Mortality in combined pulmonary fibrosis and emphysema patients is determined by the sum of pulmonary fibrosis and emphysema

To the Editor:

Emphysema is one of the most common pulmonary comorbidities of idiopathic pulmonary fibrosis (IPF), presenting in about one-third of IPF patients [1]. The term combined pulmonary fibrosis and emphysema (CPFE) has been used to describe a potential phenotype characterised by the coexistence of upper lobe-predominant emphysema, lower lobe-predominant fibrosis and relative preservation of lung volumes (forced vital capacity; FVC) in the context of a disproportionately reduced gas transfer (diffusing capacity of the lung for carbon monoxide; D_{LCO}) [1–3]. With regard to patient survival, it remains unclear whether mortality in patients with CPFE reflects the cumulative effects of two disease processes (emphysema and fibrosis), or whether CPFE represents a distinct disease phenotype where outcome is worse than the sum of disease parts (emphysema and fibrosis).

In a previous single centre study [4], we demonstrated that the CPFE phenotype (defined as the presence of emphysema on computed tomography (CT)) in IPF patients did not independently predict mortality once summed visual lobar CT extents of emphysema and interstitial lung disease (ILD) had been considered. Put another way, survival in CPFE patients was the same as for IPF patients without emphysema, once the total extents of emphysema and fibrosis on CT were considered. The findings suggested that there was no additional synergistic impact on mortality when both disease patterns (emphysema and ILD) co-existed. Past analyses of CPFE populations have shown conflicting results regarding the impact of CPFE on mortality [3, 5–11] and may relate to heterogeneous study populations, varied CPFE inclusion criteria, and inconsistent adjustment for disease severity in mortality models [12]. The aim of the current study was to confirm our earlier study findings [4] that a CPFE phenotype has no independent mortality effect beyond that described by emphysema and ILD extent. The question was evaluated using various definitions of CPFE that have been considered in the literature, with results run on independent validation datasets.

We evaluated two separate cohorts of IPF patients diagnosed by a multidisciplinary team. Cohort 1: 220 patients from two centres in Turkey and Italy, 102 deaths observed; cohort 2: 310 patients from two centres in the Netherlands and England, and from the Australian IPF Registry, 169 deaths observed. CT extents of emphysema and ILD were separately scored, averaged across the lobes and then summed to develop a total lung percentage for both patterns as previously described [4]. We also performed a sub analysis in IPF patients that fulfilled drug trial inclusion criteria (D_{LCO} >30% predicted and FVC >50% predicted) in cohort 1 (n=150, 57 deaths observed) and cohort 2 (n=239, 117 deaths observed). The median and interquartile ranges of emphysema extent were 4.17% and 11.67% in cohort 1; 2.92% and 8.33% in cohort 2. In the populations qualifying for drug trials: median and interquartile ranges of emphysema extent were 3.33% and 10.00% in cohort 1; 2.50% and 7.50% in cohort 2.

In each cohort, multivariable mixed-effects Cox regression models were used to evaluate whether the CPFE phenotype had any impact on outcome after considering the sum of visual CT extents of ILD and emphysema: VILDemph. To ensure that VILDemph and the various expressions of CPFE could be applied in the same model, we tested for collinearity using univariable linear regression. No strong collinearity was
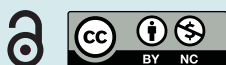
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In patients with combined pulmonary fibrosis and emphysema, emphysema and fibrosis do not have a synergistic effect that results in worsened survival when compared to IPF patients without emphysema https://bit.ly/35EJMo6

shown between VILDemph and the various expressions of CPFE (maximum R^2=0.36). All mortality models were adjusted for patient age, sex, smoking status (never *versus* ever) and antifibrotic use (never *versus* ever). Models were repeated evaluating D_{LCO} instead of VILDemph as a distinct functional measure of disease severity, thereby complimenting the models where a morphological measure of disease severity had been used (VILDemph). Different centres/countries within each cohort were modelled as multilevel with random effects between centres/countries (with a random intercept per centre/country). To encompass the breadth of published definitions of the CPFE phenotype [12], the CPFE phenotype was separately characterised as a binary emphysema variable in multivariable mixed-effects Cox regression models using four different emphysema thresholds (0%, 5%, 10% or 15% emphysema). The concordance index (C-index) was used to compare the predictive performance of the Cox models. Bootstrapping with 500 replications was used in the estimation of the C-index. p-values <0.05 were regarded as statistically significant. All analyses were implemented by R Studio.

Our results demonstrated that in both IPF cohorts, the CPFE phenotype did not independently predict mortality once summed extents of ILD and emphysema were considered in multivariable models (table 1). The results were maintained when patients fulfilling drug trial entry criteria were sub analysed in both cohorts. Results remained unchanged when the models examined baseline D_{LCO} instead of VILDemph to adjust for disease severity. 181 (82%) out of 220 patients in cohort 1, and 266 (86%) out of 310 patients in cohort 2 had baseline D_{LCO} values, whilst all patients in the drug trial population had baseline D_{LCO} values.

Our study confirms that mortality in patients with CPFE is explained by the sum of its two disease processes: the extents of fibrosis and emphysema. CPFE does not appear to manifest a malignant phenotype where survival is worse than that expected from the combination of two bad disease processes. Accordingly, once you consider emphysema and ILD patterns on CT, survival in CPFE is no different to survival in IPF patients without emphysema. The results were maintained when all of the different definitions of CPFE were separately analysed in both study cohorts and the smaller subsets of patients that would be included in drug trials.

A limitation of the study by JACOB *et al.* [4] was that the extent of emphysema in the cohort was relatively limited, with 11% (30 out of 272) patients having >15% emphysema extent (a threshold above which

TABLE 1 Multivariable mixed-effects Cox proportional hazards regression models in two cohorts of idiopathic pulmonary fibrosis (IPF) patients					
Disease severity and emphysema variables in the models	Patients for emphysema thresholds	C-index	Hazard ratio	p-value	95% CI
Cohort 1					
VILDemph	Emphysema=0%: n=79	0.76	1.05	<0.0001	(1.04–1.06)
Binary visual emphysema (threshold: 0%)	Emphysema >0%: n=141		1.03	0.931	(0.55–1.94)
VILDemph	Emphysema ⩽5%: n=123	0.76	1.05	<0.0001	(1.04–1.07)
Binary visual emphysema (threshold: 5%)	Emphysema >5%: n=97		0.62	0.090	(0.35–1.08)
VILDemph	Emphysema ⩽10%: n=155	0.76	1.05	<0.0001	(1.04–1.07)
Binary visual emphysema (threshold: 10%)	Emphysema >10%: n=65		0.75	0.273	(0.44–1.26)
VILDemph	Emphysema ⩽15%: n=179	0.76	1.05	<0.0001	(1.04–1.07)
Binary visual emphysema (threshold: 15%)	Emphysema >15%: n=41		0.71	0.244	(0.39–1.27)
Cohort 2					
VILDemph	Emphysema=0%: n=126	0.70	1.03	<0.0001	(1.02–1.04)
Binary visual emphysema (threshold: 0%)	Emphysema >0%: n=184		0.81	0.234	(0.58–1.14)
VILDemph	Emphysema ⩽5%: n=202	0.71	1.03	<0.0001	(1.02–1.04)
Binary visual emphysema (threshold: 5%)	Emphysema >5%: n=108		0.79	0.231	(0.55–1.16)
VILDemph	Emphysema ⩽10%: n=248	0.70	1.03	<0.0001	(1.02–1.04)
Binary visual emphysema (threshold: 10%)	Emphysema >10%: n=62		0.76	0.225	(0.49–1.18)
VILDemph	Emphysema ⩽15%: n=271	0.70	1.03	<0.0001	(1.02–1.04)
Binary visual emphysema (threshold: 15%)	Emphysema >15%: n=39		0.68	0.160	(0.40–1.16)

To evaluate whether the combined pulmonary fibrosis and emphysema (CPFE) phenotype had an additive impact on outcome of IPF patients after adjusting for patient age, sex, smoking status (never *versus* ever), antifibrotic use (never *versus* ever) and baseline disease severity, multivariable mixed-effects Cox regression models were used to analyse two independent cohorts of IPF patients. Separate centres/countries within cohort 1 and cohort 2 were modelled as multilevel with random effects between centres/countries (a random intercept per centre/country). Baseline disease severity was quantified as the sum of average lobar visual CT extents of emphysema and ILD: VILDemph. The CPFE phenotype was separately characterised by a binary visual emphysema variable using thresholds of emphysema extent including: 0%, 5%, 10% or 15%, which were reported in various definitions of CPFE in the literature. The impact of the four binary visual emphysema thresholds were separately analysed in multivariable models. C-index: concordance index.

emphysema has been associated with significantly reduced FVC decline [13]). The proportion of patients with emphysema >15% was higher in the current study populations, 41 (19%) out of 220 patients in cohort 1 and 39 (13%) out of 310 patients in cohort 2. There were also very few patients in whom emphysema extent was greater than fibrosis extent. Only five (2%) out of 220 patients in cohort 1 and 13 (4%) out of 310 patients had more emphysema than fibrosis. A recent CPFE study considered patients in whom emphysema was more extensive than ILD on CT [14]. Repeating our analyses with a CPFE population defined in this way would be important to confirm our findings. Yet powering such a study in IPF patients will be extremely challenging.

In summary, we have validated findings across independent datasets confirming that in CPFE patients mortality is explained by the sum of emphysema and fibrosis extents. We have demonstrated that in CPFE patients, emphysema and fibrosis do not have a synergistic effect resulting in a malignant disease phenotype. CPFE patients and IPF patients without emphysema have indistinguishable mortality once the extents of emphysema and ILD on CT have been considered.

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