The association of lung cancer with pulmonary fibrosis

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To the Editor:

Idiopathic pulmonary fibrosis (IPF) shares several pathogenetic similarities with other fibrotic lung diseases. Patients with IPF are considered to have a higher risk of concomitant lung cancer (LC) as a result of similar risk factors which include older age, smoking and male sex. Patients with IPF have a poor prognosis with a median survival time ranging from 2 to 5 years [1]. It is not yet known if LC is a significant contributor to deaths in those with IPF. To address this question, we evaluated the association between LC and IPF compared to all non-IPF decedents in the USA from 2004 to 2018.

In this large retrospective study, we used the Centers for Disease Control and Prevention Multiple Cause of Death Database. This database collects from death certificates of all US residents information related to their underlying cause of death (UCD) and other conditions contributing to their death [2]. Similar to previous studies, decedents with LC and IPF were identified using International Classification of Diseases (10th Revision) codes [3, 4]. Those <45 years old were excluded as the diagnoses of IPF and LC were rare in this age group. In comparing those with and without IPF, logistic regression was utilised to obtain the adjusted odds ratio, as in prior studies [5]. To analyse the temporal trends, Poisson regression modelling was used (negative binomial regression was used for overdispersed data). A p-value of <0.05 was considered statistically significant. SPSS version 25 (IBM Corp, Armonk, NY, USA) software was used for the analyses.

Overall, there were 35 615 442 deaths in the USA from 2004 to 2018. LC was present in 3.38% of decedents with IPF and 6.90% of decedents without IPF. The presence of LC was significantly lower in decedents with IPF (OR 0.47, 95% CI 0.46–0.48) from 2004 to 2018. The odds of LC were lower in decedents with IPF in all age groups and races, and both sexes (table 1) and in the year-by-year analysis (not shown). The odds of LC remained lower in IPF decedents even after adjusting for sex and age (OR 0.50, 95% CI 0.49–0.50) or for sex and race (OR 0.47, 95% CI 0.46–0.47) using logistic regression.

We also performed a reverse analysis to examine the proportion of LC decedents with IPF (0.48%) compared to non-LC decedents with IPF (1.01%). This also showed that the odds of having IPF in decedents with LC is lower (OR 0.47, 95% CI 0.46–0.48).

The mortality rate (crude) per 100 000 population from LC was 132 (156 in males and 111 in females). The mortality rate from LC decreased significantly in those without IPF and was unchanged in those with IPF from 2004–2018. As a result, the overall odds of LC with IPF showed a continued rise from 2010 to 2018 (0.43 in 2010 and 0.58 in 2018). In decedents without IPF, a negative trend was noted in LC mortality rates in both sexes, and all age groups and races. In decedents with IPF, a decline in mortality rate was noted in the 65–74-year age group, and an increase in mortality rate was noted in those ⩾75 years old and Hispanic people.

LC was listed as the UCD in 94.2% of LC decedents without IPF. In decedents with both LC and IPF, the UCD was listed as LC in 75.9% and IPF in 20.8%. In the inpatient setting, the percentage of deaths was higher in the LC decedents with IPF compared to those without but was lower in the home, hospice and nursing home settings. For both groups, the deaths in hospice increased significantly during the study period.

Our study is the largest to date comparing the association between IPF and LC. In our study, the prevalence of LC was 53% lower in decedents with a listed diagnosis of IPF compared to those without.

Shareable abstract (@ERSpublications)
In this study using a large database of US decedents, the overall presence of lung cancer was lower in those with idiopathic pulmonary fibrosis compared to those without idiopathic pulmonary fibrosis https://bit.ly/30d6dC4

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TABLE 1 Prevalence of lung cancer (LC) in decedents with and without idiopathic pulmonary fibrosis (IPF)

Variable	Decedents without IPF[#]					Decedents with IPF[¶]					OR[+] (95% CI)
	Total deaths	LC present	Deaths with LC, % total	LC mortality rate, % change 2004–2018	p-value for trend	Total deaths	LC present	Deaths with LC, % total	LC mortality rate, % change 2004–2018	p-value for trend	
Sex											
Female	18 002 346	1 087 001	6.04	−23.4	<0.001	160 389	3985	2.48		0.30	0.40 (0.38–0.41)
Male	17 263 723	1 346 703	7.80	−41.0	<0.001	188 984	7816	4.13		0.32	0.51 (0.50–0.52)
Age, years											
45–54	2 677 125	164 280	6.14	−48.4	<0.001	10 476	294	2.81		0.26	0.44 (0.39–0.50)
55–64	4 797 685	482 281	10.05	−34.8	<0.001	32 043	1533	4.78		0.12	0.45 (0.43–0.47)
65–74	6 566 472	767 181	11.68	−42.0	<0.001	76 494	4070	5.32	−19.1	0.04	0.42 (0.41–0.44)
75–84	9 574 477	729 948	7.62	−27.4	<0.001	126 992	4327	3.40	+22.3	0.001	0.43 (0.41–0.44)
⩾85	11 650 310	290 014	2.49	−9.2	<0.001	103 368	1577	1.53	+21.8	<0.001	0.61 (0.58–0.64)
Race											
Native-American	186 275	11 424	6.13	−12.4	0.02	2775	84	3.03		0.52	0.48 (0.38–0.59)
Asian	738 695	49 661	6.72	−17.0	<0.001	8726	214	2.45		0.85	0.35 (0.30–0.40)
Black	3 851 698	250 914	6.51	−32.4	<0.001	18 707	642	3.43		0.34	0.51 (0.47–0.55)
White	28 498 575	2 039 321	7.16	−23.1	<0.001	291 706	10 302	3.53		0.09	0.47 (0.47–0.48)
Hispanic	1 902 714	77 398	4.07	−31.2	<0.001	26 903	538	2.00	+35.0	0.03	0.48 (0.44–0.52)
UCD											
IPF	NA	NA	NA	NA	NA	NA	1863	NA		0.92	NA
LC	NA	2 292 943	NA	−28.7	<0.001	NA	8956	NA		0.40	0.19 (0.18–0.20)
Pneumonia	NA	1023	NA		0.14	NA	19	NA		1.00	3.83 (2.43–6.04)
Place of death											
Inpatient	NA	700 652	NA	−45.8	<0.001	NA	5625	NA		0.44	2.25 (2.17–2.33)
Home	NA	993 905	NA	−22.5	<0.001	NA	3687	NA		0.11	0.66 (0.63–0.68)
Hospice	NA	211 291	NA	+1130.2	<0.001	NA	847	NA	+8880.0	<0.001	0.81 (0.76–0.87)
Nursing home	NA	331 624	NA	−43.0	<0.001	NA	896	NA		0.55	0.52 (0.49–0.56)

International Classification of Diseases (10th Revision) (ICD-10) codes used for underlying cause of death (UCD) were pulmonary fibrosis (J84.1 and J84.9), lung cancer (C34–C34.9) and pneumonia (J09–J18.9). Similar to prior studies, ICD-10 codes were used to identify and exclude patients with underlying connective tissue diseases (M32–M35, M35.1, M35.5, M35.8–M36 and M05–M08.9), radiation fibrosis (J70.1), sarcoidosis (D86–D86.9), pneumoconiosis (J60–J65) and hypersensitivity pneumonitis (J67–J67.9). If no data are shown for % change in rate, the regression analysis of the data did not indicate a significant departure from a linear trend during the analysis period. NA: not applicable. [#]: n=35 266 069; [¶]: n=349 373; [+]: the overall odds of lung cancer with IPF compared to without IPF.

This finding was observed irrespective of sex, age group, race or year of death. Our findings are consistent with a previous study by Wells and Mannino [6] that reported LC in 4.8% of decedents with IPF compared to 6.5% decedents in the general US population from 1979 to 1991.

Possible explanations for the lower odds of LC with IPF are a lower prevalence of LC in patients with IPF or improved survival in those with LC and IPF. Previous studies have shown that patients with both IPF and LC have a shorter survival time [7, 8]. This is likely due to surgical procedures and treatments for LC, which have both been associated with acute exacerbations of IPF [7]. As noted in this study, the mortality rates for LC patients without IPF improved over the study period, but in those with IPF and LC, a similar improvement was not noted. Therefore, the likely explanation for our findings is the lower prevalence of LC in patients with IPF. In contrast to our findings, two previous studies in European cohorts reported an increased incident rate of LC in patients with IPF compared to the general population [9, 10]. A systematic review evaluating comorbidities in IPF reported a wide range of LC prevalence rates ranging from 3% to 48% [11]. The majority of these studies were single-centred with small sample sizes, and therefore selection and referral bias could have influenced the results. Our study population was significantly larger than those in previous studies. In IPF compared to the general population, the higher LC incident rate but lower prevalence could also be explained by the shorter survival time associated with IPF. Ascertainment and surveillance biases may have contributed to the higher reported incidence since IPF patients are more likely to seek evaluation sooner due to respiratory symptoms and thus have chest computed tomography scans performed more frequently. Our non-IPF decedent group also probably represents a sicker population (similar to the IPF patients) and is, therefore, a more appropriate comparison in contrast to the prior studies where the control group was a live population. Presumably, the frequency of LC among decedents exceeds that in a live population.

In a recent study using the UK IPF registry, LC was present in only 0.6% of patients with IPF [12]. Similar to our estimates, in recent studies of IPF patients admitted to the intensive care unit, LC was reported in 2.3–3.5% of patients [13, 14]. Since both LC and IPF have a short survival time, the lower prevalence reported in these studies and ours is likely to be because those with LC or IPF die before the other condition can develop. Unfortunately, we did not have data on the duration of the disease to determine whether long-term IPF patients have different rates of LC prevalence than short-term patients. However, given that our study extended over a 15-year period, we believe that our reported rates are reliable.

Consistent with other studies, we noted declining LC-related mortality rates in the non-IPF decedents [15]. However, in the IPF decedents, the overall rates were unchanged. The decreasing mortality rates in the 65–74-year age group is probably due to improved survival of patients with both IPF and LC in this age group. The increasing mortality rates in those $\geqslant$75 years old are probably due to improved diagnosis or increased documentation of both diseases. The increase in LC rates in Hispanic people with IPF is probably due to improved access to medical care facilitated by the Affordable Care Act.

We noted that the odds of having LC listed as the UCD was even lower in IPF decedents compared to those without IPF. This is likely to be because a significant percentage of IPF patients experience an acute exacerbation and/or pneumonia prior to the death and are therefore likely to have those diagnoses listed as the UCD instead of LC. In the IPF and LC group, 20.8% of decedents had IPF listed as the UCD. Although only a small percentage of decedents had pneumonia listed as the UCD in both groups (0.24% of LC decedents without IPF and 1.16% of LC decedents with IPF), the odds ratio was higher in the IPF group (3.83, 95% CI 2.43–6.04).

The strength of this study is the evaluation of the whole US population and the large numbers. The main drawback is that we are not able to verify the accuracy of the diagnosis or the documentation on the death certificate. Since the diagnosis of IPF may require multidisciplinary discussion and/or surgical lung biopsy, it is possible that under-reporting and misdiagnosis may have occurred. LC in early stages or remission could also be under-reported; however, this would probably not be affected by whether a person has IPF or not. Our findings are unlikely to be due to random chance alone given the large numbers. To support this claim, we analysed the prevalence of LC in decedents with COPD, a pulmonary condition that is associated with a higher prevalence of LC. The overall odds of having LC were higher in those with COPD (OR 1.59, 95% CI 1.58–1.60) compared to those without COPD. In summary, we noted that the prevalence of LC is lower in decedents with IPF compared to those without IPF.

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Author contributions: N. Jeganathan and M. Sathananthan conceived the idea and designed the study. All authors acquired the data. N. Jeganathan analysed the data. The manuscript was drafted by all authors, and all authors contributed to the data interpretation and edited the manuscript.

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