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XXXVI CICLO

*Prevalence, progression, and mortality of interstitial lung abnormalities in over 20000 unselected abdominal and thoraco-abdominal CT scans*

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## ABSTRACT

Interstitial lung abnormalities (ILA) represent radiologic abnormalities incidentally detected on computed tomography (CT) scans, potentially associated with increased risk of progression toward frank pulmonary fibrosis and mortality.

We aim at evaluating frequency, progression, and associated mortality of ILA depictable in a large cohort of unselected subjects who had undergone either abdominal CT or thoracic-abdominal CT for various clinical indications.

Consecutive abdominal or thoraco-abdominal CT scans, performed on a large cohort of inpatients and outpatients without any available prior chest CT scan, were reviewed for the presence of ILA according to the Fleischner Society recommendations. Radiological progression of ILA was evaluated by comparing the first and the last available CT timepoints. Demographic and clinical data were obtained from hospital database and regional registry. Cox proportional hazards models were used to assess factors associated with hazards of ILA progression and mortality.

ILA were observed in 362/21.118 (1.7%) subjects; with fibrotic ILA recognized in approximately 1% of either baseline abdominal or thoraco-abdominal CT scans. A definite progression was observed in 44.4% subjects. ILA were independently associated with either all-cause mortality (OR 4.158, 95%CI 2.2165-8.9908, p<0.0001) or mortality due to respiratory disease (OR 4.76., 95%CI 11.95, p=0009).

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# INTRODUCTION

## Background

The large use and continuous implementation of high-resolution computed tomography (HRCT) of the chest have revolutionised the diagnosis of interstitial lung diseases (ILD), which represent a heterogeneous group of disorders characterized by a variable degree of inflammation and/or fibrosis of the pulmonary parenchyma [1-3]. The recognition of mild interstitial abnormalities, however, can be rather challenging, and the relative ease of assessing severe and diffuse interstitial involvement contrasts with the difficulty of depicting subtle and less extensive abnormalities. Subclinical interstitial changes can be depicted in subjects undergoing either abdominal or chest CT examination, without any clinical suspicion of underlying ILD. These incidentally detected CT findings, potentially representing symptomatic ILD, are named interstitial lung abnormalities (ILA) [4].

The estimated prevalence of ILA in subjects over 60 years of age is up to 9% in smokers and 7% in non-smokers [5], reaching the rate of 9.7% [6] and 25% [7] in lung cancer screening populations.

Increasing age, tobacco smoke exposure, other inhalational exposures (e.g., gases, dusts, fumes, etc), and genetic factors are recognized risk factors for ILA [8-10]. Of note, a promoter polymorphism in the gene encoding mucin 5B, well-known to be associated with idiopathic pulmonary fibrosis (IPF) and familial interstitial pneumonia [11], has been demonstrated to be linked with both presence [8] and progression [12] of ILA.

Since ILA were first described in tobacco smokers [13-15], several studies have attempted to better characterize such abnormalities [8, 12, 16]. The Position Paper released by the Fleischer Society in 2020 provides some clarity on definition, terminology, risk factors and management of

ILA [4], addressing some of the unanswered questions around this topic. ILA are defined as non-dependent lung abnormalities [17], diffuse in distribution (i.e., non-focal) and with at least 5% extent of a lung zone (upper, middle, and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein), displayed by subjects in whom ILD is not suspected and thus, incidentally [4]. Hatabu et al also proposed three different categories of ILA: (i) subpleural fibrotic ILA, (ii) subpleural non-fibrotic ILA and (iii) non subpleural ILA. CT features of fibrosis include architectural distortion (e.g., fissures displacement, bronchovascular structures distortion) with traction bronchiectasis, and/or honeycombing (or both) [4].

Prior to the Position Paper release, an heterogeneous terminology had been used to define ILA, including (i) ILD at an early stage, (ii) early ILD, (iii) preclinical ILD and (iv) subclinical ILD [4, 18, 19], all suggesting a relentless progression toward ILD. However, ILA categories are associated with different risk of progression: non-subpleural ILA tend to remain stable, as opposite to subpleural fibrotic ILA, which are more likely to progress toward fibrosis [6, 20]. Notably, Putman et al observed that subpleural reticulations, traction bronchiectasis and lower lobe abnormalities were associated with a sixfold increase odd of progression and reported that all subjects presenting with honeycombing had progressed over the following 5 years [20]. Distinguishing clinically irrelevant ILA from clinically significant ILA is of paramount importance since the latter might benefit from early antifibrotic treatments [4], which have been proposed for ILA at a higher risk of progression.

The association between ILA and adverse clinical outcomes, including progressive respiratory function decline, hospitalization, increased risk of lung cancer and all-cause mortality, has been well established. Individuals with ILA experience respiratory symptoms, including chronic cough and shortness of breath, more than those without ILA [8, 21]. ILA is also associated with reduced exercise capacity [22], decreased total lung capacity [8, 13] and impaired gas exchange [8,

21]. The presence of ILA correlates with increased mortality in both general populations [12] and among smokers assessed for chronic obstructive pulmonary disease (COPD) or lung cancer screening [10, 13, 23].

## Open issues

To date, epidemiologic data on ILA have been mostly obtained from studies involving research population cohorts and selected populations of smokers [6, 10, 16, 24-29]. Such studies including mostly elderly [6, 30, 31] and/or smokers [13, 26] only provide data on subjects at a greater risk of having ILA as compared to the general population. In fact, although ILA have been increasingly recognized in either abdominal or thoraco-abdominal CT scan performed for any reason, data on their prevalence and mortality in unselected populations are still missing.

The 5% threshold recommended by the Fleischner Society to define the presence of ILA is rather prone to subjective interpretation. A purely visual assessment of ILA extent can be challenging and suffers from a high interobserver variability [32-34]. However, the accurate quantification of the involved parenchyma on both baseline and follow-up CT is crucial, to define their presence and longitudinal behaviour, respectively.

The recognition of interstitial abnormalities involving ≥ 5% extent of a lung zone should trigger a dedicated chest CT to confirm and characterize such abnormalities. However, to whom a dedicated CT should be offered is still debated. Notably, it might be argued whether performing additional CT examination on asymptomatic individuals is appropriate, particularly younger subjects because of the radiation exposure-related risks. On the other hand, given that ILA is detected in subjects without any clinical suspicion of underlying ILD (by definition), investigating the presence of symptoms unrelated to the clinical indication for which the patient had been referred can be challenging in clinical practice. Although radiologists play a pivotal role in

identifying and characterize ILA, a correct management of ILA requires a thorough patient assessment, and thus a multidisciplinary approach to this radiological entity should be encouraged.

Analogously to ILD, ILA may change in both extent and morphology over time, but how radiological progression should be assessed is still to be defined, as well as whether a radiological progression should be managed as progressed ILA regardless of the clinical and functional domains. Araki et al demonstrated a correlation between radiological and functional progression, reporting that ILA subjects with radiological progression experienced an accelerated pulmonary function decline [12]. However, evidence of radiological progression is not necessarily associated with worsening of respiratory symptoms and/or lung function [35]. Signs of overt progression are more easily detected as compared to subtle changes, which however, might still represent a significant increase in extent (progression from 6% to 8% extent represents a relative increase of one third). Not less importantly, the assessment of radiological progression is potentially affected by technical aspects of CT acquisition and reconstruction parameters [36].

## Aim of the study

This study aimed at evaluating frequency, progression, and associated mortality of ILA recognizable in a large cohort of unselected subjects who had undergone either abdominal CT or thoracic-abdominal CT for various clinical indications.

## MATERIALS AND METHODS

### Study population

We retrospectively selected subjects of ≥ 50 years of age, resident in Emilia Romagna (region of northern Italy), on whom an either abdominal or thoracic-abdominal CT reconstructed with a slice thickness ≤ 2.5 mm was performed at the University Hospital of Parma between January 2008 and December 2015. Subjects with a previous history of established ILD or diseases potentially associated with ILD (e.g., connective tissue disease, CTD) were excluded, as well as those who had undergone any chest CT scan before the abdominal or thoraco-abdominal CT scan to reduce the risk of bias towards ILD.

This retrospective observational study was approved by the Institutional Review Board of the University Hospital of Parma (CE AVEN; 210/2017).

### Demographic and clinical data

Demographic and clinical data were retrieved from both hospital database and regional registry from 2006 to 2018. Such data included age, sex, previous history of lung disease (i.e., lung fibrosis, COPD, CTD; etc), cardiovascular disease, oncologic disease (i.e., lung and extrapulmonary cancer) and cause of death (obtained from death certificates and defined according to the International Classification of Diseases, Ninth Revision, ICD-9).

### Radiological data

CT images were acquired in inpatient, acute care, or outpatient settings with multiple scanners and different acquisition protocols. CT scanners were:

- single-source 6 slice (Emotion 6; Siemens Healthcare, Forchheim, Germany)
- single-source 64-slice (Sensation Cardiac; Siemens Healthcare)
- second-generation dual-source 128-slice CT scanner (Somatom Definition Flash; Siemens Healthcare).

### *Imaging assessment*

At first, CT images were retrieved from the local Picture Archiving Communicating System (PACS) and evaluated by six senior radiology residents on a dedicated workstation (BARCO visualization system, Kortrijk, Belgium) to detect features of ILA. The presence of ILA was determined according to the Fleischner Society Position Paper on ILA, which are defined as nondependent imaging findings affecting at least 5% of a lung zone (i.e., upper, middle, lower) [4]. Such findings include [17]:

- ***ground-glass opacities***, defined as hazy increased opacities of the lung parenchyma, with preservation of bronchial and vascular margins;
- ***reticulations***: small linear opacities that produce an appearance resembling a net;
- ***parenchymal distortion***: the normal lung anatomy has a distorted appearance with associated volume loss, usually due to fibrosis;
- ***non-emphysematous cysts***: round parenchymal lucencies/low-attenuating areas with a well-defined interface with normal lung. Cysts have a thin wall (<2 mm) and occur without associated pulmonary emphysema;
- ***honeycombing***: clustered cystic air spaces with a diameter of 3-10 mm (occasionally as large as 2.5 cm), usually subpleural and with well-defined walls;
- and/or **traction bronchiectasis**: irregular bronchial dilatation caused by surrounding pulmonary fibrosis.

Then, the CTs showing features compatible with ILA were assessed in consensus by two highly experienced chest radiologists (with 15 years of experience in the field) who (i) confirmed or discarded the presence of ILA detected by the residents, (ii) classified established ILA as subpleural fibrotic (Figure 1), subpleural non-fibrotic (Figure 2), and non-subpleural (Figure 3), according to the Fleischner Society recommendations [4], and (iii) recorded CT findings equivocal for ILA (e.g., focal or unilateral abnormalities, <5% in extent in any lung zone).

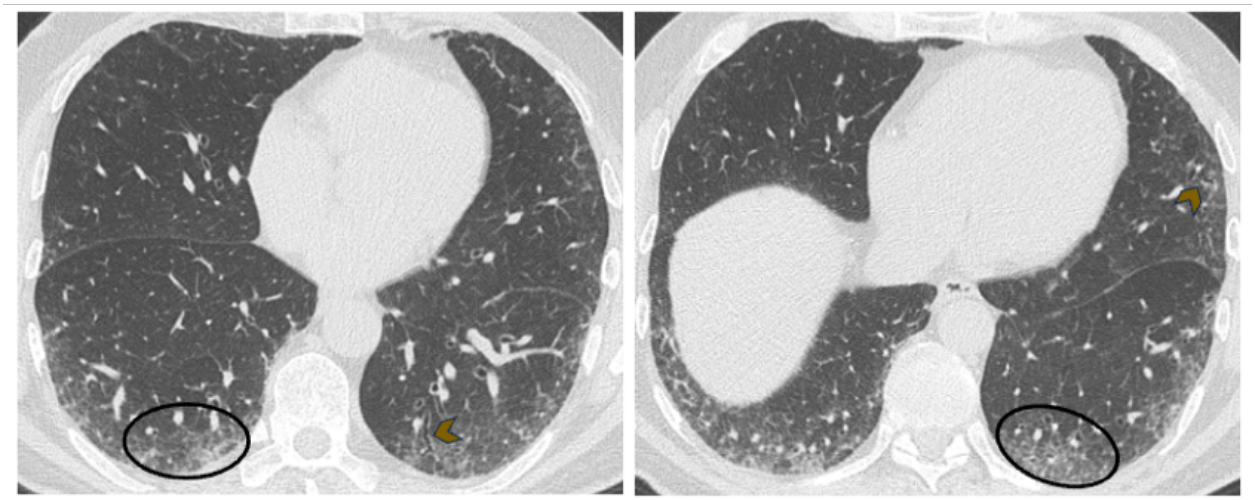

*Figure 1. Axial CT images showing evidence of subpleural fibrotic ILA: bilateral traction bronchiolectasis (arrowheads) associated with ground glass opacities and reticulations (circles).*

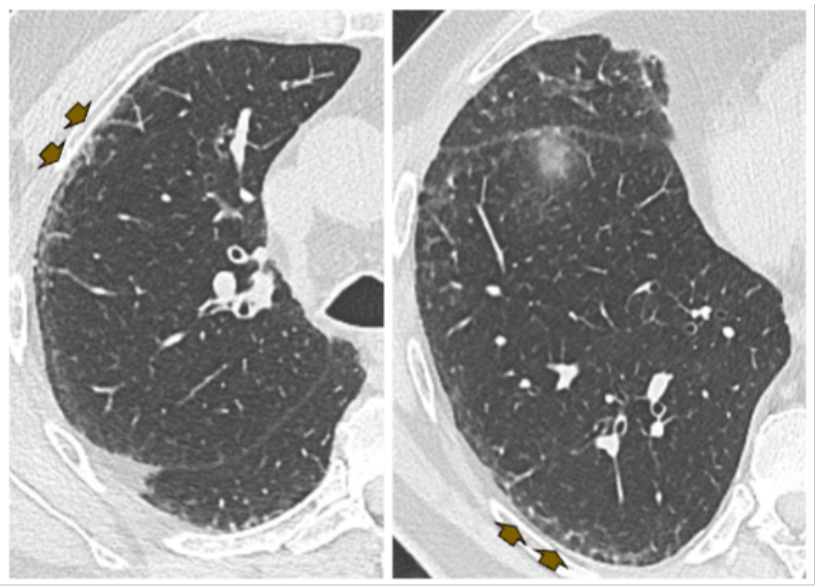

*Figure 2. Axial CT images showing evidence of subpleural non fibrotic ILA: subpleural reticular opacities (arrows) with no overt signs of fibrosis/parenchymal distortion.*

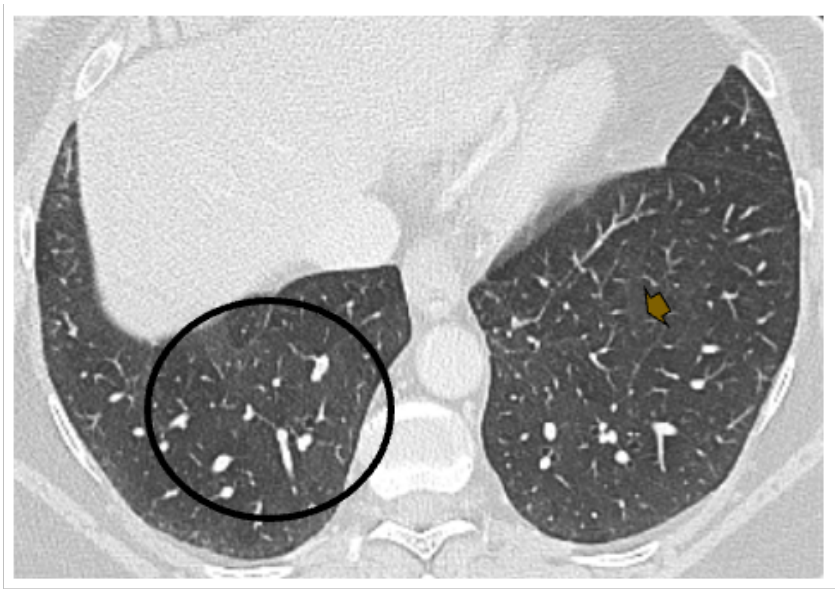

*Figure 3. Axial CT image showing ground glass opacities (circle), associated with minimal reticular opacities (arrow) both with a prevalent central distribution, compatible with non-subpleural ILA.*

For abdominal CT, ILA extent was classified as 'likely greater than 5%', or 'indeterminate'. Fibrotic patterns of ILA were classified as typical usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP, or more consistent with non-IPF diagnosis [37].

Severity of traction bronchiectasis was assessed visually by the chest radiologists through the comparison of the diameter of the airway with that of the adjacent pulmonary artery using a 5- point score:

- 0= none (no dilatation)
- 1= minimal (dilatation of bronchioles without obvious bronchiectasis or architectural distortion)
- 2= mild (dilated bronchi almost same diameters with adjacent pulmonary artery)
- 3= moderate (between mild and severe)
- 4= severe (remarkable dilatation of bronchi or honeycombing).

The score was assigned considering the lung areas where traction bronchiectasis/bronchiolectasis was most severe [38].

Traction Bronchiectasis/traction bronchiolectasis index (TBI) was defined according to the above-mentioned score:

- TBI= 0, assigned when traction bronchiectasis score was 0 (ILA without traction bronchiectasis/bronchiolectasis)
- TBI= 1, ILA with bronchiolectasis (score 1) but without bronchiectasis or architectural distortion
- TBI= 2, ILA with mild or moderate traction bronchiectasis (score 2 or 3)
- TBI= 3, ILA and severe traction bronchiectasis and/or honeycombing (score 4).

As for the 5-point bronchiectasis score, TBI was determined based on the lung regions where traction bronchiectasis/bronchiolectasis was most prominent [38].

### *ILA progression*

ILA progression was evaluated by comparing the first and the last available CT timepoints on local PACS. The disease behaviour was classified as:

- resolved
- definitely regressed
- likely regressed
- stable
- likely progressed
- definitely progressed

Progression was defined as an increased extent of non-dependent ground-glass opacities, reticular abnormalities, non-emphysematous cysts, honeycombing, and/or traction bronchiectasis, or as new appearance of at least one these abnormalities [39].

## Statistical analysis

The relationship of ILA frequency with demographic and clinical variables was assessed by logistic regression models and expressed as odds ratio (OR) and its 95% Confidence Interval (CI).

ILA progression was also evaluated using logistic regression analyses; ILA progression was dichotomized into “progressive ILA” including both “likely progressed” and “definitely progressed” and “non-progressive ILA” including “stable”, “likely regressed”, “definitely regressed”, and

“resolved” categories. The multivariable analyses were adjusted for age, sex, oncologic and cardiovascular disease.

Logistic regression models were also used for assessing time-to-mortality according to presence of ILA, patterns of ILA, and ILA progression. Multivariable models were adjusted for age, sex, race, oncologic and cardiovascular disease. All variables included in Cox models were assessed for the proportional hazards’ assumption with no violation.

All statistical analysis were performed with SAS v 8.0/9.4, Enterprise Guide 8.2/8.3 and STATA/SE v. 11.0./17.0.

## RESULTS

### Study population

The study population consisted of 23.840 subjects (53% male, median age 72 years - interquartile range, IQR, 79-63). The CT scans with their corresponding slice thickness were:

- Abdominal CT: 11.081 (46%)
  - < 2 mm: 3.103 (28.1%)
  - 2-2.5 mm: 7.967 (71.9%)
- Thoraco-Abdominal CT: 12.759 (54%)
  - < 2 mm: 6.239 (48.9%)
  - 2-2.5 mm: 6.520 (51.1%)

Detailed data on the number of CT assessed by each resident is detailed in Table 1.

| **Radiology Resident** | **Evaluated CT (N°)** | **Evaluated CT (%)** |
|---|---|---|
| *Reader 1* | 4.127/23.840 | 17.3 |
| *Reader 2* | 5.007/23.840 | 21 |
| *Reader 3* | 5.365/23.840 | 22.5 |
| *Reader 4* | 4.656/23.840 | 19.5 |
| *Reader 5* | 551/23.840 | 2.3 |
| *Reader 6* | 4.134/23.840 | 17.4 |

*Table 1. Absolute number and percentage of CT scans assessed by each radiology resident.*

### Prevalence of ILA

CT features compatible with ILA were identified in 1.041/23.840 (4.37%) subjects by the residents and in 648/23.840 (2.71%) by the chest radiologists; 401/648 (61.9%) participants

showed features of ILA, while 247/648 (38.1%) CT abnormalities equivocal for ILA (1.68% and 1.03% of the whole study population, respectively).

Medical history was available for 21.118/23.840 (88.6%) subjects and for 390/401 (97.3%) subjects with suspected ILA. Since 24 /390 (6.2%) subjects had a previous history of lung fibrosis and 4/390 (1.0%) of CTD, only 362/21.118 (1.7%) subjects were considered as having ILA (Figure 4). Subpleural fibrotic ILA was observed in 197/362 (54.4%), subpleural non-fibrotic ILA in 97/362 (26.8%), and non-subpleural ILA in 68/362 (18.8%) (Figure 5); 25/68 (36.8%) subjects with non-subpleural ILA showed signs of fibrosis. Therefore, 222 (1.1%) fibrotic ILA were depicted among all subjects.

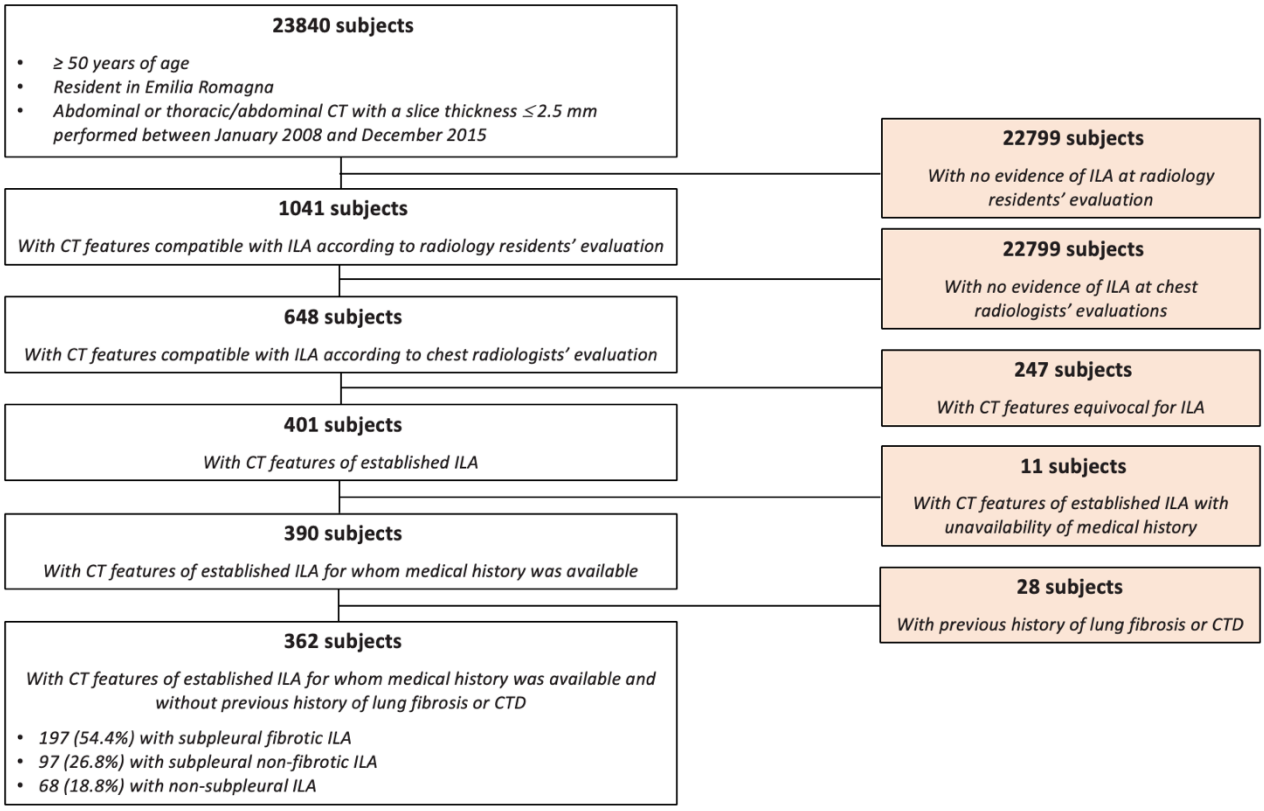


*Figure 4. Flow-chart showing the selection of subjects with ILA.*

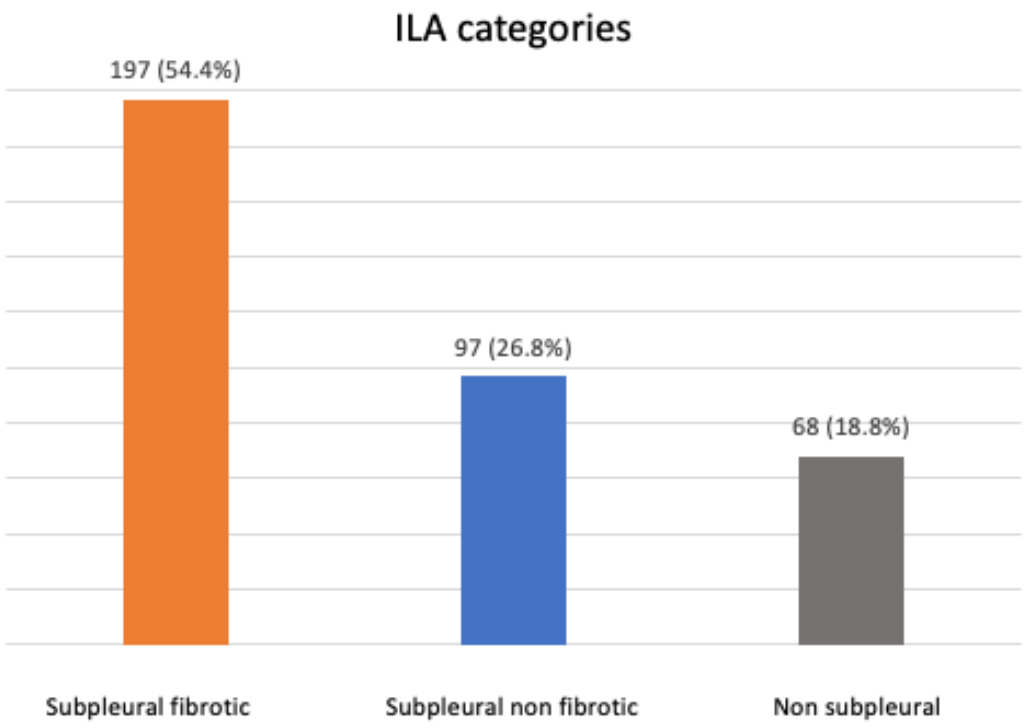


*Figure 5. Histogram showing absolute number with relative percentage of ILA categories in our population cohort.*

## CT features of ILA

ILA was mostly represented by subpleural reticular opacities (270/362, 74.6 %). The frequency of typical UIP, probable UIP, indeterminate for UIP and suggestive of alternative diagnosis CT patterns were 0.21%, 0.27%, 0.38%, and 0.18%, respectively.

Subpleural non-fibrotic ILA was characterized by subpleural reticular opacities, without obvious traction bronchiectasis or honeycombing, with (65.8%) or without (34.2%) ground-glass opacity.

Non-subpleural ILA included either peribronchovascular (42.6%) or diffuse (57.4%) ground-glass opacities/reticular abnormalities, while equivocal ILA were mostly peribronchovascular (97.6%) in distribution.

## Demographic and clinical features of ILA

Subjects with ILA were older (OR=1.05, 95%CI 1.04-1-06, p < 0.0001) and more frequently male (OR= 2.0, 95%CI 1.58-2.49, p < 0.0001), as compared to subjects without ILA (Figure 6). Subjects with ILA showed a higher frequency of previous cardiovascular disease (15.38% vs. 9.54%, p < 0.0001) or other non-fibrotic pulmonary diseases (47.4% vs. 20.3%, p<0.0001) as compared to those without. Moreover, lung cancer was more frequently observed among subjects displaying ILA (12.1% vs. 6.8%, p<0.0001), whereas no significant differences were observed for extrapulmonary cancers between the two groups (44.4% vs. 47.5%, p = 0.3).

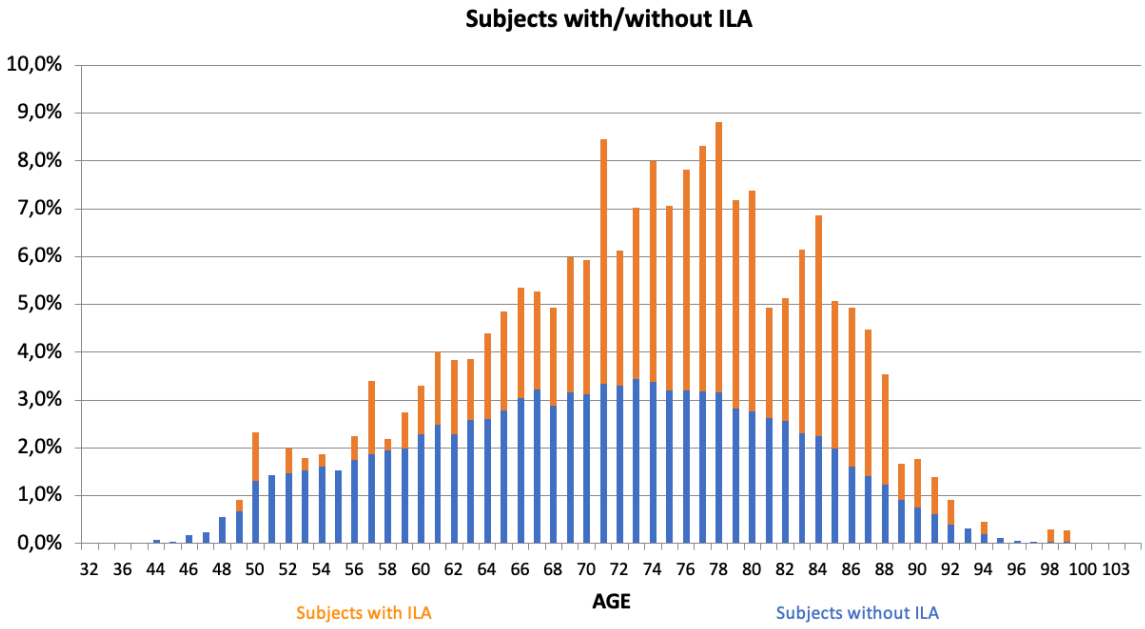


*Figure 6. ILA distribution according to age.*

## ILA and mortality

Association between ILA and cause-specific/all-cause mortality is summarized in Table 2. The median follow-up time was 3 years (IQR 1-5.5). Overall, extrapulmonary cancer was the most common cause of mortality (18.4%), with a rate of 12.1% in the ILA group.

On multivariable analysis, the presence of ILA was independently associated with all-cause (OR 2.070, 95%CI 1.628 -2.633, p<0.0001) and cause-specific mortality with the only exception of extrapulmonary cancer. The strongest association was observed between ILA and respiratory disease-related death (OR 3.790, 95%CI 2.060-6.972, p<0.0001), with subjects displaying fibrotic ILA being at a higher risk (OR= 4.581, 95%CI 2.21-8.99, p<0.0001) as compared to those with other types of ILA.

| **Covariate** | **Subjects with ILA** | **Subjects without ILA** | **OR (95%CI)** | **p-value** |
|---|---|---|---|---|
| ***All-cause mortality*** | 34.4% | 16.6% | 2.065 (1.365-2.608) | <0.0001 |
| ***Cause-specific mortality*** | | | | |
| *Respiratory disease* | 3.3% | 0.7% | 3.798 (2.109-6.839) | <0.0001 |
| *Cardiovascular disease* | 7.7% | 2.6% | 2.465 (1.661-3.659) | <0.0001 |
| *Lung cancer* | 4.4% | 1.8 | 2.464 (1.492-4.070) | 0.0004 |
| *Extrapulmonary cancer* | 9.5% | 8.3% | 1.140 (0.799-1.625) | 0.4706 |
| *Other* | 9.2% | 3.2% | 2.552 (1.766-3.686) | <0.0001 |

*Table 2. Association between ILA and mortality.*

## Progression of ILA

A total of 177/362 (50.6%) subjects with ILA at baseline CT had at least one follow-up scan; median time between the two imaging timepoints was 8 months (IQR 0 –3 years); of them, 83/177

(46.9%) showed evidence of definitely progression (Figure 6), 15/177 (8.5%) of probable progression, 68/177 (38.4%) were stable, 5/177 (2.8%) had probably improved, and 6/177 (3.4%) had definitely improved (Table 3).

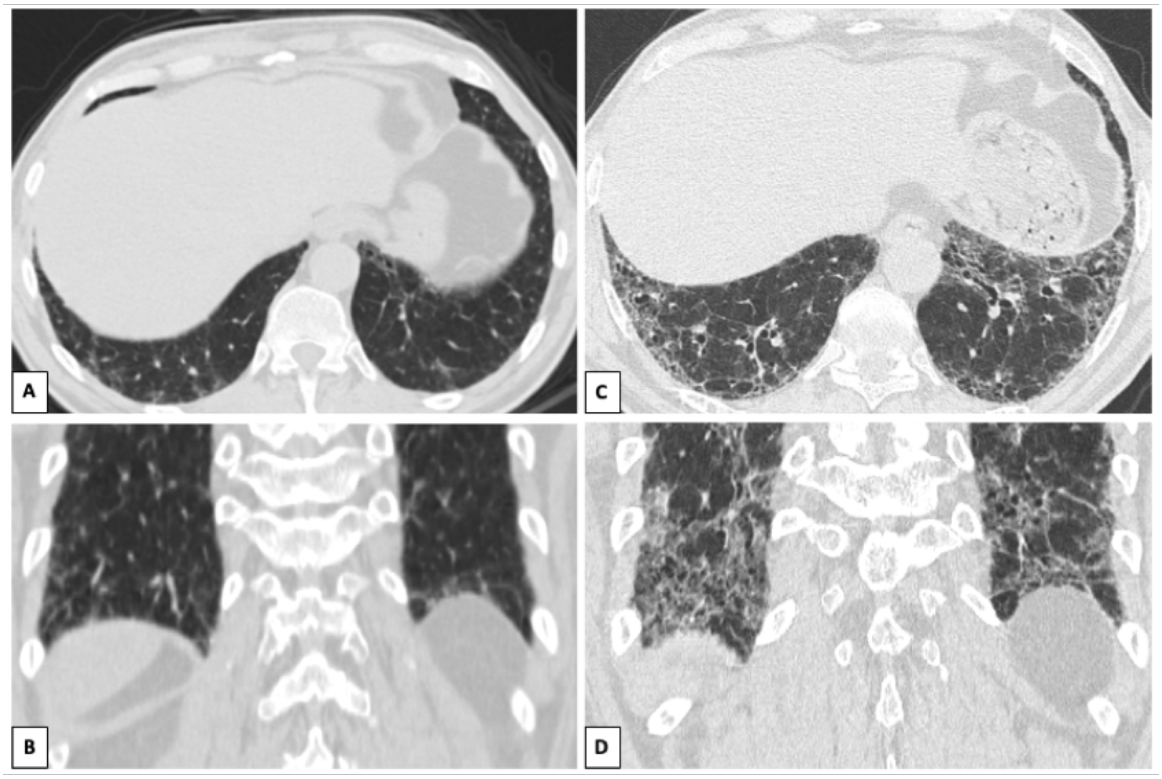


*Figure 6. Severe progression of minimal reticular opacities detected on abdominal CT in 2009 (A and B) toward overt fibrosis in four years (C and D).*

In multivariable models, ILA progression was mostly associated with subpleural fibrotic pattern (OR 2.55, 95%CI 1.36-4.79, p = 0.004) and TBI (OR 3.47, 95%CI 1.83-6.58, p<0.0001) at baseline. Among subjects with fibrotic ILA with signs of progression, 25/71 (36%) showed an indeterminate CT pattern, 20 (28%) typical UIP pattern, 15 (21%) probable UIP pattern, and 11 (15%) CT pattern suggestive of an alternate diagnosis. Finally, an increased extent of pre-existing

findings or appearance of fibrotic features was depicted on 31/71 (44%) subjects with non-fibrotic ILA at baseline CT.

| **Covariate** | **Abdominal CT scan** | | **Thoraco-abdominal CT scan** | | |
|---|---|---|---|---|---|
| | *Frequency* | *%* | *Frequency* | *%* | *p-value* |
| ***ILA*** | 122 | 1.3 | 240 | 2.1 | <0.0001 |
| ***ILA behavior over time*** | | | | | |
| *Definite progression* | 35 | 31.0 | 79 | 41.6 | 0.0028 |
| *Probable progression* | 16 | 14.2 | 15 | 7.9 | 0.4303 |
| *Stable* | 58 | 51.3 | 83 | 43.7 | 0.4093 |
| *Probable regression* | 2 | 1.8 | 7 | 3.7 | 0.1772 |
| *Definite regression* | 2 | 1.8 | 6 | 3.2 | 0.2652 |

*Table 3. ILA behavior over time.*

## DISCUSSION

We retrospectively evaluated the prevalence of ILA in a large cohort of unselected subjects who had undergone either abdominal or thoraco-abdominal CT for different clinical indications. We also assessed the association between ILA and cause-specific/all-cause mortality as well as progression of ILA for whom mortality data and/or at least a follow-up CT was available.

The frequency of ILA (1.68%) was lower as compared to that reported in previous studies (2%-17%), which, however, mostly included subjects at a high risk of having ILA [9, 12, 39-43]. A relative lower rate in our cohorts was also observed for fibrotic ILA (1.07% vs. 2-6.6%) [6, 39], while the prevalence of the typical and probable UIP CT patterns (0.5%) was similar to previous papers [39]. Such differences from prior studies might be explained by various aspects. First, our study cohort is rather heterogenous, including CT scans performed on unselected general population. Second, a considerable proportion (46%) of the included baseline CT scans were abdominal, thus limiting the assessment of ILA in the upper-mid regions of the lung. Third, a sizeable proportion (60.1%) of CT scans had been reconstructed with a slice thickness of 2-2.5 mm and thus, hampering the depiction of subtle CT abnormalities (e.g., minimal ground-glass opacities and/or fine reticulations).

Consistent with previous literature, subjects with ILA were more frequently male and older than subjects without ILA [12, 13, 41]. If male sex has been identified as a risk factor for ILA only in some studies [41, 44], increasing age is an established risk factor for ILA [45]. Washko et al observed that the prevalence of ILA raised from 4% in individuals aged less than 60 years to 6% in those aged 70 or over [26], while in the Framingham Heart Study the prevalence of ILA in subjects ≥ 70 years of age reached a remarkable 47% [12]. Albeit established, the relationship between ILA and aging is still not fully understood. Reticular abnormalities, potentially representing ILA, are commonly observed in elderly populations, in whom are deemed as part of the normal spectrum

of senescent lung, to some extent [46, 47]. In fact, Copley et al observed that in a considerable proportion of subjects over 75 years of age with ILA, these abnormalities were not associated with respiratory symptoms nor with declined pulmonary function [46]. Interestingly, Sanders et al demonstrated that some blood biomarkers of accelerated aging may partly explain the associations among age, ILA, and mortality [48]. These plasma biomarkers include the growth differentiation factor 15 (GDF15), a well-known stress-induced factor, whose levels significantly increase in chronic or acute illness conditions, as well as with aging independently from the health state [49]. Emerging evidence seems to suggest that some aging-associated pathways can increase the risk of ILA and that ILA should be considered in gerontologic studies attempting to identify biomarkers of accelerated aging [48].

In keeping with previous literature [50-53], we observed an association between ILA and lung cancer incidence. Results from the National Lung Screening Trial demonstrated an incidence rate ratio of 1.33 [16], while Axelsson et al (AGES- Reykjavik study) reported a hazard ratio (HR) of 2.77 [54]. Patel et al, on the other hand, did not prove a raised lung cancer incidence in ILA subjects among over 1600 lung cancer screening participants [55]. However, the relationship between ILA and lung cancer goes beyond the increased risk of lung cancer incidence. ILA is an important risk factor for lung injury during therapies for lung and other types of cancer. Namely, ILA increases the risk of developing severe pneumonitis as a side effect of immune checkpoint inhibitors, systemic chemotherapy, and radiation therapy [50, 53, 56-58]. Moreover, cancer patients with ILA are more likely to suffer from post-surgical complications, including pneumonia, acute respiratory distress syndrome, respiratory failure, empyema, and pneumothorax as compared to those without ILA [59, 60]. In 2022, Im et al demonstrated that lung cancer patients with ILA undergoing curative surgery had a lower rate of overall survival at 5 years (52 vs 76%) and suffered more of post-surgical pulmonary complications (OR= 9.56) as compared to patients

without ILA [61]. These results underscore the need of reporting ILA, which may have relevant clinical implications that go beyond the risk of progression toward pulmonary fibrosis, particularly in oncologic patients.

The presence of ILA was independently associated with all-cause and cause-specific mortality with the only exception of extrapulmonary cancer. Similarly, in the AGES-Reykjavik study cohort, subjects with ILA showed increased all-cause mortality compared with participants without ILA (HR= 1.5) [20]. Participants with ILA from the same cohort had also a higher OR of death from a respiratory cause as compared to those without ILA [41]. Notably, the strongest association observed in our study was between ILA and respiratory disease-related death (OR= 3.790). We also found an association between ILA and lung cancer mortality (OR= 2.464), consistent with prior studies including the AGES-Reykjavik study, the National Lung Screening Trial and the Danish Lung Cancer Screening Trial that reported a HR of 2.89, 1.51 and 3.2, respectively [10, 16, 54].

Progression of ILA was observed in 52.8% cases that had multiple CT scans. In line with the observations of Putman et al, CT fibrotic features were associated with a greater risk of ILA progression [39]. Additionally, 42% of subjects with subpleural ILA without recognizable CT features of lung fibrosis at baseline either progressed or developed CT features of lung fibrosis at follow-up, confirming the subpleural ILA are at a higher risk of progression regardless the presence of fibrotic changes at the baseline evaluation. To date, most studies have investigated the association between progressive subpleural fibrotic ILA and IPF, since the two entities have several features in common, including radiological, epidemiological, clinical, and functional ones [62]. Nonetheless, not negligible differences exist between ILA and IPF. Aside from the definition, the prevalence of ILA is significantly higher than that of IPF (7% versus <1%), suggesting that only a minority of ILA cases evolve toward IPF. This, however, does not mean that only a minority of ILA cases progress. More recent studies have attempted to investigate possible correlation with ILA

and other types of fibrotic CT patterns, including non-specific interstitial pneumonia (NSIP) [63]. In 2020, Kawano-Dourado et al reported a progression rate of subtle CT changes toward overt ILD of 57% in a rheumatoid arthritis population [64]. Such evidence suggests that a radiological progression of ILA toward a typical UIP pattern might not be the only evolution of clinical significance.

Distinguishing fibrotic from non-fibrotic ILA, however, remains crucial, yet challenging in limited/early disease (e.g., mild subpleural reticular opacities) and in non-HRCT scans. It must be acknowledged that the correlation between CT appearance and histology is imperfect in this setting. Limited subpleural reticulation may be the sole CT manifestation of histologically advanced fibrosis in some patients, but may not represent fibrosis at all in another ones [65]. Of note, Verleden et al have recently reported on the presence of histopathologic fibrosis in areas of explanted lungs that appeared normal or affected by mild reticulation on CT [66].

### Strengths

Given the heterogeneity of our study cohort, we were able to report on demographic data of ILA in the general population. We also showed that ILA can be depicted in 0.9% of abdominal CT scans, confirming that the 8-10 cm of lung parenchyma usually included in the abdominal CT scans [67] may contain important findings besides lung nodules. In fact, abdominal CT scans may reveal the presence of ILA and allow to characterize the subtype (e.g., basal, subpleural, fibrotic) potentially of clinical relevance.

### Limitations

This study has several limitations. First, the assessment of whether ILA were truly unknown before the baseline CT scan might have been incomplete, due to the retrospective nature of the

study including over 20000 subjects. Second, medical history was available for almost 90% of subjects, limiting the possibility to investigate the association of ILA with clinical outcomes in the entire population. Also, due to the limited availability of clinical information, we could not assess the association between ILA with respiratory symptoms and/or lung function. Third, baseline abdominal or thoraco-abdominal CT scan were compared with follow-up HRCT scan in some cases, and thus, technical differences may have affected the assessment of ILA behaviour, particularly for the "probably regressed" and "probably progressed" categories. Forth, we could not investigate race-related differences, being the selected subjects almost all Caucasian.

## Future perspectives

Quantitative imaging techniques, largely applied in diffuse lung diseases [68-70], have also been employed in ILA, including densitometry of high-attenuation areas, local histogram analysis, and deep learning–based textural evaluation, with different outcomes. Densitometry assesses the proportion of high-attenuation areas between -600 and 220 HU, which are thought to represent ground-glass and reticular abnormalities [71]. Such approach, however, does not seem to be successfully applicable in ILA, since high-attenuation areas are often due to inadequate inspiration, obesity, and technical issues. Significant discrepancies between visual and automated assessment have also been described in ILD. Jacob et al observed how fine reticular abnormalities overlaying on ground glass opacities were scored as merely ground glass opacities by the quantitative software [72]. Conversely, recent advances in the field of deep learning seem to offer great opportunities in such setting, allowing accurate detection and quantification of ILA [43]. Deep convolutional neural networks (CNNs)- based techniques have shown the potential to detect and classify ILA with a sensitivity of 91,41% and average specificity of 98,18% [73].

## CONCLUSIONS

In conclusion, this study suggests that the role of radiologist is crucial in triggering ILA work-up. Subpleural ILA, and particularly subpleural fibrotic ILA, should be systematically reported and fully assessed, possibly with a proper HRCT scan of the chest, given the increased risk of progression toward frank pulmonary fibrosis and mortality. A correct management of ILA, however, should be driven by both radiological and clinical features, and a multidisciplinary approach should be preferred.

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