between smoker and non-smoker COPD patients.2. To compare the CAT score, mMRC score and various spirometry parameters between smoker and non-smoker COPD patients3. To calculate the diagnostic performance, sensitivity and specificity of inflammatory markers e.g. ESR, CRP, Fibrinogen, IL-5 and IL-6 between smoker and non-smoker COPD patients. **Methods:** In this cross-sectional study 80 subjects between age group of 40 to 65 years participated. This study included category A, B and C patients of COPD included and category D of COPD patients were excluded and those who were exposed to occupational exposure to smoke. Serum levels of inflammatory markers including ESR, CRP, IL-5, IL-6, and Fibrinogen measured. **Results:** This study showed that there was statistically significant difference in ESR, CRP and fibrinogen levels between smoker and non-smoker COPD. There was also significant statistical difference between smoker and non-smoker COPD with respect to gender, old TB, haemoglobin, and the spirometry parameters. **Conclusions:** Therefore, this phenotypical categorization of patients with COPD may result in better understanding of the varied pathophysiology and help as screening tool for diagnosis of non-smoker COPD patients. ESR, CRP and fibrinogen may be used as a screening tool between smoker and non-smoker COPD patients, for a focused approach to treatment.

INTRODUCTION

As per the GOLD guidelines, COPD is a preventable, and treatable disease. Airflow limitation which is characteristic feature in COPD, is not fully reversible [1]. This airflow limitation is progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases. Currently, COPD becomes the public health challenge as mortality related to COPD is on number 4th in the world [2]. Tobacco smoking in past or current is most important risk factor for COPD development. However, not all patients with COPD have a history of smoking. As per available literature 10% to 12% of individuals with COPD have never smoked and only 50 % worldwide COPD cases are related to smoking [3, 4]. This suggests that other environmental factors are also involved, including biomass fuel exposure (outdoor and indoor air pollution), occupational hazards, passive smoking and smoking in mother during early pregnancy, childhood respiratory infections [5, 6]. OPD is a complex chronic disease, involving several types of inflammatory cells and variety of inflammatory mediators. Its pathogenesis entails complex interactions among multiple factors, including oxidative stress, extracellular matrix destruction, alterations of cell growth and repair, cellular apoptosis on exposure to air pollutants including tobacco smoke [7]. IL-1 is mainly

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produced by the airway epithelium and macrophages, and it is released along with IL-6, IL-8 and TNFα. It causes neutrophilia, macrophage activation and responses by T cells [8, 9]. Various clinical studies reported elevated levels of inflammatory cytokines in respiratory tract and/or peripheral blood of COPD patients in comparison to healthy controls [10, 11]. The major inflammatory cell in the process is the neutrophil. It has been seen that number of neutrophils in small airways is related to severity of COPD [12]. The number of circulating leukocytes, together with blood levels of markers of systemic inflammation like CRP, IL-6, TNF-alpha and fibrinogen, is regarded as an associated with lung function impairment over time [13]. The number of macrophages is increased in the Airways in COPD and these cells seem to be of direct importance of development of emphysema. Eosinophils as a marker of airway inflammation have attracted some interest in COPD. There are studies indicating the number of sputum eosinophils increases in COPD in association with acute exacerbations [14]. Only a few studies have been done globally as well as in India, which have attempted to evaluate and compare the clinical, inflammatory marker's patterns between smoker and non-smoker COPD patients. Therefore, it was planned to do this study to demonstrate any significant difference in systemic inflammatory biomarker levels between smoker and non-smoker COPD.

METHODS

This cross-sectional observational study was conducted from January 2021 to April 2022 at University College of Medical Sciences and GTB Hospital, New Delhi. 80 subjects were included in this study. Sample size of current study was calculated by Rincon M *et al.*, in 2017 t α = 5% and power = 80% [10]. This study included category A, B and C patients of COPD between ages of 40 to 65 years. We excluded patients of category D of COPD and those who were exposed to occupational exposure to smoke and patients with recent episode of febrile illness, autoimmune disorders and taking systemic corticosteroids were also excluded from study. Institutional Ethics Committee-Human Research (IEC-HR) of University College of Medical Sciences, University of Delhi, India, Reference number of ethics committee – IECHR /2020/PG/46/46 had given ethical clearance and written informed consent was taken from each study subject. Complete history and examination were done for each patient. Basic routine sampling of each patient was done by taking venous blood sample.10 mL of peripheral venous blood was collected in all patients. 2 mL of blood was collected in plain vacutainer for biochemical investigations like LFT, KFT. 4 mL of blood was collected in plain vacutainer for inflammatory biomarkers (IL-5, IL-6, CRP). 2 mL of blood was collected in EDTA vacutainer for hemogram and ESR. 2 mL of blood was collected in Sodium citrate vacutainer for plasma Fibrinogen. ESR was estimated using Westergren principle in a ROLLER 20LC Autoanalyzer (ALIFAX, ITALY). CRP was estimated using RANDOX RX Imola Autoanalyzer, (RANDOX, UK) using company reagent packs. Serum IL-6 was estimated using commercially available IL-6 ELISA kit (Diaclone, France) following manufacturer's protocol. Serum IL-5 was estimated using commercially available IL-5 ELISA kit (FineTest, China) following manufacturer's protocol. Plasma fibrinogen was estimated using commercially available Fibrinogen ELISA kit (FineTest, China) following manufacturer's protocol. Flow Sensing Spirometer was used to assess PFT on basis of FEV1, FEV1 as percent predicted, FVC, FVC as percent predicted, FEV1/FVC. Biochemical investigations like Hemogram, LFT, KFT and inflammatory markers ESR, CRP, Fibrinogen, IL-5 and IL-6 levels were measured. PFT, CAT (COPD Assessment test) score and mMRC (Modified Medical Research Council (mMRC)) score were also assessed and compared in between smoker and non-smoker COPD patients. Data were analysed using SPSS version 20.0 software. For comparing the clinical and investigational profile and inflammatory markers, unpaired t-test/Wilcoxon-Mann-Whitney U test was used, depending upon the nature of the data. All tests were two tailed. P-value of <0.05 was statistically significant. ROC curve was used to measure diagnostic performance, sensitivity and specificity of each inflammatory marker.

RESULTS

In current study (Table 1) mean age of the patients was 56.69 ± 6.78 years. The mean age of patients categorized under smoker COPD was 57.58 ± 6.53 years, while in other non-smoker COPD group it was 55.80 ± 7.00 years. Of the 40 patients categorized under smoker COPD, 38 (95%) were male and 2 (5%) were female. While 28 (70%) of the patients categorized under non-smoker COPD were male and 12 (30%) were female. Significant difference between the two groups in terms of distribution of Gender (p = 0.003) was observed. Out of all the comorbidities, the association between the two groups in terms of distribution of Old TB was significant (p = <0.001). Out of the routine blood investigations, there was significant difference between the two groups in terms of haemoglobin level (mg %) (p = 0.031), with the mean haemoglobin (mg %) being highest in the smoker COPD group. In the inflammatory markers p-value were significant for ESR, CRP and Fibrinogen. Difference between groups for IL5 and IL-6 were not significant.

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Table 1: Distribution of Age, Comorbidity, Routine Investigations and Inflammatory Biomarkers

Gender	Smokers COPD Mean ± SD / N (%)	Non-Smokers COPD Mean ± SD / N (%)	p-Value
Male	38 (95.0%)	28 (70.0%)	0.003
Female	2 (5.0%)	12 (30.0%)	
Mean Age	57.58 (6.53%)	55.80 (7.00%)	0.215
Comorbidity	**Present**	**Absent**	
HTN	6 (7.5%)	74 (92.5%)	-
T2DM	9 (11.2%)	71 (88.8%)	
Thyroid Disease	2 (2.5%)	78 (97.5%)	
CAD	5 (6.2%)	75 (93.8%)	
CVA	3 (3.8%)	77 (96.2%)	
CKD	4 (5.0%)	76 (95.0%)	
Old TB	25 (31.2%)	55 (68.8%)	
Asthma	2 (2.5%)	78 (97.5%)	
Investigations			**p-Value**
Hemoglobin (mg%)	12.40 ± 2.03	11.30 ± 2.43	0.031
TLC (mL)	8142.75 ± 2972.73	8577.25 ± 3090.02	0.427
Platelets Counts (mL)	230395.00 ± 89757.88	229800.00 ± 71762.50	0.946
Eosinophil Count (%)	4.10 ± 2.35	3.42 ±1.74	0.240
Absolute Eosinophil Count (mL)	335.58 ± 203.82	298.58 ± 188.95	0.303
Neutrophil Count (%)	69.00 ± 6.62	66.95 ± 7.08	0.138
Absolute Neutrophil Count (mL)	5790.65 ± 2483.31	5875.68 ± 2646.40	0.866
Urea (mg/dL)	43.38 ±18.28	44.67 ± 22.99	0.950
Creatinine (mg/dL)	0.98 ± 0.66	1.14 ± 1.26	0.706
Total Bilirubin (mg/dL)	0.94 ± 0.33	0.94 ± 0.56	0.395
Direct Bilirubin (mg/dL)	0.41 ± 0.25	0.42 ± 0.31	0.911
SGOT (U/L)	68.03 ± 95.95	50.23 ± 33.43	0.450
SGPT (U/L)	48.27 ± 28.32	44.83 ± 25.60	0.433
ALP (IU/L)	90.35 ± 26.28	87.03 ± 19.93	0.513
Inflammatory Biomarkers			**p-Value**
ESR (mm/Hr)	24.50 ± 7.04	19.10 ± 7.09	0.001
CRP (mg/L)	43.76 ± 24.62	28.31 ± 27.22	<0.001
Fibrinogen (ng/mL)	349.61 ± 126.53	416.85 ± 88.06	0.006
Il-5 (pg/mL)	50.60 ± 35.95	50.67 ± 31.04	0.847
Il-6 (pg/mL)	56.23 ± 50.38	40.07 ± 34.99	0.204

The mean of ESR in smoker COPD group was 24.50 ± 7.04) and non-smoker COPD group was 19.10 ± 7.09). Between the 2 groups in terms of ESR p- value was 0.001 which was statistically significant, with the median ESR being highest in the smoker COPD group. The area under the ROC curve (AUROC) for ESR showing smoker versus non-smoker COPD was 0.723 (95% CI: 0.609 - 0.836), thus explaining fair diagnostic performance and this difference was statistically significant (p = 0.001). At a cut-off of ESR (mm/Hr) ≥18, it predicts smoker COPD with a sensitivity of 85%, and a specificity of 50%.

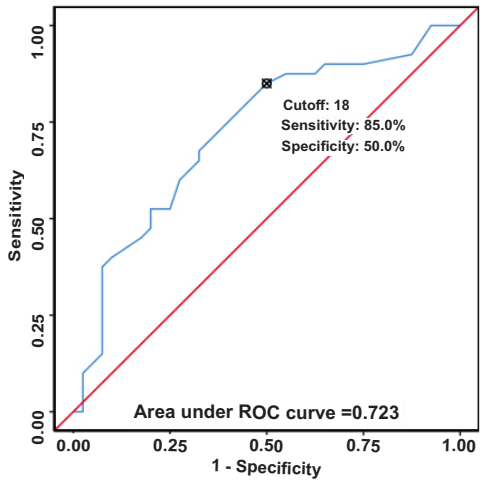

Figure 1: ROC Curve Analysis Depicting Diagnostic Performance of ESR (mm/Hr) in Predicting Smoker versus Non-Smoker COPD

CRP: The mean of CRP in smoker COPD group was 43.76 (± 24.62) and in non-smoker COPD group was 28.31 ± 27.22); this difference in CRP was significant. Median CRP being highest in the smoker COPD group. The area under the ROC curve (AUROC) for CRP predicting smoker versus non-smoker COPD was 0.762 (95% CI: 0.649 - 0.876), thus demonstrating fair diagnostic performance. Difference between two groups for CRP was statistically significant (p0.001). At a cut-off of CRP (mg/L) ≥24.3, it predicts patients with smoker COPD with a sensitivity of 90%, and a specificity of 67.5%.

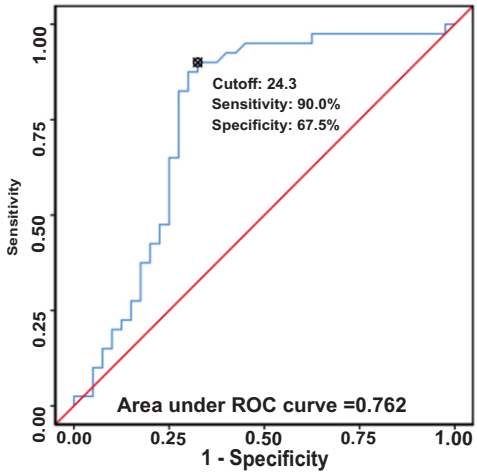

Figure 2: ROC Curve Analysis Depicting Diagnostic Performance of CRP (mg/L) in Predicting Smoker versus Non-Smoker COPD

The mean fibrinogen (ng/mL) were 349.61 ± 126.53 and 416.85 ± 88.06 in smoker and non-smoker COPD groups respectively; p – value between groups were significant (p= 0.006). The area under the ROC curve (AUROC) for Fibrinogen predicting smoker versus non-smoker COPD

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was 0.68 (95% CI: 0.559 - 0.801), hence depicting poor diagnostic performance. Difference between two groups were statistically significant (p = 0.006). At a cut-off of fibrinogen (ng/mL) ≤396, it predicts patients with smoker COPD with a sensitivity of 62.5%, and a specificity of 72.5%.

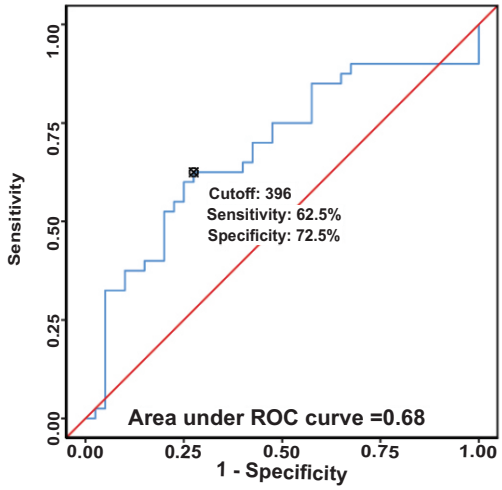

Figure 3: ROC Curve Analysis Showing Diagnostic Performance of Fibrinogen (ng/mL) in Predicting Smoker versus Non-Smoker COPD

The mean of Il-5 (pg/mL) in smoker COPD group was 50.60 ± 35.95, in nonsmoker COPD group was 50.67 (± 31.04). The AUROC for Il-5 (pg/mL) predicting smoker versus non-smoker was 0.513 (95% CI: 0.382 - 0.643), hence its diagnostic value was not good. It was not statistically significant (p = 0.847). At a cut-off of Il-5 (pg/mL) ≥50, it predicts smoker COPD with a sensitivity of 62%, and a specificity of 60%. The mean of Il-6 (pg/mL) in smoker COPD group was 56.23 (± 50.38), in non-smoker COPD group was 40.07 (± 34.99). AUROC for Il-6 predicting smoker versus non-smoker COPD was 0.583 (95% CI: 0.455 - 0.71), thus diagnostic performance of Il-6 was not good. Difference between groups were statistically not significant (p = 0.204). At a cut-off of Il-6 (pg/mL) ≥47.69, it predicts smoker COPD with a sensitivity of 50%, and a specificity of 75%.

Table 2 below depicted the mean of various spirometric test parameters among patients under smoker COPD and non-smoker COPD. There was significant difference between the two groups regarding all the spirometric test parameters, with all the parameters being greater in the patients categorized under smoker COPD group.

Table 2: Comparison of Mean of Spirometric Parameters between Smoker and Non-Smoker COPD

Variables	Smoker COPD (Mean ± SD)	Non-smoker COPD (Mean ± SD)	p-Value
FEV_1 (Liter)	1.75 ± 0.62	1.31 ± 0.52	0.001
FEV_1 (%)	67.80 ± 16.24	57.25 ± 18.33	0.010
FVC (Liter)	3.60 ± 0.71	3.09 ± 0.67	0.001
FVC (%)	106.60 ± 15.06	98.70 ± 15.93	0.0019
FEV_1/FVC	62.91 ± 9.37	57.03 ± 12.88	0.012

In table 3 variables between three sub-groups of COPD according to Refined ABCD Assessment Tool was described. The mean of mMRC Score was 1.20 ± 0.91 and 1.20 ± 0.82 in smoker COPD versus non-smoker COPD respectively. However, this difference between groups were not significant. (p = 0.946) Out of the patients under smoker COPD, 22.5% had mMRC-0, 45.0% had mMRC-1, 22.5% had mMRC-2 and 10% had mMRC-3. Out of patients under non-smoker COPD, 20.0% had mMRC-0, 48.8% had mMRC-1, 22.5% had mMRC-2 and 8.8% had mMRC-3. The mean of CAT score in smoker COPD group was 18.00 (± 8.48) non-smoker COPD group was 18.65 (± 6.76). There was no significant difference between the groups in terms of total CAT score, or in any individual component of CAT score. Out of all the patients recruited for the study, it was found that 9 patients belonged to category A (6 in smoker COPD, 3 in non-smoker COPD), 66 patients belonged to category B (30 in smoker COPD, 36 in non-smoker COPD), and 5 patients belonged to category C subgroup (4 in smoker COPD, 1 in non-smoker COPD), according to the Refined ABCD Assessment Tool. Category D patients were not included in this study. The parameters which had significant difference (p-value<0.05) between various subgroups of COPD were Eosinophil Count (%), mMRC Score, CAT Score: Cough, CAT Score: Phlegm, CAT Score: Chest Tightness, CAT Score: Breathlessness, CAT Score: Activities, CAT Score: Confidence, CAT Score: Energy, CAT Score: Total, FEV1 (%), FVC (Litre), FVC (%), FEV1/FVC. Rest other parameters were not statistically significant.

Table 2 : Comparison of Parameters with significant difference between three Sub-groups of COPD according to Refined ABCD Assessment Tool

Variables	Category A Mean ± SD / Frequency (%)	Category B Mean ± SD / Frequency (%)	Category C Mean ± SD / Frequency (%)	p-Value
Eosinophil Count	2.78 ± 1.92	4.00 ± 2.05	2.40 ± 2.19	0.045
mMRC Score	0.56 ± 0.53	1.33 ± 0.87	0.60 ± 0.55	0.008
mMRC Score				0.122
0	4 (44.4%)	10 (15.2%)	2 (40.0%)	-
1	5 (55.6%)	31 (47.0%)	3 (60.0%)	
2	0 (0.0%)	18 (27.3%)	0 (0.0%)	
3	0 (0.0%)	7 (10.6%)	0 (0.0%)	
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	
CAT Score: Cough	0.78 ± 0.83	2.98 ± 1.48	2.40 ± 0.55	<0.001
CAT Score: Phlegm	1.00 ± 0.87	2.88 ± 1.57	1.60 ± 1.52	0.002
CAT Score: Chest Tightness	1.89 ± 1.17	3.15 ± 1.32	1.40 ± 0.89	0.002

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CAT Score: Breath lessness	1.56 ± 1.24	3.08 ± 1.52	1.40 ± 1.52	0.005
CAT Score: Activities	1.00 ± 0.87	2.45 ± 1.38	0.80 ± 0.84	0.012
CAT Score: Confidence	0.78 ± 1.09	2.03 ± 1.40	1.00 ± 0.71	0.012
CAT Score: Energy	0.78 ± 0.83	1.92 ± 1.44	0.40 ± 0.55	0.004
CAT Score: Total	8.67 ± 1.50	20.30 ± 6.90	9.60 ± 0.55	<0.001
FEV_1 (%)	73.00 ± 19.33	60.59 ± 17.05	69.20 ± 23.88	0.044
FVC (Liter)	3.82 ± 0.56	3.25 ± 0.71	3.65 ± 0.94	0.042
FVC (%)	113.56 ± 13.45	100.59 ± 15.38	110.20 ± 19.56	0.041
FEV_1/ FVC (%)	63.53 ± 13.91	59.38 ± 11.09	61.24 ± 15.00	0.043

DISCUSSION

Multiple studies have been done in the past to compare the phenotypic difference as well as the systemic inflammation profile between the patients of smoker and non-smoker COPD. One such study was done by Rincon M *et al.* in 2017, significant difference was not observed between the two groups for age, body mass index, dyspnea, or oxygen saturation. Pulmonary function tests were also similar in both groups. Almost all inflammatory biomarkers were significantly higher in both COPD groups than in controls. Differences between tobacco COPD and biomass COPD were only significant in IL-6, IL-8 and IL-5, which were higher in the former group [10]. This was in contrary to this study, which established a significant difference between the two groups regarding ESR, CRP level and fibrinogen level. However, there was no significant statistical difference in terms of IL-5 and IL-6 in this study. Similar to this observations Garth J *et al.*, in 2024 from Lucknow (India) reported that males predominated in S-COPD (80.3%), while females predominated in NS-COPD (60.54%) because of more biomass fuel exposure in females during cooking. They also found 19% of non-smokers had TB. Contrary to this, we found 68.8% old TB cases in Nonsmoker group. This might be because in this hospital we get more patients from various states [15]. Pandey AK *et al.*, in 2020 observed higher levels of IL-8 and TNF-α in patients with COPD and higher smoking rate in the COPD group was considered to have contributed to these findings [16]. In another study by Yazici O *et al.*, in 2020, it was concluded that the mean age of the non-smoker COPD (NS-COPD) subjects was significantly less. The smoker COPD (S-COPD) patients were all male; whereas 53% of NS-COPD were male and 47% were female. NS-COPD subjects had lower FVC values than S-COPD, but no differences were observed for other spirometric parameters. NS-COPD subjects had similar CAT score to S-COPD subjects. Further, NS-COPD subjects had significantly greater serum CRP levels than healthy subjects and no difference from S-COPD subjects. Also, S-COPD subjects had higher blood hemoglobin, RBC counts, PCV and MCV compared to NS-COPD subjects [17]. This was in part similar to this study, where it was shown that smoker COPD patients were predominantly males, had higher hemoglobin, greater spirometric parameters. While, on the contrary, we had established significant difference in CRP levels between the two groups. Studied by Salvi SS *et al.*, in 2020 on an Egyptian population, they estimated IL-6 levels and correlated with severity and frequency of COPD. They observed that decrease in smoking index will associate the increased in IL-6 levels, this negative correlation was significant. But this was contrary to this study results. Moreover, they found significant positive correlation with between the level of IL-6 and each CAT score and MMRC among cases with COPD [18]. Reported by Huhang H that levels of IL-6 was a better predictor of the frequency of acute exacerbation of COPD rather than in stable COPD cases; hence in this study we could not find significant difference between these groups as they were stable cases as we have excluded Group D patients [19]. IL-5 was a homodimer cytokine involved in eosinophil differentiation, recruitment, maturation, activation and degranulation. Stated by Narendra DK *et al.*, that airway eosinophilia has been shown to predict an increased risk of exacerbations and lung tissue and airway remodelling as well as an increased expression of interleukin (IL)-5. In current study differences between eosinophil level and IL-5 were not significant, this might be due to only stable COPD cases were taken in this study [20]. Strengths of this study was that it has a good sample size of 80 patients thus giving a more accurate prediction of prevalence and association of smoking with inflammatory biomarkers.This study also had certain limitations. Patients were from single center only. So, the results of this study cannot be applied to a larger population or to a different geographical region. In current study healthy controls were not enrolled; so unable to know the baseline values of studied inflammatory markers in healthy control group.

CONCLUSIONS

This study found significant difference between smoker versus nonsmoker COPD patients, hence these inflammatory biomarkers can be used as a screening tool between smoker and non-smoker COPD patients, for a more focused approach to treatment. This also recommended large multi-centric studies to identify cut off for inflammatory biomarkers for bedside screening of non-smoker COPD patients.

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Authors Contribution

Conceptualization: SDM, AKV
Methodology: AKV, MM
Formal analysis: MM, EAA
Writing, review and editing: SDM, SN

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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