BEYOND SMOKING: PREVALENCE OF INTERSTITIAL LUNG ABNORMALITIES AMONG CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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Article History: **Received:** 14.02.2023 **Revised:** 31.03.2023 **Accepted:** 15.05.2023

Abstract

Background: Prevalence data of Interstitial lung abnormalities (ILAs) in asymptomatic smokers are rising. However, there are insufficient data about the association between ILAs and Chronic obstructive pulmonary disease (COPD).

Objective: this study was planned to detect the prevalence of ILAs in a cohort of smokers to know the effect of the presence or absence of COPD on the development of ILAs.

Methods: This study examined 102 men smokers. The studied participants were divided according to the presence or absence of COPD into a group of COPD patients and a group of non-COPD smokers. A non-contrast examination with CT scanner was used to detect ILAs.

Results: 49.1% of COPD patients had definite ILAs and 14.5% had equivocal ILAs. However, 8.5% of non-COPD smokers had definite ILAs and 12.8% had equivocal ILAs. All reported ILAs in non-COPD smokers were non fibrotic. Nevertheless, 40% of reported ILAs in COPD group were fibrotic. The presence of ILAs in COPD patients in this study not significantly associated with age, COPD group and severity of airflow limitation.

Conclusion: ILAs are more frequent among COPD smokers than non-COPD smokers. CT might give important diagnostic data about ILAs especially in absence of symptoms or pulmonary function abnormalities.

Keywords: Interstitial lung abnormalities; COPD; ILAs; smoking; definite ILAs; fibrotic ILAs

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DOI: 10.31838/ecb/2023.12.s3.327

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease distinguished by persistent airflow limitation. [1] COPD-associated comorbidities affect the patients' management and prognosis, particularly in patients with severe airway obstruction.[2,3] Nevertheless, these comorbidities might be ignored as their clinical characteristics often overlap with COPD. [4]

Interstitial lung abnormalities (ILAs) are defined as specific patterns of increased lung density observed on chest computed tomography (CT) scans in contributors with no previous history of interstitial lung disease. [5] Because these changes in the lungs have similar but milder clinical characteristics than interstitial lung disease (ILD), they are supposed to be early or mild manifestations of ILD. [6]

The association between exposure to tobacco smoke and COPD is well defined. In addition, there is improving knowledge that smoking may also result in areas ILAs. [7]Although prevalence data of ILAs in asymptomatic smokers are rising, there are insufficient data about the association between ILAs and COPD. [4] So, this study was planned to detect the prevalence of ILAs in a cohort of smokers to know the effect of the presence or absence of COPD on the development of ILAs.

2. PATIENTS AND METHODS

This comparative cross-sectional study examined 102 men smokers, 40 years and above. The studied participants were divided according to the presence or absence of COPD into a group of COPD patients and a group of non-COPD smokers. The diagnosis and assessment of COPD was built on the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines 2021.[8] Patients with history of interstitial lung diseases (e.g., idiopathic, granulomatous, connective tissue diseases, occupational exposure), history of tuberculosis, pleural effusion, malignancy, chemotherapy, radiotherapy, or chronic lung diseases such as bronchial asthma , patients with congestive heart failure and patients with suspected or confirmed COVID-19 were excluded.

The study was conducted at chest medicine and radiology departments. Ethical approval from our university institutional research Board was taken (code MD.21.03.432). Informed written consent also was taken from all included participants.

All involved participants were subjected to: a; the whole history taking, b, computed tomography (CT), c, pulmonary function testing and 6-minute walk test (6MWT)

Cigarette and shisha smoking status were recorded. Current smoker was defined as person who smoked at least 100 cigarettes in lifetime and currently smokes. Former (ex-smoker) was defined as person who smoked at least 100 cigarettes in lifetime but not currently smoking. Non-smoker was defined as person who never smoked at all or smoked less than 100 cigarettes in lifetime.[9] Pack-years index 10and Shisha smoking index (SSI) 11were also calculated.

The lung function test and the 6MWT was conducted in line with the requirements of the American Thoracic Society (ATS).[12,13] Each patient was advised to walk in six minutes, through which peripheral oxygen saturation (SpO2) and 6minute walk distance (6MWD) were recorded. Changes in SpO2 (ΔSpO2) during the 6MWT were analysed by subtracting the measurements at the starting point from those immediately after walking 6 minutes [14]

Detection of ILAs:

A non-contrast examination with 128-detector row CT scanner (Philips Ingenuity Core 128 Scanner, Philips Medical Systems®, Eindhoven, The Netherlands) in both supine and prone positions was used. Also. CT scan was performed during the inspiratory and expiratory breath-holding periods. Image analysis was performed by one radiologist (A E); 20 years' experience in chest imaging.

Images were evaluated for presence of ILAs which are demarcated as incidental detection of non-dependant abnormalities (comprising ground-glass opacity, reticular abnormalities, traction bronchiectasis, lung distortion, honey comping, and non-emphysematous cysts) involving ≥ 5% of a lung zone in people not suspected to have interstitial lung disease.[15]

ILAs were classified as definite ILAs, equivocal ILAs, no evidence of ILAs. [7,4,16] Any ILAs (definite or equivocal) was further classified into: Fibrotic ILAs or Nonfibrotic ILAs. [4,16,17,18]A five-point scale for grading the extent of CT findings was also measured. [16].

STATISTICAL ANALYSIS:

Data were analysed using SPSS v. 26. Frequencies and percentages were used to present nominal variables, while means (SD), or Median (min-max) used to present continuous data according to the results of Shapiro-Wilk testing of normality of variables. Significance testing was done using Chi-Square test and Fisher's exact test for discrete variables, Welch's t-test for parametric data, Mann Whitney U test for non-parametric variables. The 5% was set as a significance level.

3. RESULTS

The study included 102 men smokers, 53.9% of them were diagnosed as COPD (mean age 59.4±8.3) and 46.1% were non-COPD smokers (mean age 55 ± 9.8). Most of studied participants were cigarette smokers (84.3%). Apart from the shisha index no significant differences between both groups regarding

smoking status, smoking duration, and smoking indices **table (1).** 20.6% of COPD patients had group D COPD. However, group A presented in 16.7% of them. regarding airflow limitation severity, 22.5% had GOLD 3, and 20.6% had GOLD 2.

According to CT results, ILAs not reported in 36.4% of COPD patients and in 78.7% of non-COPD smokers. This difference in results between the two groups was statistically significant (p< 0.001). Consequently, the remainder of the two groups had ILAs. 49.1% of COPD patients had definite ILAs and 14.5% had equivocal ILAs. However, 8.5% of non-COPD smokers had definite ILAs and 12.8% had equivocal ILAs **table (2)**, **figure (1).**

All reported ILAs in non-COPD smokers were non fibrotic and had CT extent score of 1 (1-25%). Nevertheless, 40% of reported ILAs in COPD group were fibrotic (figure 2). Most of ILAs in COPD group (71.4%) had CT extent score of 1 followed by CT extent score of 2 (14.3%) (table 2).

The presence of ILAs in COPD patients in this study not significantly associated with age (p:0.06), BMI (p:0.9), previous use of inhaled steroid (0.4), COPD group (p: 0.4), severity of airflow limitation (p: 0.2), lung volumes and capacities from pulmonary function (TLC, FVC, RV/TLC, DLCO) and 6MWD from 6MWT(p:0.3). However, significant association was reported between the presence of ILAs and numbers of hospitalization in last year (p:0.04). Significant higher Δ SPO2 from 6MWT (p:0.02) was found in COPD patients with ILAs **table (3).**

The presence of fibrotic ILAs in COPD patients in this study not significantly associated with functional assessment of COPD patients **table (4).**

Table (1): Demographic characteristics of the studied groups.

Parameters	**COPD group (N :55)**	**Non-COPD smokers (N: 47)**	**significance**
Age mean±SD	59.4±8.3	55 ± 9.8	t:2.4 p:0.01
Cigarette Smoking status: N (%) Current (r) Ex-smokers Nonsmokers	 17 (30.9%) 31(56.4%) 7 (12.7%)	 19 (40.4%) 19 (40.4%) 9 (19.2%)	X^2:2.6 p:0.2
Duration of Cigarette smoking (year) median (min-max)	20(2-50)	27(3-45)	Z: -0.2 p:0.8
Pack year index median (min-max)	30(1.5-150)	30 (0.7-120)	Z: -0.17 p:0.8
shisha Smoking status: N (%) Current (r) Ex-smokers Nonsmokers	 4 (7.3%) 21(38.2%) 30 (54.5%)	 8 (17%) 15 (31.9%) 24 (51.1%)	X^2:2.3 p:0.3
Duration of shisha smoking (year) median (min-max)	18.5 (1-50)	15 (5-30)	Z: -0. 7 p:0.4
Shisha smoking index median (min-max)	31.5(7-210)	21 (14-70)	Z: -1.9 p:0.05
BMI mean±SD	28.1±4.9	30.5 ±5.2	t: -2.3 p:0.02

BMI (body mass index)

Table (2): Interstitial lung abnormalities (ILAs) among studied groups

Parameters	**COPD group (N :55)**	**Non-COPD smokers (N: 47)**	**significance**
ILA N (%) • Definite ILAs (r) • Equivocal ILAs **No evidence non-ILAs**	 27 (49.1%) 8 (14.5%) 20 (36.4%)	 4 (8.5%) 6 (12.8%) 37 (78.7%)	X^2:21.9 p< 0.001
ILA N (%) Fibrotic Non fibrotic	 14 (40%) 21 (60%)	 0 (0%) 10 (100%)	X^2:5.2 p 0.04
ILA distribution Non subpleural (r) Subpleural fibrotic Subpleural non fibrotic	 1 (2.9%) 15 (42.8%) 19 (54.3%)	 0(0%) 0(0%) 10 (100%)	X^2:7.1 p 0.02
CT extent score N (%) 1: 1-25% (r) 2: 26-50% 3: 51-75% 4: 76-100%	 25 (71.4%) 5 (14.3%) 2(5.7%) 3 (8.6%)	 10 (100%) 0(0%) 0 (0%) 0 (0%)	X^2:2.2 p1: 0.3 X^2:0.7 p2: 0.5 X^2:1.1 p3: 0.5

r: reference, p1: p value between r and score 2; p2; p value between r and score 3; p3; p value between r and score 4

Table (3): Association between ILAs and characteristics of COPD patients

Parameters	**ILA**	**Non- ILA**	
Age mean±SD	61 ± 7.9	56.7 ± 8.4	t: -1.9 p:0.06
BMI mean±SD	28.1 ±4.5	28.1± 5.7	t: 0.02 p:0.9

COPD group A/B (N=29) C/D (N=26)	 17 (58.6%) 18 (69.2%)	 12 (41.4%) 8 (30.8%)	X^2 :0.6 p: 0.4
mMRC ≥2 yes no	 19 (57.6%) 16 (72.7%)	 14 (42.6%) 6 (27.3%)	X^2 :1.3 p: 0.2
ICS use Yes No	 31 4	 19 1	X^2 :0.6 p: 0.4
Hospitalization in last year	0 (0-4)	0 (0-2)	Z: -1.9 p:0.04
GOLD classification 1/2 (N=25) 3/4(N=30)	 14 (56%) 21(70%)	 11(35%) 9 (30%)	X^2 :1.1 p: 0.2
FVC % mean±SD	70 ±16.8	68 ± 20.8	t: -0.2 p:0.7
DLCO % mean±SD	69.1 ± 22.9	73.1 ± 18.6	t: 0.6 p:0.5
TLC % mean±SD	101.6 ± 20.9	107.6 ± 38	t: 0.7 p:0.4
RV/TLC mean±SD	54.3 ± 15.5	52.9 ± 16.3	t: -0.3 p:0.7
6MWD median (minimum-maximum)	390(48-540)	277.5(45-720)	Z: -0. 9 p:0.3
Δ SPO2 from 6MWT median (minimum-maximum)	2(0-18)	0(0-7)	Z: -2.2 p:0.02

BMI (body mass index); mMRC (modified medical research council scale); ICS (inhaled corticosteroid); 6MWD (6minute walk distance), DLCO (diffusion capacity of carbon monoxide)

Table (4): Association between fibrotic ILAs and characteristics of COPD patients

Parameters	**Fibrotic ILA**	**Non-fibrotic ILA**	
Age mean±SD	63.2± 7	59.5 ± 8	t: 1.3 p:0.1
COPD group a/b c/d	 6 8	 11 10	X^2 :0.3 p: 0.5
mMRC ≥2 yes no	 8 6	 11 10	X^2 :0.07 p: 0.7
GOLD 1/2 ¾	 7 7	 7 14	X^2 :0.9 p: 0.4
FVC % mean±SD	73.9 ± 17.4	67.4 ± 16.2	t: 1.1 p:0.2
DLCO % mean±SD	66.4 ±22.3	70.9 ± 23.6	t: -0.5 p:0.5
TLC % mean±SD	96.7 ± 17.9	105± 22	t: -1.1 p:0.2
RV/TLC mean±SD	51.4 ± 11.4	56 ±17.3	t: -0.9 p:0.3
6MWD median (minimum-maximum)	375(48-540)	390(115-540)	Z: -0.8 p:0.4
Δ SPO2 from 6MWT median (minimum-maximum)	2(0-14)	1(0-18)	Z: -1.7 p:0.08
Hospitalization	0.5(0-2)	0(0-4)	Z: -0.7 p:0.5

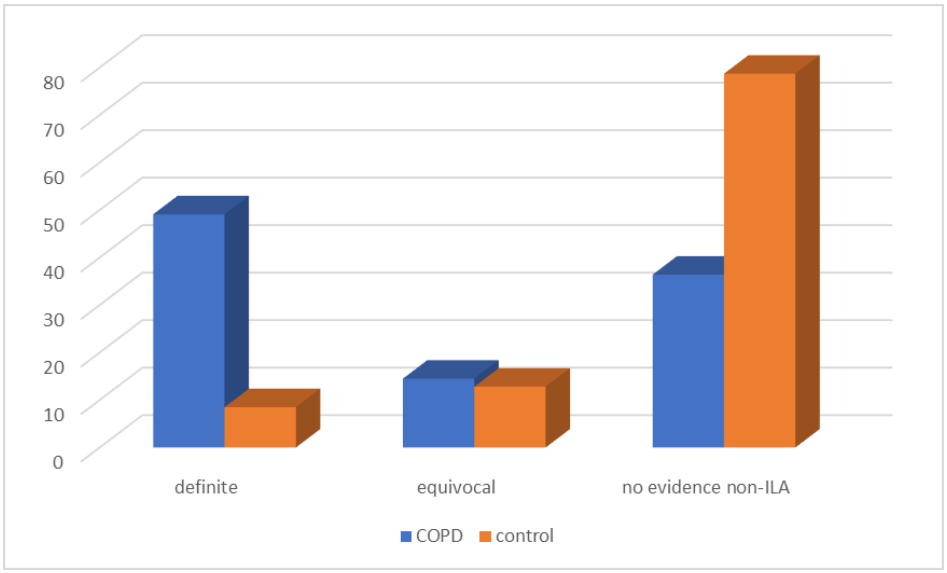

Figure (1): prevalence of ILAs among studied groups

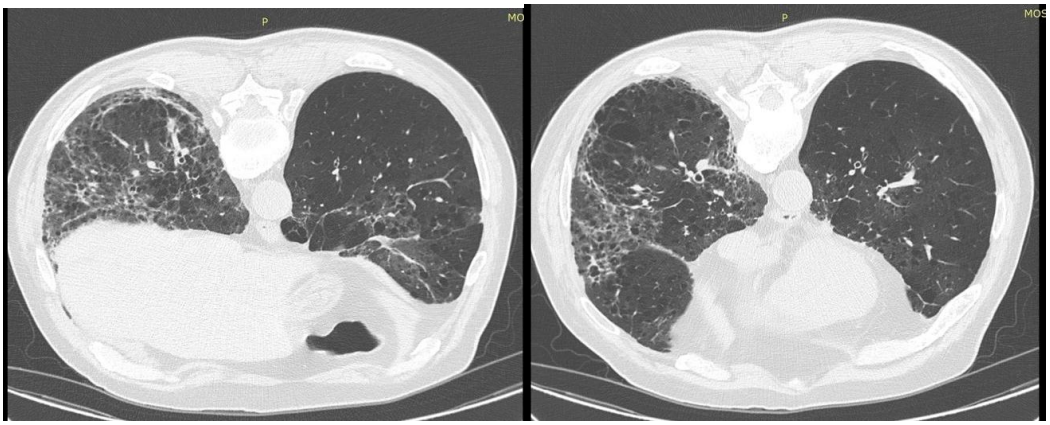

Figure (2): Fibrotic ILAs: right lower lobe reticular abnormalities and traction bronchiectasis

4. DISCUSSION

Cigarette smoking is a known risk factor for some of the idiopathic interstitial pneumonias such as desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease 19.

In this study, ILAs more prevalent among COPD patients (63.6%) than non-COPD smokers (21.3%). So, smoking not associated with the presence of ILAs in COPD patients especially since COPD group was matched to non-COPD smokers regarding smoking history. These results are contrary to Bozzetti et al 4 that found that the current smoking status was the strongest element associated with definite ILA in the group of cases.

Our results could be explained by, in addition to smoking, genetic and biomarkers may be implicated in pathogenesis of ILAs. Ding et al and Wang et al 20,21 have been reported that some genes, such as FAM13A and TERT gene, are associated with both COPD and idiopathic pulmonary fibrosis (IPF) progression.

Cornwell et al. 22 compared levels of inflammatory biomarkers in post-mortem lung tissue after categorized lung tissue into emphysema only, idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE), and healthy control groups. Comparisons of biomarkers revealed biomarkers elevated in emphysema alone (e.g., Interleukin [IL]-6}; biomarkers reduced in emphysema alone (e.g. IL-13, matrix metalloproteinase [MMP] 1); biomarkers that were similar among emphysema, IPF, and CPFE, but different from the healthy control group (e.g. sCD14, CCL5, SP-D).

In addition, Chiba et al 23 found that patients with asthma-COPD overlap and ILAs showed higher levels of Klebs von den Lungen-6 (KL-6), compared with patients with asthma-COPD overlap without ILAs. Consequently, the immunological pathogenesis of CPFE may be more closely associated with IPF development.24

In this study, 49.1% of COPD patients had definite ILAs and 14.5% had equivocal ILAs. But a retrospective study by Lee et al 18 found that 12.1%

of COPD patients had definite ILAs and 28.4% had equivocal ILAs.

In this study, all reported ILAs in non-COPD smokers were non fibrotic. Nevertheless, 40% of reported ILAs in COPD group were fibrotic. The presence of fibrotic ILAs in COPD patients in this study not significantly associated with age or functional assessment of COPD patients. Bozzetti et al 4 reported that 2.8% of COPD patients had fibrotic ILAs and, demonstrated that male sex and age were the only factors clearly linked with the presence of fibrotic ILA.

Washko et al 7 found definite ILAs in 13.4% of cigarette smokers with GOLD 1–4 COPD. Most of the abnormalities in these participants were nonfibrotic, but 1.8% participants had fibrotic ILA.

In this study, significant association was reported between the presence of ILAs and numbers of hospitalization in last year.in agreement with our results, Lee et al 18 found that ILAs were associated significantly with moderate to severe acute exacerbation in patients with COPD.

In this study, the presence of ILAs in COPD patients not significantly associated with COPD group, severity of airflow limitation, lung volumes and capacities. These results could be explained by most of ILAs in COPD group had CT extent score of 1. So, ILAs may be mild with no effect on lung volumes 7,25. Additionally, it is still not obvious which percentages of emphysema and ILAs are necessary to generate either predominant obstructive or predominant restrictive functional pattern.4

Since emphysema and ILAs have opposite influences on lung volume, CT might give important diagnostic data in smokers whose total lung capacity is normal. 7 So, absence of symptoms or pulmonary function abnormalities doesn't mean patient is diseases free.

Washko et al 7 found reverse association between ILAs and the severity of COPD. This finding could be explained by that ILAs would result in an inaccurate underestimation of the quantity of emphysema by enhancing the overall lung density.

As oxygen desaturation plays a key role in exercise limitations in COPD patients,26 significant higher Δ SPO2 from 6MWT was found in COPD patients with ILAs in this study.

This study has several limitations. First, small sample size. Second, most of the study COPD patients had CT extent score of 1 and 2, and data on subjects with more advanced scores are little. Third, the lack of quantitative data for pulmonary emphysema. Such data could explain how ILAs and emphysema interplay to define the functional insufficiency of COPD patients. So further longitudinal studies on large numbers of COPD patients with ILAs will be required to determine whether these CT abnormalities are transient or permanent, or whether they will progress to clinically significant disease.

5. CONCLUSION

Interstitial lung abnormalities are more frequent among COPD smokers than non-COPD smokers.

Absence of symptoms or pulmonary function abnormalities doesn't mean that the patient is diseases free. So, CT might give important diagnostic data about interstitial lung abnormalities.

6. REFERENCES

1. Celli BR, Decramer M, Wedzicha JA, et al. An Official American Thoracic Society/European Respiratory Society Statement: research questions in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;191(7): e4–e27
2. Gershon AS, Mecredy GC, Guan J, Victor JC, Goldstein R, To T. Quantifying comorbidity in individuals with COPD: a population study. Eur Respir J. 2015;45(1):51–59.
3. Smith MC, Wrobel JP. Epidemiology and clinical impact of major comorbidities in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2014; 9:871–888.
4. Bozzetti F, Paladini I, Rabaiotti E, Franceschini A, Alfieri V, Chetta A, Crisafulli E, Silva M, Pastorino U, Sverzellati N. Are interstitial lung abnormalities associated with COPD? A nested case-control study. Int J Chron Obstruct Pulmon Dis. 2016 May 26; 11:1087-96.
5. Hunninghake GM, Hatabu H, Okajima Y, et al. MUC5B promoter polymorphism and interstitial lung abnormalities. N Engl J Med. 2013;368(23):2192-2200.
6. Putman RK, Hatabu H, Araki T, Gudmundsson G, Gao W, Nishino M, et al. Association between interstitial lung abnormalities and all-cause mortality. JAMA. 2016; 315:672–81.
7. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, Ross JC, Estépar RS, Lynch DA, Brehm JM, Andriole KP, Diaz AA, Khorasani R, D'Aco K, Sciurba FC, Silverman EK, Hatabu H, Rosas IO; COPDGene Investigators. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. 2011 Mar 10;364(10):897-906.
8. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Varela MVL. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2021.
9. Schoenborn, c.a., p.f. adams, and j.a. peregoy, health behaviors of adults: united states, 2008-2010. Vital and health statistics. Series 10, data from the national health survey, 2013(257): p. 1-184

10. Lee, y.-h., et al., cumulative smoking exposure, duration of smoking cessation, and peripheral arterial disease in middle-aged and older korean men. Bmc public health, 2011. 11(1): p. 1-7.
11. Israel, e., et al., water pipe (sisha) smoking in cafes in egypt. J egypt soc parasitol, 2003. 33(3 suppl): p. 1073-85.
12. Miller MR, Hankinson J, Brusasco V, et al.; ATS/ERS Task Force. Standardization of spirometry. Eur Respir J. 2005;26(2):319–33
13. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111–117.
14. Xavier Alsina, Isabel Blanco, Yolanda Torralba, Maria Palomo, Felip Burgos, Joan Albert Barbera. Modified Desaturation Distance Ratio (mDDR) predicts prognosis in patients with Pulmonary Arterial Hypertension European Respiratory Journal 2017 50: PA2390.
15. Hata, A., et al., Interstitial Lung Abnormalities: State of the Art. Radiology, 2021. 301(1): p. 19-34.
16. Jin, G.Y., et al., Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. Radiology, 2013. 268(2): p. 563-571.
17. Chae, K.J., et al., Interstitial Lung Abnormalities: What Radiologists Should Know. Korean Journal of Radiology, 2021. 22(3): p. 454
18. Lee TS, Jin KN, Lee HW, Yoon SY, Park TY, Heo EY, Kim DK, Chung HS, Lee JK. Interstitial Lung Abnormalities and the Clinical Course in Patients With COPD. Chest. 2021 Jan;159(1):128-137.
19. Fraig M, Shreesha U, Savici D, Katzenstein AL. Respiratory bronchiolitis: a clinicopathologic study in current smokers, ex-smokers, and never-smokers. Am J Surg Pathol 2002; 26:647–653.
20. Ding Y, Li Q, Wu C, Wang W, Zhao J, Feng Q, et al. TERT gene polymorphisms are associated with chronic obstructive pulmonary disease risk in the Chinese Li population. Mol Genet Genomic Med. 2019;7: e773.
21. Wang H, Zhuang Y, Peng H, Cao M, Li Y, Xu Q, et al. The relationship between MUC5B promoter, TERT polymorphisms and telomere lengths with radiographic extent and survival in a Chinese IPF cohort. Sci Rep. 2019; 9:15307
22. Cornwell WD, Kim C, Lastra AC, Dass C, Bolla S, Wang H, et al. Inflammatory signature in lung tissues in patients with combined pulmonary fibrosis and emphysema. Biomarkers. 2019; 24:232–9.
23. Chiba S, Tsuchiya K, Nukui Y, Sema M, Tamaoka M, Sumi Y, et al. Interstitial changes in asthma-COPD overlap syndrome. Clin Respir J. 2017; 11:1024–31.
24. Choi JY, Song JW, Rhee CK. Chronic Obstructive Pulmonary Disease Combined with Interstitial Lung Disease. Tuberc Respir Dis (Seoul). 2022 Apr;85(2):122-136.
25. Alhamad EH, Lynch JP, 3rd, Martinez FJ. Pulmonary function tests in interstitial lung disease: what role do they have? Clin Chest Med. 2001;22(4):715–750. Ix
26. Abdelwahab HW, Radi AA, Shata HM, Ehab A. ΔSpO2/distance ratio from the six-minute walk test in evaluation of patients with chronic obstructive pulmonary disease. Adv Respir Med. 2022 Feb 24.