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Original Article

Internal Medicine Section

Correlation of Serum Surfactant Protein-B with Lung Function and Diffusion Abnormalities in Chronic Obstructive Pulmonary Disease: A Case-control Study

SAURAV SURESH[1], KEERTIVARDHAN D KULKARNI[2]

ABSTRACT

Introduction: Spirometry remains the cornerstone for the diagnosis and assessment of Chronic Obstructive Pulmonary Disease (COPD). However, it may not fully reflect the underlying structural lung injury, particularly in early disease and in older individuals. Surfactant Protein-B (SP-B) is a lung-specific molecule of particular interest, although its relationship with pulmonary function impairment in COPD is not well established.

Aim: To evaluate the correlation of serum SP-B levels with pulmonary function parameters and diffusion abnormalities in patients with COPD and to compare these findings with age-matched healthy controls.

Materials and Methods: This case-control study conducted in the Department of Respiratory Medicine, Shri B. M. Patil Medical College, Vijayapura, Karnataka, India. The study included 70 participants- 35 COPD patients and 35 age-matched healthy controls. Individuals over 50 years of age with either a smoking index greater than 10 pack-years or biomass exposure index above 30 were enrolled in the study. All participants underwent spirometry with Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) assessment as per American Thoracic Society (ATS) and European Respiratory Society (ERS) 2022 standards. Venous blood samples were collected, centrifuged and stored at -80°C and plasma SP-B levels were measured using a Human SP-B Sandwich ELISA Kit (AQTE01771, Aliquot Biotech). Parameters studied included COPD Assessment Test (CAT), modified Medical Research Council (mMRC) score, Forced Expiratory Volume in 1 second (FEV1%) predicted, post-bronchodilator FEV_1/FVC ratio, FEV_1 and FVC z-scores, DLCO, KCO (Carbon Monoxide Transfer Coefficient) and plasma SP-B levels. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 27.0, with p-value <0.05 considered statistically significant.

Results: A total of 70 participants were included in the study, comprising 35 COPD cases and 35 age-matched controls. The COPD group consisted of 26 males and nine females with a mean age of 66.31±6.45 years, while controls included 23 males and 12 females with a mean age of 64.34±7.03 years. Mean serum SP-B levels were significantly higher in COPD cases compared to controls (3.00±0.58 ng/mL vs 1.79±0.63 ng/mL). COPD patients demonstrated significantly lower mean FEV_1% predicted (42.97±12.18 vs 75.55±15.35), FVC % predicted (59.57±11.41 vs 74.31±14.18), post-bronchodilator FEV_1/FVC ratio (54.28±10.60 vs 78.14±6.11), and DLCO values (13.47±4.99 vs 16.13±5.79) compared to controls. Serum SP-B levels showed significant inverse correlations with FEV_1 % predicted, FVC % predicted, corresponding z-scores, and FEV_1/FVC ratio.

Conclusion: Serum SP-B is significantly elevated in COPD patients and demonstrated an inverse relationship with lung function parameters. SP-B shows considerable promise as a biomarker reflecting physiological impairment and alveolar injury in COPD patients.

Keywords: Airway obstruction, Biomarkers, Diffusing capacity of lung, Spirometry

INTRODUCTION

The COPD is a progressive lung disorder that occurs as a result of persistent inflammation and damage to the airways and alveoli. Nearly 400 million people worldwide are affected and the disease is on a rising trend. India alone accounts for 16.7% of the global disease burden, ranking second in both COPD prevalence and death [1]. The development of COPD reflects a complex interaction between genetic susceptibility and chronic exposure to noxious inhaled particles. These exposures result in inflammation driven structural and functional changes in the lungs that predominantly affect the small airways, which ultimately leads to airway wall thickening, luminal narrowing and parenchymal destruction [2]. According to Global initiative for Chronic Obstructive Lung Disease (GOLD) consensus, a diagnosis of COPD is made when a patient has symptoms of chronic cough or dyspnoea and spirometry shows a postbronchodilator FEV_1/FVC ratio below 0.7. This threshold is a mandatory criterion to establish a diagnosis of COPD [3].

Although this approach is convenient for routine clinical use, it often leads to overdiagnosis of the disease in elderly and does not account for physiological age-related decline in lung function. Moreover, this criterion has limited sensitivity in early disease and may not always align with the symptom burden [4,5]. The progression of COPD involves a complex interplay of chronic inflammatory pathways that produce structural and functional changes extending beyond the conducting airways to the alveolar-capillary interface. Since these pathological changes may occur long before significant deterioration in spirometric parameters is detected, there is growing interest in identifying circulating biomarkers that can reflect the ongoing pulmonary injury and disease severity. However, despite extensive research efforts, no blood-based biomarker has yet been incorporated into routine clinical practice for COPD [6,7].

Pulmonary surfactant is a complex mixture of phospholipids and proteins that maintains alveolar stability by reducing surface tension and preventing alveolar collapse during respiration. Approximately, 90% of surfactant consists of phospholipids, while the remaining

10% comprises surfactant-associated proteins, namely SP-A, SP-B, SP-C and SP-D. These proteins contribute not only to surfactant function but also to host defence, alveolar integrity and epithelial repair mechanisms [8]. Among these proteins SP-B and SP-C are highly hydrophobic molecule that are incorporated directly into the phospholipid layer of pulmonary surfactant. SP-B is synthesised almost exclusively by alveolar type II pneumocytes and non-ciliated bronchiolar epithelial cells and is essential for the spreading, stability and recycling of surfactant molecules within the alveoli [9]. Studies of SP-B deficiency have demonstrated severe disturbances in alveolar stability and gas exchange, underscoring its importance in maintaining normal respiratory physiology. This, combined with its high degree of lung specificity has led to interest in SP-B as a potential circulating marker of alveolar epithelial integrity [9,10].

Under normal physiological conditions, SP-B remains confined to the alveolar space and is largely absent from the systemic circulation. However, disruption of the alveolar–capillary barrier caused by inflammation, mechanical stress, emphysematous destruction or increased epithelial permeability permits the leakage of SP-B into bloodstream [10,11]. Elevated circulating SP-B levels have therefore been reported in conditions associated with alveolar injury, including cardiogenic pulmonary oedema, acute lung injury, severe pneumonia and Respiratory Syncytial Virus (RSV) infection [11-13]. Among the surfactant-associated proteins, SP-A and SP-D have received the greatest attention as potential biomarkers of lung disease. Elevated levels have been described in several lung diseases including COPD, interstitial lung diseases, pneumonia and acute respiratory distress syndrome [14,15]. However, since these proteins are not confined to the lungs and are also expressed in a number of extra-pulmonary tissues, their specificity for lung injury remains uncertain. SP-B differs in this regard, as its expression is largely restricted to the respiratory tract, making it a promising marker of alveolar epithelial disruption [9]. Despite this biological plausibility, evidence regarding its role in COPD remains limited [7]. Available studies [15,16] have involved relatively small sample sizes and have primarily focused on airflow obstruction and spirometric indices. Although elevated circulating SP-B levels and associations with lung function decline have been reported, its relationship with diffusion abnormalities, particularly DLCO, remains poorly characterised. Furthermore, data from populations with substantial exposure to both smoking and biomass fuel combustion are scarce [16,17]. To address these existing gaps, this study seeks to provide further evidence regarding the utility of SP-B as a marker of alveolar injury and disease severity in COPD. Therefore, the present study aimed to investigate the relationship between serum SP-B levels, pulmonary function parameters and diffusion abnormalities in patients with COPD and to compare these parameters with those observed in age-matched controls.

MATERIALS AND METHODS

This hospital-based case-control study was conducted in the Department of Respiratory Medicine at BLDE (Deemed to be University), Shri B.M. Patil Medical College, Vijayapura, Karnataka, India over an 18-month period from March 2024 to September 2025, involving 70 voluntary participants attending the outpatient clinic. A written informed consent was obtained from all participants prior to enrolment and the study protocol was approved by the Institutional Ethics Committee of BLDE (Deemed to be University) before commencement of the study (IEC no- BLDE (DU)/IEC-SBMPMC/021/2023-24), in accordance with ethical guidelines.

Sample size calculation: Based on the anticipated mean±SD, SP-B plasma levels in COPD patients and healthy smokers (4.72±3.2 and 1.78±1.50, respectively) reported in a previous study by D'Ascanio M et al., sample size was calculated using the formula $N=2\{(Z\alpha+Z\beta)\times SD/d\}^2$, where $Z\alpha$ corresponds to the standard normal deviate for a two-sided significance level of 5% (95% confidence level), $Z\beta$ corresponds to a study power of 95%, SD represents the common standard deviation, and d denotes the clinically significant difference between the two groups, a minimum sample size of 35 participants per group and a total of 70 participants was calculated to achieve 95% power and a two-sided significance level of 5% for detecting a true difference between the two groups [16].

Inclusion criteria: Individuals aged over 50 years with either a smoking index greater than 10 pack-years or a biomass exposure index exceeding 30 were included in the study.

Exclusion criteria: Participants with active tuberculosis, anaemia (defined as haemoglobin <13 g/dL in men and <12 g/dL in women), known cardiac disease, recent surgery, and pregnant or lactating women were excluded from the study.

Initially 78 patients were included in the study, seven were excluded due cardiac disease and one participant was excluded due to a diagnosis of tuberculosis during the course of the study.

Spirometry and DLCO were performed on all participants while adhering to 2022 ERS/ATS standards [18] and Third National Health and Nutrition Examination Survey (NHANES III) reference equations [19].

Study Procedure

The participants of the study were divided into COPD cases and controls on the basis of Global Initiative for Chronic Lung Disease 2025 COPD criteria [3] (post-bronchodilator $FEV_1/FVC < 0.7$).

Controls were age-matched individuals with similar smoking or biomass exposure but without spirometric evidence of COPD, defined as a post-bronchodilator FEV_1/FVC ratio of 0.7 or higher [3].

General and subjective measurements: After obtaining due consent for the study from all participants, the following parameters was recorded: anthropometric data (age, sex and body mass index), smoking status with number of packs per year or number of years of biomass exposure. In all patients, CAT [20], an eight-item questionnaire with scores ranging from 0 to 40 and mMRC dyspnoea scale [21] scores were assessed.

Lung function tests: Pulmonary function tests were conducted using ndd Easy One Pro Advanced Spirometer (Nachdruckdiagnostik Medical Technologies) adhering to 2022 ERS/ATS standards. Spirometry was performed to determine FEV_1, FVC, FEV_1/FVC and DLCO was measured using single breath technique to determine gas diffusion across the alveolar capillary barrier.

SP-B analysis: Following spirometry, a venous blood sample was obtained from all participants. Blood samples were collected into sodium citrate containing vacutainers and immediately centrifuged to separate plasma. The resulting plasma was separated, aliquoted and stored at -80°C until biomarker analysis was performed at the CAMR Laboratory, BLDEDU, Vijayapura [16].

Citrate-anticoagulated plasma was selected for this study because prior circulating SP-B biomarker studies by Magrì D et al., (2009), D'Ascanio M et al., (2023) and Agostoni P et al., employed citrate plasma for ELISA-based quantification of SP-B. SP-B concentrations were measured using a human SP-B Sandwich ELISA kit (AQTE01771 by Aliquot Biotech), following the manufacturer's instructions [11,16,22]. All laboratory measurements and clinical variables were recorded and compiled into a master chart database for subsequent statistical analysis.

STATISTICAL ANALYSIS

Data were analysed using SPSS Software, Version 27.0. Continuous variables were expressed as mean±standard deviation and comparisons were performed using student's t-test. Independent student's t-test was used for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed variables and Chi-square test for categorical variables. Correlation between SP-B and spirometry parameters was assessed using Spearman's

rho two tailed test. A two tailed p-value < 0.05 was considered statistically significant.

RESULTS

The COPD cases had significantly higher symptom burden (mMRC and CAT scores) and markedly elevated serum SP-B levels compared to controls, despite comparable age, sex distribution and BMI. All male COPD patients were smokers, whereas all female COPD patients had a history of significant biomass fuel exposure [Table/Fig-1].

Data	Cases (n=35) M±SD	Controls (n=35) M±SD	p-value
Age (years)	66.31±6.45	64.34±7.03	0.226
BMI (kg/m^2)	22.02±4.27	22.84±4.38	0.312
mMRC score	2.94±0.34	2.11±0.47	p<0.001
CAT score	25.17±4.13	17.51±4.95	p<0.001
Mean SP-B (ng/mL)	3.00±0.58	1.79±0.63	p<0.001
Gender, M/F	26/9	23/12	0.434

[Table/Fig-1]: Baseline demographic and clinical profile of COPD cases and controls.

The COPD patients demonstrated significantly greater airflow limitation and impaired gas-transfer capacity as evidenced by lower FEV_1% predicted, FVC% predicted, FEV_1 and FVC Z-scores, FEV_1/FVC ratio and DLCO values compared with controls. However, KCO did not differ significantly between groups, suggesting that an overall diffusion impairment was more prominent than diffusion efficiency per unit lung volume [Table/Fig-2].

Parameter	Cases (mean±SD)	Controls (mean±SD)	p-value (Mann-Whitney test)
FEV1 % predicted	42.97±12.18	75.55±15.35	<0.001
FVC % predicted	59.57±11.41	74.31±14.18	<0.001
Post Bronchodilator FEV1/FVC	54.28±10.60	78.14±6.11	<0.001
Z score FEV1	-3.58±1.24	-1.54±1.19	<0.001
Z score FVC	-3.16±0.79	-1.48±0.85	<0.001
DLCO Z-score	-2.04±1.31	-1.37±1.43	0.035
DLCO (mL/min/mmHg)	13.47±4.99	16.13±5.79	0.035
KCO (mL/min/mmHg/L)	4.19±2.67	3.97±1.22	0.573

[Table/Fig-2]: Baseline pulmonary function and diffusion parameters in COPD cases and controls.

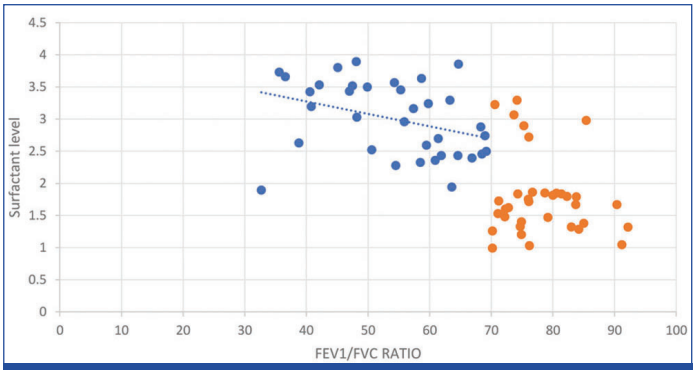
Increasing serum SP-B levels were associated with worsening airflow limitation and reduced lung volumes in COPD patients. In contrast, no consistent relationship between SP-B and spirometric indices were observed among controls [Table/Fig-3].

Parameter	Correlation of cases (ρ, p-value)	Correlation of controls (ρ, p-value)
FEV_1 % predicted (NHANES III)	ρ=-0.520, p=0.001	ρ=0.155, p=0.374
FEV_1 Z score (NHANES III)	ρ=-0.428, p=0.010	ρ=0.197, p=0.258
FVC % predicted (NHANES III)	ρ=-0.569, p<0.001	ρ=0.164, p=0.347
FVC Z score (NHANES III)	ρ=-0.752, p<0.001	ρ=-0.212, p=0.221
FEV_1/FVC Z score (NHANES III)	ρ=-0.403, p=0.017	ρ=0.069, p=0.695
DLCO Z-score (NHANES III)	ρ=-0.275, p=0.111	ρ=-0.392, p=0.020
DLCO (mL/min/mmHg)	ρ=-0.318, p=0.063	ρ=-0.386, p=0.022
KCO (mL/min/mmHg/L)	ρ=-0.243, p=0.159	ρ=-0.155, p=0.373

[Table/Fig-3]: Spearman correlation of serum SP-B with lung function parameters in COPD cases and controls.

Serum SP-B levels showed a negative association with post-bronchodilator FEV_1/FVC ratio, indicating that increasing SP-B concentrations were associated with worsening airflow limitation [Table/Fig-4].

Mean serum SP-B levels increased progressively from GOLD stage II to GOLD stage IV COPD, demonstrating a stepwise relationship between SP-B concentration and disease severity [Table/Fig-5].



[Table/Fig-4]: Scatter plot of serum SP-B levels versus post-bronchodilator FEV_1/FVC ratio among COPD cases and controls.

Mean serum SP-B levels showed a progressive increase across categories of worsening DLCO impairment; however, correlation analysis did not demonstrate a statistically significant association between SP-B and DLCO in COPD patients [Table/Fig-6].

GOLD Stage	COPD Severity	N (%)	Mean serum SP-B Level (ng/mL) and SD
GOLD I	Mild COPD	0	No participants included
GOLD II	Moderate COPD	9 (25.7)	2.5 (2.42±0.21)
GOLD III	Severe COPD	22 (62.9)	3.0 (3.14±0.55)
GOLD IV	Very severe COPD	4 (11.4)	3.3 (3.53±0.14)

[Table/Fig-5]: Distribution of COPD cases according to GOLD stage and corresponding mean serum SP-B levels.

DLCO severity-(Cases)	DLCO Z-score range	n	Mean SP-B (ng/mL) and S.D	DLCO severity-(Controls)	DLCO Z-score range	n	Mean SP-B (ng/mL) and SD
Normal DLCO	> -1.64	11	2.73±0.48	Normal DLCO	>-1.64	18	1.55±0.39
Mild DLCO reduction	-1.65 to -2.50	7	3.05±0.57	Mild DLCO reduction	-1.65 to -2.50	11	2.02±0.73
Moderate DLCO reduction	-2.51 to -4.00	15	3.30±0.61	Moderate DLCO reduction	-2.51 to -4.00	6	2.62±0.72
Severe DLCO reduction	<-4.1	2	3.31±0.16	Severe DLCO reduction	<-4.1	0	—

[Table/Fig-6]: Mean serum Surfactant Protein-B (SP-B) levels across stages of DLCO in cases and controls.

DISCUSSION

This study evaluated the relationship between serum SP-B levels, pulmonary function parameters and diffusion abnormalities in patients with COPD, compared with age-matched controls who had significant exposure to known risk factors. COPD patients had a significantly greater symptom burden, reflected by higher CAT and mMRC scores than controls. A male predominance was observed among COPD cases, with smoking being the principal exposure among men, while biomass fuel exposure was observed as the cause for COPD among women. BMI did not differ significantly between cases and controls and showed no significant relationship with serum SP-B levels. The observed male predominance was consistent with the systematic review and meta-analysis by Al Wachami N et al., which reported a higher global prevalence of COPD among men which was largely attributed to greater tobacco exposure and occupational risk factors [23]. Although smoking remains the leading risk factor for COPD worldwide, biomass fuel exposure continues to contribute substantially to disease burden in low- and middle-income countries, particularly among women exposed to indoor biomass smoke [17,23].

With regard to anthropometric characteristics, Wu Z et al., reported that a lower BMI was associated with poorer lung function and greater disease severity in COPD patients [24]. In contrast, the present study found no significant relationship between BMI and serum SP-B levels, suggesting that circulating SP-B may reflect alveolar epithelial injury independent of nutritional status. This finding was supported by Mathur S et al., who noted that many COPD patients maintain a normal BMI despite significant skeletal muscle loss due to preservation of fat mass [25]. Collectively, these findings indicate that serum SP-B is more closely associated with pulmonary structural injury than with anthropometric measures such as BMI.

The principal finding of this study was that serum SP-B levels were significantly higher in COPD patients than in controls and were inversely correlated with FEV_1% predicted, FVC% predicted, and the FEV_1/FVC ratio. Similar associations were observed when spirometric indices were analysed using Global Lung Function Initiative (GLI) derived Z-scores in accordance with the 2022 ERS/ATS interpretative recommendations [26]. The use of NHANES III reference equations further ensured standardisation and comparability of spirometric measurements with previous studies. These results are consistent with those of Kim SJ et al., who demonstrated a progressive decline in lung function with increasing COPD severity and advancing age [27]. SP-B is a lung-specific protein synthesised by type II pneumocytes and non-ciliated bronchiolar epithelial cells. Under normal conditions, it remains confined to the alveolar space and enters the circulation only when the alveolar-capillary membrane is disrupted by mechanical, inflammatory or hydrostatic stress. Given its essential role in maintaining alveolar stability, SP-B dysfunction may contribute to alveolar collapse, reduced lung compliance and worsening hyperinflation [10].

Supporting these observations, Leung JM et al., reported that pro-SP-B a precursor of SP-B produced by type II pneumocytes, showed significant negative correlations with airflow obstruction and was strongly associated with emphysema burden on CT imaging [28]. Spearman correlation analysis demonstrated significant inverse relationships between serum SP-B levels and major spirometric indices, with higher SP-B concentrations associated with lower FEV_1 % predicted, FVC % predicted and FEV_1/FVC ratio. The stronger correlation observed with FVC may suggest a closer relationship between SP-B and emphysematous remodelling rather than airway obstruction alone. This interpretation is supported by the progressive increase in SP-B levels across GOLD stages II-IV. Similar inverse correlations between SP-B, FEV_1% predicted, and FEV_1/FVC ratio were reported by D'Ascanio M et al., in COPD patients compared with smokers without COPD [16]. Diffusion studies demonstrated significantly lower DLCO and KCO values in COPD patients than in controls. Reduced DLCO Z-scores likely reflect loss of alveolar-capillary surface area and impairment of gas exchange associated with emphysematous lung damage. Although D'Ascanio M et al., did not observe a significant relationship between SP-B and DLCO, this study identified a weak negative correlation between SP-B and DLCO Z-score, suggesting a trend toward higher SP-B levels with worsening diffusing capacity. However, this association did not reach statistical significance [16]. Similarly, no significant correlation was observed between SP-B and KCO. Overall, these findings suggest that serum SP-B reflects alveolar epithelial damage and may provide additional insight into the structural component of COPD when interpreted alongside conventional measures such as spirometry and DLCO.

Previous studies have shown that circulating SP-Bs increase in response to pulmonary epithelial injury. Wang SZ et al., reported significantly elevated plasma SP-B levels in infants with RSV bronchiolitis, supporting the sensitivity of SP-B as a marker of acute viral epithelial injury in the lungs [13]. Among surfactant-associated proteins, SP-D has been extensively studied as a biomarker of alveolar-capillary membrane injury. Cedzyński M and Świerzko AS reviewed evidence demonstrating elevated circulating SP-D levels in a range of respiratory disorders, including interstitial lung diseases, asthma, COPD, ARDS and bacterial/viral pneumonia, reflecting its role in innate immunity and surfactant homeostasis [29]. Elevated SP-D levels have also been reported in metabolic conditions such as obesity and diabetes, likely through inflammatory pathways involving adipocytes and vascular endothelium [29]. This broader association may be explained by the presence of SP-A and SP-D in several extra-pulmonary tissues, including the skin, gastrointestinal tract, kidneys, reproductive organs, brain, cornea and vascular endothelium, which limit their specificity for lung injury [29].

In contrast, SP-B is synthesised almost exclusively by alveolar type II pneumocytes and bronchiolar epithelial cells, making it a highly lung-specific marker of alveolar integrity and a potentially valuable biomarker for diseases such as COPD [9].

Limitation(s)

The absence of a radiological quantification, including High-Resolution Computed Tomography (HRCT)-based emphysema scoring, prevents direct comparison of SP-B levels with the extent of parenchymal destruction. In addition, SP-B is a small, highly hydrophobic molecules that require strict subzero preservation, posing challenges in its storage, transport and analytical stability. Another limitation is the lack of standardisation in SP-B measurement. Variability between commercially available assay platforms may contribute to differences in reported values across studies, thereby complicating comparisons and limiting the establishment of clinically applicable reference ranges.

CONCLUSION(S)

In this case-control study, serum SP-B levels were significantly higher in patients with COPD than in age-matched controls. Elevated SP-B showed consistent inverse correlations with key spirometry indices, particularly FEV_1 and FVC, underscoring its close association with physiological impairment. Unlike SP-A and SP-D, which lack lung specificity due to extra-pulmonary expression, SP-B appears to be a more lung-specific indicator of alveolar-capillary injury. The absence of correlation with symptom scores suggests that SP-B reflects underlying structural and functional lung damage rather than subjective disease burden. These findings highlight the potential clinical utility of SP-B as a complementary biomarker for detecting alveolar injury, refining disease severity assessment.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Resident, Department of Respiratory Medicine, Shri B.M. Patil Medical College, Vijayapura, Karnataka, India.
2. Professor and Head, Department of Respiratory Medicine, Shri B.M. Patil Medical College, Vijayapura, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Saurav Suresh,
211, Agasthya Boys Hostel, Shri B.M. Patil Medical College, Bangaramma Sajjan Campus, BLDE DU, Solapur Road, Vijayapura-586103, Karnataka, India.
E-mail: sauravsuresh@gmail.com

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