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

**Take Home Message**: 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.

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The care of patients with idiopathic pulmonary fibrosis (IPF) has been transformed by the widespread approval of anti-fibrotic therapies(1){Richeldi, 2018, Pharmacological management of progressive-fibrosing interstitial lung diseases: a review of the current evidence}. Within primary care-based healthcare systems the diagnosis of IPF and commencement of anti-fibrotic therapy typically requires 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 multi-disciplinary team (MDT) discussion, a diagnosis of IPF is made and anti-fibrotic therapy may be commenced.

To maximise the benefit of anti-fibrotic therapy early diagnosis of IPF has been widely advocated (3-5). However whilst patient surveys and questionnaires consistently report significant delays in time 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 first primary care physician referral for symptom investigation to ILD specialist centre review and anti-fibrotic 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 Hospitals 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, anti-fibrotic commencement, anti-fibrotic 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.** Date of census was April 2018. The study was approved by the London-Hampstead Research Ethics Committee (REC 17/LO/2037). Statistical analysis was conducted using IBM-SPSS® version 25.

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

Patients reviewed in the ILD clinic within 12 months of primary care referral (n=142) were non-significantly younger (mean age 72 years, SD=8.8) than patients reviewed between 12-24 months (n=41) (73.5 years, SD=7.39) or after 24 months (n=63) (73.3 years, SD=6.6). Patients reviewed in the ILD clinic within 12 months of primary care referral had a significantly preserved mean FVC (83% predicted, SD=22) compared to those reviewed between 12-24 months (75%, SD=22, p=0.036) and >24 months (71%, SD=17, p=<0.001) respectively **(Figure 1A)**. There was a trend to decreasing TLCO% with longer time to ILD clinic review; 49.7% for <12 months (SD=16.7) versus 48.0% for 12-24 months (SD=20.95) and 45.6% for >24 months (SD=13.3) (p=0.089 <12months vs. >24months).

165 patients (67%) commenced anti-fibrotic therapy prior to census date. Kaplan-Meier analysis identified that patients seen in the ILD clinic within 12 months from initial primary care referral had significantly longer time to discontinuation of therapy compared to those seen at 12-24 months or greater than 24 months. Median time to discontinuation 774 days (95%CI 508-1040) vs. 531 days (95%CI 193-869) vs. 390 days (95%CI 247-533) respectively p=0.005 **(Figure 1B)**. Multivariate cox-regression analysis including age at diagnosis, gender, smoking-status, FVC% predicted, DLCO% predicted, and time to ILD clinic, identified a trend towards 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, whilst age (HR 1.04, 95% CI 1.01 – 1.07, p=0.005) and TLCO % 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 time of census. Patients seen in the ILD specialist clinic within 12months of primary care referral had significantly longer time to death compared to those reviewed at 12-24months and >24months, with median survival 1558 days (95% CI 1217-1898) vs. 883 days (551-1215) vs. 1063 days (608-1518) respectively p=0.022 **(Figure 1C)**. In multivariate regression analysis (age, smoking status, FVC% predicted, DLCO% predicted, time to ILD clinic), time to ILD specialist review was not a significant independent predictor for mortality whilst age (HR 1.04, 95% CI 1.02-1.07, p=0.001) and TLCO% 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 health care 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(8).

Prior to the approval of anti-fibrotic therapies Lamas *et al* 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(7). 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 retrospective and includes the period following the approval of anti-fibrotics, although findings were consistent across 2 distinct primary care healthcare based systems. Further investigation is required to understand the identified heterogeneity in 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 NICE criteria for anti-fibrotic prescribing (FVC 50-80% predicted).

Whilst 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 that prospective studies should be considered 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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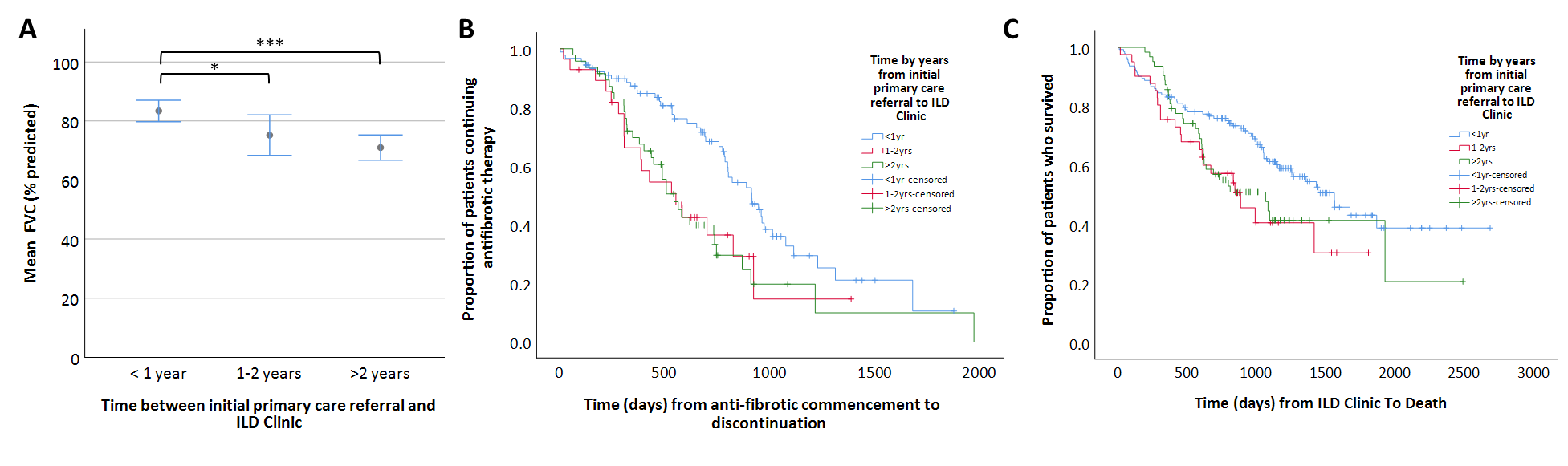
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**Figure 1:** Patients diagnosed with IPF stratified by time from first primary care referral to first review within an ILD clinic. **A)** Error-Bar chart showing mean FVC % predicted (error bars represent 95% confidence intervals, \* p<0.05 \*\*\* p<0.001) **B)** Kaplan Meier analysis of anti-fibrotic duration and **C)** Kaplan Meier analysis of survival.