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Prevalence and progression of interstitial lung abnormalities in the general population: A longitudinal study

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Abstract

Background: Interstitial lung abnormalities (ILAs) are increasingly recognized on chest Computed tomography (CT) scans. There has been no prior evaluation of ILA prevalence and progression in the general population in China. Therefore, we conduct a longitudinal study to investigate the prevalence and progression of ILA in the general population in China, and to provide a reference for the management of ILA and further researches.

Method: CT images of 10820 participants who underwent chest CT scans at the Health Management Centre of Nanjing Drum Tower Hospital in 2017 were evaluated. The temporal change of the ILA was evaluated at 2-5 years follow up. Logistic regression models were used to determine factors associated with development and progression of ILA.

Results: Interstitial lung abnormalities were noted in 715(6.6%) participants. Of whom, 83 participants were assessed as false or non-ILA changes, mainly due to gravity effect or inadequate inspiration. Age was associated with the prevalence of ILA. Of 497 participates with sequential chest CT scans during the five-year follow-up period, 165(33.2%) subjects had progressed ILA and 287(57.7%) patients had stable ILA, and 45(9.1%) patients had improved ILA. Compared to female, ILA in male are more likely to progress.

Conclusions: ILA is relatively common in the general population and the presence of ILA is associated with increasing age. ILA progression is common and more common in male. Early management may be the best option for these patients. Further studies are needed to validate management strategies and treatment benefits.

Keywords: Interstitial lung abnormalities (ILA); Prevalence; Progression; Management; Imaging pattern.

Introduction

ILA has been described since decades ago, initially discovered in clinically unaffected members of families with an idiopathic pulmonary fibrosis or smokers [1,3]. With the widespread use of high-resolution computed tomography (HRCT) in clinical setting, especially lung cancer screening, ILA has become more widely detected in asymptomatic and undiagnosed individuals. ILA has been shown to be associated with respiratory symptoms, functional impairment, risk of disease progression and increased all-cause mortality, possibly an early state of interstitial lung disease (ILD) [3,8]. In recent years, as studies on ILA have increased, the 2020 Fleischner Society position paper standardized the definition of ILA based on the available published literature and the Multidisciplinary consensus [9]: ILA is an incidental identification of non-dependent abnormalities involving at least 5% of a lung zone, including ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts. Moreover, the position paper addressed the predisposing risk factors; clinical outcomes; initial evaluation, monitoring and management of ILA and future research needs, which may increase the awareness of ILA identification and help primary care providers and pulmonary specialists to evaluate and treat subjects with incidentally discovered ILA.

However, our understanding of ILAs is still minimal, currently epidemiological data are mainly derived from several large early cohort studies [6,7], with more longitudinal studies are lacking. It was also proposed in the Fleischner position paper that the preliminary radiological criteria for ILA presented in the paper required evaluation to determine their reproducibility and application to clinical practice. There has been no prior evaluation of ILA prevalence and progression in the general population in China. Therefore, we conducted a longitudinal study to explore the prevalence of ILA in the general population and the progression rate of ILA over a five-year follow-up period, and hope to provide more statistical evidence for development and progression of ILA in clinical practice and make recommendations for further research.

Methods

Study population

We retrospectively reviewed the CT images of 10820 participants who underwent low-dose CT at the Health Management Centre of Nanjing Drum Tower Hospital from January 2017 to December 2017. Subjects who were reported interstitial abnormalities and had serial chest CT scan from 2018 to 2022 (two to five years follow-up period) were selected, which were used for ILA progression evaluation. The Neusoft (v5.5.0 Diagnostic imaging systems) were used to view the image information. The study was approved by Medical Ethics Committee of Nanjing Drum Tower Hospital Affiliated to Nanjing University School of Medicine (NO.2022-046-01) and individual consent for this retrospective analysis was waived.

CT scan

In this study, participants underwent CT chest without contrast (Definition Sensation 64; Siemens Medical Solutions, Forchheim, Germany). Images were obtained after full inspiration and hold in the supine position.

ILA evaluation

To ensure the accuracy of the evaluation, the images of these participants were initially evaluated by radiologists (two radiologists, one reported and one reviewed) and the CT images were re-evaluated by experienced pulmonologists (physicians from respiratory department), who were blind to prior radiologic interpretations of other readers and all subjects-specific information. Inconsistencies between the evaluation were resolved by common discussions. ILA evaluation was objectively based on the radiological imaging and referenced to the fleischner paper criteria for ILA.

Statistical analysis

The demographic data between participants with and without ILA were compared by using an unpaired t test (for normal distribution data) or Mann-Whitney test (for non-normal distribution data). Chi-square test was performed to test for any differences in the distribution of categorical variables among two groups. Logistic regression models were used to assess the associations between ILA and demographic data (age, sex); the corresponding odds ratios with 95% confidence interval (CI) were computed. A two-sided p value less than 0.05 was considered to be statistically significant. All analyses were performed with statistical software (SPSS 25.0, Chicago) and GraphPad Prism9.0.0.

Results

Baseline characteristics and interstitial lung abnormalities

We reviewed images on a total of 10,820 subjects who had chest Computed Tomography (CT) from January 2017 to December 2017 at the Health Management Centre of Nanjing Drum Tower Hospital. The flowchart of participant inclusion and evaluation in this study is shown in figure 1. Table 1 shows the baseline characteristics of the participants. The participants consisted of 6833(63.2%) men and 3987(36.8%) women, with a mean age of 58.2±12.6 years (median: 57years, range: 19–100 years). ILA were noted in 715(6.6%) patients. As compared to participants had normal CT images, those reported to be ILA were more likely to be older (median age: 73 vs 56 years old, p<0.0001) (Figure 2). Increasing age was associated with ILA prevalence (OR: 1.103, 95%CI: 1.095-1.111, P<0.0001) (Table 2).

Prognostic evaluation of ILA at follow-up CT

The detection rate of ILA in the baseline radiologic reports were 6.6%(715/10820). After re-evaluation by experienced respiratory physicians reference to the fleischner's ILA criteria, 83 patients were assessed as non-ILA ("false-positive" or "not-real") changes, mainly due to gravity effect or insufficient inspiration. 497 patients underwent at least two serial imaging evaluations during the five-year follow-up period were included in prognostic evaluation. Of the 497 participants with sequential chest CT scans, 165(33.2%) subjects had progressed ILA and 287 (57.7%) patients had ILA stable state, and 45(9.1%) patients had ILA improved (3 of them were after treated) (Table 3). Logistic regression showed that compared to male, female are a protective factors of ILA progression (OR:0.614, 95%CI:0.409-0.923, p=0,019) (Table 4).

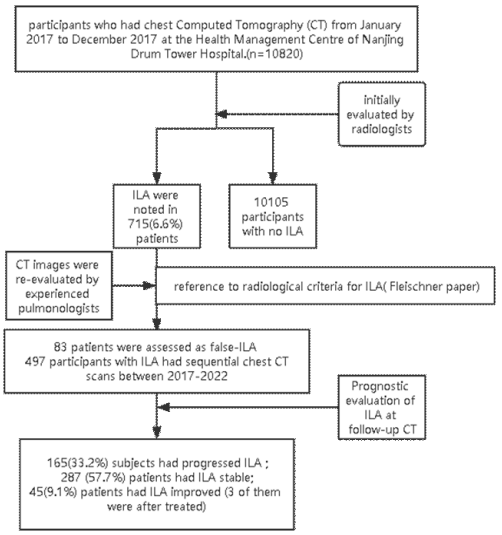

Figure 1: The flowchart of participant inclusion and evaluation in this study.

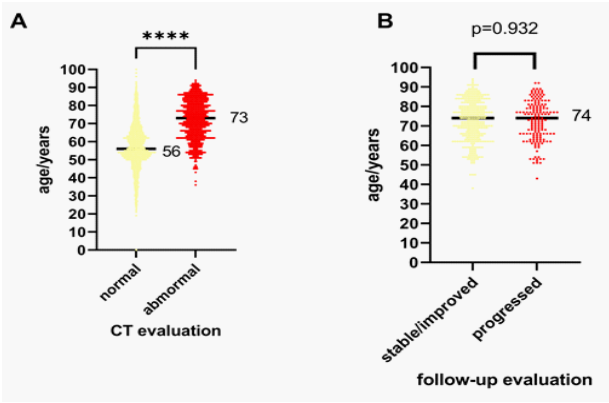

Figure 2: Mann-Whitey test of age between participants. **(A):** of 10820 participants with or without ILA; **(B):** of 497 participants with or without ILA progression.

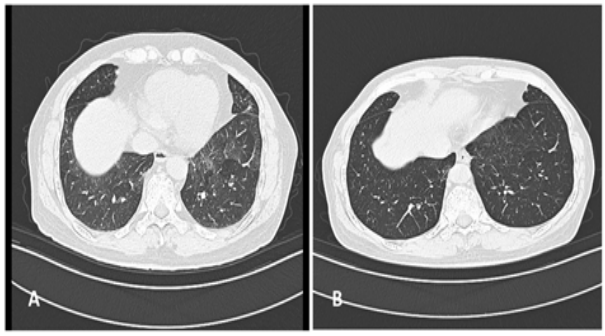

Figure 3: Imaging abnormalities that do not represent interstitial lung abnormalities (false ILA): A 69 years old male, CT images in 2017year **(A):** CT showed Ground-glass shadow with air retention; in 2021 year **(B):** the abnormality disappeared.

Representative CT images

Notably, we found that some patients have "false" ILAs, which were caused by transient factors such as incomplete inspiration during examination and gravity fall effect, infection, aspiration, and drugs. We need to carefully identify the radiological abnormalities (Figure 3). Some patients' ILA progressed slowly during our 2-5year follow-up (Figure 4), and some patients' ILA progressed rapidly during the treatment of lung cancer (Figure 5). We showed some CT images, hoping to provide some references to clinical physicians about the image patterns of ILA.

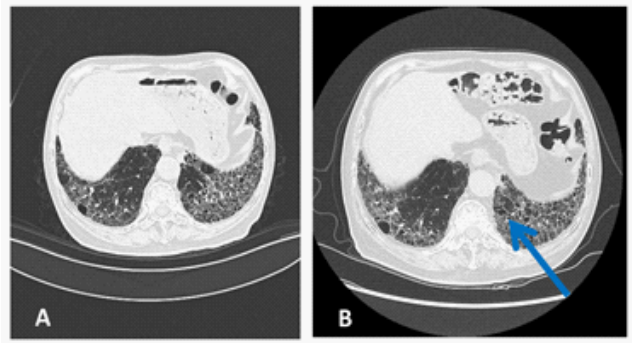

Figure 4: Progression of ILA: CT examination obtained in a 76 years old male, CT images in 2017 **(A)** CT showed subpleural reticular pattern, ground-glass opacity and traction bronchiectasis; **(B)** CT obtained 4 years later showed ground-glass shadows have increased significantly at left lower lobe (arrow).

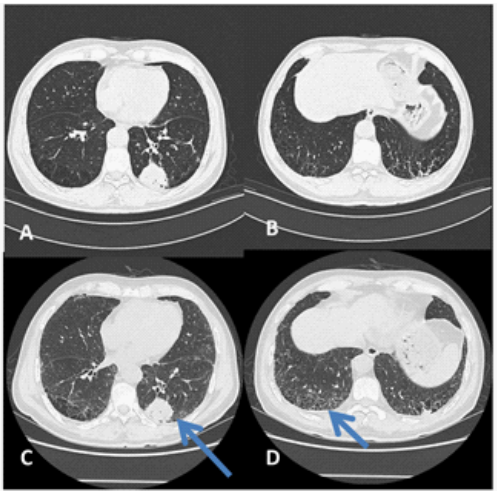

Figure 5: Interstitial lung abnormalities after therapy for lung cancer: a 62 years old male, with lung cancer., CT images in 2017 (A,B), 2018 (C,D); **(A-B)** CT showed lung tumor with minimal emphysema with interstitial changes (fibrosis); **(C-D)** After one year treatment of lung cancer, CT showed tumor progression is not obvious, but notable reticular pattern and ground-glass abnormality (arrows).

Discussion

This study was a longitudinal visual assessment of chest CT images for the purposes of characterizing ILA prevalence and progression. One of significance of this study was to conduct a robust evaluation about the preliminary radiological criteria for ILAs presented in Fleischner Position Paper, to determine their reproducibility and application to clinical practice. For the first time, this study provided some descriptive statistics on the prevalence and progression rate of ILA in the general population in China. ILA progression was relatively common, which may be the point that clinical physicians should pay more attention to.

The prevalence of ILA in the general population in our study (6.6%; 715 of 10820 participants) was similar with prior reports. In Framingham Heart Study (FHS), a longitudinal study originally designed to investigate risk factors for cardiovascular disease in the general population, ILA was prevalent on 3% of the initial scans and the progression rate of ILA was 43% over approximately 5 years of follow-up time [7]. In a National Lung Screening Trial population, the prevalence of ILA was 9.7% (86 of 884 participants) [4].

Table 1: Characteristics of 10820 participates with normal/abnormal interstitial lung images.

	Total n=10820	Normal n=10105	Abnormal n=715	P
Age*	57(58.2±12.6)	56(57.2±12.1)	73(72.0±11.2)	<0.0001
Age-layer				<0.0001
<=40	808	806(8.0%)	2(0.3%)	
41-50	1617	1605(15.9%)	12(1.7%)	
51-60	4005	3902(38.6%)	103(14.4%)	
61-70	2678	2476(24.5%)	202()28.3%	
71-80	1108	902(8.9%)	206(28.8%)	
>80	604	414(4.1%)	190(26.6%)	
sex				0.781
male	6833	6387(63.1%)	455(63.6%)	
female	3987	3727(36.9%)	260(36.4%)	

*: age was shown as the median (mean±SD). Categorical variables (sex, age-layer) were analyzed by chi-square test.

Table 2: logistics regression of factors associated with ILA detected at baseline CT.

Factor	Model 1			groups	Model 2		
	OR	95%CI	P		OR	95%CI	P
Sex (f/m)	0.925	0.782-1.094	0.360	(f/m)	0.903	(0.764-1.067)	0.230
age	1.103	1.095-1.111	**0.000**	vs.<=40 years			
				41-50	3.014	(0.673-13.501)	0.149
				51-60	10.494	(2.584-42.621)	**0.001**
				61-70	32.722	(8.109-132.036)	**0.000**
				71-80	91.712	(22.709-370.376)	**0.000**
				>80	184.564	(45.594-747.114)	**0.000**

f/m: female vs male; model 1 logistic regression included factors: sex and age(years), model 2: logistic regression when age were categorical variables.

Table 3: Characteristics of 497 participates with ILA at 2-5year Follow-up.

	Total n=497	Stable/ improved n=10105	progressed n=715	P
Age*	74(72.6±10.4)	74(72.6±10.6)	74(72.6±10.2)	0.77
Age-layer				0.858
<=40	1	1(0.3%)	0(0.0%)	
41-50	4	3(0.9%)	1 (0.6%)	
51-60	57	41(12.3%)	16(9.7%)	
61-70	145	94(28.3%)	51(30.9%)	
71-80	165	109(32.8%)	56(33.9%)	
>80	125	84(25.3%)	41 (24.8%)	
sex				**0.019**
male	323	204(61.4%)	119(72.1%)	
female	174	174(38.6%)	46(27.9%)	

*: age was shown as the median (mean±SD). Categorical variables (sex, age-layer) were analyzed by chi-square test.

Table 4: logistics regression of factors associated with the progression of ILA.

factors	OR	95%CI		P
		lower	upper	
Sex (f/m)	0.614	0.409	0.923	**0.019**
age	1.002	0.984	1.02	0.863

f/m: female vs male.

Participants with ILA were significantly older in our study, which is similar to previous reports. The main known risk factors for ILA are advanced age, smoking, and familial history of ILD [10,13]. In addition, researchers have suggested that increased copies of the MUC5B promoter, occupational exposure (including steam, dust and fumes), air pollution, nitrogen oxide exposure, and arsenic content in edible rice may all be related to the occurrence of ILA [14,18]. Notably, there were "false" and transient ILA in our research, which were caused by factors such as incomplete inspiration during examination and gravity fall effect, infection, aspiration, and drugs [3,13]. we need to carefully identify the radiological abnormalities, some of them may be "real" ILA, with a danger to progression, such patients need to be paid close attention and management; False, transient lung shadows due to position, infection, aspiration, etc., may usually resolve automatically when the cause is relieved.

In our study, participants with ILA had lung cancer rapidly progressing or worsening to death. Studies have shown an association between ILA and cancer treatment toxicity and mortality [19]. Studies suggest that ILA may increase lung injury risk caused by cancer therapies (e.g., surgery, radiation therapy, and drugs). This includes the development of associated ILD after immune checkpoint inhibitor (ICI) therapy (ICI-ILD) [20], acute respiratory distress syndrome (ARDS) after pulmonary surgery [21]. Extensive radiation pneumonitis (RP) is probably the most common and fatal complication in patients with pre-existing ILA treated with stereotactic body radiotherapy [22,27].

Despite the increasing attention to ILA in research Settings, it may be easier to ignore these interstitial lung changes in an actual clinical setting, mainly because they are often found incidentally and are usually asymptomatic. The clinical management strategy for ILA outlined in the fleischner position paper may help improve this situation and help clinicians manage these abnormalities. Our findings demonstrate that ILA is widespread in the general population and carries a risk of progression, calling for clinicians to pay more attention to this inconspicuous abnormality in clinical practice.

Our study has some limitations. First, as a single-center study, there may be some regional bias in the physical examination population. Second, the basic information we included was not comprehensive, and multivariable models were not adjusted for potential covariates (including body mass index, smoking status, pack-years of smoking, etc.). Third, all assessments were assessed by physicians based on CT images, with little understanding of the patient's diagnosis and treatment process. At the same time, the presence or pattern of parenchymal abnormalities could not be demonstrated histologically, so the physiological correlation of imaging abnormalities could not be matched. Considering the deficiency of our study and current situation of ILA research, we put forward some ideas for further research.

Quantitative evaluation of ILA may be one of the further research directions, which may be applied to large-scale studies or mass screening. High-attenuation areas (HAA) is defined as the percentage of lung volume with CT attenuation value between -600 and -250 HU[28]. Nowadays, the clinical significance of HAA remains unclear, and assessment in individual patients is limited [9]. The feasibility of optimizing thresholds of HAA for large-scale ILA clinical identification and risk assessment need to be further explored.

Overall considering the current research status there are still some doubts about ILA: the appropriate follow-up cycle of ILA patients found by chance, the specific relationship between different imaging characteristics and the risk of progression, the biomarkers that predict disease progression effectively, and the effective criteria for progress risk assessment are still unclear. More longitudinal studies of ILA are needed to provide more statistical evidence and to investigate reasonable management and treatment strategies. Our study revealed that the prevalence and progression of ILA is common in Chinese populations, improving physicians' attention in clinical practice and providing a reference for subsequent management.

Conclusions

Our study demonstrates that ILA is relatively common in the general population and is associated with advanced age. ILA progression is relatively common over a 5-year period. Early management and multidisciplinary discussions may be better managed for these people.

Declarations

The study was approved by Medical Ethics Committee of Nanjing Drum Tower Hospital Affiliated to Nanjing University School of Medicine (NO.2022-046-01).

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Conflict of Interest: The authors have no conflicts of interest to declare.

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