The increasing mortality of idiopathic pulmonary fibrosis: fact or fallacy?

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There are likely multiple reasons that IPF-related mortality appears to be increasing in most European countries http://ow.ly/Maty30gRrDl

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There is no debate that idiopathic pulmonary fibrosis (IPF) is a devastating disease that has a significant impact on patient morbidity and mortality. Patients with IPF experience symptoms throughout most of their disease, with disabling dyspnoea and cough that reduce quality of life. Most IPF patients eventually succumb to respiratory failure with a median survival of approximately 3 years from the time of diagnosis [1]. Two antifibrotic medications slow progression of IPF [2–5]; however, it has yet to be shown whether IPF mortality will change substantially with the availability of these therapies.

IPF qualifies as a rare disease in most regions [6] but recent studies have suggested that the incidence and prevalence of IPF are increasing over time [7–9]. It is unknown whether this increasing incidence simply reflects earlier detection of patients with milder disease, a change in diagnostic criteria or labelling of patients, or a true increase in the number of patients who develop IPF. Related to this, it is also unclear whether this increasing incidence has translated into a higher rate of IPF-related mortality. These are important questions for regulatory agencies and healthcare organisations that need to ensure appropriate resources are available to support this complex group of patients.

A study by Marshall *et al.* [10] published in this issue of the *European Respiratory Journal* describes trends in IPF mortality between 2001 and 2013, based on deaths recorded in the World Health Organization (WHO) mortality database. This large dataset clearly shows that age-standardised IPF-related mortality is increasing over time in most European countries, adding to a recent study reporting similar findings in several European and non-European nations [11]. The present study also identifies significant heterogeneity in IPF-related mortality across countries, ranging from less than 1 per 100 000 for both sexes in Croatia, Lithuania and Romania to 12 per 100 000 for males in the United Kingdom. However, it is important to note that this study does not explain why IPF mortality appears to be increasing over time, nor does it identify which factors account for these differences. In addition, this study does not provide data on the risk of mortality for an individual IPF patient and the reported findings are therefore more important for their overall population impact rather than for patient-specific prognostication.

As discussed by the authors, there are two main possibilities for the finding that IPF mortality is increasing over time, either a worsening prognosis for IPF in recent years, or, more likely, that greater numbers of patients are now being labelled with IPF and consequently a higher number of deaths are

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being attributed to the disease. The first possibility, essentially that the median survival of patients with IPF has worsened in recent years, could conceivably be related to more frequent use of harmful medications recommended in consensus guidelines published in 2000 [12]. However, this seems unlikely given the consistent increase in mortality rate over time in most countries, including for the most recent years of the current study's observation period, which followed both the 2011 guideline recommendation against these therapies and a 2012 publication showing clear harm from immunosuppressive therapy in patients with IPF [1, 13].

To further illustrate this point we searched Medline for "idiopathic pulmonary fibrosis", combined with either "mortality" or "survival", in order to identify publications that reported median survival of well-characterised, clinic-based IPF cohorts. We identified a total of 1494 citations between January 01, 2000 and November 10, 2017 after limiting results to articles in English with an available abstract. From these, we identified 24 distinct cohorts that reported median survival for at least 50 consecutively enrolled IPF patients over a specified date range. These cohorts had an overall median survival of only 3.2 years despite many of the patients having only mild-to-moderate IPF. Although meta-regression of these heterogeneous data was not possible, median survival increased by 0.09 years for each 1-year increase in the mean year of study enrolment, as determined by using an unweighted linear regression with adjustment for baseline diffusing capacity of the lung for carbon monoxide (*D*LCO) as an indicator of overall disease severity (p=0.015) (figure 1). This finding suggests that the increasing IPF-related mortality in the study by MARSHALL *et al.* is unlikely to be caused by a worsening prognosis at an individual patient level.

The alternative explanation for the finding that IPF-related mortality is increasing is that IPF is being identified more frequently in recent years, with a greater number of deaths subsequently attributed to this diagnosis. The authors discuss several potential reasons for an increasing prevalence of IPF [10]. One of these possibilities is that major IPF risk factors are becoming more common over time, resulting in a higher actual prevalence of IPF in recent years. However, the two most likely possibilities, an aging population and an increasing rate of cigarette smoking, are largely refuted by the age-standardised analysis of the current study as well as epidemiological data showing stable or declining smoking rates in most European countries since 1980 [14]. Neither of these possibilities therefore appears to account for the magnitude of change in IPF-related mortality seen in many European countries over the relatively short study period (2001–2013). In fact, it is more likely that increasing IPF-related mortality is predominantly driven by a greater number of patients being labelled with IPF without there being a true change in IPF prevalence. Again there are several potential reasons for this, as discussed by the authors, most of which relate to increased detection rates and diagnosis of IPF patients earlier in the course of their disease. On

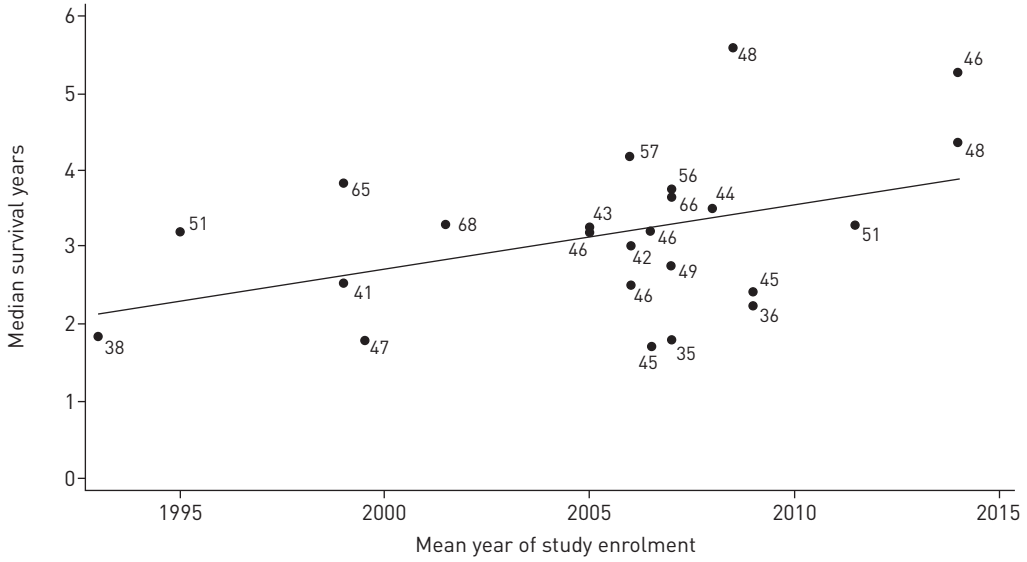

FIGURE 1 Association of median survival and mean year of study enrolment. Data are shown from 24 selected studies that included a total of 5013 patients with a weighted mean age of 67 years, forced vital capacity (FVC) of 72% and diffusing capacity of the lung for carbon monoxide (*D*LCO) of 47%. The mean *D*LCO is shown for each cohort. With adjustment for baseline *D*LCO, the median reported survival increased by 0.09 years for each 1-year increase in the mean year of study enrolment based on an unweighted linear regression analysis (p=0.015). Median survival among all cohorts was 3.2 years.

the face of it, earlier detection would not necessarily lead to higher IPF-related mortality but there are still potential mechanisms by which earlier diagnosis could increase the number of patients with cause of death attributed to IPF. For example, once IPF is identified in the patient record as a comorbid disease both physicians and other individuals responsible for completing and coding death certificates are more likely to attribute death to a highly mortal disease, like IPF, even if the IPF was mild in severity and not a clear cause of death. An additional factor is that clinicians may be more likely to assign an IPF diagnosis with the recent availability of antifibrotic therapies. This could simply be due to increased awareness of IPF or to reduced nihilism concerning its management now that there are approved therapies. Another possibility is that IPF incidence and prevalence can increase subsequent to clinicians shifting diagnostic thresholds for IPF in the context of new diagnostic criteria and an evolving evidence base, or potentially as a consequence of regional funding criteria for antifibrotic therapy. Specifically, clinicians may label patients with a more confident diagnosis than is fully justified in order to satisfy funding criteria for antifibrotic therapy in patients who do not quite meet formal diagnostic criteria (the appropriateness of this practice is an entirely different question!). These possibilities will likely impact future studies but will have had little impact on the findings of the current study given the relatively recent approval of antifibrotic therapy in Europe.

In summary, the study by Marshall *et al.* [10] is a significant step forward in improving our understanding of IPF epidemiology and its societal impact; however, these findings also raise several important questions that reflect on the limitations of large administrative databases. In the end, there are likely to be multiple explanations that account for increasing IPF-related mortality over time in most European countries. These limitations and uncertainties do not diminish the impact of these findings but instead provide direction for the additional studies that are needed to clarify the reasons for this change in mortality. Future studies with more granular data are needed to better inform on this changing epidemiology and to accurately predict IPF-related mortality at a population level and thus justify the appropriate resources necessary to care for this complex group of patients.

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