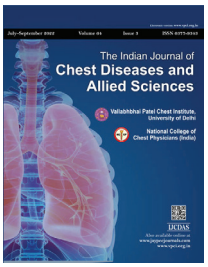
ORIGINAL ARTICLE

High-resolution Computed Tomography Findings and Serum Biomarker of Subclinical Interstitial Lung Disease in Moderate-to-severe Obstructive Sleep Apnea Patients



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Abstract

Background: Obstructive sleep apnea (OSA) has association with many comorbidities. Based on the postulated hypothesis from few studies, the primary objective of this study was to assess the occurrence of subclinical interstitial lung disease in moderate-to-severe OSA patients.

Materials and methods: It was a prospective observational study, conducted at a tertiary care chest institute of India, 43 moderate-to-severe OSA patients diagnosed by level-I polysomnography were enrolled. All the patients underwent detailed clinical examination with high-resolution computed tomography (HRCT) chest, pulmonary function test (PFT), and serum markers MMP-1,7, SP-A, and Krebs von den Lungen-6 (KL-6). Subclinical interstitial lung disease (ILD) was identified based on the two validated measures: high-attenuation areas (HAA), defined as the percentage of imaged lung volume having computed tomography (CT) attenuation between −600 and −250 HU and interstitial lung abnormalities (ILA), defined as the presence of ground-glass, reticular abnormality, diffuse centrilobular nodularity, honeycombing, traction bronchiectasis, nonemphysematous cysts, or architectural distortion in at least 5% of nondependent portions of the lung in HRCT chest without respiratory symptoms with preserved lung function.

Results: The mean age was 54.33 ± 11.5 years with 22 (51%) males. The mean apnea–hypopnea index (AHI) was 42.38 ± 27.6 with BMI >30 kg/m^2 in 18 (42%) patients. The subclinical ILD was diagnosed in 12 patients. The HRCT finding of ILA was seen in 12 and high-attenuation areas (HAA) in 5 patients. The serum markers were higher in subclinical ILD compared with non-ILD OSA patients, however, only the level of MMP-7 was significantly higher in subclinical ILD patients.

Conclusion: It was concluded that subclinical ILD is quite common among OSA patients with HRCT findings seen in nearly 30% of cases. This supports the hypothesis that OSA may be considered as a risk factor of subclinical ILD.

Keywords: Biomarker, High-resolution computed tomography chest, Obstructive sleep apnea, Subclinical ILD.

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Abbreviations used in this Article

AHI = Apnea–hypopnea index; CT = Computed tomography; HAA = High-attenuation areas; HRCT = High-resolution computed tomography; HP = Hypersensitivity pneumonitis; IPF = Idiopathic interstitial fibrosis; ILD = Interstitial lung diseases; ILA = Interstitial lung abnormalities; KL-6 = Krebs von den Lungen-6; *MMP = Matrix metalloproteinase;* OSA = Obstructive sleep apnea; PFT = Pulmonary function test; SP = Surfactant protein; 6MWT = 6-minute walk test; oAHI = Obstructive apnea–hypopnea index; FVC = Forced vital capacity

Introduction

Obstructive sleep apnea is defined as a sleep-related breathing disorder characterized by the recurrent collapse of the pharyngeal airway during sleep, resulting in substantially reduced (hypopnea) or complete cessation (apnea) of airflow, despite ongoing breathing efforts.[1] Obstructive sleep apnea is classified into mild, moderate, and severe as per AHI. The prevalence of OSA varies according to age, study population, and definition of hypopnea.[2,3] The estimated prevalence of symptomatic OSA is 3–8% in men and 1–5% in women.[4] Obstructive sleep apnea is associated with increased incidence of hypertension, diabetic mellitus, heart failure, coronary artery disease, stroke, and death.[1,5] There is lack of data on true prevalence of OSA from India. Various studies in the last decade in India reported that the prevalence of OSA was nearly 3–4%.[6,7]

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Interstitial lung disease refers to a heterogeneous collection of more than one hundred distinct lung disorders that tend to be grouped together because they share clinical, radiographic, and pathologic features.[8] The overall prevalence and incidence of total ILDs are varying according to the study population and geographical location with sarcoidosis and idiopathic interstitial fibrosis (IPF) being the common subtypes.[9,10] The studies from India also have shown variable prevalence of different subtypes of ILD with slight difference from developed countries. The common types of ILDs documented in India are IPF, sarcoidosis, and HP.[11–13] The subclinical ILD encompasses a group of individuals who have specific radiological, physiological, and in some cases, histopathological abnormalities but are either asymptomatic or have symptoms that have not been attributed to ILD. As per the available studies, the prevalence of subclinical ILD in a few selected populations were 35% in familial pulmonary fibrosis, 46% in connective-tissue disease, 5% in smoker, and 15% in postoperative patients.[14] The study of preclinical/subclinical disease before the advent of advanced parenchymal disease could help in understanding the novel biological pathways involved in the pathogenesis of ILD at an earlier stage amenable for intervention.[15] Subclinical interstitial lung disease has two validated phenotypes – high-attenuation areas (HAA), a quantitative assessment marker, and ILA, a qualitative marker visually evident in HRCT chest.[16,17] Obstructive sleep apnea causes subclinical lung injury due to tractional stress and oxidative free radical-induced damage through hypercapnic microRNA induction.[18–20] The sleep-related breathing disorders are quite common in ILD patients and as per recent review, it was seen in 44–72% patients.[21] The coexistence of both the diseases further increases the symptoms, makes difficulty in diagnosis, increases the morbidity, and decreases the quality of life. Kim et al. in a cross-sectional analysis found that 32% of the case population who had an obstructive apnea–hypopnea index (oAHI) >15, was associated with 4% HAA increment and 35% increased odds of ILA with higher serum surfactant protein-A (SP-A) and *matrix metalloproteinase-7* (MMP-7) levels.[16] The aim of this study is to assess the occurrence of subclinical ILD in patients with moderate-to-severe OSA and correlate the AHI with various biomarkers of subclinical lung injury.

Materials and Methods

This study was a prospective cross-sectional study conducted at one of the tertiary care chest institutes of India from April 2018 to March 2019. The study was carried out after the approval of the Institutional Ethics Committee. We enrolled 43 cases of moderate-to-severe OSA patients diagnosed by level-I polysomnography as per AASM guidelines[1] with the following inclusion and exclusion criteria. The inclusion criteria were: (1) age>18 years, (2) diagnosed cases of moderate-to-severe OSA, and (3) consent of the patients for participation, and exclusion criteria included were: (1) patients with insignificant sleep-disordered breathing, (2) pregnant females, (3) already diagnosed ILD, (4) history of exposure to any known risk factors of ILD, and (5) hemodynamically unstable and hypoxic patients. The enrolled patients underwent detailed history, clinical examination, and baseline laboratory evaluation followed by HRCT chest, PFT, 6-minute walk test (6MWT), and serum biomarkers of lung injury, including KL-6, MMP-1,7, and SP-A for the detection of subclinical interstitial lung disease.

High-resolution Computed Tomography Scan

The HRCT chest was performed on Toshiba Aquilion 64 machine (model TSX-102A). High-resolution computed tomography chest was done with 1 mm collimation for thin-section images to study the interstitial portion with contiguous 5 mm section for the whole lung at supine position and at prone position (if needed). All HRCT chest reports were reported by the radiologist as a standard hospital practice.

Subclinical ILD

Subclinical ILD was diagnosed based on the two validated measures of HRCT chest, as mentioned earlier, such as HAA and ILA with preserved forced vital capacity (FVC) without respiratory symptoms.[16]

Interstitial Lung Abnormalities

Interstitial lung abnormalities on HRCT chest was defined by the presence of centrilobular nodularity, reticular shadows, ground glass opacities, traction bronchiectasis, ill-defined subpleural opacities, nonemphysematous cysts, and honeycombing in >5% of nondependent portions of the lung.[16,17,22]

High-attenuation Areas

High-attenuation areas were a validated computed tomography (CT)-derived, quantitative phenotype of subclinical ILD, which was defined as the percentage of imaged lung volume with attenuation between −600 and −250 Hounsfield units.[16,17,23]

Serum Biomarkers

Serum levels of biomarkers of alveolar injury, including MMP-1, MMP-7, SP-A, and KL-6, are measured by ELISA technique with standardized kits according to the manufacturer's protocol and compared among the subclinical ILD and non-ILD groups. The correlation between the AHI and the above-mentioned serum biomarkers was also done.

6-minute Walk Test

The 6-minute walk test was performed in accordance with ATS guidelines.[24] The distance covered in 6 minutes was recorded in meters. To avoid interobserver variability, all tests were done by the same investigator.

Pulmonary Function Testing

Pulmonary function testing such as spirometry, detection of static lung volumes, and diffusion capacity of lung were done as per ATS guidelines.

Statistical Analysis

The variables collected were entered in Microsoft Excel (Office 2007 or higher) and analyzed using SPSS (version 19 or higher). Continuous data were presented as mean and standard deviation, while categorical data were presented as percentages. The data variables between the two groups were compared using unpaired *t*-test. The correlation coefficient was calculated by Pearson's correlation coefficient method. The value of $p < 0.05$ was considered statistical significance.

Results

The mean age was 54.33 ± 11.5 years with 22 (51%) males and 21 (49%) females. The mean AHI was 42.38 ± 27.6, with moderate OSA

in 19 (44.1%) and severe OSA in 24 (55.9%) cases. Only three patients among the males were smokers who had severe form of OSA, while there was no single smoker among the female patients. The mean BMI of all the enrolled patients was 31.19 ± 7.2 kg/m^2. The BMI was >30 kg/m^2 in 18 (42%), 25–30 kg/m^2 in 19 (44%), and <25 kg/m^2 in six patients. The most common symptoms were snoring in 40 (93%) and daytime sleepiness in 21 (48.8%) patients. The demographic details of the patients are shown in Table 1.

On chest X-ray, lung volume was reduced in four with overall abnormalities in nine patients. The most common abnormalities on X-ray were reticulonodular shadow in five, followed by reticular and nodular shadows in two patients each. On HRCT chest, the subclinical ILD was seen in 12 patients. Interstitial lung abnormalities such as centrilobular nodules in six, ground-glass opacities in five, reticular abnormalities in three, and one in each case of traction bronchiectasis with subpleural opacities and nonemphysematous cysts. The HAA were found in five patients. The details of HRCT findings and various patterns of abnormalities are shown in Table 2 and Figure 1. Out of 12 subclinical ILD findings, the HRCT findings were single abnormality in eight patients and multiple abnormalities in other four patients. Isolated centrilobular nodularity was seen in three patients who were non-smokers, isolated reticular abnormalities in two, and nonemphysematous cyst in a single patient. The details of various patterns of abnormalities in 12 subclinical ILD patients are shown in Figure 2.

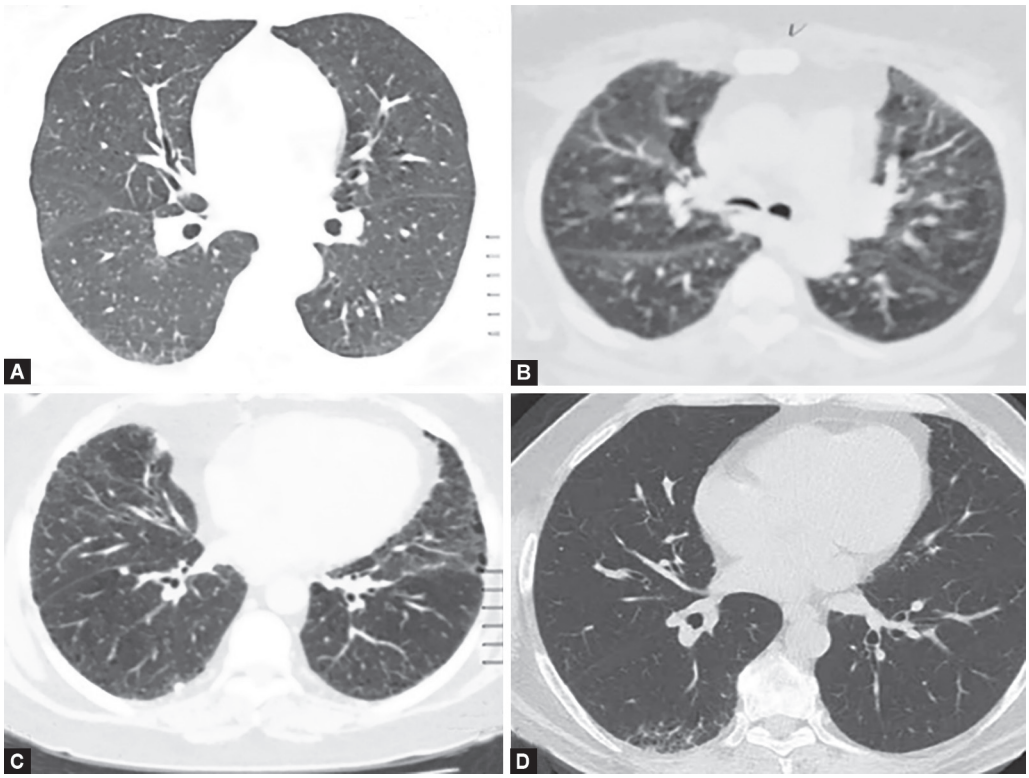
The PFT was done on all the enrolled patients. The lung function was preserved with mean forced vital capacity (FVC

Table 1: The demographic characteristics of OSA patients

Variable	*Number (%)*
Age in years (mean + SD)	54.33 ± 11.5
Male	22 (51)
Female	21 (49)
Symptoms	
Snoring	40 (93.0)
Daytime sleepiness	21 (48.8)
Witness apnea	6 (14.0)
Dryness of mouth	8 (18.6)
Morning headache	2 (4.7)
Smoker	3 (7%)
BMI (mean ± SD)	31.19 ± 7.2 kg/m^2
AHI (mean ± SD)	42.38 ± 27.6

Table 2: HRCT finding of subclinical ILD in OSA patients

HRCT finding	*Moderate OSA N (%)*	*Severe OSA N (%)*	*Total N (%)*
Centrilobular nodularity	2 (10.6)	4 (16.7)	6 (13.9)
Ground glass opacity	2 (10.6)	3 (12.5)	5 (11.7)
Reticular abnormality	2 (10.6)	1 (4.3)	3 (6.9)
Traction bronchiectasis	–	1 (4.3)	1 (2.3)
Non-emphysematous cyst	–	1 (4.3)	1 (2.3)
Subpleural opacities	–	1 (4.3)	1 (2.3)
High-attenuation areas	2 (10.6)	3 (12.5)	5 (11.7)



Figs 1A to D: (A) HRCT chest of OSA patient showing bilateral centrilobular nodularity; (B) Ground glass opacities in both lungs; (C) Bilateral nonemphysematous cystic lesions; (D) Reticular abnormality in right lower lobe

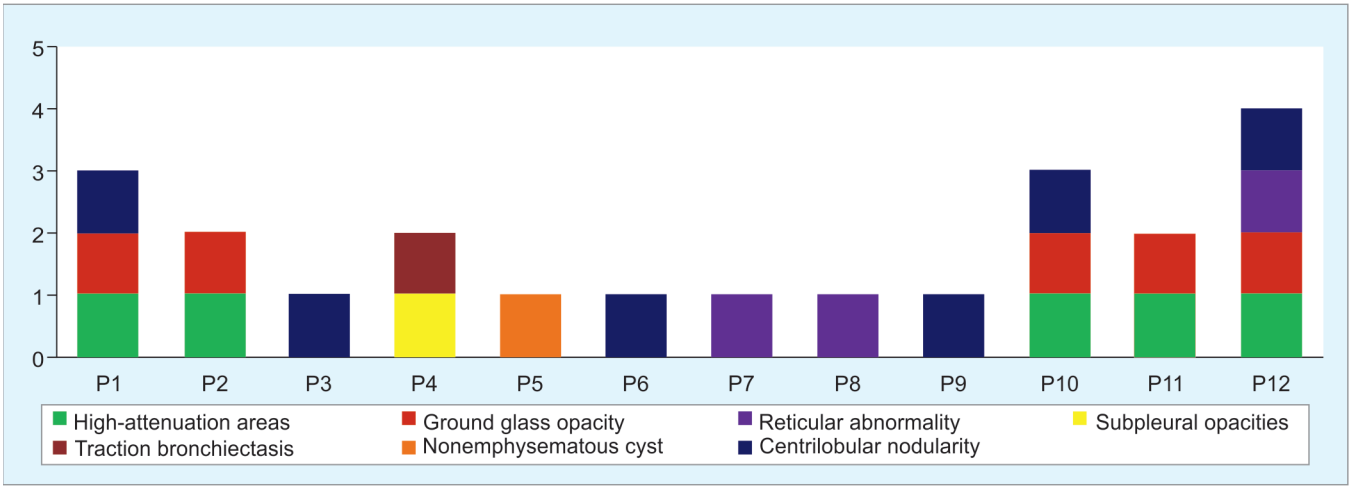


Fig. 2: The detail of various HRCT abnormalities in subclinical ILD patients. Each box represents one ILA or HAA as per above color code

pred. %) of 79.49 ± 17.13, forced expiratory volume in 1st second (FEV_1 pred. %) of 75.71 ± 20.87, FEV_1/FVC of 75.34 ± 14.32, total lung capacity (TLC pred. %) of 91.53 ± 21.68, diffusion for carbon monoxide (DLCO pred. %) of 94.41 ± 29.50, and residual volume (RV pred. %) of 106.93 ± 50.00 in all the patients. Even on comparison between the groups of subclinical ILD and non-ILD, there was no significant difference in the lung function parameters. The mean distance covered in 6MWT was 298.33 ± 90.64 meters. The majority of the patients, 41 (85%), covered >250 meters without desaturation of >4%. The mean distance covered by patients was 291.5 ± 32.65 meters in subclinical ILD and 304.34 ± 41.75 meters in non-ILD patients, with a statistically significant difference.

The serum biomarkers of alveolar injury, such as MMP-1, MMP-7, SP-A, and KL-6, were measured, and their levels were compared between the subclinical ILD and non-ILD patients. The mean value of MMP-1 was 909.5 ± 990.8 pg/mL in subclinical ILD and 802.2 ± 367.4 pg/mL in non-ILD patients, with no significant difference. The mean value MMP-7 was 1162.08 ± 816.7 pg/mL in subclinical ILD and 842 ± 65.8 pg/mL in non-ILD patients, with statistically significant difference ($p = 0.03$). The mean value of SP-A was 160.6 ± 109.04 ng/mL in subclinical ILD and 150.3 ± 73.6 ng/mL in non-ILD patients, with no significant difference. The mean value of serum KL-6 was 117 ± 69.03 ng/mL in subclinical ILD and 104.32 ± 52.8 ng/mL in non-ILD patients, with no significant difference. All the serum markers were elevated in subclinical ILD group, among which MMP-7 was elevated with a statistically significant difference ($p = 0.03$). The details of various serum biomarkers are shown in Table 3. The correlation between the serum biomarkers and AHI was done. Among subclinical ILD patients, MMP-7 showed positive correlation with AHI ($r = 0.74$, $p = 0.005$), while the level of MMP-1, SP-A, and KL-6 showed no significant correlation with AHI. The correlation of AHI with serum biomarkers is shown in Figure 3.

Table 3: Serum biomarker in subclinical ILD patients

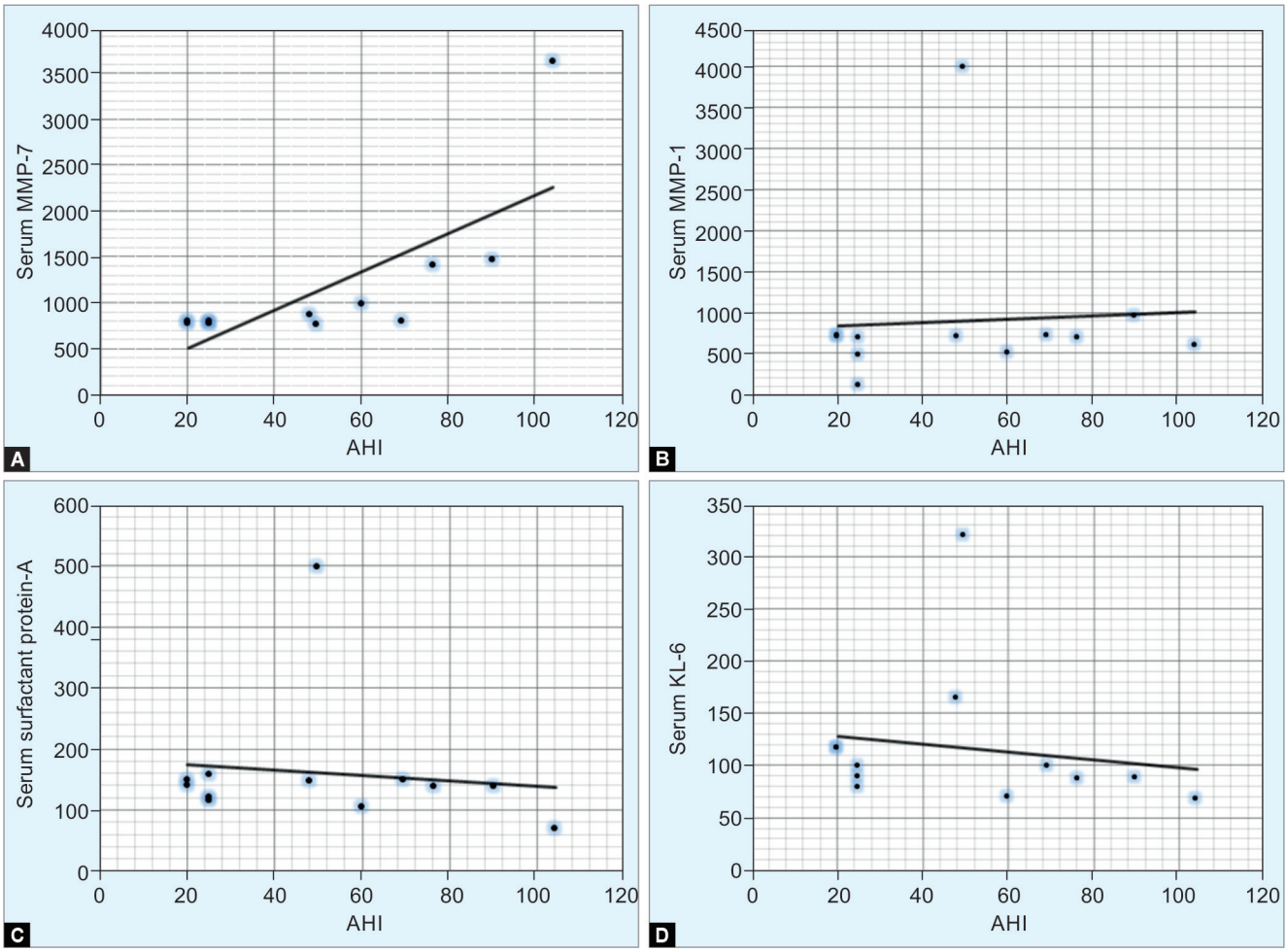
Serum markers	*Subclinical ILD*	*Non-ILD*	*p-value*
MMP-1	909.5 ± 990.8	802.2 ± 367.4	0.6
MMP-7	1162.08 ± 816.7	842 ± 65.8	0.03
SP-A	160.6 ± 109.04	150.3 ± 73.6	0.7
KL-6	117 ± 69.03	104.32 ± 52.8	0.5

Discussion

The clinical presentation of a disease in the form of various signs and symptoms is important for early diagnosis, treatment, and prevention of associated complications. However, the subclinical disease has been considered as an early stage of the disease before the development of a full-blown disease. Several epidemiologic studies had begun since the 1980s with an objective to measure the subclinical form of diseases and risk factors identified. Several studies have reported the incidence of subclinical ILD, among which most are from other countries, and the data from India are very scarce.[14,16,22] This study was done to generate evidence on the existing data of the occurrence of subclinical ILD in the moderate-to-severe OSA patients from India.

The standard radiological tool for diagnosis of subclinical ILD is HRCT chest which shows two phenotypes – ILA and HAA.[16] In our study that was done between April 2018 and March 2019, the subclinical ILD was defined based on the updated definition at that time period as mentioned earlier. The recently updated definition states that the subclinical ILD was defined as the extent of ILD <5% by semiquantitative assessment of baseline HRCT, preserved lung function with FVC >80%, and without respiratory symptoms.[25]

Podolanczuk et al. in a study concluded that HAA in the lungs of community-dwelling adults was associated with raised levels of serum MMP-7, IL-6, reduced FVC, reduced exercise capacity, increased odds of ILA on a 10-year follow-up, and higher mortality supporting that HAA is a novel quantitative phenotype of subclinical lung injury.[17] Choi et al. in a study found that the greater regional HAA in all lung regions was associated with higher odds of overall ILA. Their findings support the validity of HAA measurement for the detection of subclinical ILD.[26] Kim et al. in a cross-sectional analysis of 1690 community-dwelling adults of MESA study found that 32% subjects had an oAHI >15. An oAHI >15 was associated with a 4% HAA increment and 35% increased odds of ILA. Greater oAHI was associated with higher serum SP-A and MMP-7 levels. This large analysis concluded that moderate-to-severe OSA is associated with subclinical ILD along with the evidence of alveolar epithelial injury and extracellular-matrix remodeling.[16] In this study, it was found that 12 patients of moderate-to-severe OSA had subclinical ILD in the form of ILA in 12



Figs 3A to D: Correlation of serum biomarker with AHI. MMP-7 showed positive correlation with AHI while all other biomarkers showed no correlation with AHI

and HAA in five patients with preserved lung function. The presence of raised levels of serum biomarkers of alveolar injury supports the diagnosis of subclinical ILD. The role of serum biomarkers was investigated since last 30 years. However, till now, none are identified as a definitive marker for the diagnosis of ILD and many are under investigation.[27,28] The commonly studied markers for the diagnosis of various ILD are MMP-1, MMP-7, SP-A, SP-D, KL-6, MUC1, lactate dehydrogenase, angiotensin-converting enzyme, and tumor necrosis factor.[21,27,29] The elevated serum biomarkers represent alveolar epithelial cell injury and extracellular-matrix remodeling and support the hypothesis that OSA may be one of the risk factors for ILD. Aihara et al. in a study measured the serum levels of KL-6, SP-D, and CRP in 197 OSA-suspected patients. They showed that the AHI had a significant positive correlation with serum KL-6 ($r = 0.20$, $p = 0.01$) and CRP ($r = 0.17$, $p = 0.03$), while the correlation was not significant with SP-D level ($r = 0.06$, $p = 0.48$). It was concluded that KL-6 could be a potential serum biomarker of subclinical ILD in OSA. Armstrong et al. in a study found that each increment in MMP-7 level was associated with a 3.7% absolute decrement in FVC%, 1.6-fold increased odds of exertional dyspnea, 1.5-fold increased odds of ILAs, and a 2.2-fold increased all-cause mortality rate. They concluded that MMP-7 may be a quantitative biomarker of subclinical ECM remodeling.[29] The present study also found the positive correlation of MMP-7 with AHI. The serum level of MMP-1, SP-A, and KL-6 was also higher in subclinical ILD, but there was no significant correlation with AHI. These studies supported the hypothesis that OSA is characterized by repetitive forced inspiration against increased airway resistance that is likely to decrease lung interstitial pressures resulting in alveolar epithelial and pulmonary endothelial injury and pro-inflammatory capillary response[18,30] and also, through the generation of oxidative stress induced by cyclical local hypoxia and re-oxygenation in the alveoli, it promotes endothelial injury and increases its permeability which fits the hypothesis that OSA may lead to subclinical ILD.[21]

To the best of our knowledge, this is the first study on subclinical ILD in OSA patients from India. The advantage of the diagnosis of subclinical diseases is to detect them noninvasively before they develop into a full-blown clinical disease, so that it may help in the prevention of disease progression, better clinical outcome, and improve the quality of life. There is a need of a larger multicenter study for further evaluation of serum biomarkers and its correlation in subclinical ILD among OSA patients.

There are few limitations of this study. The present study was of one-year duration, hence the number of population was limited to 43 patients. The other limitation was that it was a single-center study

with moderate-to-severe OSA patients without control population. There was no follow-up with HRCT or serum biomarker for further assessment and progression of ILD. Hence, it is suggested that there is a need for a larger multicenter study with the OSA patients of all severity types with control population for detecting the real estimation of subclinical ILD in OSA patients and to prove the hypothesis of OSA as one of the risk factors for future ILD.

Conclusion

Subclinical ILD is quite common among moderate-to-severe OSA patients. High-attenuation areas and ILA are standard HRCT chest findings of subclinical ILD seen in nearly 30% cases. Obstructive sleep apnea may be considered as one of the risk factors for ILD in the near future, however, a larger multicenter study is needed to confirm our findings.

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