Title: Temporal progression of mediastinal lymphadenopathy in idiopathic pulmonary fibrosis

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Take home message

In two separate cohorts of patients with idiopathic pulmonary fibrosis, mediastinal adenopathy was common and an increase in the size of lymphadenopathy independently predicts mortality

Keywords: Idiopathic Pulmonary Fibrosis, Lymphadenopathy, Survival Analysis

ABSTRACT

Background

The presence of mediastinal lymphadenopathy (MLN) in patients with idiopathic pulmonary fibrosis (IPF) has been associated with poor prognosis. We investigated temporal trends in MLN and its relationship with patient outcomes.

Methods

Patients with at least two consecutive CT chest scans were identified from two independent IPF cohorts. Assessment of MLN size by short-axis diameter was performed by independent radiologists for each cohort, with MLN defined as ≥ 10 mm. Patients with alternative causes of MLN were excluded. Survival outcomes were calculated using Kaplan-Meier and multivariable Cox-regression analysis (co-variates; gender, smoking-status, age, antifibrotic therapy, and either FVC% or DLCO% predicted).

Results

In the two IPF cohorts (derivation n=51, validation n=92) MLN≥10mm was present in 71% (derivation n=36) and 84% (validation n=77) of patients at baseline. At follow-up, MLN size increased in approximately 50% of patients in both cohorts with a mean unidirectional temporal change in adenopathy of 1.83mm/year (derivation) and 1.43mm/year (validation). The rate of temporal progression in lymphadenopathy (mm/year) was associated with an increased mortality risk in multivariable analysis in both the derivation (HR 1.30 [95% 1.05-1.62]) and validation cohort HR 1.83 [1.19-2.58]). Comparing 'Progressors' (MLN≥10mm with ≥1mm/year increase in nodal size) to 'Non progressors' (No significant MLN, or MLN≥10mm with <1mm/year increase) identified Progressors to have a significantly increased mortality risk in both the derivation (multivariable analysis: HR 4.56 [95%CI 1.64-12.62]), and validation cohorts (multivariable analysis: HR 3.15 [95%CI 1.32-7.53]).

Conclusions

MLN is common in patients with IPF and temporal progression confers an additive, independent increased mortality risk.

MANUSCRIPT

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic interstitial lung disease (ILD) with limited therapeutic options and poor prognosis. Progressive disease is characterised by worsening breathlessness, exercise limitation and impaired quality of life.(1)

Average life expectancy from diagnosis of IPF is 2-4 years(2) however the disease course for an individual patient may vary significantly. Some patients experience rapid decline in lung function and physical capacity with associated early mortality, whilst others have a more indolent disease course.(3) Predicting an individual patient disease trajectory is challenging and there are no established clinically available disease biomarkers.(4)

Computed tomography (CT) scanning of the chest is an essential part of the diagnostic pathway in IPF(5). In addition to characteristic lung parenchymal changes of usual interstitial pneumonia pattern (UIP) fibrosis,(6) mediastinal lymphadenopathy (MLN) has been described with high prevalence (52-92%) in IPF cohorts.(7-11) The underlying mechanism for MLN in IPF remains unknown but it may reflect immunological activation.(12) Previous studies have identified that the presence of MLN is linked to disease severity and can independently predict reduced survival in IPF(13, 14) and ILD.(11) The presence of MLN has been shown to persist on longitudinal imaging in the majority of patients with IPF who have MLN at baseline.(14) However, whilst temporal progression of MLN has been shown to correlate with worsening CT fibrosis score,(8) whether temporal progression of MLN in IPF confers an additional impact on mortality is unknown.

In this study we investigated temporal trends in MLN in patients with IPF in two independent cohorts. Using a derivation and validation cohort study design we identify that in IPF patients with MLN temporal progression occurs in approximately 50% of patients and the rate of temporal progression is associated with an additive increase in mortality risk.

METHODS

Study population

Patients with a multidisciplinary team diagnosis of IPF and at least two consecutive volumetric inspiratory CT examinations were identified from two medical centres. The derivation cohort consisted of patients presenting to University Hospital Southampton Foundation NHS Trust (UHSFT) between 2011 and 2016. The validation cohort consisted of patients presenting to Ege Hospital Izmir, Turkey between 2008 and 2015. Patient demographic and clinical information were extracted from electronic clinical records.

CT analysis for mediastinal lymphadenopathy

Derivation cohort CTs were assessed by two experienced radiologists (KV and SB). CTs in the validation cohort were assessed by an experienced radiologist (JJ). All radiologists were blinded to clinical information and study outcomes. CTs were reviewed for mediastinal lymphadenopathy (MLN) in accordance with the International Association for the Study of Lung Cancer (IASLC) classifications.(15) Mediastinal node stations 1-9 were assessed,(8, 11) with significant MLN defined as a short-axis diameter ≥10mm (16-19), an approach consistent with previous studies of MLN in lung fibrosis (8, 11, 13, 14). Subjects with alternative identified causes for MLN (concurrent pulmonary infection or malignancy [except basal skin cancer]) were excluded. The rate of temporal progression/regression was calculated by dividing the difference in size between the largest mediastinal lymph node (on either baseline or follow-up scan) and the same node on the other timepoint CT, by the CT interval (years).

Ethical Approvals

Ethical approval was obtained from the London-Hampstead Research Ethics Committee (REC:17/LO/2037) and Leeds East Research Ethics Committee: (REC:134 20/YH/0120).

Statistical analysis

Between group comparisons for continuous variables were made using independent two-tailed t-tests. Assessment of difference in distribution of categorical variables between independent groups was made using the Chi-squared test (χ^2) or Fisher's Exact test as appropriate.

Time-to-event analysis was computed using Kaplan-Meier analysis and Cox proportional-hazard models to determine any association between a) the influence of presence of MLN≥10mm on baseline CT b) the rate of progression of mediastinal lymphadenopathy, between baseline and follow-up CT, on a linear scale (mm/year) c) rate of progression of mediastinal lymphadenopathy stratified as ≥1mm/year or <1mm/year - a value which would be the smallest reliable measurable interval change. Survival analysis was conducted from baseline CT (CT1) to death/censor for baseline analysis and from follow-up CT (CT2) to death/censor for temporal progression analysis. Multivariable Cox-regression survival analysis was adjusted for the following covariates; age at diagnosis, gender, smoking-status (ever smoker vs. never smoker), antifibrotic therapy (ever taken vs. never taken), and either forced vital capacity percentage predicted (FVC% predicted), or diffusion capacity of the lung for carbon monoxide percentage predicted (DLCO% predicted). P values of <0.05 were deemed significant. Statistical analysis was conducted using IBM®-SPSS® version 26.

RESULTS

51 patients were identified for study inclusion from the derivation cohort and 92 patients were identified for inclusion from the validation cohort **(CONSORT (20) Diagram Figure 1**).

Patient Characteristics

Baseline demographic information for the two cohorts is summarised in **Table 1.** There was a male predominance in both cohorts. Patients in the validation cohort were significantly younger than those in the derivation cohort (63.9 years vs. 72.5 years $p<0.001$) and a significantly greater proportion of patients in the validation cohort were taking antifibrotic therapy (77% vs. 56% $p=0.01$). There was no significant difference between cohorts in gender, baseline lung function parameters, smoking history, or body mass index (BMI).

Presence of Mediastinal Lymphadenopathy at Baseline

71% (n=36) and 84% (n=77) of patients had MLN≥10mm at baseline in the derivation and validation cohorts respectively. In patients with MLN, the mean (standard deviation [SD]) size of the largest node ≥10mm in the derivation cohort was 13.3 mm (2.8), and in the validation cohort 12.5 mm (3.4) (Supplemental Table 1). Compared to those without MLN, patients with MLN≥10mm in both cohorts had greater impairment in lung function. There was no statistical difference between those with, and those without MLN≥10mm, in either cohort for gender, the use of antifibrotic therapy, age at baseline, or body mass index (BMI) **(Supplemental Table 2)**. Kaplan-Meier survival analysis identified that the presence of MLN≥10mm at baseline was associated with a trend to reduced median survival time in the derivation cohort and significantly reduced median survival time in the validation cohort (**Supplemental Table 3)**. However, the presence of MLN≥10mm at baseline was not observed to have a significant effect on survival in multivariate analysis in either cohort (**Supplemental Table 4**).

Temporal Change in Mediastinal Lymphadenopathy

Having confirmed the presence of baseline adenopathy in our cohorts we investigated temporal trends in MLN and whether progression of MLN has a negative impact on prognosis using a derivation and validation cohort approach.

Derivation Cohort

The mean (SD) interval between baseline and follow-up CT in the derivation cohort was 2.17 years (1.6). At follow-up 82% (n=42) of patients in the derivation cohort had MLN≥10mm (**Supplemental Table 1**). 24% (n=12) of patients changed MLN status between CTs, with 18% (n=9) of patients progressing from no MLN at baseline to presence of MLN≥10mm at follow-up. In total 88% (n=45) of patients in the derivation cohort had MLN at either time point.

In the derivation cohort the size of the largest node increased from baseline to follow-up in 57% (n=28) of patients, decreased in 39% (n=10), and remained unchanged in 14% (n=8). The mean unidirectional rate of change of the largest lymph node correcting for the imaging interval was 1.83 mm/year (1.8).

In univariable analysis the rate of temporal progression of adenopathy (mm/year) trended toward increased mortality risk HR 1.15 (95%CI 0.96-1.38). Further in multivariable Cox analysis regardless of the measure used to estimate disease severity in IPF patients (FVC %predicted or DLCO %predicted), the rate of temporal change in adenopathy was identified as a significant independent predictor of mortality risk (**Table 2**).

Using a binary threshold of ≥10 mm on short axis diameter to define the presence of pathologically significant adenopathy we stratified patients into; '***Progressors***' those with MLN≥10mm and a ≥1 mm/year increase in nodal size, and '***Non progressors***' those with either MLN≥10mm and a <1 mm/year increase in nodal size or no significant MLN on either CT. Using this stratification identified 'Progressors' to have a significantly increased mortality risk HR 4.56 (95%CI 1.64-12.62) p=0.004. (**Figure 2a, Table 3)**

Validation Cohort

The mean (SD) interval between baseline and follow-up CT in the validation cohort was 1.40 years (0.7). At follow-up CT 82% (n=75) of patients in the validation cohort had MLN≥10mm (**Supplemental Table 1**). 17% (n=16) of patients changed MLN status between CTs with 7.6% (n=7) of patients progressing from no significant MLN at baseline to presence of MLN≥10mm at follow-up. In total 91% (n=84) of patients in the validation cohort had MLN≥10mm at either time point.

In the validation cohort the size of the largest node increased from baseline to follow-up in 57% (n=52), decreased in 21% (n=19), and remained unchanged in 23% (n=21) of patients. The mean unidirectional rate of change in largest lymph node size correcting for the imaging interval was 1.43 mm/year (2.3).

In the validation cohort, the rate of change in MLN size demonstrated a trend to increased mortality risk in univariable analysis HR 1.84 (95%CI 0.92-1.51) p=0.18. When correcting for covariates and adjusting for disease severity using either FVC% predicted or DLCO% predicted in separate models, the rate of change in MLN size was confirmed as a significant independent predictor of increased mortality risk (**Table 2**). Further stratifying patients as *Progressors* (MLN≥10mm with a ≥ 1 mm/year increase in size of the largest node) and *Non progressors* (MLN≥10mm with <1mm/year increase in nodal size, or no significant MLN on either CT) conferred a significant increased risk of death between groups (HR 3.15 [95%CI 1.32-7.53] p=0.010 **(Figure 2b, Table 3**).

DISCUSSION

In this study we investigated the temporal progression of MLN in patients with IPF in two independent cohorts using a derivation and validation study design. In patients with lymphadenopathy at baseline, persistence of adenopathy at follow-up imaging was common and the size of the largest node increased in approximately 50% of patients. We identified that the rate of temporal progression in mediastinal lymphadenopathy was found to predict increased mortality risk. Further stratifying patients using a cut off of a 1mm/year increase in the size of largest node identified a group with additive poor prognosis.

MLN was common in both cohorts, with MLN identified on baseline CT in 71% (derivation cohort) and 84% (validation cohort) of patients. This frequency is consistent with that observed by Adegunsoye et al. (11) in which 75% of 342 patients with IPF had MLN≥10mm. Whilst a lower proportion (66%) was identified in a series of 133 consecutive patients with pathologically proven idiopathic pulmonary fibrosis(7), this was performed using non-contiguous HRCT at 10-mm intervals, and so the authors acknowledged that this was likely an underestimate in the prevalence of MLN. Thus, our findings and previous reports (7-11) identify that the majority of patients with IPF have mediastinal adenopathy. Whilst current ATS/ERS/JRS/ALAT diagnostic IPF guidelines recognise that mediastinal lymphadenopathy may be present in patients with IPF, they recommend consideration to other aetiologies be given when extensive lymph node enlargement is present(21), The Fleischner Society White Paper proposing diagnostic criteria for IPF acknowledges mild mediastinal lymph node enlargement may be evident on CT in patients with IPF, although does not define mild MLN(22). Given the high frequency of adenopathy of variable size we and others have identified in patients with IPF, further prospective investigation into the distribution of mediastinal lymph node sizes in IPF and the definition of extensive node enlargement not consistent with IPF is warranted to inform future guidelines.

We observed that approximately 90% of patients maintained MLN≥10mm status from baseline to follow-up, with a total of 17-24% of patients changing MLN status between CTs; these observed rates are similar to those identified by Sgalla et al. (14). Whilst in univariate analysis the presence of baseline mediastinal adenopathy predicted survival in the validation cohort, in both the derivation and validation cohorts no significant association with survival was identified in multivariate analysis. This observation is similar to that of Sgalla et al. (14) and may be a consequence of a type II statistical error due to the small number of deaths in those without MLN in our cohorts.

The pathological mechanism underlying lymphadenopathy in lung fibrosis remains uncertain. Proposed mechanisms include an early response to lung injury facilitating recruitment of inflammatory and fibrotic cells to fibroblastic foci(23, 24) or secondary to local macrophage

activation.(12) Further evidence supporting the role of MLN in ILD reflecting immunological activation comes from Adegunsoye et. al (11) who identified that MLN in various ILDs are associated with an increased circulating peripheral blood lymphocyte count and other immunological markers including lower plasma concentrations of the cytokine sCD40L and the mitogenic protein Epidermal Growth Factor (EGF). Further, a recent study by Rotondo et al.(25) identified that the presence of MLN significantly predicted progression to ILD in patients with systemic sclerosis without parenchymal lung involvement at baseline.

Despite the observed association between presence of MLN on Chest CTs in IPF patients and increased mortality risk, it remains uncertain whether the development, and the progression in size, of MLN is the driver of, or a reaction to, disease progression. Consistent with our observation of temporal progression of MLN influencing patient mortality, and the supposition that it is a driver of disease pathology in this group of patients, it has previously been identified that development of MLN between baseline and follow-up CT was significantly associated with worsening fibrosis score in four patients with IPF (8). In both our cohorts, temporal progression of lymphadenopathy occurred in approximately 50% of patients, the rate of temporal progression was found to confer a negative impact on survival. Our finding that a cut-off of a 1mm/year increase in nodal size confers a significant additive mortality risk suggests this finding is of clinical relevance. It is notable that the finding was reproduced by independent radiologists for each cohort, suggesting potential utility in standard clinical practice as a screening tool on interval scanning to identify patients at increased risk of poor outcome.

This study is, to our knowledge, the first to assess the impact of temporal progression of MLN on survival in IPF. The strength of our study is the replication of the novel association between temporal progression of MLN and increased mortality risk in two independent cohorts of IPF patients. However, there are a number of methodological limitations. In both cohorts the analysis was retrospective and had a relatively small sample size (derivation n=51, validation n=92). The CT scans analysed occurred at varying intervals as part of standard clinical care, rather than in the rigorous constructs of a clinical

trial. It is also important to highlight occult malignancy as a potential confounder due to the known association between IPF and both lung cancer(26-28) and tobacco smoking.(29) We aimed to reduce this potential bias by excluding patients with any known active malignancy (except basal skin cancer) and all CT images were screened for suspected malignancy.

In summary we identify in two independent cohorts of IPF patients, using a derivation and validation study design, that temporal progression of mediastinal lymphadenopathy is frequent and confers an additive and independent increase in mortality risk.

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DISCLOSURE STATEMENT:

JJ reports fees from Boehringer Ingelheim, Roche, NHSX and GlaxoSmithKline unrelated to the submitted work.
L.R. reports fees from Biogen, Roche, ImmuneWorks, Boehringer Ingelheim, Celegene, Nitto, FibroGen, Promedior,
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TABLES

Table 1

	Derivation Cohort mean (SD) or % (n)	**Validation Cohort** mean (SD) or % (n)	**p value**
Total (n)	n=51	n=92	
Age (years)	72.52 (8.4)	63.93 (8.3)	<0.001**
Gender (Male)	82.4% (42)	78.3% (72)	0.560
BMI (kg/m^2)[1]	26.48 (4.2)	27.62 (3.9)	0.109
Ever smoker[2]	58.8% (30)	57.6% (49)	0.444
Pack-years[2]	17.89 (18.1)	21.07 (27.7)	0.480
Antifibrotic (% Ever taken)	56.9% (29)	77.2% (71)	0.011*
FEV1%[3]	86.84 (18.9)	79.41 (22.9)	0.066
FVC (L)[3]	2.80 (0.71)	2.47 (0.75)	0.091
FVC (%)[3]	80.10 (18.1)	75.47 (21.5)	0.220
DLCO (%)[4]	51.19 (13.7)	54.29 (18.1)	0.330

Table 1: Baseline characteristics for the Derivation and Validation Cohorts. Derivation cohort (n=51) Validation cohort (n=92). Scale variables presented as mean (standard deviation [SD]) categorical variables presented % (n). FEV1% - forced expiratory volume 1 sec % predicted. FVC (L) - absolute forced vital capacity litres, FVC% - FVC % predicted. DLCO% - diffusion capacity of the lung for carbon monoxide % predicted. [1]BMI data available in derivation cohort for n=50 and validation cohort n=91.[2]smoking history available in derivation cohort n=51 and validation cohort n=85. [3]Spirometry (FEV1%, FVC (L), and FVC%) data available in derivation cohort for n=50 and validation cohort n=68. [4]DLCO% predicted data available in derivation cohort for n=48 and validation cohort n=61. p values independent two-tailed t-test for continuous variables, Chi-squared test (χ^2) or Fisher's exact test for categorical variables as appropriate. **p<0.01 *p<0.05

TABLE 2

MLN Temporal Progression Survival Analyses	(n)	Hazard Ratio	95% Confidence Interval	p value
Univariable Analyses				
Derivation Cohort	51	1.15	0.96-1.38	0.12
Validation Cohort	92	1.84	0.92-1.51	0.18
Multivariable Analysis (Covariates[&] and FVC% predicted)				
Derivation Cohort	50	1.31	1.07-1.61	0.010*
Validation Cohort	66	1.41	1.06-1.89	0.020*
Multivariable Analysis (Covariates[&] and DLCO% predicted)				
Derivation Cohort	48	1.30	1.05-1.62	0.019*
Validation Cohort	57	1.83	1.19-2.58	0.001**

Table 2: Cox Univariable and Multivariable Regression Analyses for influence of Temporal Progression of mediastinal lymphadenopathy (MLN) on survival. [&]All multivariable models were adjusted for smoking status (Ever smoker vs. never smoker), Gender, Antifibrotic therapy (Ever taken vs. never taken), Age, and one of two measures of baseline disease severity, either forced vital capacity percent predicted (FVC% predicted) or diffusion capacity of the lung for carbon monoxide percent predicted (DLCO% predicted) *p<0.05 **p<0.01

TABLE 3

MLN Temporal Progression Survival Analyses for Progressors vs. Non progressors	**(n)**	**Hazard Ratio**	**95% Confidence Interval**	**p value**
Univariable Analyses				
Derivation Cohort	51	2.49	1.13-5.47	0.023*
Validation Cohort	92	1.97	0.96-4.06	0.065
Multivariable Analysis (Covariates[&] and DLCO% predicted)				
Derivation Cohort	48	4.56	1.64-12.62	0.004*
Validation Cohort	57	3.15	1.32-7.53	0.010*

Table 3: **Cox Univariable and Multivariable Regression Analyses for influence of Temporal Progression of mediastinal lymphadenopathy (MLN) on survival grouping patients as 'Progressors' (MLN≥10mm with a ≥1 mm/year increase in size of largest node) vs. 'Non progressors' (MLN≥10mm with a <1 mm/year increase in nodal size or No significant MLN on either CT).** [&]Multivariable analysis adjusted for smoking status (Ever smoker vs. never smoker), Gender, Antifibrotic therapy (Ever taken vs. never taken), Age, and diffusion capacity of the lung for carbon monoxide percent predicted (DLCO% predicted). *p<0.05.

FIGURE LEGEND:

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patients in the study analysis.
UHSFT- University Hospital Southampton Foundation Trust. CT- Computed Topography Scan.

Figure 2: Kaplan-Meier cumulative survival curves from Follow-up CT (CT2) to death or censor date (years) for temporal progression of lymphadenopathy stratified as Progressor vs. Non progressor. Progressor (MLN≥10mm with ≥1mm/year increase in nodal size). **Non progressor** (MLN≥10mm with <1mm/year increase in nodal size or no significant MLN), **(A)** Derivation Cohort total n=51. Number of deaths per group; Non progressor n=15, Progressor n=12. Log rank p=0.019. (**B**) Validation Cohort n=92. Number of deaths per group; Non progressor n=20 Progressor n=13. Log rank p=0.060

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