ORIGINAL RESEARCH LETTER

Time taken from primary care referral to a specialist centre diagnosis of idiopathic pulmonary fibrosis: an opportunity to improve patient outcomes?

To the Editor:

The care of patients with idiopathic pulmonary fibrosis (IPF) has been transformed by the widespread approval of antifibrotic therapies [1]. Within primary care-based healthcare systems, the diagnosis of IPF and commencement of antifibrotic therapy typically requires a patient referral from a primary care physician to a respiratory physician in secondary care, with referral then made to a specialist interstitial lung disease (ILD) centre [2]. Following ILD centre review and multidisciplinary team (MDT) discussion, a diagnosis of IPF is made and antifibrotic therapy may be commenced.

To maximise the benefit of antifibrotic therapy, early diagnosis of IPF has been widely advocated [3–5]. However, while patient surveys and questionnaires consistently report significant delays to a definitive IPF diagnosis, understanding of any impact upon patient outcomes is limited [6]. The objective of this study was to investigate, within primary care healthcare systems, the time taken from the first primary care physician referral for symptom investigation to ILD specialist centre review and antifibrotic therapy commencement.

We identified patients with an MDT diagnosis of IPF between January 2012 and December 2017 in two specialist ILD clinics in two countries with a primary care healthcare system (University Hospital Southampton, Southampton, UK, and Mater Misericordiae University Hospital, Dublin, Ireland). The dates of primary care referral, first secondary care respiratory clinic contact, first ILD clinic review, antifibrotic commencement, antifibrotic discontinuation and date of death were determined through electronic case note review. Patients who were discussed in the MDT but not seen in the ILD clinic, or had insufficient clinical information, were excluded. The date of the census was April 2018. The study was approved by the London-Hampstead Research Ethics Committee (REC 17/LO/2037). Statistical analysis was conducted using SPSS version 25 (IBM, Armonk, NY, USA)

247 patients were identified (194 from Southampton and 53 from Dublin). 183 (74%) were male and 162 (66%) were ex-smokers. The median (interquartile range) time from primary care referral to secondary care respiratory clinic review was 47 (25–84) days, to ILD clinic 290 (133–773) days and to antifibrotic commencement 540 (282–1024) days.

We used Cox regression analysis to investigate for demographic variables associated with a >12 month period from general practitioner (GP) referral to ILD clinic. Male sex (hazard ratio (HR) 1.935, 95% CI 1.141–3.281; p=0.014), increasing body mass index (HR 1.081, 95% CI 1.028–1.136; p=0.002) and gastro-oesophageal reflux (HR 1.559, 95% CI 1.010–2.405; p=0.045) were significantly associated with a >12 month period from GP referral to ILD clinic. Age, smoking status, ILD centre and other comorbidities (COPD, diabetes and ischaemic heart disease) were not significantly associated.

Patients reviewed in the ILD clinic within 12 months of primary care referral (n=142) were nonsignificantly younger (mean±SD age 72±8.8 years) than patients reviewed between 12 and 24 months

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For patients with IPF, length of time in healthcare systems prior to review in an ILD clinic reflects disease severity and may impact upon patient outcome https://bit.ly/2TkO26r

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(n=41) (73.5±7.39 years) or after 24 months (n=63) (73.3±6.6 years). Patients reviewed in the ILD clinic within 12 months of primary care referral had a significantly preserved mean forced vital capacity (FVC) (83±22% predicted) compared to those reviewed between 12 and 24 months (75±22%, p=0.036), and >24 months (71±17%, p≤0.001), respectively (figure 1a). There was a trend to decreasing transfer capacity of the lung for carbon monoxide (T_{LCO}) with longer time to ILD clinic review; 49.7±16.7% predicted for <12 months *versus* 48.0±20.95% for 12–24 months and 45.6±13.3% for >24 months (p=0.089, <12 *versus* >24 months).

165 (67%) patients commenced antifibrotic therapy prior to the census date. Kaplan–Meier analysis identified that patients seen in the ILD clinic within 12 months from the initial primary care referral had significantly longer time to discontinuation of therapy compared to those seen at 12–24 or >24 months. The median (95% CI) time to discontinuation was 774 (508–1040) *versus* 531 (193–869) *versus* 390 (247–533) days, respectively, p=0.005 (figure 1b). Multivariate Cox regression analysis, including age at diagnosis, sex, smoking status, FVC % predicted, T_{LCO} % predicted and time to ILD clinic, identified a trend towards the time of first ILD clinic review being an independent predictor of time to discontinuation of antifibrotic therapy (12–24 months, HR 1.63 (95% CI 0.90–2.92, p=0.104), and >24 months, HR 1.50 (95% CI 0.95–2.51, p=0.077)), while age (HR 1.04, 95% CI 1.01–1.07; p=0.005) and T_{LCO} % predicted (HR 0.98, 95% CI 0.96–1.00; p=0.011) were significant independent predictors of time to antifibrotic discontinuation.

116 patients (47%) were deceased at the time of the census. Patients seen in the ILD specialist clinic within 12 months of primary care referral had significantly longer time to death compared to those reviewed at 12–24 and >24 months, with median survival 1558 days (95% CI 1217–1898 days) *versus* 883 days (95% CI 551–1215 days) *versus* 1063 days (95% CI 608–1518 days), respectively (p=0.022) (figure 1c). In multivariate regression analysis (age, smoking status, FVC % predicted, T_{LCO} % predicted to time to ILD clinic), time to ILD specialist review was not a significant independent predictor for mortality while age (HR 1.04, 95% CI 1.02–1.07; p=0.001) and T_{LCO} % predicted (HR 0.95, 95% CI 0.94–0.97; p<0.001) were significant independent predictors of mortality.

Research into IPF is typically undertaken in specialist centres, with a patient receiving a diagnosis of IPF at this point and the time taken in the healthcare system prior to this point often not available or recorded. Whilst primary care case finding strategies have been advocated, our findings identify that following primary care physician referral, there can be significant variation in referral to a specialist centre. Consistent with our findings, a recent review of Medicare patients identified that one-third of patients visited a respiratory physician more than 3 years prior to an IPF diagnosis [7].

Prior to the approval of antifibrotic therapies, Lamas *et al.* [8] identified that a longer delay from the onset of dyspnoea until evaluation at a tertiary care centre was associated with a higher rate of death from IPF independent of disease severity. We identified that patients with IPF who were reviewed in the ILD clinic within 12 months of primary care referral, compared to those seen later, had significantly preserved lung function, significantly longer total duration of antifibrotic therapy and significantly longer time to death.

Our study has a number of limitations. It is a two-centre retrospective study and includes the period following the approval of antifibrotics, although findings were consistent across two distinct primary care healthcare-based systems. Further investigation is required to understand the identified heterogeneity in

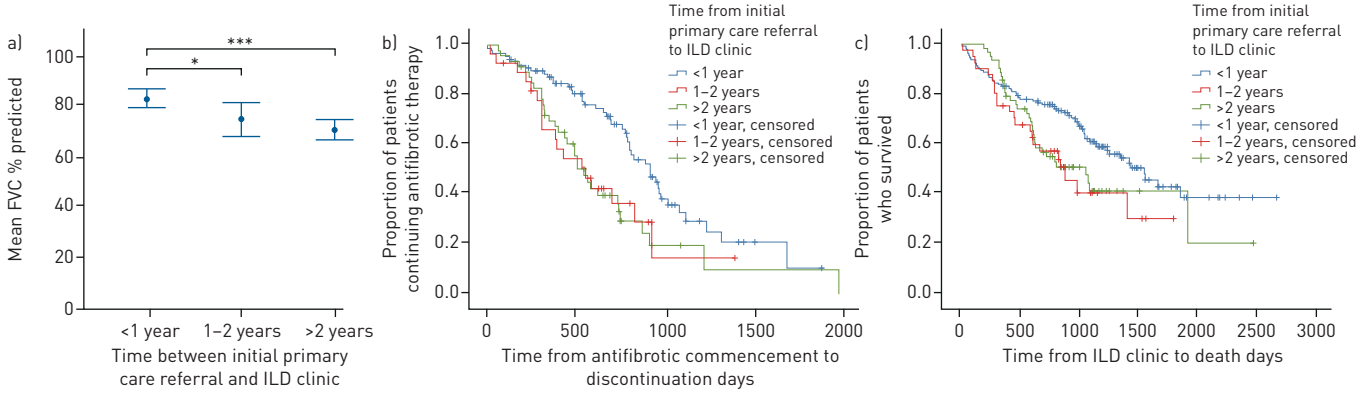

FIGURE 1 Patients diagnosed with idiopathic pulmonary fibrosis stratified by time from first primary care referral to first review within an interstitial lung disease (ILD) clinic. a) Error-bar chart showing the mean forced vital capacity (FVC) % predicted (error bars represent 95% confidence intervals). b) Kaplan–Meier analysis of antifibrotic duration and c) Kaplan–Meier analysis of survival. *: p<0.05; ***: p<0.001.

the patient pathway, with potential factors including resource limitations, alternative diagnoses or a period of observation prior to referral, and within the UK cohort, lung function outside of National Institute for Health and Care Excellence criteria for antifibrotic prescribing (FVC 50–80% predicted).

While the use of cancer service quality measures for the time within cancer pathways is well established to improve patient outcomes [9], no such clinical benchmarks are routine for patients with fibrotic lung diseases. Our findings identify a need for multinational prospective studies to investigate whether the introduction of such standards of care for the time taken within lung fibrosis diagnostic and treatment pathways could improve patient outcomes.

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References

1 Richeldi L, Varone F, Bergna M, *et al.* Pharmacological management of progressive-fibrosing interstitial lung diseases: a review of the current evidence. *Eur Respir Rev* 2018; 27: 180074.
2 Hoyer N, Prior TS, Bendstrup E, *et al.* Risk factors for diagnostic delay in idiopathic pulmonary fibrosis. *Respir Res* 2019; 20: 103.
3 Maher TM, Strek ME. Antifibrotic therapy for idiopathic pulmonary fibrosis: time to treat. *Respir Res* 2019; 20: 205.
4 Valeyre D. Towards a better diagnosis of idiopathic pulmonary fibrosis. *Eur Respir Rev* 2011; 20: 108–113.
5 Purokivi M, Hodgson U, Myllärniemi M, *et al.* Are physicians in primary health care able to recognize pulmonary fibrosis? *Eur Clin Respir J* 2017; 4: 1290339.
6 Maher TM, Swigris JJ, Kreuter M, *et al.* Identifying barriers to idiopathic pulmonary fibrosis treatment: a survey of patient and physician views. *Respiration* 2018; 96: 514–524.
7 Mooney J, Chang E, Lalla D, *et al.* Potential delays in diagnosis of idiopathic pulmonary fibrosis in Medicare beneficiaries. *Ann Am Thorac Soc* 2019; 16: 393–396.
8 Lamas DJ, Kawut SM, Bagiella E, *et al.* Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. *Am J Respir Crit Care Med* 2011; 184: 842–847.
9 National Cancer Intelligence Network, Public Health England. www.ncin.org.uk/cancer_information_tools/profiles/serviceprofiles Date last accessed 18 October 2019