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ORIGINAL RESEARCH

Impact of Interstitial Lung Abnormalities on Disease Expression and Outcomes in COPD or Emphysema: A Systematic Review

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Background: Both COPD and interstitial lung abnormalities (ILAs) are conditions associated with smoking and age. The impact of coexistent ILAs on the manifestations and outcomes of COPD or emphysema awaits evaluation.

Methods: We searched PubMed and Embase using Medical Subject Headings terms in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results: Eleven studies were included in the review. The sample size of the studies ranged from 30 to 9579. ILAs were reported in 6.5% to 25.7% of the patients with COPD/emphysema, higher than that reported in the general populations. COPD/emphysema patients with ILAs were older, mostly male, and had a higher smoking index than those without ILAs. Hospital admission and mortality were increased in COPD patients with ILAs compared to those without ILAs, whereas the frequency of COPD exacerbations was discrepant in 2 of the studies. The FEV_1 and FEV_1% predicted tended to be higher in the group with ILAs, but not significantly in most of the studies.

Conclusion: ILAs were more frequent in subjects with COPD/emphysema than in the general population. ILAs may have a negative impact on hospital admission and mortality of COPD/emphysema. The impact of ILAs on lung functions and exacerbations of COPD/emphysema was discrepant in these studies. Further prospective studies are warranted to provide high-quality evidence of the association and interaction between COPD/emphysema and ILAs.

Keywords: COPD, emphysema, interstitial lung abnormalities, review

Introduction

Chronic obstructive pulmonary disease (COPD), characterized by persistent airflow limitation, small airway inflammation, and parenchymal destruction (emphysema), is one of the top causes of death worldwide.[1] The main risk factor for COPD is cigarette smoking, influenced by host factors such as accelerated aging, abnormal lung development, and so on.[2,3] Interstitial lung diseases (ILDs), also associated with smoking and aging,[4] are characterized by parenchymal inflammation or fibrosis, and physiologically by restrictive ventilatory abnormalities. COPD coexisting with pulmonary fibrosis has been reported in previous studies,[5] while emphysema combined with idiopathic pulmonary fibrosis (IPF) has been identified as a syndrome which is designated combined pulmonary fibrosis and emphysema.[6] In recent years, interstitial lung abnormalities (ILAs) not meeting the diagnosis of ILDs by chest CT, previously named as early ILDs or subclinical ILDs, have been increasingly recognized. ILAs were first described by Washko et al[7] in 2011, and later Hobbs et al[8] revealed that, while ILAs shared common genetic pathways with IPF, they had some independent pathways, suggesting that ILAs may be pathologically similar to ILDs or an early stage of ILDs, but it may also have unique characteristics in terms of disease development. In 2020, the Fleischner Society defined ILAs as interstitial lung changes

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on HRCT which did not meet the radiological diagnosis of ILDs including IPF, and indicated that these abnormalities in high-risk groups including those with connective tissue diseases and familial ILD should not be considered as ILAs.[9]

The prevalence of ILAs ranged from 4–9% in smoking individuals, and 2–7% in non-smoking populations.[7,10–14] Accumulating evidence indicated that ILAs are associated with increased mortality, decreased pulmonary function tests (PFTs), and poorer physical activity.[7,11–13,15] Since ILAs and COPD share several risk factors, and previous studies have reported the coexistence of COPD and ILAs, the clinical implications of ILAs in COPD are gaining attention.

Several studies evaluated the impact of ILAs on the clinical manifestations, PFTs, and outcomes of COPD and/or emphysema, showing that the exacerbation rate and mortality tended to be higher in COPD patients with ILAs compared to those without.[13,16] Some investigators also reported decreased PFTs, poorer physical activity, and more respiratory symptoms in COPD or emphysema patients with ILAs.[16,17] However, there are discrepancies in the results. The impact of ILAs on the disease expression and clinical outcomes of COPD and/or emphysema needs to be comprehensively evaluated. Therefore, we performed a systematic review to assess the demographic data, PFTs, radiological features as well as the impact of coexistent ILAs in patients with COPD/emphysema.

Methods

The study protocol was prepared in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and prospectively registered in the International Prospective Register of Systematic Reviews (registration number CRD42022339506). Eligible studies included cohort studies, case-control studies, and cross-sectional studies reporting the association between COPD/emphysema and ILAs.

The primary objective was to evaluate the impact of comorbid ILAs on the clinical manifestations, clinical course, outcomes, PFTs, and chest CT features of COPD/emphysema.

We searched PubMed and Embase in March 2022 using the Medical Subject Headings (MESH) and keyword searches detailed in Figure 1. All titles and abstracts were screened independently by two reviewers (YJ.L. and JY.T.). Any discrepancies/disagreements were resolved by discussion between reviewers and included a third party (YC.S.) if

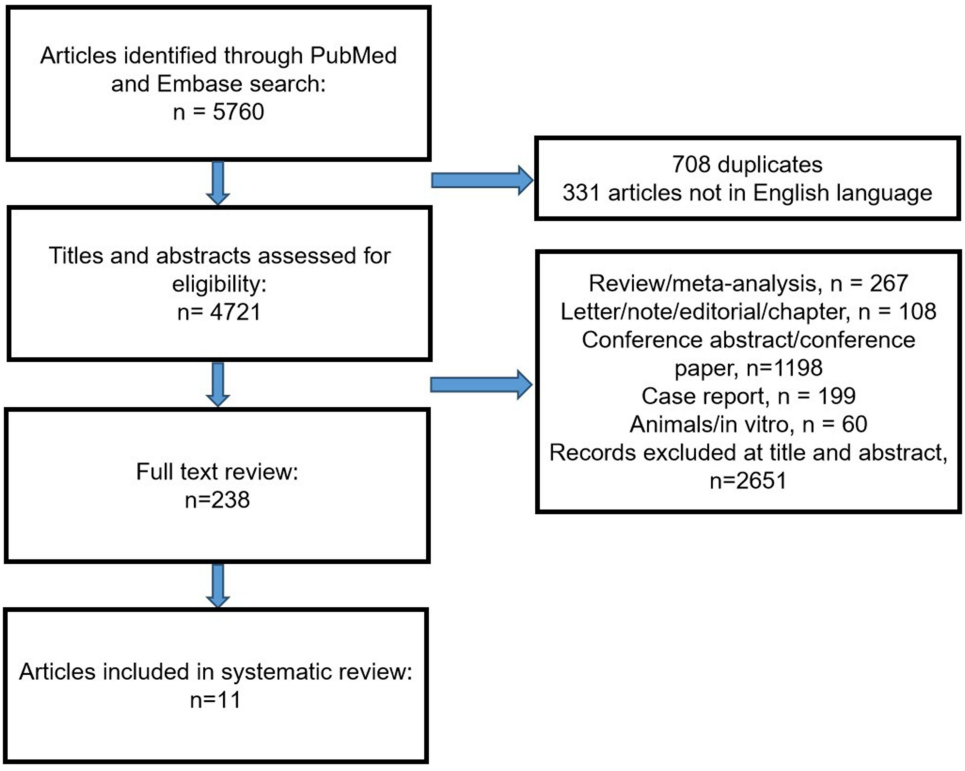

Figure 1 Flowchart of critical review and selection for inclusion of article.

necessary. Studies not written in English were excluded. Studies investigating IPF, combined pulmonary fibrosis and emphysema, or COPD/emphysema complicated with connective tissue disease-related ILDs were also excluded.

Results

We reviewed 4721 titles and abstracts; from these, we included 238 in a full-text review (Figure 1). A further 227 articles were excluded after a full review, providing a total of 11 articles eligible for inclusion.

The quality of cohort studies and case-control studies was assessed by Newcastle-Ottawa Scale (NOS), while the quality of cross-sectional studies was assessed by the scale of the Agency for Healthcare Research and Quality (AHRQ).

General Description

Totally 11 studies were included in this review, with 5 cross-sectional studies, 4 case-control studies, and 2 cohort studies. In the study by Bozzetti et al[18] the subjects included were COPD patients and current- or ever-smokers without airflow obstruction as matching control subjects. Three studies included COPD patients alone.[16,19,20] The study by Chiba et al[21] investigated patients with Asthma-COPD overlap syndrome (ACOS), a subtype of COPD which is recognized as a syndrome of the characteristics of both asthma and COPD.[22] The study by Putman et al[13] included 4 cohorts, including the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study,[23] the Genetic Epidemiology of COPD Study (COPDGene) cohort,[24] the Framingham Heart Study (FHS) cohort,[25] and the Age Gene/Environment Susceptibility-Reykjavik study.[26] ECLIPSE is a study of COPD patients and control subjects including smoking or non-smoking subjects free from airflow obstruction.[23] Notably, only the COPD patients in the ECLIPSE were included in the study by Putman et al.[13] The COPDGene study recruited smoking individuals with or without COPD.[24] The FHS is a cohort recruiting a well-characterized general population.[25] In this systematic review, we included the data of ECLIPSE, and the data about COPD or smoking population from the COPDGene and FHS in the study by Putman et al.[13] The data of the other cohort were excluded because the COPD/emphysema subpopulation was not defined. Studies by Washko et al.[7] Ash et al[17] and Menon et al[27] analyzed the COPDGene cohort. We included these 3 studies in this systematic review because Ash et al[17] and Menon et al[27] investigated the impact of ILAs on individuals with emphysema, and Washko et al[7] examined the interaction between ILAs and COPD/emphysema. Araki et al[28] investigated subjects in the FHS, which was included because they analyzed paraseptal emphysema and ILAs in the cohort. Hoyer et al[29] studied the cohort of the Danish Lung Cancer Screening Trial,[30] which included smoking populations. The study was included as they reported the association between ILAs and hospital admission for COPD.

The sample size of the studies ranged from 30 to 9579. Measurements and outcomes varied in the 11 studies. Age, body mass index (BMI), PFTs, and chest CT were measured in 10 studies.[7,13,16–21,27,28] Gender and smoking status were reported in 9 studies,[7,13,16–19,21,27,28] and the smoking amount was described in 8 studies.[7,13,16–18,21,27,28] Mortality was reported in 3 studies.[13,17,19] Six minutes walk distance (6MWD),[16,17] COPD exacerbations,[16,19] comorbidities,[16,21] serum Krebs Von den Lungen-6 (KL-6)[20,21] were measured in 2 of the studies, respectively. Respiratory symptoms,[28] Modified British Medical Research Council (mMRC) Questionnaire,[19] COPD Assessment Test (CAT),[19] St. George's Respiratory Questionnaire (SGRQ),[17] positive bronchodilator response,[16] right ventricular-to-left ventricular (RVLV) volume ratio,[17] serum surfactant protein D (SP-D),[21] serum total and antigen-specific immunoglobulin E (IgE),[21] and hospital admission[29] were measured in 1 of the studies, respectively.

The quality of cross-sectional studies was relatively high in studies by Lee et al.[16] Washko et al[7] and Araki et al[28] and moderate in studies by Chiba et al[21] and Ohgiya et al[20] assessed by the AHRQ scale. The quality of case-control studies and cohort studies was relatively high in studies by Bozzetti et al.[18] Ono et al.[19] Putman et al[13] and Menon et al[27] and moderate in studies by Ash et al[17] and Hoyer et al.[29] Details were presented in Table 1.

The Definition of ILAs

Six studies[7,13,16,18,27,28] evaluated ILAs as definite ILAs and equivocal or indeterminate ILAs. The definition of ILAs they shared was first described by Washko et al[7] in 2011. Definite ILAs were defined by the following features: nondependent ground-glass opacity (GGO) or reticular abnormality, diffuse centrilobular nodularity, honeycombing, traction bronchiectasis, nonemphysematous cysts, or architectural distortion (affecting > 5% of any lung zone). Equivocal

Table 1 Characteristics of Included Studies Focusing on the Association Between ILAs and COPD/Emphysema

Author (Year)	Type of Study	Quality of Study Assessed by NOS Tool or AHRQ Scale[a]	Image Features, Image Subtypes, and Classification Assessed by Chest CT	Measurement Parameters	Main Manifestations and Outcomes	Sample Size	Prevalence of ILAs	Main Results
Washko GR (2011)[7]	Cross-sectional study	8	Classification 1: Definite ILAs, equivocal ILAs Classification 2: Centrilobular, subpleural, mixed centrilobular and subpleural, radiologic ILD	Age, gender, BMI, smoking status, smoking pack-years, PFTs, chest CT	1. PFTs 2. Prevalence of COPD and Emphysema	2416 smokers in COPDGene cohort (1210 with COPD and 905 without COPD, others are unclassified)	Definite ILAs: 194(8%) participants indeterminate ILAs: 861(36%) participants	1. The participants with ILAs were significantly older, had a higher BMI, and had greater smoking pack-years than those without ILAs. 2. The participants with ILAs were less likely to have COPD, and had a lower percentage of emphysema. 3. ILAs were associated with reduced total lung capacity in individuals with or without COPD. The reductions in total lung capacity were similar between the two groups after adjustment for emphysema. 4. ILAs odds were associated with smoking pack-years and smoking status.
Araki T (2015)[28]	Cross-sectional study	7	Definite ILAs, indeterminate ILAs	Age, gender, BMI, smoking status, smoking pack-years, Respiratory symptoms, PFTs, chest CT	Subtypes of emphysema	2633 participants in the FHS	Definite ILAs: 177(7%) participants Indeterminate ILAs: 1086(41%) participants	Participants with paraseptal emphysema had a higher rate of combined ILAs than those without paraseptal emphysema (24% vs 6%).

Bozzetti F (2016)[18]	Case-control study	********	Classification 1: definite UIP, possible UIP, RB, indeterminate Classification 2: fibrotic, nonfibrotic	Age, gender, BMI, smoking status, smoking pack-years, PFTs, LDCT, GOLD stage	PFTs	457 COPD and 914 control subjects	Definite ILAs: 32(7%)in COPD and 89(9%)in control subjects Equivocal ILAs: 14(3.1%) in COPD and none in control subjects	1. The prevalence of ILAs was similar between COPD cases and control subjects. 2. ILAs was distributed across GOLD stages homogeneously. There is no significant difference between the PFTs of individuals with and without ILAs. 3. Definite ILAs were associated with current smoking status (OR 4.05) and increasing smoking index (OR 1.01). 4. Individuals with fibrotic ILAs were more likely to be older (OR 1.17) and male (OR 8.58). 5. RB was more frequent in control subjects whereas the indeterminate pattern was more frequent in COPD cases. Equivocal ILAs were observed only among COPD cases. Fibrotic ILAs was less frequent in control subjects as compared to subjects with GOLD 1, 2, 3, or U of COPD.

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Table 1 (Continued).

Author (Year)	Type of Study	Quality of Study Assessed by NOS Tool or AHRQ Scale[a]	Image Features, Image Subtypes, and Classification Assessed by Chest CT	Measurement Parameters	Main Manifestations and Outcomes	Sample Size	Prevalence of ILAs	Main Results
Putman RK (2016)[13]	Cohort study	*******	Definite ILAs, indeterminate ILAs	Age, race, gender, BMI, smoking status, smoking pack-years, PFTs, chest CT, GOLD stage	1. All-cause mortality with a median follow-up of 3–9 years 2. PFTs	2068 participants from the COPDGene cohort and 1670 COPD patients from the ECLIPSE cohort	Definite ILAs: 156 (8%) in the COPDGene cohort, and 157 (9%) in the ECLIPSE cohort Indeterminate ILAs: 739 (36%) in the COPDGene cohort, and 985 (59%) in the ECLIPSE cohort	1. In the individuals with ILAs, compared to those without ILAs, age was older in the COPDGene cohort and the ECLIPSE cohort, gender was not different, BMI was higher in the COPDGene cohort and no different difference in the ECLIPSE cohort. Smoking pack-year was higher in the COPDGene cohort but no difference in the ECLIPSE. COPD prevalence was lower in the COPDGene but higher in the FHS. 2. ILAs were associated with a high FEV_1 and FEV_1-to-FVC ratio in the COPDGene and the ECLIPSE. In contrast, ILAs were associated with a higher prevalence of COPD and a lower FEV_1-to-FVC ratio in the FHS cohort. TLC was lower in the COPDGene but no difference in the ECLIPSE. 3. ILAs were associated with a higher mortality compared to those without ILAs. (HR, 1.8 in the COPDGene cohort, and HR, 1.4 in the ECLIPSE cohort)

Chiba S (2017)[21]	Cross-sectional study	6	Unclassifiable, nonspecific interstitial pneumonia	Age, gender, BMI, smoking status, smoking pack-years, prevalence and number of comorbidities, serum KL-6, serum SP-D, serum total and antigen-specific IgE, PFTs, HRCT	1. PFTs 2. IgE, SP-D, and KL-6	30 ACOS	7(23.3%) with interstitial changes	1. In ACOS with interstitial changes, the age was older, and smoking pack-years were higher, the airway walls in HRCT were thicker and serum KL-6 was higher than those in ACOS without interstitial changes significantly. 2. PFTs were similar between the two groups. 3. The fungal-specific IgE was higher in ACOS with interstitial changes but not significantly. There was no significant difference in serum total IgE and SP-D between the two groups.
Ohgiya M (2017)[20]	Cross-sectional study	4	Honeycombing, reticular abnormalities, GGOs	Age, BMI, serum KL-6, PFTs, HRCT	PFTs	349 COPD	20(10.3%) patients in Group A, 17 (22.5%) patients in Group B, 3 (5.6%) patients in Group C, 10 (23.1%) patients in Group D, total 50(14.3%) in all	1. In Group B, the frequency of ILAs was higher and the area of ILAs was greater significantly compared with those in Group C. 2. In Group B, patients with ILAs had higher FEV_1% predicted and low attenuation area scores than patients without ILAs, but not significantly. 3. The area of honeycombing in Group B was significantly greater than that in Group C. The rates and severity of GGOs were similar in all 4 groups.
Ash SY (2018)[17]	Case-control study	******	-	Age, gender, BMI, smoking status, smoking pack-years, 6MWD, SGRQ, mortality, PFTs, chest CT, The RVLV volume ratio	1. Mortality with a median follow-up of 6.3 years 2. PFTs 3. 6MWD, RVLV volume ratio, and SGRQ score	8266 participants in COPDGene cohort	1069 (12.9%) participants with interstitial features	Subjects with emphysema and interstitial features had a higher FEV_1% predicted, a lower D_{LCO}% predicted, a higher RVLV ratio, a shorter 6MWD, a higher SGRQ score, and higher mortality, compared with the subjects with emphysema alone. Interstitial features enhanced the effect of emphysema on D_{LCO}% predicted, 6MWD, RVLV volume ratio, and SGRQ score.

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Table 1 (Continued).

Author (Year)	Type of Study	Quality of Study Assessed by NOS Tool or AHRQ Scale[a]	Image Features, Image Subtypes, and Classification Assessed by Chest CT	Measurement Parameters	Main Manifestations and Outcomes	Sample Size	Prevalence of ILAs	Main Results
Hoyer N (2020)[29]	Cohort study	****	-	Age, gender, BMI, smoking status, smoking pack-years, PFTs, LDCT, comorbid disease, hospital admission	Hospital admission	1990 participants (322 with ILA, 214 with COPD)	55(25.7%) subjects in COPD patients	1. Frequency of comorbid COPD was increased in ILAs subjects. 2. In COPD patients, those with ILAs had more frequent hospital admissions (HR 2.1) when considering the primary and contributing discharge diagnoses, whereas the hospital admissions for COPD were not associated with ILAs when only considering the primary discharge diagnosis.
Ono M (2020)[19]	Case-control study	*******	-	Age, gender, BMI, smoking status, mMRC scales, CAT scores, exacerbation frequency, PFTs, HRCT	1. Exacerbations of COPD 2. PFTs	463 COPD (30 patients with ILAs and 90 patients without ILAs after propensity score matching)	30(6.5%) patients with ILAs	1. The annualized rate of COPD exacerbations per patient was lower in the ILAs compared with those without ILAs (0.06 vs 0.23). 2. Patients with ILAs showed greater FEV_1 and FEV_1% predicted, as well as lower mMRC scale and CAT scores compared with those without ILAs, but not significantly.

Lee TS (2021)[16]	Cross-sectional study	7	Classification 1: Definite ILAs, equivocal ILAs Classification 2: Centrilobular, subpleural, mixed, radiologic ILD	Age, gender, BMI, smoking status, smoking pack-years, annual incidence of acute exacerbations of COPD (history and follow-up), Charlson Comorbidity Index, 6MWD, PFTs (baseline and follow-up), positive bronchodilator response, chest CT (baseline and follow-up)	1. Exacerbation of COPD 2. Longitudinal decline in lung function	363 COPD	Definite ILAs: 103(28.4%) patients Equivocal ILAs: 44(12.1%) patients	1. The COPD patients with ILAs were significantly older and had lower FEV_1 and FVC than patients without ILAs. 2. ILAs were significantly associated with the annual incidence of moderate to severe acute exacerbation of COPD and with the risk of frequent exacerbation (HR 2.04). 3. The patients with ILAs had lower FEV_1% predicted, FVC%predicted, D_{LCO}, and 6MWD, but not significantly. Smoking status and intensity were similar between the two groups. 4. Patients with progressive ILAs showed a significantly higher rate of annual decline in FEV_1 and FVC than those showing no change in, or improved, ILAs. The decline in D_{LCO} was not significantly different according to ILAs status. 5. The changes of PFTs showed no significantly different according to ILAs subtype during the follow-up.

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Table 1 (Continued).

Author (Year)	Type of Study	Quality of Study Assessed by NOS Tool or AHRQ Scale[a]	Image Features, Image Subtypes, and Classification Assessed by Chest CT	Measurement Parameters	Main Manifestations and Outcomes	Sample Size	Prevalence of ILAs	Main Results
Menon A (2022)[27]	Case-control study	*******	Definite ILAs, indeterminate ILAs	Age, gender, BMI, smoking status, smoking pack-years, PFTs, chest CT	1. PFTs 2. Emphysema	9579 participants from phase 1 and 5277 participants from phase 2 in the COPDGene cohort	Definite ILAs: 528 (6%) in phase 1, and 580 (11%) in phase 2	1. Participants with ILAs were older, have a higher BMI, a heavier smoking intensity, a lower FEV_1, a lower FVC, a lower D_{LCO}% predicted, a lower TLC, and a lower emphysema score compared with those without ILAs. FEV_1-to-FVC ratios were not different between the two groups with and without ILAs. In phase 1, the FRC to TLC ratio and measures of Pi10 were higher in participants with ILAs compared with those without ILAs, but not in phase 2. 2. The decrement in FVC associated with increased emphysema was less in the ILAs group than that in the group without ILAs. In phase 1, the FVC was negatively associated with the amount of emphysema in participants without ILAs, whereas in participants with ILAs, the reduction of FVC was not associated with an increase in the amount of emphysema. In the longitudinal analysis, in participants with ILAs (in phase 1), the decline in FVC associated with emphysema was less than that noted in those without ILAs. ILAs modified the effect of emphysema on FEV_1 and the FEV_1-to-FVC ratio, but not the TLC and D_{LCO}.

Note: [a]The quality of studies assessed by the NOS tool is presented as stars, and the quality of studies assessed by the AHRQ scale is presented as numbers.

Abbreviations: 6MWD, Six minutes walk distance; ACOS, Asthma-COPD overlap syndrome; AHRQ, Agency for Healthcare Research and Quality; BMI, body mass index; CAT, COPD Assessment Test; COPDGene, Genetic Epidemiology of COPD Study; D_{LCO}, diffusion capacity of the lung for carbon monoxide; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; FHS, Framingham Heart Study; FRC, functional residual capacity; GGO, ground-glass opacity; GOLD, global initiative for chronic obstructive lung disease; HRCT, High Resolution Computed Tomography; IgE, immunoglobulin E; ILAs, interstitial lung abnormalities; ILD, interstitial lung disease; KL-6, Krebs Von den Lungen-6; LDCT, Low-Dose Computed Tomography; mMRC, Modified British Medical Research Council; NOS, Newcastle-Ottawa Scale; PFTs, pulmonary function tests; Pi10, square root of wall area of airway with internal perimeter of 10 mm; RB, respiratory bronchiolitis; RVLV, right ventricular to left ventricular; SGRQ, St George's Respiratory Questionnaire; SP-D, serum surfactant protein D; TLC, total lung capacity; UIP, usual interstitial pneumonia.

or indeterminate ILAs were defined by the presence of focal or unilateral GGO, focal or unilateral reticulation, or patchy GGO (affecting < 5% of the lung). Ash et al[17] defined interstitial features as reticular changes, honeycombing, centrilobular nodules, linear scar, nodular changes, subpleural lines, and GGOs, but they did not include traction bronchiectasis or nonemphysematous cysts as ILAs. Hoyer et al[29] defined ILAs as GGO, honeycombing, reticulation, pleural nodules, centrilobular nodules, paraseptal/subpleural nodules, mosaic attenuation, and mass. Two studies[19,20] described ILA patterns as honeycomb-like lesions, reticular abnormalities, and GGO. Chiba et al[21] defined interstitial changes as bilateral GGOs and reticular opacities with peripheral and basal predominance (Table 1).

Prevalence of ILAs in COPD and/or Emphysema Patients

The reported prevalence of ILAs in COPD/emphysema ranged from 6.5% to 68%, including definite ILAs and equivocal or indeterminate ILAs.[13,16,18–21,29] In the studies that did not define ILAs as definite or equivocal/indeterminate, the prevalence of ILAs in COPD/emphysema ranged from 6.5% to 25.7%.[19–21,29] In the studies that reported definite and equivocal/indeterminate ILAs separately, the prevalence of definite ILAs ranged from 7% to 28.4%, and that of equivocal/indeterminate ILAs ranged from 3.1% to 59%.[13,16,18] In the study[18] which included COPD cases and non-COPD control subjects, the prevalence of ILAs was similar between the two groups. Hoyer et al[29] reported an increased frequency of comorbid COPD in subjects with ILAs. In contrast, Washko et al[7] found that those with ILAs were less likely to have COPD, and had a lower percentage of emphysema. In the study by Putman et al,[13] the prevalence of COPD in those with ILAs was lower in the COPDGene cohort, but higher in the FHS cohort, as compared to those without ILAs. Araki et al[28] investigated the association between different subtypes of emphysema and the prevalence of ILAs, and they found that those with paraseptal emphysema had a higher prevalence of ILAs (Table 1).

Demographic Characteristics

COPD patients with ILAs were older as compared to those without, as demonstrated in Lee's study[16] and the ECLIPSE corhort.[13] A similar finding was reported in patients with ACOS.[21] In contrast, In Bozzetti's study,[18] which recruited COPD patients and non-COPD control subjects, age was not different between individuals with and without ILAs. In Ono's study,[19] the age was not different between patients with and without ILAs after propensity score matching. In the COPDGene cohort, in which the participants were smokers with or without COPD, the age of individuals with ILAs was older than those without ILAs.[7,13,17,27]

As reported in Bozzetti's study,[18] individuals with ILAs were more frequently male compared with those without ILAs.[18] However, in another study of COPD patients, the reported frequency of ILAs was not different between males and females, similar to the results in ACOS patients.[16,21] In the COPDGene cohort, the prevalence of ILAs was not different between the two genders.[7,10,13,27]

In COPD patients and ACOS patients, BMI was not significantly different between individuals with and without ILAs.[13,16,21] In the COPDGene cohort, BMI was higher in individuals with ILAs as compared to those without ILAs.[7,13,17,27]

The smoking index was higher in patients with ILAs in COPD and control subjects compared with those without ILAs, reported by Bozzetti et al[18] as well as in ACOS patients reported by Chiba et al.[21] However, the smoking index was similar between subjects with ILAs and those without ILAs in COPD patients from the ECLIPSE cohort,[13] and in COPD patients reported by Lee et al.[16] In the COPDGene cohort, Washko et al.[7] Menon et al[27] and Putman et al reported that the smoking index was higher in subjects with ILAs compared to those without ILAs. A similar tendency was observed in the study by Ash et al,[17] but the difference was not significant.

In patients with COPD, current smokers were more in COPD patients with ILAs than those without ILAs, as reported in the ECLIPSE cohort by Putman et al.[13] In the study by Bozzetti et al[18] the current smoking status was a factor associated with ILAs. However, smoking status was not different between COPD patients with and without ILAs in the study by Lee et al,[16] and a similar result was found in ACOS patients in the study by Chiba et al.[21] In the COPDgene cohort, the odds of having ILAs were 67% higher in current smokers in the adjusted model, reported by Washko et al.[7] Similarly, Ash et al[17] also reported the ratio of current smokers was higher in participants with ILAs. While in the study by Menon et al,[27] the ratio of current smokers was not significantly different between the groups with and without ILAs.

In summary, COPD/emphysema patients with ILAs had a propensity to be older, male, to have more current smokers, and to have a heavier smoking intensity compared with those without ILAs, although some studies showed no significant differences.

The Impact of ILAs on Symptoms and Outcomes of COPD

One study showed that the SGRQ score was higher, indicating poorer quality of life, in subjects with both emphysema and interstitial changes as compared to those with emphysema alone.[17] However, in the study by Ono et al, the CAT score and mMRC grades tended to be lower in COPD patients with ILAs, though the difference was not significant.[19] The 6MWD was shorter in COPD/emphysema subjects with ILAs as compared to those without ILAs, the difference being significant in subjects with emphysema from Ash's study[17] but not in COPD patients from Lee's study.[16] The prevalence of comorbidities was not different between COPD patients with and without ILAs,[16] so as that in ACOS patients.[21]

Two studies investigated the frequency of COPD exacerbations, but the results were discrepant. Ono et al[19] reported that the annualized rate of COPD exacerbations was lower in patients with ILAs compared with those without ILAs (0.06 vs 0.23), while that reported by Lee et al[16] was higher in COPD patients with ILAs (HR=2.04). Hoyer et al[29] reported a higher hospital admission rate in COPD patients with ILAs when considering the primary and contributing discharge diagnoses. In COPD patients from the ECLIPSE cohort, the mortality was higher in subjects with ILAs,[13] whereas no difference was reported by Ono et al between COPD patients with and without ILAs.[19] The mortality in ILAs subjects was also higher compared to those without ILAs, found in the COPDGene cohort.[13,17]

The Impact of ILAs on PFTs in COPD

The data of PFTs presented in the 11 studies were listed in Table 2. In COPD patients from the ECLIPSE corhort,[13] patients with ILAs had higher FEV_1% predicted and FEV_1-to-FVC ratio compared to those without ILAs. In another study[19] of COPD patients, higher FEV_1 and FEV_1% predicted were reported in the ILA group, but the difference was not significant. Similarly, in COPD patients of Group B (defined by GOLD 2011), FEV_1% predicted tended to be higher in patients with ILAs compared with those without ILAs.[20] In contrast, Lee et al[16] found that COPD patients with ILAs had a lower FEV_1, with the FEV_1% predicted and FEV-to-FVC ratio not different between the groups with and without ILAs. Furthermore, they found that patients with progressive ILAs showed a higher rate of annual decline in FEV_1 than those with unchanged or improved ILAs. Bozzetti et al[18] reported that the FEV_1% predicted and FEV_1-to-FVC ratios were not associated with the prevalence of ILAs in COPD patients.

In individuals with emphysema in the COPDGene cohort, subjects with interstitial features had a higher FEV_1% predicted than those without.[17] However, in the whole population from the COPDGene cohort, no difference was found in FEV_1% predicted between subjects with and without ILAs,[10,13] whereas FEV_1 was lower in the ILAs groups.[27] Putman et al[13] showed that FEV_1-to-FVC ratios were higher in the ILAs group, while no difference was found between the two groups from the same cohort by Washko et al[7] and Menon et al.[27] In summary, the changes in FEV_1, FEV_1% predicted, and FEV_1-to-FVC ratio modified by ILAs in COPD patients were discrepant in these articles.

Abnormality in the diffusing capacity is a feature of ILDs, and also of COPD/emphysema. Lee et al[16] found that the D_{LCO} tended to be lower in COPD patients with ILAs, though the difference was not significant, and the decline of D_{LCO} over time was not different between those with and without ILAs. However, in the COPDGene cohort, Ash et al[17] and Menon et al[27] showed that subjects with emphysema and ILAs had a lower D_{LCO}% predicted than those with emphysema only.

In COPD patients, FVC was found to be lower in patients with ILAs than those without ILAs, reported by Lee et al,[16] whereas no difference was found between the two groups in the study by Ono et al.[19] FVC% predicted showed no difference in the 3 studies including COPD patients.[13,16,18] In a longitudinal observation, the annual decline in FVC was higher in patients with progressive ILAs compared to those with unchanged or improved ILAs.[16] In the COPD cohort, Menon et al[27] found that FVC was lower in subjects with ILAs compared to those without. FVC% predicted was lower in the study by Ash et al[17] while not in the studies by Washko et al[7] and Putman et al.[13]

Total lung capacity (TLC) was not different between COPD patients with and without ILAs from the ECLIPSE cohort.[13] In the COPDGene cohort, ILAs were associated with reduced TLC and TLC% predicted,[7,13,27] and the reductions were not different between COPD and non-COPD patients, after adjustment for emphysema.[7] Furthermore, they assessed the change of PFTs longitudinally by different subtypes of ILAs, and found that those with radiographical

Table 2 PFTs in Subjects with and without ILAs in Included Studies

	Populations	Subjects with ILAs		Subjects without ILAs	*P* value	Author (Year)
		Total or Definite ILAs	Equivocal/Indeterminate ILAs			
FVC % predicted (%) (mean (SD))	COPD patients	102.7 (17.8)	–	104.8 (17.4)	0.6	Bozzetti F (2016)[18]
		80 (20)	–	79 (19)	0.78	Putman RK (2016)[13]
		86.4 (18.0)	81.5 (18.4)	87.0 (18.0)	0.222	Lee TS (2021)[16]
	Smoking subjects	88 (77–98)	87 (74–99)	88 (75–100)	0.80	Washko GR (2011)[7]
		99.5 (17.7)	–	101.7 (15.3)	0.04	Hoyer N (2020)[29]
		88 (17)	–	87 (19)	0.49	Putman RK (2016)[13]
		87.0 (17.5)	–	89.8 (18.0)	<0.001	Ash SY (2018)[17]
FVC (L)	COPD patients	3.13 (0.63)	–	3.02 (0.68)	0.442	Ono M (2020)[19]
		3.0 (0.7)	2.9 (0.8)	3.2 (0.8)	0.032	Lee TS (2021)[16]
	Smoking subjects	4.03(1.0)	–	4.13 (0.99)	0.10	Hoyer N (2020)[29]
		2.98 (2.5–3.7)	–	3.32 (2.7–4.1)	< 0.0001	Menon A (2022)[27]
		2.94 (2.37–3.63)	–	3.13 (2.52–3.90)	< 0.0001	
FEV_1% predicted (%)	COPD patients	92.8 (17.8)	–	94.6 (18.9)	0.3	Bozzetti F (2016)[18]
		68.1 (19.5)	–	64.0 (21.4)	0.354	Ono M (2020)[19]
		61.9 (20.0)	58.2 (18.2)	62.8 (18.0)	0.264	Lee TS (2021)[16]
		47 (14)	–	44 (15)	0.02	Putman RK (2016)[13]
	Smoking subjects	76.8 (23.8)	–	77.8 (27.0)	0.200	Ash SY (2018)[17]
		87.9 (18.6)	–	92.4 (16.3)	< 0.001	Hoyer N (2020)[29]
		82 (67–93)	77 (55–92)	80 (52–97)	0.15	Washko GR (2011)[7]
		78 (22)	–	75 (28)	0.10	Putman RK (2016)[13]

(*Continued*)

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Table 2 (Continued).

	Populations	Subjects with ILAs		Subjects without ILAs	*P* value	Author (Year)
		Total or Definite ILAs	Equivocal/Indeterminate ILAs			
FEV_1 (L)	COPD patients	1.74 (0.50)	–	1.58 (0.59)	0.184	Ono M (2020)[19]
		1.5 (0.5)	1.5 (0.6)	1.6 (0.5)	0.025	Lee TS (2021)[16]
	Smoking subjects	2.75 (0.76)	–	2.91 (0.75)	< 0.001	Hoyer N (2020)[29]
		2.06 (1.6–2.6)	–	2.35 (1.7–3.0)	< 0.0001	Menon A (2022)[27]
		2.06 (1.61–2.57)	–	2.26 (1.61–2.83)	0.0005	
FEV_1-to-FVC ratio (%)	COPD patients	71.8±12	–	72.8 (12.5)	0.7	Bozzetti F (2016)[18]
		48.6 (12.3)	49.6 (12.7)	50.4 (11.5)	0.585	Lee TS (2021)[16]
		48 (11)	–	45(12)	0.006	Putman RK (2016)[13]
	Smoking subjects	71 (60–80)	–	72 (60–80)	0.37	Menon A (2022)[27]
		72(64–78)	–	73 (62–79)	0.76	
		71 (61–77)	68 (53–76)	70 (51–79)	0.32	Washko GR (2011)[7]
		67 (14)	–	64 (18)	0.03	Putman RK (2016)[13]
D_{LCO} % predicted (%)	COPD patients	82.1 (25.0)	77.1 (27.2)	81.0 (23.7)	0.718	Lee TS (2021)[16]
	Smoking subjects	50.9 (20.8)	–	49.8 (20.5)	0.764	Ash SY[17]
		70.6 (57.7–84.5)	–	83.4 (68–97.9)	< 0.0001	Menon A (2022)[27]
D_{LCO}(mL/mmHg/min)	COPD patients	12.7 (4.5)	13.3 (6.0)	14.0 (4.9)	0.147	Lee TS (2021)[16]
TLC (L)	COPD patients	5.7 (1.4)	–	5.9 (1.5)	0.16	Putman RK (2016)[13]
	Smoking subjects	5.0 (4.1–6.0)	–	5.6 (4.7–6.7)	< 0.0001	Menon A (2022)[27]
		5.04 (4.22–6.05)	–	5.38 (4.57–6.54)	< 0.0001	
		5.02 (4.15–5.96)	5.21 (4.38–6.27)	5.70 (4.80–6.78)	<0.001	Washko GR (2011)[7]
		5.2 (1.4)	–	5.8 (1.4)	<0 0.001	Putman RK (2016)[13]
TLC % predicted (%)	Smoking subjects	95 (81–109)	100 (84–112)	107 (92–120)	<0.001	Washko GR (2011)[7]
FRC-to-TLC ratio (%)	Smoking subjects	0.6 (0.5–0.7)	–	0.6 (0.5–0.7)	0.0001	Menon A (2022)[27]
		0.56 (0.50–0.63)	–	0.56 (0.49–0.65)	0.87	

Note: Data are presented as No. (%) or mean (SD), unless otherwise indicated.

Abbreviations: D_{LCO}, diffusion capacity of the lung for carbon monoxide; FRC, functional residual capacity; ILAs, interstitial lung abnormalities; TLC, total lung capacity.

ILDs had the greatest reduction in TLC, while those with subpleural lesions, mixed patterns and centrilobular lesions showed milder decrease of TLC. The FRC to TLC ratio was higher in participants with ILAs in Phase 1 but not in Phase 2 in the COPDGene cohort.[27]

Different Patterns of ILAs on Chest CT

In the study by Bozzetti et al[18] the indeterminate pattern was more frequent in COPD cases with definite ILAs, whereas respiratory bronchiolitis (RB) was more frequent in non-COPD control subjects. The frequencies of usual interstitial pneumonia (UIP) and fibrotic ILAs were similar between COPD cases and control subjects in definite ILAs, while equivocal ILAs were observed only in COPD cases. Subpleural abnormalities were the most common subtype of ILAs, reported by Washko et al[7] and Lee et al.[16] The area of honeycombing in Group B COPD was significantly greater than that in Group C. As reported by Ohgiya et al,[20] the rates of GGOs were similar in all 4 COPD groups defined by GOLD 2011.

In ACOS patients, airway walls were thicker in patients with interstitial changes as compared to those without.[21] In phase 1 of the COPDGene cohort,[27] measurements of Pi10 were higher in participants with ILAs compared with those without.

Lee et al[16] evaluated the longitudinal changes of ILAs on chest CT, and found that 70% of the COPD patients without ILAs remained free of ILAs, whereas ILAs occurred in the remaining 30%. In the equivocal ILAs group, ILAs were inconsistent in nearly half of the patients; progression to definite ILAs in about 20% and disappearance in about 30%. In the definite ILAs group, definite ILAs remained in about 70% of the patients, while about 10% converted to equivocal ILAs, and 20% disappeared.

Interaction Between ILAs and Emphysema

In the COPDGene cohort, Menon et al[27] reported a lower emphysema score in the participants with ILAs, compared to those without ILAs. This result was similar to that reported by Washko et al[7] that individuals with ILAs had a lower percentage of emphysema than those without ILAs. However, in COPD patients, emphysema was not different between groups with and without ILAs, reported by Lee et al.[16]

Menon et al[27] reported that the decrease in FVC associated with increased emphysema was less in the ILA group. In their phase 1 study, the FVC was negatively associated with the amount of emphysema in participants without ILAs, whereas in participants with ILAs, the reduction of FVC was not associated with an increase in the amount of emphysema. In longitudinal observations, in participants with ILAs (in phase 1), the decline in FVC associated with emphysema was less than that noted in those without ILAs. ILAs modified the impact of emphysema on FEV_1 and the FEV_1-to-FVC ratio, but not the TLC and D_{LCO}. In addition, Ash et al[17] found that interstitial features enhanced the impact of emphysema on D_{LCO}% predicted, RVLV volume ratio, 6WMD, SGRQ score, and mortality.

Discussion

To our knowledge, this is the first systematic review that focuses on the impact of coexistent ILAs on the disease expression and clinical outcomes of COPD/emphysema. In this review, we found that the prevalence of ILAs tends to be higher in COPD/emphysema patients than that in general populations. COPD/emphysema patients with ILAs had a propensity to be older and male, and have a heavier smoking intensity, a shorter 6MWD, a higher mortality, and a lower D_{LCO}, as compared to those without ILAs, while the impact of ILAs on COPD exacerbation and spirometry was discrepant.

The prevalence of ILAs in COPD/emphysema patients was 6.5% - 28.4%, which was higher than that in general populations (2% −7%) and smoking populations (4–9%). The higher prevalence of ILAs in COPD/emphysema might be attributable to the older age and heavier smoking in the COPD/emphysema population. It is interesting to note that, MUC5B promoter polymorphism was associated with ILAs,[11] while MUC5B was one of the major polymeric mucins in the airways of COPD patients,[31] suggesting that the interaction between ILAs and COPD might be also associated with the dysregulation of MUC5B.

This review found that in the COPD/emphysema populations, individuals with ILAs tended to be older, male, have more current smokers, and have a heavier smoking intensity, which was similar to those found in smoking and general populations.[11,12,32,33] Subjects with emphysema and ILAs had more respiratory symptoms and a reduced 6MWD, and

similar findings were also reported in smoking individuals. Unexpectedly, in COPD patients, the deterioration in respiratory symptoms and exercise capacity tended to be alleviated by coexistent ILAs, which needs further investigation.

Acute exacerbations and mortality are major outcomes of COPD, and factors associated with these outcomes are of critical significance. Our review here found that the impact of ILAs on the exacerbation rate of COPD was discrepant in these studies. Therefore, more evidence is needed to reveal the impact of ILAs on the frequency of exacerbation of COPD. Consistent with findings that ILAs were associated with all-cause mortality in both smoking and general populations,[13,14,34] our review showed that the mortality in COPD patients with ILAs was higher than in those without ILAs.

It is predictable that ILAs aggravated the decrease of D_{LCO} and/or D_{LCO}% predicted in COPD patients. However, the changes in FEV_1, FVC, FEV_1-to-FVC ratio, and TLC modified by ILAs in COPD patients varied in these studies. These findings might be related to the different performances of PFTs between ILAs and COPD subjects. The airflow limitation of COPD is manifested as obstructive ventilation dysfunction, with decreased FEV_1, FEV_1% predicted, and FEV_1-to-FVC ratio in PFTs. Oppositely, ILAs lead to restrictive dysfunction with a decreased FVC and an increased or normal FEV_1-to-FVC ratio in PFTs. Similarly, the lung volume is increased in emphysema whereas decreased in ILAs. As a result, the dysfunction in PFTs of COPD might be pseudonormalized or attenuated when combined with ILAs, depending on the severity of COPD/emphysema and ILAs.

There are several limitations in this review. Firstly, because the studies focused on the interaction between ILAs and COPD/emphysema were limited and heterogenous, we were unable to perform a meta-analysis, and therefore we only narratively presented the results. Secondly, most of the included studies were cross-sectional or retrospective in design, which makes it hard to understand the real impact of ILAs in patients with COPD. Importantly, the definition of ILAs varied among the studies included in this review, which may influence the results and partially account for the discrepancies in the results of different studies.

Therefore, a standard and comprehensive definition of ILAs is needed for further investigations. In 2020, a definition of ILAs was proposed by the Fleischner Society,[9] in which centrilobular nodularity was not included, because it was recognized as a presentation of smoking-related respiratory bronchiolitis, and was typically non-progressive. Subcategories of ILAs were also defined by the Fleischner Society as non-subpleural, subpleural non-fibrotic, and subpleural fibrotic.[9] Since the progression of ILAs may be varied in different subcategories,[35] future studies should also observe the impact of ILAs by different subcategories. In addition, the severity of ILAs and COPD/emphysema should be quantified to better understand the interaction between COPD/emphysema and ILAs.

Conclusion

In conclusion, the prevalence of ILAs was higher in subjects with COPD/emphysema than that in general populations. ILAs may have a negative impact on exercise capacity, hospital admission and mortality of COPD/emphysema patients. The impact of ILAs on PFTs and exacerbations of COPD/emphysema was discrepant in the current studies. To further understand the association and interaction between COPD/emphysema and ILAs, more high-quality evidence from prospective studies is needed.

Abbreviations

6MWD, Six minutes walk distance; ACOS, Asthma-COPD overlap syndrome; AHRQ, Agency for Healthcare Research and Quality; BMI, body mass index; CAT, COPD Assessment Test; COPDGene, Genetic Epidemiology of COPD Study; D_{LCO}, diffusion capacity of the lung for carbon monoxide; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; FHS, Framingham Heart Study; FRC, functional residual capacity; GGO, ground-glass opacity; GOLD, global initiative for chronic obstructive lung disease; HRCT, High Resolution Computed Tomography; IgE, immunoglobulin E; ILAs, interstitial lung abnormalities; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs Von den Lungen-6; LDCT, Low-Dose Computed Tomography; mMRC, Modified British Medical Research Council; NOS, Newcastle-Ottawa Scale; PFTs, pulmonary function tests; Pi10, square root of wall area of airway with internal perimeter of 10 mm; RB, respiratory bronchiolitis; RVLV, right ventricular to left ventricular; SGRQ, St George's Respiratory Questionnaire; SP-D, serum surfactant protein D; TLC, total lung capacity; UIP, usual interstitial pneumonia.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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