Temporal progression of mediastinal lymphadenopathy in idiopathic pulmonary fibrosis

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic interstitial lung disease (ILD) with limited therapeutic options and poor prognosis. [1] The average life expectancy from diagnosis is 2 to 4 years [2]; however, predicting an individual patient disease trajectory is challenging and there are no established clinically available disease biomarkers [3]. Computed tomography (CT) scanning of the chest is an essential part of the diagnostic pathway in IPF with characteristic appearances of usual interstitial pneumonia (UIP) [4]. In addition, mediastinal lymphadenopathy (MLN) has been described with high prevalence (52–92%) in IPF cohorts [5–9]. Previous studies have identified that the presence of MLN is linked to disease severity and can independently predict reduced survival in IPF [10, 11] and ILD [9]. The presence of MLN has been shown to persist on longitudinal imaging in the majority of patients with IPF who have MLN at baseline [11]. However, whilst temporal progression of MLN has been shown to correlate with worsening CT fibrosis score [6], whether temporal progression of MLN in IPF confers an additional impact on mortality is unknown. In this study we investigated temporal trends in MLN and their impact on survival in patients with IPF in two independent cohorts.

Consecutive patients with a confirmed specialist multidisciplinary team diagnosis of IPF based on consensus guidelines [4] with at least two consecutive volumetric inspiratory CT examinations were identified from two medical centres: cohort 1: University Hospital Southampton, UK between 2011 and 2016; and cohort 2: Ege Hospital Izmir, Turkey between 2008 and 2015. Lung biopsies were performed as part of the diagnostic pathway in 22% (n=11) and 26% (n=24) of patients in cohort 1 and 2, respectively. Ethical approval was obtained from the London-Hampstead Research Ethics Committee (Cohort 1) (REC: 17/LO/2037) and from the Leeds-East Research Ethics Committee (Cohort 2) (REC: 134 20/YH/0120).

CT scans were assessed for MLN independently for each cohort by experienced radiologists blinded to the study outcomes (cohort 1, K. Vedwan and S. Battison; cohort 2, J. Jacob). CT images were reviewed for MLN in accordance with the International Association for the Study of Lung Cancer classifications [12], with significant MLN defined as a short-axis diameter ⩾10 mm [6, 9–11]. Subjects with alternative identified causes for MLN (concurrent pulmonary infection, granulomatous disease, 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).

Survival analysis was computed using Kaplan–Meier and Cox proportional hazard models to determine any association between 1) the rate of progression of mediastinal lymphadenopathy on a linear scale (mm per year) and 2) rate of progression of mediastinal lymphadenopathy stratified as ⩾1 mm per year or <1 mm per year (a value which would be the smallest reliable measurable interval change). Survival analysis was conducted from time of the follow-up CT to death or censor. Multivariable survival analysis was adjusted for age, antifibrotic therapy (ever *versus* never taken), and either forced vital capacity (FVC) % predicted or diffusing capacity of the lung for carbon monoxide (D_{LCO}) % predicted. p-values <0.05 were deemed significant. Statistical analysis was conducted using IBM-SPSS version 26.0.
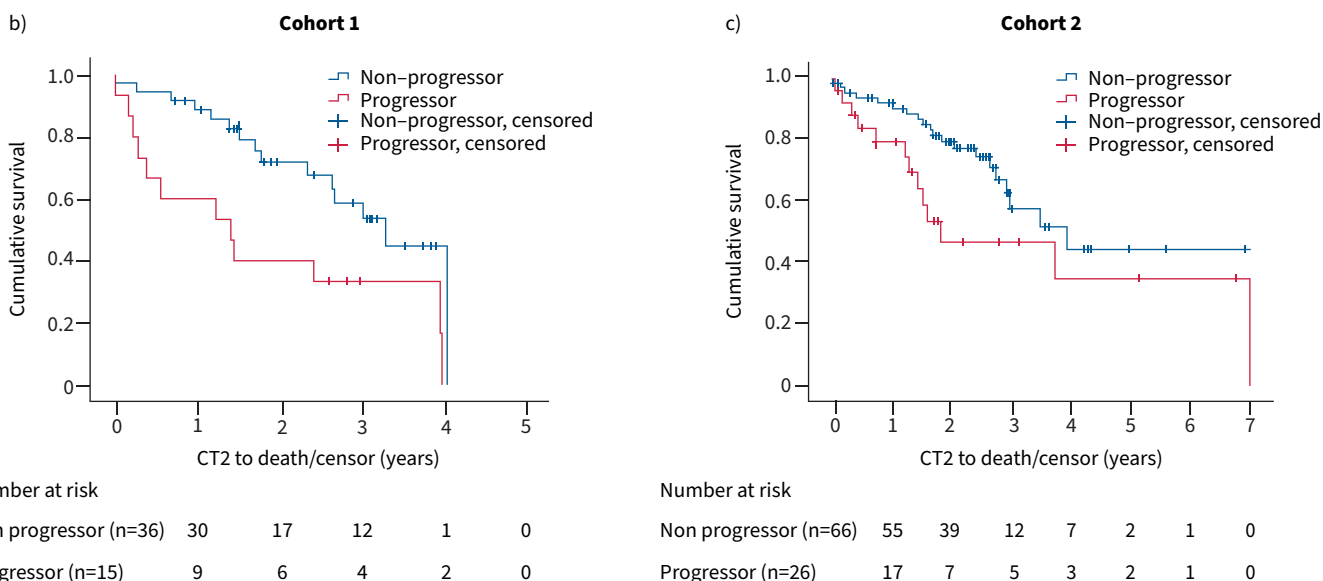
Shareable abstract (@ERSpublications)
In two separate cohorts of patients with idiopathic pulmonary fibrosis, mediastinal adenopathy was common and an increase in the size of lymphadenopathy independently predicts mortality https://bit.ly/32vEMnX

a)

		Linear temporal progression (mm per year)			Stratified temporal progression (progressors *versus* non-progressors)	
Univariable analysis						
	n	HR (95% CI)		p-value	HR (95% CI)	p-value
Cohort 1	51	1.15 (0.96–1.38)		0.12	2.49 (1.13–5.47)	0.023*
Cohort 2	92	1.84 (0.92–1.51)		0.18	1.97 (0.96–4.06)	0.065
Multivariable analysis (covariates and FVC % pred)						
	n	HR (95% CI)		p-value	HR (95% CI)	p-value
Cohort 1	50	1.32 (1.07–1.61)		0.008**	3.02 (1.26–7.26)	0.014*
Cohort 2	68	1.43 (1.07–1.91)		0.036*	1.86 (0.84–4.12)	0.126
Multivariable analysis (covariates and D_{LCO} % pred)						
	n	HR (95% CI)		p-value	HR (95% CI)	p-value
Cohort 1	48	1.38 (1.11–1.71)		0.004**	4.71 (1.72–12.94)	0.003**
Cohort 2	59	1.84 (1.30–2.60)		0.001**	3.30 (1.39–7.83)	0.007**

b) Cohort 1

Number at risk

Non progressor (n=36)	30	17	12	1	0
Progressor (n=15)	9	6	4	2	0

c) Cohort 2

Number at risk

Non progressor (n=66)	55	39	12	7	2	1	0
Progressor (n=26)	17	7	5	3	2	1	0

FIGURE 1 Influence of temporal progression of mediastinal lymphadenopathy (MLN) on survival. a) Cox univariable and multivariable regression analyses for influence of temporal progression of MLN on survival. All multivariable models were adjusted for age, antifibrotic therapy (ever taken *versus* never taken), and one of two measures of baseline disease severity, either forced vital capacity (FVC) % predicted or diffusion capacity of the lung for carbon monoxide (D_{LCO}) percent predicted. HR: hazard ratio. "Progressors" refers to those with MLN ⩾10 mm with a ⩾1 mm per year increase in size of largest node; "non-progressors" to those with MLN ⩾10 mm with a <1 mm per year increase in nodal size or no significant MLN on either computed tomography (CT) image. *: p<0.05; **: p<0.01. b and c) Kaplan–Meier cumulative survival curves from follow-up CT (CT2) to death or censor date (years) for temporal progression of MLN stratified as progressor *versus* non-progressor. b) Cohort 1, total n=51. Number of deaths per group: non-progressor n=15, progressor n=12. Log-rank p=0.019. c) Cohort 2, total n=92. Number of deaths per group: non-progressor n=20, progressor n=13. Log-rank p=0.060.

51 patients were included in cohort 1 and 92 patients in cohort 2. The mean±SD CT imaging interval was 2.17±1.6 years and 1.40±0.7 years in cohort 1 and 2, respectively. The inter-radiologist agreement for presence on MLN in cohort 1 was 86%, kappa 0.681, standard error 0.078, p<0.001.

There was no significant difference observed between patients in cohorts 1 and 2 for any of: sex (males, 82% *versus* 78%; p=0.56), mean FVC (87% *versus* 79% pred; p=0.07), D_{LCO} (52% *versus* 54% pred; p=0.33), or smoking history (59% *versus* 58%; p=0.44). Patients in cohort 1 were significantly older (72.5 years *versus* 63.9 years; p<0.001) and fewer had ever taken antifibrotic therapy (56% *versus* 77%; p=0.01). Concomitant historic diagnosis of left ventricular dysfunction was present in five patients in cohort 1 and six patients in cohort 2.

Significant MLN was identified in 71% (cohort 1) and 84% (cohort 2) of patients at baseline. The incidence of significant MLN increased at follow-up CT and was identified in 88% (cohort 1) and 91%

(cohort 2) of patients on either CT scan. At follow-up CT, the size of the largest node increased in approximately 50% of patients (55% in cohort 1 and 57% in cohort 2). The mean unidirectional rate of temporal progression of adenopathy was 1.83 mm per year (cohort 1) and 1.43 mm per year (cohort 2). In univariable analysis the rate of temporal progression of adenopathy (mm per year) trended toward increased mortality risk in both cohorts (figure 1a). However, in multivariable analysis the rate of temporal change in adenopathy was identified as a significant independent risk factor for mortality in both cohorts (figure 1a). As a $\geqslant 1$ mm per year increase would be considered the smallest reliable change, we stratified patients into: "progressors", those with significant MLN and a $\geqslant 1$ mm per year increase in nodal size; and "non-progressors" those with either significant MLN with a <1 mm per year increase in nodal size, or no significant MLN on either scan. Using this stratification within the D_{LCO} multivariate model identified progressors to have a significantly increased mortality risk in both cohorts 1 and 2; hazard ratio (HR) 4.71, p=0.003; and HR 3.30, p=0.007, respectively (figure 1a–c).

In this study we investigated the temporal progression of MLN in patients with IPF in two independent cohorts. 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 $\geqslant 1$ mm per year increase in size of the largest node identified a group with additive poor prognosis.

Despite the observed association between presence of MLN on chest CT images 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. Proposed mechanisms underlying lymphadenopathy in lung fibrosis include an early response to lung injury facilitating recruitment of inflammatory cells to fibroblastic foci [13, 14] or secondary to local macrophage activation [15]. 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 [6].

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 including the retrospective analysis, relatively small sample size, and varying intervals of the CT scans performed as part of standard care. Further although CTs were screened for malignancy, it is also important to highlight occult malignancy as a potential confounder.

In summary we identify in two independent cohorts of patients with IPF that temporal progression of mediastinal lymphadenopathy is frequent and confers an additive and independent increase in mortality risk.

Tim J.M. Wallis[1,2], Eyjólfur Gudmundsson[3], Katarina Pontoppidan[1], Nesrin Mogulkoc[4], Recep Savaş[5], Ömer Selim Unat[4], Katharine Vedwan[6], Sobana Battison[6], Fiona J. Thompson[1], Christopher J. Brereton [1,2], Ben G. Marshall [1,2], Sophie V. Fletcher[1,2], Luca Richeldi[1,7], Joseph Jacob [3,8] and Mark G. Jones [1,2]

[1]National Institute for Health Research Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, UK. [2]School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK. [3]Centre for Medical Image Computing, University College London, London, UK. [4]Dept of Respiratory Medicine, Ege University Hospital, Izmir, Turkey. [5]Dept of Radiology, Ege University Hospital, Izmir, Turkey. [6]Dept of Cardiothoracic Radiology, University Hospital Southampton, Southampton, UK. [7]Unità Operativa Complessa di Pneumologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico A. Gemelli, Rome, Italy. [8]UCL Respiratory, University College London, London, UK.

Corresponding author: Tim J.M. Wallis (Timothy.Wallis@soton.ac.uk)

References

1   Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. *Lancet* 2017; 389: 1941–1952.
2   Ley B, Collard HR, Talmadge E, *et al.* Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183: 431–440.
3   Drakopanagiotakis F, Wujak L, Wygrecka M, *et al.* Biomarkers in idiopathic pulmonary fibrosis. *Matrix Biology* 2018; 68–69: 404–421.
4   Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis. an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.
5   Souza CA, Muller NL, Lee KS, *et al.* Idiopathic interstitial pneumonias: prevalence of mediastinal lymph node enlargement in 206 patients. *AJR Am J Roentgenol* 2006; 186: 995–999.
6   Attili AK, Kazerooni EA, Gross BH, *et al.* Thoracic lymph node enlargement in usual interstitial pneumonitis and nonspecific-interstitial pneumonitis: prevalence, correlation with disease activity and temporal evolution. *J Thorac Imaging* 2006; 21: 288–292.
7   Bergin C, Castellino RA. Mediastinal lymph node enlargement on CT scans in patients with usual interstitial pneumonitis. *AJR Am J Roentgenol* 1990; 154: 251–254.
8   Niimi H, Kang EY, Kwong JS, *et al.* CT of chronic infiltrative lung disease: prevalence of mediastinal lymphadenopathy. *J Comput Assist Tomogr* 1996; 20: 305–308.
9   Adegunsoye A, Oldham JM, Bonham C, *et al.* Prognosticating outcomes in interstitial lung disease by mediastinal lymph node assessment. An observational cohort study with independent validation. *Am J Respir Crit Care Med* 2019; 199: 747–759.
10 Sin S, Lee KH, Hur JH, *et al.* Impact of mediastinal lymph node enlargement on the prognosis of idiopathic pulmonary fibrosis. *PLOS ONE* 2018; 13: e0201154.
11 Sgalla G, Larici AR, Golfi N, *et al.* Mediastinal lymph node enlargement in idiopathic pulmonary fibrosis: relationships with disease progression and pulmonary function trends. *BMC Pulm Med* 2020; 20: 249.
12 Goldstraw PMBF, Crowley JJP, on behalf of the IISP. The international association for the study of lung cancer international staging project on lung cancer. *J Thorac Oncol* 2006; 1: 281–286.
13 Lara AR, Cosgrove GP, Janssen WJ, *et al.* Increased lymphatic vessel length is associated with the fibroblast reticulum and disease severity in usual interstitial pneumonia and nonspecific interstitial pneumonia. *Chest* 2012; 142: 1569–1576.
14 Sarah M, Abigail L. Lymphangiogenesis and its role in physiologic wound healing and the pathogenesis of pulmonary fibrosis. *J Vasc Med Surg* 2015; 3: 236.
15 El-Chemaly S, Malide D, Zudaire E, *et al.* Abnormal lymphangiogenesis in idiopathic pulmonary fibrosis with insights into cellular and molecular mechanisms. *Proc Natl Acad Sci USA* 2009; 106: 3958–3963.