The detection, assessment and clinical evolution of interstitial lung abnormalities identified through lung cancer screening

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Shareable abstract (@ERSpublications)
Lung cancer screening in a high-risk population identified ILAs in 3.9% of subjects, of whom 40.7% were subsequently diagnosed with ILD, 25.9% died and 53.8% suffered disease progression within 5 years of identification https://bit.ly/3EehGlr

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Abstract

Introduction Interstitial lung abnormalities (ILAs) are common incidental findings in lung cancer screening; however, their clinical evolution and longer-term outcomes are less clear. The aim of this cohort study was to report 5-year outcomes of individuals with ILAs identified through a lung cancer screening programme. In addition, we compared patient-reported outcome measures (PROMs) in patients with screen-detected ILAs to newly diagnosed interstitial lung disease (ILD) to assess symptoms and health-related quality of life (HRQoL).

Methods Individuals with screen-detected ILAs were identified, and 5-year outcomes, including ILD diagnoses, progression-free survival and mortality, were recorded. Risk factors associated with ILD diagnosis were assessed using logistic regression and survival using Cox proportional hazard analysis. PROMs were compared between a subset of patients with ILAs and a group of ILD patients.

Results 1384 individuals underwent baseline low-dose computed tomography screening, with 54 (3.9%) identified as having ILAs. 22 (40.7%) were subsequently diagnosed with ILD. 14 (25.9%) individuals died, and 28 (53.8%) suffered disease progression within 5 years. Fibrotic ILA was an independent risk factor for ILD diagnosis, mortality and reduced progression-free survival. Patients with ILAs had lower symptom burden and better HRQoL in comparison to the ILD group. Breathlessness visual analogue scale (VAS) score was associated with mortality on multivariate analysis.

Conclusions Fibrotic ILA was a significant risk factor for adverse outcomes including subsequent ILD diagnosis. While screen-detected ILA patients were less symptomatic, breathlessness VAS score was associated with adverse outcomes. These results could inform risk stratification in ILA.

Introduction

Screening for lung cancer with low-dose computed tomography (LDCT) identifies early-stage disease and reduces lung cancer-specific mortality [1, 2]. While not the primary aim of screening, LDCT scans can also identify other incidental findings including parenchymal lung changes. These changes have been recognised as a distinct clinical entity, termed interstitial lung abnormalities (ILAs), by the Fleischner Society and defined as an incidental finding of nondependent abnormalities involving ⩾ 5% of a lung zone [3]. ILA detection in screening is common, ranging between 4% and 20% across lung cancer screening studies [4–7]. The detection of ILAs is associated with disease progression and mortality [8–10], and

radiological pattern, especially the presence of traction bronchiectasis, is an important predictor of adverse outcomes [8, 11]. Three subtypes of ILA have been described: nonsubpleural nonfibrotic, subpleural nonfibrotic and subpleural fibrotic [3]. Subpleural fibrotic ILA is characterised by the presence of traction bronchiectasis and is most likely to progress.

The presence of ILA increases the likelihood of a subsequent diagnosis of ILD up to five times [6]. Identifying which cases of ILA will evolve into clinically significant ILD is of key importance, given the increased utility of lung cancer screening programmes. A recent report from a United Kingdom (UK) screening population identified that 65% of patients with ILA were diagnosed with ILD on initial clinical assessment [12]. However, there is a lack of longitudinal data describing the evolution of ILA to ILD, with associated risk factors, within the context of lung cancer screening.

The aim of this study is to report the 5-year clinical outcomes of individuals with ILA identified during the Manchester Lung Health Check (MLHC) lung cancer screening pilot. We describe the proportion of patients with subsequent disease progression, ILD diagnosis and mortality. Furthermore, we explore potential risk factors associated with adverse outcomes. In addition, in a smaller substudy, we compare patient-reported outcome measures (PROMs) in a subset of patients with screen-detected ILAs to a cohort of patients with newly diagnosed ILD to assess symptoms and health-related quality of life (HRQoL) burden. Finally, we examine whether baseline PROMs predict subsequent adverse outcomes in ILAs.

Methods

MLHC and recruitment

Individuals were recruited from the MLHC pilot, which evaluated the impact of implementing LDCT screening in three socially disadvantaged areas of Manchester, UK. The design of the MLHC pilot has been described previously [13]. In brief, ever-smokers aged 55–74 years were invited to attend a community-based lung health check at which 6-year lung cancer risk, respiratory symptoms and spirometry were assessed. Those at high risk of lung cancer, defined as having a Prostate Lung Colorectal and Ovarian cancer risk prediction model ($PLCO_{M2012}$) score of $\geqslant$1.51%, were offered annual LDCT screening over two rounds, starting with an immediate LDCT in a co-located mobile unit.

Radiology reporting, ILA diagnosis and 5-year clinical outcomes

All participants who underwent a baseline LDCT scan were included in this study. Individuals with ILA, as defined by the Fleischner Society [3], were identified. All screening LDCT scans with reported ILA were reviewed centrally as part of a specialist ILD multidisciplinary team meeting. Participants with respiratory bronchiolitis interstitial lung disease (RB-ILD) or features not in keeping with ILA were excluded. In those with confirmed ILA, all relevant computed tomography scans were reviewed retrospectively to determine ILA subtypes.

Clinical outcomes over a 5-year period from the point of ILA identification were retrospectively collected from electronic patient records. This included subsequent radiology reports, lung function tests, diagnoses and all-cause mortality. Disease progression was defined using one of the following three criteria adapted from guidelines defining progressive pulmonary fibrosis [14]: 1) death; 2) absolute decline in forced vital capacity (FVC) % predicted >10% from baseline; or 3) two out of symptom progression, absolute decline in FVC % predicted 5–10% from baseline and radiological progression from baseline. Baseline spirometry for all screening participants was performed on the community-based mobile unit while subsequent lung function testing, when clinically indicated, was performed at the hospital lung function laboratories.

The ILD in Screening Study

A subset of patients with ILA were prospectively recruited to a substudy, the ILD in Screening Study, to assess baseline PROMs. These were compared to a control group of consecutive ILD patients attending a new patient clinic at a tertiary ILD centre. Recruited patients completed the following questionnaires: University of California San Diego Shortness of Breath Questionnaire (UCSD-SOBQ) [15], Fatigue Severity Scale [16], Leicester Cough Questionnaire [17], King's Brief Interstitial Lung Disease questionnaire [18], Medical Outcomes 36-item Short Form Survey (SF-36) [19] and visual analogue scales (VAS) for cough, breathlessness and fatigue [20]. Further details can be found in supplementary table S1.

Ethical approval

The MLHC pilot and the ILD in Screening Study (reference 17/WM/0365) were both approved by the North West-Greater Manchester West research ethics committee. Clinical data from screening were recorded on an ethically approved database (reference 16/NW/0013).

Statistical analysis

Continuous data were tested for normality using the Shapiro–Wilk test and analysed using independent t-test (parametric data) or the Mann–Whitney U-test (nonparametric data). Categorical data were analysed using the Chi-squared test. Associations between baseline characteristics and subsequent diagnosis of ILD were tested using binary logistic regression. Univariable analysis was performed to identify significant associations using a p-value threshold of 0.05. Variables included were baseline demographics (age, sex, smoking status, smoking pack-years, body mass index, indices of multiple deprivation rank, $PLCO_{M2012}$ score), FVC % predicted, ILA subtype, Medical Research Council (MRC) dyspnoea score and comorbidities and medications reported in >10% of the cohort. A multivariate model was then constructed using forward selection which included all significant variables, to identify those which were independently associated with a subsequent ILD diagnosis. For ease of analysis, nonsubpleural nonfibrotic and subpleural nonfibrotic subtypes were merged into one group (nonfibrotic ILA) and subpleural fibrotic was renamed "fibrotic ILA". MRC dyspnoea score was split into two groups: <3 and ⩾3. ILA survival analysis was performed using a Cox proportional hazard model to identify risk factors for mortality. Univariable analysis was performed initially using the same variables included in logistic regression. Significant variables ($p<0.05$) were then selected for multivariate analysis using forward selection to identify independent risk factors for mortality. The same analysis was performed for progression-free survival, which was measured in months from ILA identification to disease progression as defined earlier. Statistical analysis was performed using SPSS (version 25; IBM, Armonk, NY, USA).

Results

Screening outcomes and ILA diagnosis

1384 individuals underwent baseline LDCT screening as part of the MLHC pilot between June 2016 and October 2016. Interstitial changes were reported in 87 (6.3%) initial LDCT reports. 33 were deemed not to have ILA (31 RB-ILD; two interstitial oedema) and were excluded, leaving 54 individuals with ILA. This equates to 3.9% of the screened cohort at baseline. Screening participants with identified ILA were older (67.5±4.8 years *versus* 64.7±5.5 years; p=0.0002), had a higher proportion of men (68.5% *versus* 48.7%; p=0.005) and a lower proportion of current smokers (38.9% *versus* 53.5%; p=0.04) than those without ILA (table 1). Baseline FVC % predicted was lower in the ILA cohort (89.9%±21.3 *versus* 99.9%±24.4; p=0.002), and fewer individuals had obstructive spirometry (33.3% *versus* 51.0%; p=0.01). Figure 1 describes the distribution of ILA subtypes and the most common radiological features identified.

Evolution to ILD diagnosis

All 54 individuals with ILA were offered an assessment at a tertiary ILD clinic. 15 chose not to attend and were managed in primary care. A significantly higher proportion of those seen in tertiary care had fibrotic ILA compared to those managed in primary care (46.6% *versus* 13.3%; p=0.03) (supplementary table S3). Overall, 22 (40.7%) patients with ILA were formally diagnosed with ILD (figures 2 and 3), equating to 1.6% of the population screened. Idiopathic pulmonary fibrosis (IPF) was the most common diagnosis (seven out of 22, 31.8%). In 15 (68.2%) of those diagnosed with ILD, the diagnosis was made at the first clinic visit. Among individuals diagnosed with ILD at subsequent visits, the median (interquartile range (IQR)) time to diagnosis from the first clinic visit was 14 (17) months. All diagnoses were clinicoradiological. Four patients were initiated on treatment with medication: three with IPF received antifibrotic therapy (one pirfenidone; two nintedanib); and one with hypersensitivity pneumonitis received oral corticosteroids.

Univariate logistic regression identified that a fibrotic ILA subtype (OR 3.6, 95% CI 1.1–11.5; p=0.03) and an MRC score ⩾3 (OR 5.6, 95% CI 1.0–31.2; p=0.04) were predictors of subsequent diagnosis of ILD. All other variables tested were nonsignificant. After multivariate analysis, fibrotic ILA remained independently associated with progression to ILD (OR 3.6, 95% CI 1.1–11.5; p=0.03). 60.0% (12 out of 20) of patients with fibrotic ILA were subsequently diagnosed with ILD compared to 39.4% (10 out of 34) of patients with nonfibrotic ILA (p=0.03).

Survival

14 (25.9%) individuals died within 5 years of ILA identification. Cox proportional hazard analysis identified fibrotic ILA (hazard ratio (HR) 13.7, 95% CI 3.0–61.3; p=0.001), hypertension (HR 6.0, 95% CI 1.3–26.2; p=0.002), self-reported breathlessness (HR 3.9, 95% CI 1.2–12.4; p=0.02), history of cancer (HR 3.4, 95% CI 1.0–11; p=0.04), MRC score ⩾3 (HR 3.1, 95% CI 1.0–9.9; p=0.04) and use of angiotensin-converting enzyme inhibitors (HR 3.0, 95% CI 1.0–9.0; p=0.04) as predictors of mortality on univariate analysis. In the multivariate model, fibrotic ILA was identified as the sole independent predictor of mortality (HR 27.1, CI 3.5–209.3; p=0.002). Figure 4 shows survival curves for fibrotic and nonfibrotic ILA subtypes.

TABLE 1 Baseline demographics for individuals with screen-detected interstitial lung abnormalities (ILAs) and those with no ILAs

	ILA	Non-ILA	p-value
Participants	54	1330	
Age years	67.5±4.8	64.7±5.5	0.0002
Male	37 (68.5)	648 (48.7)	0.005
Smoking status			0.04
Current smoker	21 (38.9)	711 (53.5)	
Ex-smoker	33 (61.1)	619 (46.5)	
Pack-years	46.8±24.6	51.6±26.8	NS
BMI kg·m^{-2}	29.0±4.2	28.4±5.5	NS
$PLCO_{M2012}$ score	4.5±3.6	5.0±4.0	NS
IMD rank, median (IQR)	2868 (3476)	2866 (4033)	NS
Asbestos exposure	16 (29.6)	335 (25.2)	NS
Self-reported breathlessness	24 (44.4)	461 (34.7)	NS
Self-reported cough	17 (31.5)	561 (42.2)	NS
MRC dyspnoea score			NS
1	32 (59.3)	869 (65.3)	
2	14 (25.9)	281 (21.1)	
3	6 (11.1)	112 (8.4)	
4	2 (3.7)	66 (5.0)	
5	0	2 (0.2)	
Baseline FVC L	3.26±1.02	3.19±1.00	NS
Baseline FVC % predicted	89.5±21.3	99.9±24.4	0.002
FEV_1/FVC <0.7	18 (33.3)	678 (51.0)	0.01
Radiological evidence of emphysema	37 (68.5)	843 (63.4)	NS

Data are presented as n, mean±SD or n (%), unless otherwise stated. BMI: body mass index; $PLCO_{M2012}$: Prostate Lung Colorectal and Ovarian lung cancer risk prediction model; IMD: indices of multiple deprivation; IQR: interquartile range; MRC: Medical Research Council; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; NS: nonsignificant.

Disease progression

22 (40.7%) individuals reported increased symptoms of breathlessness or cough within 5 years of ILA identification. 43 (79.8%) individuals had repeat lung function tests within 5 years of ILA identification. There was a general increase in FVC at 1 year with mean±SD absolute change in FVC of 6.3±12.1% pred followed by subsequent decline over time with a change of 0.1±17.1% predicted at 5 years. There was a larger decline in fibrotic ILA (−3.7±15.1% pred) compared to nonfibrotic (2.7±18.1% pred), although this was not statistically significant. Further details are provided in supplementary table S4 and figure S1.

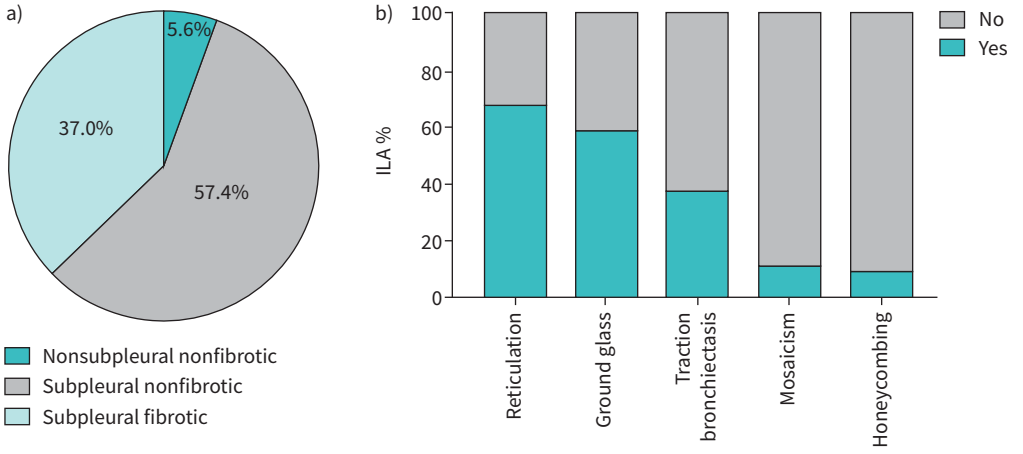

FIGURE 1 a) Distribution of interstitial lung abnormality (ILA) subtypes and b) radiological features contributing to ILA, presented as a percentage of the total (n=54).

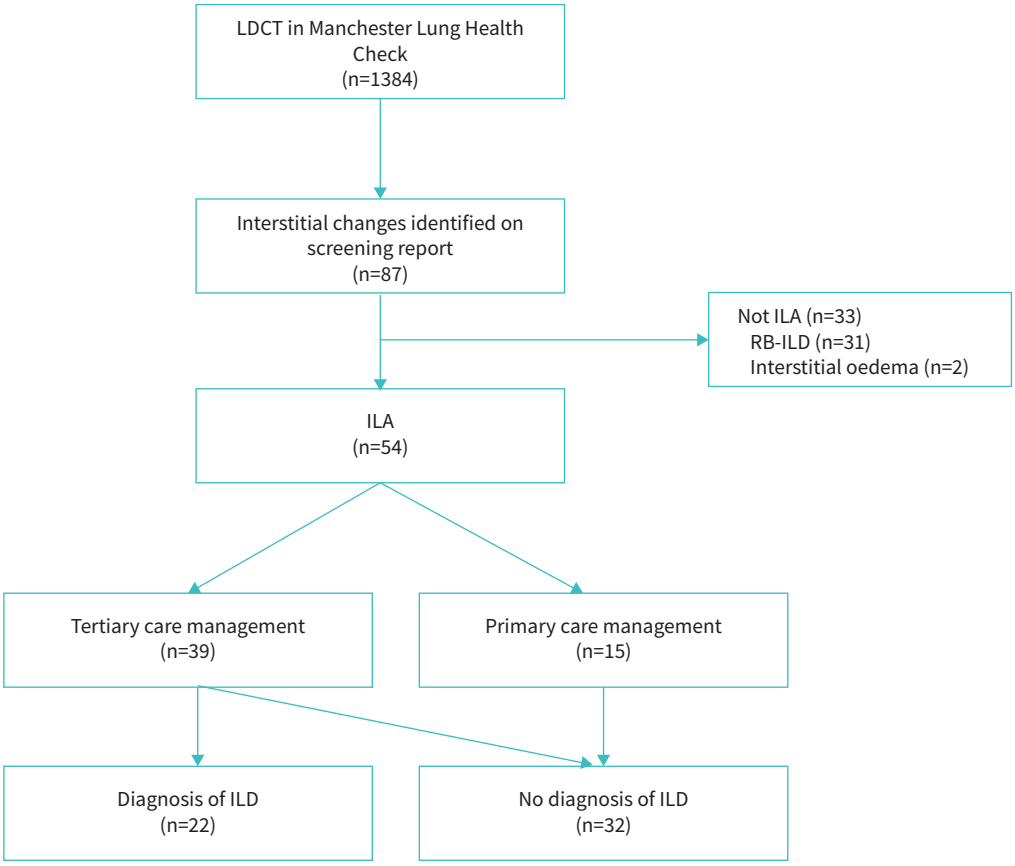

FIGURE 2 Flow diagram of patients identified with interstitial lung abnormality (ILA) on low-dose computed tomography (LDCT) and subsequent diagnosis of interstitial lung disease (ILD). RB-ILD: respiratory bronchiolitis ILD.

Of 46 patients who had a repeat computed tomography scan at 1 year, 17 (37.0%) demonstrated radiological progression. Almost all the ILA cohort (52 out of 54, 96.3%) had at least one further CT within 5 years. Half of these (26 out of 52, 50.0%) had evidence of radiological progression.

Just over half of individuals (28 out of 52, 53.8%) with 5 years' follow-up data met the criteria for disease progression (supplementary table S5). The median (IQR) progression-free survival was 51 (47) months.

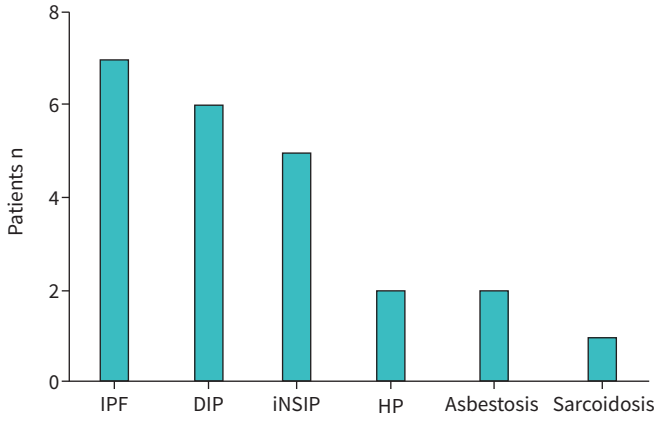

FIGURE 3 Frequency of interstitial lung disease diagnoses in patients identified with interstitial lung abnormality (n=22). IPF: idiopathic pulmonary fibrosis; DIP: desquamative interstitial pneumonia; iNSIP: idiopathic nonspecific interstitial pneumonia; HP: hypersensitivity pneumonitis.

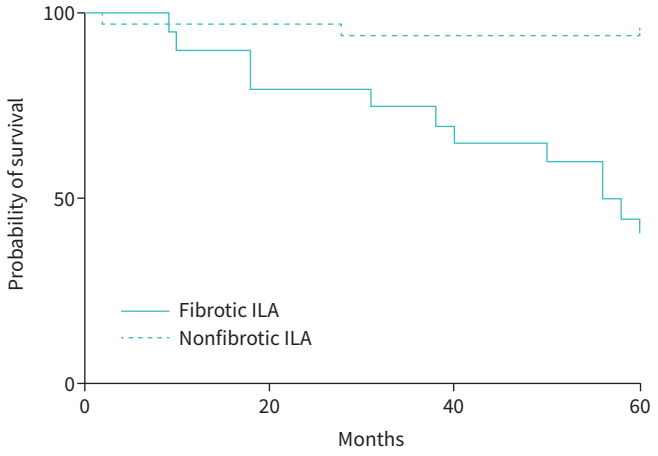

FIGURE 4 Survival curve for individuals split by interstitial lung abnormality (ILA) subtype (fibrotic *versus* nonfibrotic). Mean±SD survival 46.2±19.0 months for fibrotic ILA and 57.4±11.2 months for nonfibrotic ILA. Hazard ratio 27.1, 95% CI 3.5–209.3; p=0.002.

Cox proportional hazard analysis was performed, and fibrotic ILA subtype (HR 3.4, 95% CI 1.6–7.3; p=0.002), male sex (HR 3.7, 95% CI 1.3–10.6; p=0.02) and the presence of hypertension (HR 2.5, 95% CI 1.1–5.5; p=0.03) were identified as risk factors for reduced progression-free survival on univariate analysis. Fibrotic subtype was again identified as the sole independent risk factor following multivariate analysis (HR 3.8, 95% CI 1.7–8.2; p=0.001). Figure 5 shows survival curves for progression-free survival stratified by ILA subtype.

PROMs

19 individuals with ILA were recruited to the ILD in Screening substudy and completed PROMs at baseline. A further 16 consecutive new attendees at the ILD clinic were recruited for the control group. Table 2 shows the baseline demographics of these two groups. There was a higher proportion of current smokers in the screening ILA group and a significantly higher pack-year smoking history, but the groups were otherwise well matched. There were no differences in the total number and frequency of common comorbidities and medications between the two groups (supplementary table S6).

The results of the PROMs are summarised in table 3. All outcome measures with the exception of the VAS for breathlessness and four domains of the SF-36 questionnaire were significantly different between

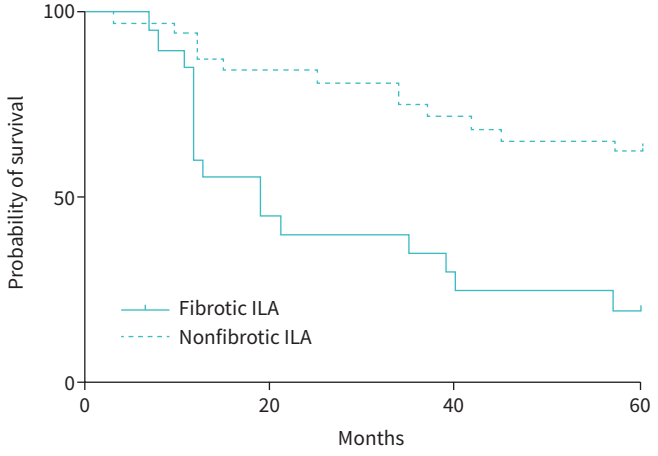

FIGURE 5 Survival curve for progression-free survival in individuals split by interstitial lung abnormality (ILA) subtype (fibrotic *versus* non-fibrotic). Mean progression-free survival 28.5 (±SD 20.6) months for fibrotic ILA and 47.7 (±SD 18.8) months for non-fibrotic ILA. HR 3.8, CI 1.7–8.2, p=0.001.

TABLE 2 Baseline demographics of the ILD in Screening substudy participants, comparing those with screen-detected interstitial lung abnormalities (ILAs) and clinically detected interstitial lung disease (ILD)

	Screen-detected ILA	Clinically detected ILD	p-value
Participants	19	16	
Age years	67.6±5.2	68.7±8.0	NS
Males	11 (57.9)	11 (68.8)	NS
Smoking status			0.02
Current	8 (42.1)	1 (6.3)	
Ex-smoker	11 (57.9)	13 (81.3)	
Never-smoker	0	2 (12.5)	
Pack-years	44.2±25.6	21.6±18.9	0.004
BMI kg·m^{-2}	28.7±3.5	30.3±4.9	NS
Asbestos exposure	4 (21.1)	6 (37.5)	NS
FVC L	3.2±1.1	3.1±1.2	NS
FVC % pred	89.9±23.0	86.0±26.2	NS
T_{LCO} mmol·min^{-1}·kPa^{-1}	5.1±1.6	4.7±2.7	NS
T_{LCO} % pred	67.9±17.7	58.8±25.8	NS
Individuals with FEV_1/FVC <0.7	5 (26.3)	4 (25.0)	NS
ILA subtype			
Fibrotic	8 (42.1)		
Nonfibrotic	11 (57.9)		
ILD diagnosis			
IPF		8 (50.0)	
iNSIP		2 (12.5)	
CTD-ILD		2 (12.5)	
Unclassifiable		2 (12.5)	
HP		1 (6.25)	
DIP		1 (6.25)	

Data are presented as n, mean±SD or n (%), unless otherwise stated. The proportion of diagnoses within the ILD group is listed. BMI: body mass index; FVC: forced vital capacity; T_{LCO}: transfer factor of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; IPF: idiopathic pulmonary fibrosis; iNSIP: idiopathic nonspecific interstitial pneumonia; CTD-ILD: connective tissue disease related ILD; HP: hypersensitivity pneumonitis; DIP: desquamative interstitial pneumonia; NS: nonsignificant.

the two groups. All the results indicated a lower symptom burden and better HRQoL in the screen-detected ILA group in comparison to the clinically detected ILD group. The results that did not reach statistical significance also followed this trend. We compared PROMs between individuals with fibrotic and nonfibrotic ILA subtypes. Individuals with fibrotic ILA had significantly higher UCSD-SOBQ scores (mean 42.4±26.6 *versus* 16.3±26.6) and breathlessness VAS scores (54.2±33.1 *versus* 16.4±19.9) compared to those with nonfibrotic ILA, indicating significantly increased symptoms of breathlessness. There were no significant differences in any of the other outcome measures reported.

We assessed whether PROMs predicted subsequent mortality and reduced progression-free survival in the ILA group using Cox hazard proportional analysis. UCSD-SOBQ score (HR 1.1, 95% CI 1.0–1.1; p=0.04), cough VAS score (HR 1.1, 95% CI 1.0–1.1; p=0.03), breathlessness VAS score (HR 1.1, 95% CI 1.0–1.1; p=0.003) and fatigue VAS score (HR 1.1, 95% CI 1.0–1.1; p=0.04) were all significantly associated with mortality on univariate analysis. Breathlessness VAS score remained significantly associated with mortality after inclusion in a multivariate model (HR 1.1, 95% CI 1.0–1.1; p=0.003), and remained significant after controlling for ILA subtype. None of the PROMs were associated with progression-free survival.

Discussion

In this study, we report clinical outcomes for individuals 5 years after identification of ILA in a lung cancer screening programme. We found an ILA prevalence rate of 3.9%, of which 40.7% were subsequently diagnosed with ILD within 5 years. This was equivalent to 1.6% of the total population screened, supporting recent findings from another UK screening study [12]. We observed a mortality rate of ∼25% at 5 years. Previous mortality estimations have varied, being reported to be as high as 56% in the Age Gene/Environment Susceptibility Reykjavik study (median follow-up 8.9 years) [10]; however, data from lung cancer screening populations are limited.

TABLE 3 Summary of results of patient-reported outcome measures between interstitial lung abnormality (ILA) and interstitial lung disease (ILD) groups

	ILA	ILD	p-value
Participants	19	16	
Fatigue Severity Score	3.3±2.0	5.1±1.3	0.01
UCSD-SOBQ	27.3±29.8	52.7±29.5	0.02
Visual analogue score			
Cough	22.6±9.6	52.7±12.2	0.04
Breathlessness	32.3±31.9	60.3±46.6	NS
Fatigue	32.2±41.3	67.0±50.5	0.008
Leicester Cough Questionnaire			
Total	18.2±3.3	13.4±1.3	0.003
Physical	5.5±1.1	4.4±2.2	0.01
Psychological	6.3±1.4	4.2±2.0	0.004
Social	6.4±1.1	4.8±1.8	0.005
K-BILD questionnaire			
Total	79.1±22.4	59.2±19.6	0.003
Breathlessness and activities	73.3±26.1	51.3±24.4	0.02
Psychological	83.7±22.3	60.2±19.7	0.001
Chest symptoms	80.2±24.2	65.9±19.2	0.04
SF-36			
Physical functioning	61.7±32.5	38.4±26.4	0.04
Role limitations due to physical health	62.5±46.2	21.9±40.7	0.03
Role limitations due to emotional problems	58.2±46.8	45.8±48.5	NS
Energy/fatigue	56.8±22.1	39.3±6.1	0.03
Emotional wellbeing	66.3±24.1	70.5±25.2	NS
Social functioning	81.6±26.8	53.9±7.4	0.004
Pain	75.3±36.4	64.5±27.2	NS
General health	51.1±22.9	38.1±26.6	NS

Data are presented as n or mean±SD, unless otherwise stated. UCSD-SOBQ: University California San Diego Shortness of Breath Questionnaire; K-BILD: King's Brief Interstitial Lung Disease; SF-36: 36-item Short Form Survey; NS: nonsignificant.

Among patients diagnosed with ILD, IPF was most common and desquamative interstitial pneumonia (DIP) the second most common diagnosis. DIP is considered to be a rare form of ILD, although the true incidence is unknown [21]. Tobacco smoke exposure is a strong risk factor for the development of DIP, which may explain an increased incidence in this cohort with high tobacco consumption.

The identification of ILA could offer the potential for early diagnosis and intervention of ILD, which may be life-prolonging. Incorporation of smoking cessation within lung cancer screening programmes is recommended and may benefit not only smoking-related ILD, but also IPF, in which tobacco smoke is associated with pathogenesis and disease progression [22]. IPF diagnosis is hampered by delays in diagnosis, and treating disease at an early stage with antifibrotics may slow the trajectory of decline [23].

Another potential benefit of screening is the identification of early ILD in high-risk populations with reduced access to healthcare. The MLHCs were designed to target populations in areas of high social deprivation at higher risk of lung cancer and in whom access to health services is low [13]. This is also an important issue in fibrotic lung disease, in which reduced socioeconomic status has been associated with reduced survival [24, 25]. The reasons for this are likely to be multifactorial, but may include increased exposure to atmospheric air pollution [26]. This has been identified as a risk factor for the presence of ILA and development and progression of ILD [27–29].

The incidental detection of ILA through screening risks placing additional burden on already overstretched healthcare resources. There is a clear need to risk-stratify ILA to identify individuals at highest risk of progression. Fibrotic ILA, as defined by the presence of traction bronchiectasis, appears to be the strongest risk predictor for adverse outcomes. In this study it was an independent risk factor for both disease progression and all-cause mortality, consistent with previous observations [8, 11]. We also found that individuals with fibrotic ILA were three times more likely to be subsequently diagnosed with ILD. Limiting criteria for follow-up to patients with a fibrotic subtype would appear to be a simple method of

managing healthcare resources. However, a recent large population-based study identified no difference in radiological progression between subpleural fibrotic and nonfibrotic subtypes of ILA, with reticulation being an independent risk factor for radiological progression [30].

The inclusion of symptom assessment in risk stratification models may be useful. Symptoms may be present in up to 60% of individuals with ILA [31]. We found that individuals with ILA were significantly less symptomatic and had better HRQoL scores than patients with ILD. We found that breathlessness scores were higher in individuals with fibrotic ILA and the breathlessness VAS score was an independent predictor of mortality. A simple objective measure of breathlessness may therefore be a useful addition in ILA assessment.

There are several limitations to this study. A lung cancer screening cohort may not provide an accurate representation of the true prevalence of ILA or the natural evolution of changes, due to a higher smoking prevalence. A high incidence of DIP diagnosis may be testament to this. However, the anticipated implementation of lung cancer screening suggests that this will provide a significant proportion of ILA referrals into respiratory services. All baseline lung functions were performed in a community-based mobile unit, while subsequent tests were performed in a hospital lung function laboratory. This may explain some of the variation in FVC results and the trend towards higher values on initial repeat assessment. Spirometry values may be influenced by multiple factors and even in the context of a randomised controlled trial, significant variability in repeated FVC values is observed in IPF [32]. The definition for disease progression that we used in this study was modified from the recently published guidelines for progressive pulmonary fibrosis, which limit assessment of progression to a 1-year period [14]. We applied these criteria over the broader timeframe of 5 years, since progression of disease in ILA is not clearly defined; however, modest changes in physiology or radiological features over a prolonged period may not be of clinical importance. We did not include measurements of transfer factor, as these were not performed at baseline. We did not include a negative control group in the substudy assessing PROMs. It is therefore difficult to fully estimate the symptom and HRQoL burden associated with ILA.

In conclusion, we found an ILA prevalence rate of 3.9% in our lung cancer screening population, of which 40.7% were subsequently diagnosed with ILD within 5 years. Fibrotic ILA is a significant risk factor for progression to ILD, reduced progression-free survival and mortality at 5 years. Individuals with screen-detected ILA have less symptom burden and HRQoL in comparison to patients newly diagnosed with ILD; however, increased breathlessness VAS was associated with increased risk of mortality in ILA. Such data could help inform risk stratification and management of screening-detected ILA as implementation is expanded.

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