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# Does the presence of connective tissue disease modify survival in patients with pulmonary fibrosis?

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**Summary**

*Objectives:* Previous studies into the survival differences between individuals with idiopathic pulmonary fibrosis and those with connective tissue disease associated pulmonary fibrosis (CTD-PF) have yielded mixed results. The aim of this study is to compare the survival of individuals with CTD-PF to those with idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) using data derived from The Health Improvement network, a large primary care database in the UK.
*Methods:* Incident cases of CTD-PF and IPF-CS between the years 2000—2009 were identified. Survival analysis was performed using Kaplan—Meier methods, stratified by type of connective tissue disease. Cox regression was then used to compare mortality rates between the groups, adjusting for age, gender and year of diagnosis.
*Results:* A total of 324 cases of CTD-PF and 2209 cases of IPF-CS were followed up over a mean period of 2.3 years. During this period, 113 (34.9%) cases of CTD-PF and 1073 (48.6%) cases of IPF-CS died. The mortality rates for cases with CTD-PF and IPF-CS were 123.6 per 1000 person years (95%CI: 102.8—148.9) and 229.8 per 1000 person years (95% CI: 216.4—244.0) respectively. After adjusting for age, sex and year of diagnosis, cases with CTD-PF had a better prognosis compared to those with IPF-CS (HR 0.76,95%CI: 0.62—0.92).
*Conclusion:* The prognosis of individuals with CTD-PF appears to be significantly better than those with IPF-CS, but remains an important cause of death in patients with connective tissue disease, and requires more effective treatment options.
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## Introduction

The pulmonary complications that are associated with connective tissue diseases are well recognised, but the clinical course of pulmonary fibrosis that accompanies this group of diseases is unclear. Despite these uncertainties, it is acknowledged that pulmonary fibrosis associated with connective tissue diseases is an important and serious complication that can be under-recognised. This is particularly true with rheumatoid arthritis, the commonest type of connective tissue disease, whereby almost 20% of individuals seen in hospital with this type of connective tissue disease will have some evidence of pulmonary fibrosis on high resolution computed tomography (HRCT).[1]

For a long time, patients with connective tissue disease associated pulmonary fibrosis (CTD-PF) were thought to be identical to those with cryptogenic fibrosing alveolitis (CFA) as they had similar radiological and histopathological patterns.[2,3] This resulted in both groups of patients being managed in the same fashion. There is now increased recognition that the underlying histology of lung fibrosis associated with connective tissue disease may vary from that of idiopathic pulmonary fibrosis (IPF), particularly in those individuals with scleroderma associated pulmonary fibrosis. This has resulted in individuals with CTD-PF being excluded from clinical trials involving cases with IPF, on the argument that individuals with CTD-PF suffer from a different disease entity, and hence should not be treated in the same way as individuals with IPF.

It is currently uncertain if there is a difference in survival between individuals with CTD-PF compared to those with IPF as studies in to the subject so far have yielded varying results.[4–7] We have previously looked at the differences in survival between cases of CTD-PF and cases with CFA using primary care data, which showed little difference in median survival between the two groups.[7] A significant time period has passed since our study, and with the reclassification of interstitial lung diseases, we have revisited the same question to re-evaluate the burden and outcome of recognised disease among individuals with CTD-PF.

The aim of this study is to compare the survival of individuals with idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) to those with connective tissue disease associated pulmonary fibrosis (CTD-PF) using data from a large general practice database.

## Methods

The dataset used in this study was extracted from The Health Improvement Network (THIN) which is a large computerised primary care database in the United Kingdom. Information is recorded as part of routine clinical care, after face to face consultations and following communication with secondary care referrals. THIN has previously been used to estimate incidence and mortality rates of idiopathic pulmonary fibrosis.[8,9] The version of THIN used in this study includes all information available until July 2009 from 446 general practices.

We identified all individuals who had a new diagnosis of pulmonary fibrosis made after the 1st of January 2000. Cases were included into our cohort if they had at least one recorded diagnosis of pulmonary fibrosis, the first recorded diagnosis was at least 12 months after their practice registration date and they were at least 40 years of age. This definition enabled us to capture incident cases of pulmonary fibrosis and the age cut off improved diagnostic specificity. We excluded individuals with a coexisting diagnosis of extrinsic allergic alveolitis, sarcoidosis, pneumoconiosis and asbestosis (see Appendix 1), because it is not clear in this subset which diagnosis was correct, and this approach provided a more conservative estimate of disease mortality rates. Individuals with pulmonary fibrosis and a coexisting diagnosis of connective tissue disease (Rheumatoid Arthritis/Systemic Sclerosis/Systemic Lupus Erythematosus/Polymyositis/Dermatomyositis/Mixed Connective Tissue Disease) were defined as having connective tissue disease associated pulmonary fibrosis (CTD-PF) (see Appendix 2). Individuals with pulmonary fibrosis and without a coexistent diagnosis of connective tissue disease were defined as having idiopathic pulmonary fibrosis clinical syndrome (IPF-CS). The data were grouped into five-year age bands over the age of 55 years.

All cases of pulmonary fibrosis were assigned a start date which was defined as the date of diagnosis, and a stop date that was defined as the earliest of either last date of data collection within THIN or date of death. We initially compared survival between cases with IPF-CS and CTD-PF, and then repeated the analysis, stratifying cases of CTD-PF by type of connective tissue disease using Kaplan–Meir methods. We used Cox regression modelling to compare survival between cases with IPF-CS and CTD-PF and then repeated the analysis, stratifying cases of CTD-PF by type of connective tissue disease, adjusting for year of diagnosis, age categories and gender.

Stata version 11 (Texas) was used for all statistical analyses and likelihood ratio tests for all hypotheses testing.

## Results

The total number of incident cases of pulmonary fibrosis over the study period was 2533, of which 324 (13%) had a coexistent diagnosis of connective tissue disease. Within this subset of connective tissue disease associated pulmonary fibrosis (CTD-PF), rheumatoid arthritis (8.4%) and scleroderma/systemic sclerosis (1.6%) were the most common coexistent diagnoses (see Table 1). Cases with CTD-PF were predominantly female compared to cases with idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) (56.5 vs 37.1%; chi squared test $p < 0.0001$). Cases with CTD-PF were also younger at time of diagnosis compared to those with IPF (mean age at time of diagnosis 68 years vs 74 years, $t$ test $p < 0.0001$).

The mean follow up period after diagnosis was 2.3 years and during this period 1073 (48.6%) of cases with IPF-CS and 113 (34.9%) of all cases with CTD-PF died. This equates to an overall crude mortality rate of 229.8 per 1000 person years (95% Confidence Interval: 216.4–244.0) in individuals with IPF-CS and 123.6 per 1000 person years (95% Confidence Interval: 102.8–148.7) for all cases with CTD-PF (see Table 2 for mortality rates stratified by type of connective tissue disease).

**Table 1** Demographics of incident cases of pulmonary fibrosis in The Health Improvement Network dataset.

| Connective tissue disease | Cases (n = 2533) | Mean age (years) at time of diagnosis (standard deviation) | Percentage of cases that are female |
|---|---|---|---|
| None | 2209 (87.2%) | 74.4 (10.1) | 37.1% |
| Rheumatoid arthritis | 213 (8.4%) | 69.7 (9.2) | 51.2% |
| Scleroderma/Systemic sclerosis | 40 (1.6%) | 61.8 (11.1) | 75.0% |
| Other (SLE, dermatomyositis, polymyositis, mixed connective tissue disease) | 71 (2.8%) | 66.2 (10.7) | 62.0% |

The median survival for cases with IPF-CS was approximately 3.1 years compared to 6.5 years in cases with CTD-PF. This difference in survival was statistically significant ($p = 0.0043$) (see Fig. 1). Using Cox regression modelling, we found that after adjustment for age, sex and year of diagnosis, the presence of connective tissue disease had a beneficial effect on mortality in individuals with pulmonary fibrosis (Hazard Ratio 0.76, 95% Confidence Interval: 0.62−0.92). This reduction in mortality was still evident when the analysis was repeated, stratifying those with CTD-PF by type of connective tissue disease. (see Table 2, Fig. 2).

## Discussion

Using data from primary care, we found a significant difference in survival between individuals with idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) and those with connective tissue disease associated pulmonary fibrosis (CTD-PF), after adjusting for age, year of diagnosis and sex. We have also found that the presence of connective tissue disease is more common among individuals with pulmonary fibrosis within our current dataset (13%) in comparison to the primary care dataset used in our previous study (10%) ten years ago.[7]

One of the strengths of our study is the large number of cases included into our dataset and the long period of time over which this information was obtained. This allows us to give a detailed analysis of mortality rates and median survival stratified by type of connective tissue disease. Studies of this length and magnitude would be difficult to conduct in a clinical setting. Historically, studies into pulmonary fibrosis associated with connective tissue disease are conducted in tertiary referral centres and have only small numbers of cases included in the dataset.[1,4,10]

A potential weakness of the study is the validity of diagnoses of pulmonary fibrosis and connective tissue disease in our dataset. We have previously shown the diagnosis of pulmonary fibrosis in primary care data to be valid.[8,11,12] We acknowledge that cases within our dataset are likely to represent the full spectrum of chronic fibrotic lung disease of unknown aetiology, the majority of which will have idiopathic pulmonary fibrosis. For this reason, we think it is more appropriate to label these individuals as having idiopathic pulmonary fibrosis clinical syndrome (IPF-CS). We also believe that it is unlikely for an individual to have a diagnosis of pulmonary fibrosis recorded in primary care without confirmation from a specialist secondary opinion. Further reassurance of the diagnostic validity of pulmonary fibrosis is demonstrated by the fact that the median survival of individuals with IPF-CS in this study is similar to other population based studies.[12−15] We believe the same high validity applies for the diagnosis of connective tissue disease within our dataset. Although we have not formally validated the diagnosis of connective tissue disease within this dataset, we are reassured by previous studies that have demonstrated high validity of a recorded diagnosis of connective tissue disease in the General Practice Research Database (GPRD),[16,17] a computerised primary care database in the United Kingdom that is similar to The Health Improvement Network (THIN). Both databases record patient information and code data in a similar fashion, and hence we would expect the same high validity of recording shown in GPRD to apply to THIN. In addition to this, we also believe that a diagnosis of connective tissue disease would typically be established by a rheumatologist and it is unlikely that such a diagnosis would be recorded without confirmation from secondary or tertiary care.

Another potential weakness is the potential overlap between the different types of connective tissue disease. It

**Table 2** Mortality rates and Cox regression modelling in individuals with pulmonary fibrosis stratified by type of connective tissue disease.

| Connective tissue disease | Number of deaths | Person years | Mortality rate (95%CI)per 1000 person years | Hazard ratio[a] (95% CI) | Median survival (years) |
|---|---|---|---|---|---|
| None | 1073 | 4669.6 | 229.8 (216.4−244.0) | 1.0 | 3.1 |
| Rheumatoid arthritis | 75 | 564.5 | 132.9 (106.0−166.6) | 0.75 (0.59−0.96) | 6.6 |
| Scleroderma/Systemic sclerosis | 9 | 126.9 | 70.9 (36.9−136.3) | 0.55 (0.28−1.06) | 8.8 |
| Other (SLE, dermatomyositis, polymyositis, mixed connective tissue disease) | 29 | 222.5 | 130.3 (90.6−187.5) | 0.86 (0.59−1.25) [b]$p = 0.019$ | 5.6 $p = 0.0217$ |

a Hazards ratios adjusted for year of diagnosis, age and gender.
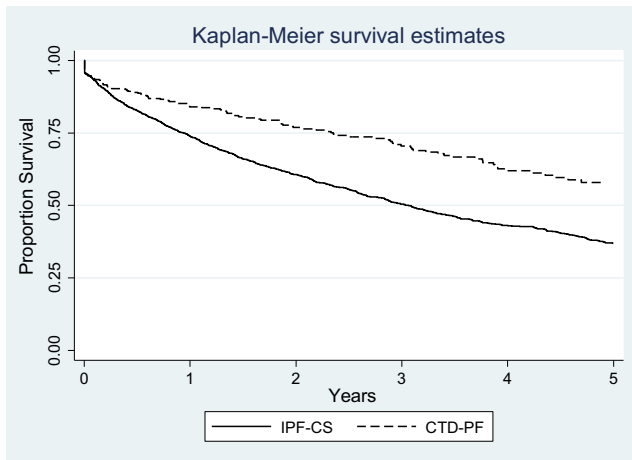b p value for likelihood ratio test.

**Figure 1**  Kaplan—Meir plot of survival among cases of idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) compared to cases of connective tissue disease associated pulmonary fibrosis (CTD-PF).

has been observed in clinical practice that individuals can move between the different subtypes of connective tissue disease or have their diagnosis altered after an initial prodrome. The overall aim of our study was to investigate the difference in survival between individuals with IPF-CS and those with CTD-PF and to see if any difference in survival was altered after stratification by type of underlying connective tissue disease. Hence, any misclassification in the subtype of connective tissue disease associated with pulmonary fibrosis is unlikely to alter our findings. We are also unable to exclude the possibility that a small number of cases within our CTD-PF subset may have pulmonary fibrosis secondary to treatment received for the underlying connective tissue disease. However, this does not change our conclusion that individuals with pulmonary fibrosis associated with connective tissue disease have a better prognosis compared to those who do not have a coexisting diagnosis of CTD.

There is limited data available on median lengths of survival stratified by type of connective tissue disease. We
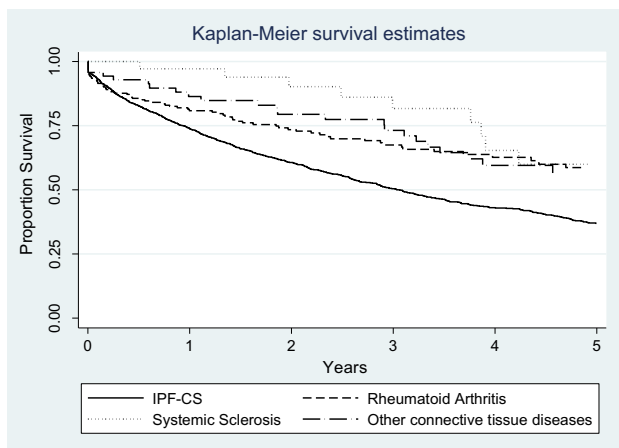


**Figure 2**  Kaplan—Meir plot of survival amongst cases of pulmonary fibrosis stratified by type of underlying connective tissue disease.

have previously looked at the differences in survival between cases with lone cryptogenic fibrosing alveolitis (CFA) and cases with connective tissue disease associated fibrosing alveolitis (FA-CTD) using data from primary care.[7] The previous study showed no difference in survival between the two groups (median survival 2.6 years vs 2.4 years). The overall prevalence of connective tissue disease in our current dataset is slightly higher at 13% compared to 10% in our previous cohort of cases. This raises the possibility that the difference in survival could be due to increased case ascertainment and in individuals with connective tissue disease, due to increased recognition of pulmonary fibrosis by rheumatologists. The introduction of a multidisciplinary approach to the management of patients with connective tissue disease has resulted in rheumatologists being more aware of the pulmonary complications that can occur. It is also more common for patients with connective tissue disease to undergo baseline radiological investigations prior to commencing disease modifying treatment, as many of these drugs have toxic pulmonary side effects. The widespread use of high resolution computed tomography scans (HRCT) to aid the diagnosis of suspected interstitial lung disease raises the possibility that milder cases of pulmonary fibrosis are being identified within the CTD-PF group. If milder cases of pulmonary fibrosis are being diagnosed in the CTD-PF group, this would offer an explanation as to why we have found a difference in survival within this cohort when previously there was no significant difference in survival.

Previous studies done to date on the potential differences in survival have yielded mixed results and one of the limitations is that most of them have only a small numbers of patients. A study in Newcastle followed up patients with rheumatoid arthritis associated interstitial lung disease(RA-ILD) and with cryptogenic fibrosing alveolitis over 5 years and found that median survival was significantly longer in the RA-ILD group.[4] This differs from the findings of Early Rheumatoid Arthritis Study (ERAS) who reported a median survival of 3 years following a diagnosis of RA-ILD within their cohort. This median survival is similar to reported lengths of survival within IPF cohorts.[5]

Studies have consistently shown that the prognosis of pulmonary fibrosis associated with systemic sclerosis or scleroderma is better than other connective tissue diseases, and certainly better compared to IPF, and our findings in this study confirm this.[10,18] It has been speculated that the reason behind this difference in survival either stems from lead time bias or that pulmonary fibrosis secondary to scleroderma is a completely different disease entity to IPF. In a study conducted in the Brompton Hospital, researchers matched patients with lone CFA and those with scleroderma associated pulmonary fibrosis on the basis of CT scans to try and remove the problem of lead time bias.[18] They found that the cases with scleroderma associated lung fibrosis had a better outcome compared to those with lone CFA.[18] It has been established that the predominant histopathological pattern in patients with scleroderma associated pulmonary fibrosis is non-specific interstitial pneumonia (NSIP)[19] which may have a better prognosis. In comparison, the majority of cases with pulmonary fibrosis associated with rheumatoid arthritis have been shown to have a usual interstitial pneumonia (UIP),[20] similar to the histopathological pattern found in IPF. The

importance of the underlying histological pattern as a prognostic factor in patients with rheumatoid arthritis associated pulmonary fibrosis remains unclear. Recently, a study among patients with rheumatoid arthritis associated interstitial lung disease reported that the survival between patients with rheumatoid arthritis and a definite UIP pattern on their HRCT was worse in comparison to those with a non-UIP pattern.[6] The same study also suggested that the survival between the rheumatoid arthritis UIP cases was similar to patients with idiopathic pulmonary fibrosis. These findings are different to those reported by Park and colleagues who found that the prognosis of patients with connective tissue disease and a UIP histopathological pattern was better compared to those with IPF.[21]

In summary, our study suggests that individuals with connective tissue disease pulmonary fibrosis (CTD-PF) have a better prognosis than individuals with idiopathic pulmonary fibrosis clinical syndrome (IPF-CS). This could be due to the fact that interstitial lung disease is now increasingly recognised as a complication of connective tissue disease and hence milder cases of pulmonary fibrosis are being diagnosed. The fact remains that both groups of patients have a considerable burden of morbidity and mortality in comparison to the general population. Aside from cyclophosphamide, which has been shown to have some modest effect on lung function and symptoms in patients with scleroderma,[22] there are no other disease modifying drugs that have been proven effective in treating this subgroup of patients. Given the fact that individuals with CTD-PF are now excluded from clinical trials involving patients with IPF, it is necessary to push forward in closing the gaps in our knowledge between these two groups of patients so we can understand how best to manage them.

## Ethics

Nottingham Ethics Committee.

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## Disclosure

The authors declare no conflicts of interest.

## Conflict of interest statement

All authors on this manuscript declare no conflicts of interest.

## Appendix
### Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.rmed.2011.08.015.

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