Manchester University
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Interstitial lung disease within a lung cancer screening programme

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List of abbreviations

BTS	British Thoracic Society
COPD	Chronic obstructive pulmonary disease
CXR	Chest x-ray
FSS	Fatigue Severity Scale
HADS	Hospital Anxiety and Depression score
HRQoL	Health related quality of life
ILA	Interstitial lung abnormalities
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
K-BILD	Kings Brief Interstitial Lung Disease
LCQ	Leicester Cough Questionnaire
LDCT	Low dose computed tomography
LHC	Lung health check
MDT	Multidisciplinary team
MFT	Manchester University NHS Foundation Trust
NHS	National health service
NLST	National lung screening trial
NSCLC	Non-small cell lung cancer
PI	Principle investigator
PIS	Patient information sheet
PLCO	Prostate, lung, colorectal and ovarian study
QoL	Quality of life
RCTs	Randomised controlled trials

UCSD-SBQ University of California San Diego Shortness of Breath Questionnaire

VAS Visual Analogue Scale

1 Background

1.1 Interstitial Lung Disease

Interstitial lung disease (ILD) represents a heterogeneous group of diseases of either known or unknown aetiology with different pathogenesis and prognosis. Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrotic lung disease and the most common form of ILD. It is characterised by an irreversible loss of lung function with the development of debilitating breathlessness that ultimately leads to death. The prognosis of IPF is worse than most cancers with an average life expectancy of three to five years [1]. For decades immunosuppression with a combination of corticosteroids and azathioprine was the standard treatment; however it was subsequently shown that this regimen was actually associated with increased mortality [2]. Until recently there has been a dearth of evidence-based treatment options available for managing IPF. Over the last 5 years, disease modifying anti-fibrotic agents have been developed which have been shown to slow the progression of the disease [3,4]. As a consequence, earlier diagnosis through a specialist multidisciplinary team (MDT) has become an essential step in the management of ILD [5]. However, patients with IPF often report significant delays before receiving the correct diagnosis [6]. The British Thoracic Society (BTS) IPF registry demonstrates that patients often have symptoms for over 12 months and have a significant disease burden before presenting to a specialist [7]. With the availability of disease modifying management strategies it is important to identify patients early in their disease course to have maximal impact on the natural progression of ILDs specifically IPF. Lung cancer screening strategies provide a unique opportunity to identify patients with previously undiagnosed ILDs.

1.2 Lung Cancer

Lung cancer is the world's leading cause of cancer-related death (1.6 million deaths/year) [8]. The main risk factor is smoking [9]. Prevention through smoking cessation is paramount [10-12], however unaided quit rates are <5% at 12 months [13]. There are 9 million smokers in England [13], smoking-related morbidity and mortality will remain a major public health burden for many years to come [14]. In the UK, 45,500 people are diagnosed with lung cancer each year. Most patients (≈70%) present with advanced incurable disease, often as an emergency [15]. Survival is poor (1-yr 32%, 5-yr 9.5%) [16,17] and lower than other equivalent nations [18,19]. Manchester has the highest rate of premature death in the country and lung cancer is the leading cause, responsible for more deaths than all other cancers combined [20]. Detection and radical treatment of early stage disease is associated with long-term survival. However, early stage lung cancer is often clinically silent or associated with non-specific symptoms, therefore the window for curative treatment is frequently lost. More effective diagnosis of symptomatic lung cancer through awareness campaigns, e.g. 'Be Clear on Cancer', is valuable but this approach alone is unlikely to transform outcomes, as symptoms are most commonly associated with advanced disease [21].

1.3 Low dose CT screening for lung cancer

Numerous observational [22-24] and randomised controlled trials (RCTs) [25-30], in asymptomatic at risk populations, have demonstrated the efficacy of low dose computed tomography (LDCT) to detect early stage non-small cell lung cancer (NSCLC), the most common pathological subtype (≈88%). The largest study, the National Lung Screening Trial (NLST, n=53,454), demonstrated a reduction in lung cancer specific (20%) and overall mortality (6.7%) with annual LDCT screening compared to chest x-ray (CXR) [26]. The US Preventative Services Task Force now recommends individuals aged 55-80 with a smoking exposure compatible with NLST be offered annual LDCT screening [31]. Recently, the UK Lung Cancer Screening Pilot (UKLS) confirmed the benefit of screening high-risk smokers with LDCT in a UK setting [28]. Most cancers detected were early stage (85.7%, n=36/42) and 83.3% underwent surgical resection (national resection rate 16%) [32]. Estimated cost effectiveness was £8,466 per quality adjusted life year (QALY) [28], well below the NICE threshold for UK implementation (£20-30,000/QALY). Mortality data from the European NELSON randomised trial (n=15,822) is awaited [25]. Several important issues that remain unresolved include optimisation of identification of high-risk individuals for screening, embedding smoking-cessation in screening programmes, ensuring participation in 'hard to reach' at-risk populations [33,34], and understanding how best to deal with additional non-lung cancer findings.

1.3.1 Optimising screening participation

Current smoking and lower socio-economic status (SES) were associated with reduced participation in UKLS [35], this participation bias has been reported in other RCTs [36,37] and inequalities in uptake according to SES is common to other screening programmes [38,39]. Several studies report differences in attitudes to screening between current and never smokers [40-42]; how best to identify and engage this 'hard-to-reach' population remains a critical issue [43-45] and a priority area for implementation [46,47]. Travel was the most common reason for non-participation in UKLS [48], therefore the Manchester Early Detection of Lung Disease Pilot used a mobile CT scanner located in convenient community settings to improve accessibility, an approach that has been effective in breast cancer screening [49].

1.3.2 Defining the threshold for screening

Retrospective analysis of NLST, after stratification according to lung cancer risk, demonstrated that the majority of cancers (88%) were detected in the three highest risk quintiles and only 1% in the lowest [50]. The number needed to screen (NNS) to save 1 life was 161 in the highest risk group and 5,276 in the lowest; higher lung cancer risk was also associated with lower screening-related harms [51]. The more precise selection of higher risk smokers may improve screening efficacy, but the optimal method to select participants is unclear. In UKLS, screening was offered if 5-year lung cancer risk was ≥5%, as calculated by the Liverpool Lung Project model (LLP_{v2}) [52]. Another model ($PLCO_{m2012}$), developed using the much larger Prostate, Lung, Colorectal,

Ovarian RCT (PLCO, n= 154,901) [53], performed significantly better than NLST selection criteria (sensitivity 83% vs. 71%) and 41.3% fewer cancers were missed [54]. Further analysis indicated that the mortality benefit of LDCT screening was evident only above a 6-year lung cancer risk threshold of 1.5% when NNS to prevent one LC death was lower than NLST (NNS: PLCO 255 vs. NLST 320) [55].

1.4 ILD and lung cancer screening

Several common features in the pathogenesis of ILD and lung cancer have been determined. There is evidence to suggest an association between various forms of ILD and lung cancer [56]. Several studies have published data on the prevalence of interstitial lung disease in patients undergoing low-dose CT for lung cancer screening. A trial at Mayo Clinic in current and former smokers identified "diffuse lung disease" in 9 (0.9%) of 1,049 participants [22]. An Irish trial identified idiopathic pulmonary fibrosis in 6 (1.3%) of 449 current smokers who underwent low-dose CT screening for lung cancer [57]. Sverzellati et al evaluated 692 participants in the Multicentric Italian Lung Detection CT screening study and reported a respiratory bronchiolitis pattern in 109 (15.7%), a usual interstitial pneumonia pattern in 2 (0.3%), and other patterns of chronic interstitial pneumonia in 26 (3.8%) [58]. The National Lung Screening Trial reported that the frequency of "clinically significant" incidental findings (including pulmonary fibrosis) in all participants was 7.5%. A retrospective analysis of 884 participants at a single site in this trial identified interstitial lung abnormalities (ILA) in 86 participants (9.7%) [59]. These abnormalities were further categorized as nonfibrotic in 52 (5.9%) of 884, fibrotic in 19 (2.1%) of 884, and mixed fibrotic and nonfibrotic in 15 (1.7%) of 884. Follow-up CT at 2 years in this trial demonstrated improvement in 50% and progression in 11% of patients who had nonfibrotic abnormalities, while fibrotic abnormalities improved in no cases and progressed in 37%. Interstitial lung abnormalities were more common in those who currently smoked and in those with more pack-years of cigarette smoking. These trials suggest that low-dose CT screening for lung cancer can detect the most common forms of interstitial lung disease in this at-risk population which is important for prognosis and subsequent management. Interstitial lung abnormalities progression on CT has been shown to be associated with increased rate of pulmonary function decline and increased mortality [60]. No direct comparison has been made between ILD patients diagnosed through a screening programme and those diagnosed through a 'standard' non-screening pathway and the impact this may have on long term outcomes.

2 Rational for study

A number of lung cancer screening programmes are underway in the UK with the aim of establishing a national screening programme in the future. As well as identifying early stage lung cancer, these programmes also provide a unique opportunity to diagnose other prevalent respiratory diseases, including ILD, at an early asymptomatic stage. Early detection of ILD through these programmes provides an opportunity to diagnose and establish treatment early and potentially have a significant impact on disease progression and symptomatic burden.

3 Aims and Objectives

3.1 Objectives

3.1.1 Primary Objectives

To determine the prevalence of ILD in a community-based lung cancer screening programme.

3.1.2 Secondary Objectives

To compare patients diagnosed with ILD in a lung cancer screening programme to those diagnosed through routine care, assessing a number of parameters:

1. Quality of life, symptoms and psychological burden at diagnosis.
2. MDT agreed type and radiological pattern of disease as depicted by ATS/ERS ILD criteria [61].
3. Lung function (Forced vital capacity (FVC) and transfer factor (DLCO) at diagnosis.
4. Treatment strategies

3.2 Outcome Measures

3.2.1 Primary Measures

The prevalence and incidence of ILD in participants of a community-based lung cancer screening programme.

3.2.2 Secondary Measures

- Symptom burden and duration as per standardised clinical history proformas.
- Quality of life and symptom burden using the following questionnaires:
    - **SF-36**: a widely used validated non-disease-specific questionnaire to assess QoL in multiple diseased populations [62]. The SF-36 is a generic HRQoL instrument, comprising 36 items, grouped into eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Scores are converted into a 100-point scale, higher scores indicating better QoL. The SF-36 has been validated for use in ILD groups including IPF [63].
    - **Kings Brief Interstitial Lung Disease** (K-BILD) [64]: developed and validated for specific use in ILD patients. It comprises 3 domains (psychological, breathlessness and activities, chest symptoms and a total score). Scores range from 0-worst to 100-best.
    - The **University of California San Diego Shortness of Breath Questionnaire** (UCSD-SBQ): a 24-item dyspnea questionnaire that asks respondents to rate themselves from 0 (“Not at all”) to

5 (“Maximally or unable to do because of breathlessness”) in two areas: 1) how short of breath they are while performing various activities (21 items); and 2) how much shortness of breath, fear of hurting themselves by over exerting, and fear of shortness of breath limit them in their daily lives (3 items). Scores range from 0–120, with higher scores indicating greater dyspnea has demonstrated validity in ILDs trials [65,66].

- **Leicester Cough Questionnaire** (LCQ) [67] : is a 19-item questionnaire exploring the impact of cough severity across three domains: physical (eight items), psychological (seven items) and social (four items). The total severity score ranges from 3 to 21, with a lower score indicating greater impairment of health status due to cough. The LCQ has been used as an outcome measure in clinical trial including ILD patients [68].
- **Fatigue Severity Scale** (FSS) [69]: contains nine items developed to assess disabling fatigue. Item responses are measured on a seven-point Likert type scale ranging from strongly disagree to strongly agree. The nine items are combined into a total score; a lower total score indicates less effect of fatigue on everyday life. The FSS scale has been used in ILD populations [70].
- **Visual Analogue Scale (VAS)** [71]: a single item scale for each symptom - patients are asked to mark cough, breathlessness and fatigue severity on a linear 100 mm visual analogue scale for the past 2 weeks. The extremes of each scale are marked from 'no cough' to 'worst cough'/’no breathlessness’ to ‘worst breathlessness’ and ‘no fatigue’ to ‘worst fatigue’.

- Diagnosis and radiological pattern through clinical MDT proformas
- Full pulmonary function tests
- Shuttle walk tests: distance walked and oxygen saturation (pre and immediately post test)
- Initiated treatments

4 Patient Selection Criteria

4.1 Inclusion criteria

- Age 50-80
- Ever-smokers (current or previous)
- MDT diagnosis of ILD detected through lung cancer screening or through a non-screening pathway
- Attending the regional ILD clinic

4.2 Exclusion criteria

- Unable to complete self-report questionnaire measures e.g. due to cognitive impairment or English not first language

- Unable to provide written informed consent.

Individuals who do not consent to participation in this study will not be disadvantaged in anyway. They will continue to receive ILD clinic assessment, treatment and follow-up as per standard practice.

5 Study Design

4.1 Screening service: Invitation letters, endorsed by GPs to improve participation [46,72,73], were sent to all individuals (n=16, 402), age 55-74, registered at participating GP practices (n=14), asking ever smokers to attend a community-based Lung Health Check (LHC). The LHC, which took place in supermarket carparks in deprived areas of Manchester, assessed symptoms, lung cancer risk ($PLCO_{m2012}$) and measured spirometry. All participants with a 6-year lung cancer risk >1.5% were offered entry into the screening programme (n=1,450), which involved a non-contrast low dose CT scan at baseline and 12 months later. The first screening round was in 2016 and the second and final screening round in 2017.

4.2 Screening LDCT scans: All LDCT scans (Optima 660, GE Healthcare) use helical acquisition of axial images from lung apices to the costophrenic angles. Imaging is performed without intravenous contrast, in suspended maximal inspiration, with the patient supine and arms above head (scan time 5-10 seconds). Acquisition parameters (kVp and mAs) vary with body weight to achieve a CT dose index below 3.0 millisieverts. Images are reconstructed at 1.25 mm thickness and at 1.25 mm increments. Most CT scans are reported within 2 weeks by practising National Health Service (NHS) Consultant Radiologists with a specific interest in thoracic radiology.

4.3 ILD MDT: Any ILAs detected on screening LDCT scans were highlighted in the CT report and referred to the regional ILD MDT for review and discussion. The MDT consisted of three ILD respiratory physicians, a thoracic radiologist with an interest in ILD, two specialist ILD nurses and an MDT co-ordinator. Once discussed at the MDT, those deemed to have changes suggestive of significant ILD have been referred to the regional ILD service for assessment in the clinic.

4.4 Study population: Individuals attending the regional ILD clinic as a 'new referral' will be invited to participate. Inclusion and exclusion criteria will be evaluated and suitable participants will be provided with a

patient information sheet (PIS) prior to written consent being obtained for enrolment into the study. We will recruit patients from two groups:

- **Group 1**: ILD diagnosed through the Manchester early detection of lung disease pilot (lung cancer screening programme) and
- **Group 2**: age and sex matched individuals with ILD diagnosed through standard non-screening pathway.

Participation at the clinic will involve collection of demographic information, medical history including co-morbidities and medication history, full lung function tests (within 6 weeks), shuttle-walk test (within 6 weeks), MDT outcome proforma, clinic visit outcome including initiation of any treatments and completed questionnaires.

6 Data storage and analysis

Data will be stored on a specially designed research database and analysed using SPSS. The original signed consent form and completed questionnaire are stored within a secured location accessible only to the research team at MFT. Statistical significance will be set at <0.05. Clinical and demographic data analyses will be descriptive. Questionnaire scores will be calculated according to corresponding scoring algorithms, and mixed-modelling will used to examine the changes in the various scores between the three time-points, explore factors associated with HRQOL and differences between Group 1 and Group 2.

7 Adverse events

It is not anticipated that any adverse outcomes will occur; direct study participation will only be on the day of clinic visit.

8 Quality assurances

Data entry will be the responsibility of all members of the research team who will check data control as a matter of standard practice.

9 Ethical considerations

9.1 Patient protection

The principal investigator (PI) will ensure that this study is conducted in agreement with the Guidelines for Good Clinical Practice after appropriate ethical review and approval.

9.2 Subject confidentiality

Each participant's completed questionnaire and consent form will be stored in a locked filing cabinet in a secure location in the North West Lung Centre at Manchester University NHS Foundation Trust (MFT). This is where the regional ILD clinic is held. Patients recruited to the study have a unique study number. Data both clinical and laboratory will be coded according to the unique study number and not linked directly to patient identifiable information. The research database is hosted on a secure MFT network with access limited to the research team.

9.3 Informed consent

All participants will be asked to provide written informed consent (signed and personally dated by the patient) to study participation. This will take place during their first visit to the regional clinic. Patient data collected as part of the study is kept strictly confidentiality, but medical records may be reviewed for study purposes by authorized individuals other than their treating physician.

10 Administrative responsibilities

The study will be administered by the research team directly with oversight from the R+D department at MFT.

10.1 Amendments

Ethical approval covers only the information contained in the protocol. It does not include extensions or amendments to the study. All amendments need to be signed by the PI. Amendments will be communicated to the patients within the scope of the patient information / informed consent.

10.2 Reporting

The final evaluation and reporting will be done after completion of the study. All information in that report is strictly confidential.

11 Study sponsorship and insurance

The study sponsor will be the Manchester University NHS Foundation Trust; the study is covered by standard NHS indemnity.

12 Publication policy

The PI will be responsible for determining the final publication or public presentation of data. Protection of data from subjects and participating physicians must be guaranteed in all publications. Publication will be aimed at peer-reviewed scientific journals.

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