In patients with idiopathic pulmonary fibrosis the presence of hiatus hernia is associated with disease progression and mortality

To the Editor:

In idiopathic pulmonary fibrosis (IPF), the role of gastro-oesophageal reflux (GOR) and its treatment remain unclear [1]. Both acid and non-acid components of GOR contribute to lung inflammation and fibrosis [2, 3]. There are conflicting data on the use of proton pump inhibitors (PPIs) in IPF, which do not act on the non-acid component of GOR and may be associated with higher rates of respiratory infection [4, 5]. Hiatus hernia (HH) is strongly linked to GOR [6] and is common in IPF patients [7]. One previous study pre-dating the era of anti-fibrotic therapy found an association between HH and increased mortality in IPF [8]. However, it did not control for immunosuppressive therapy, at that time routinely used in IPF treatment but now recognised as harmful, thereby limiting the applicability to patients with IPF today. Furthermore, the impact of HH on lung function in IPF has not been reported in any study to date. The WRAP-IPF study, which randomised patients to fundoplication or medical therapy, has generated interest in the role of surgical GOR interventions [9]. Patient selection for WRAP-IPF was dependent on a positive DeMeester score, a measure of acid reflux that has not been examined in relation to IPF outcomes. We aimed to assess the impact of HH and acid reflux as measured by DeMeester score in IPF, hypothesising that HH, which is associated with both acid and non-acid GOR, may be an important contributor to IPF progression.

A retrospective cohort of IPF patients receiving pirfenidone between 2011 and 2017 was analysed. The study was restricted to patients prescribed a single anti-fibrotic agent to minimise potential confounding. HH was scored qualitatively as "present" or "absent" and estimated for size on the first available chest computed tomography (CT) scan, by a thoracic radiologist (S.R. Desai) blinded to outcome measures, in a randomised order. A separate cohort of IPF patients, who underwent 24-h oesophageal pH impedance testing between 2008 and 2017 was analysed. The majority of pH impedance studies were performed prior to the advent of anti-fibrotic therapy, therefore the few who received an anti-fibrotic drug were excluded to minimise confounding. A positive pH study for acid reflux was defined using DeMeester score (>14.72) and Lyon Consensus Criteria (pH <4 for >6% time or >80 total events) [10, 11].

Serial forced vital capacity (FVC) was calculated as change in mL at approximately 12 months from the first available test. Transplant-free survival was measured from the first date. Appropriate parametric (t-tests), non-parametric (Mann–Whitney U-tests) and categorical (chi-square) analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA). Survival was analysed using Kaplan–Meier and Cox proportional hazards methods.

HH was present in 37/89 (42%) patients (figure 1). Patients with HH were significantly younger and experienced greater relative and absolute annual FVC decline (−250 mL (interquartile range −421 to −19 mL) *versus* −36 mL (interquartile range −261 to +104 mL); p=0.01). Prescription of PPIs was 86% and 71% in the HH present and absent groups, respectively. HH size did not correlate with FVC decline. The mean length of follow-up was 37 months and the unadjusted median transplant-free survival was significantly shorter in patients with HH (31 *versus* 55 months; p=0.049). Using a Cox proportionate

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For IPF patients, the presence of hiatus hernia is associated with lung function decline and increased mortality. This observation supports the view that hiatus hernia may influence pathogenic mechanisms involved in IPF disease progression. http://ow.ly/hPAY30omE9o

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a)

	IPF cohort scored for presence of HH on CT scan		IPF cohort scored for acid reflux using DeMeester score by 24 h pH study	
	HH present (n=37)	HH absent (n=52)	Acid reflux positive (n=19)	Acid reflux negative (n=42)
Sex	30 male (81%)	42 male (81%)	15 male (79%)	23 male (55%)
Age years	65.5±9.3	70.4±8.3**	66±10	67±9
PPI	86%	71%	84%	83%
BMI	28.2 (26.3 to 31.2)	28.2 (26.0 to 31.0)	27.2 (24.7 to 28.2)	28.1 (24.4 to 30.0)
Baseline FVC % pred	65 (55 to 74)	69 (60 to 75)	74±18	81±18
Baseline *D*LCO % pred	36.7±11.4	37.7±10.0	49±16	46±14
CPI	56.2±8.3	55.7±8.9	45.7±12.6	43.8±11.1
Discontinued pirfenidone (for GI side-effects)	2 (5.4%)	9 (17.3%)		
FVC decline mL	−250 (−421 to −19)	−36** (−261 to +104)	−87 (−239 to +127)	−183 (−502 to +25)
FVC decline %	−8.7 (−15.2 to −1.6)	−1.0** (−8.7 to +5.2)	−2.2±11.7	−9.9±15.4
Median survival months	31 (1 transplant, 24 deaths)	55* (1 transplant, 24 deaths)	50 (1 transplant, 11 deaths)	53 (22 deaths)

b)

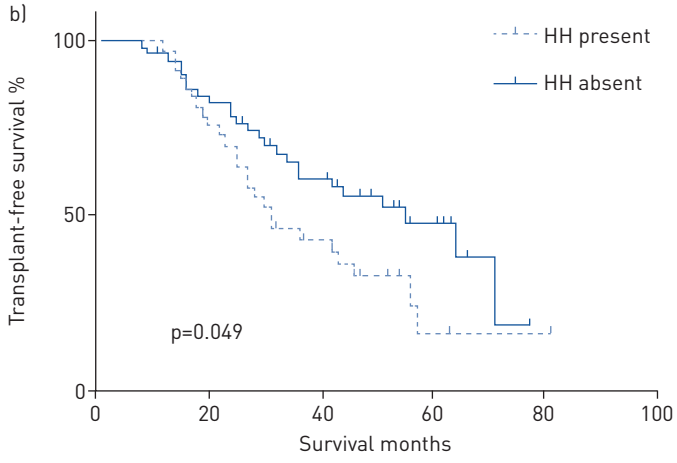

FIGURE 1 a) Baseline demographic, serial lung function and survival data for both hiatus hernia (HH) and acid reflux analyses. b) Unadjusted Kaplan–Meier survival curve for the presence of HH in idiopathic pulmonary fibrosis (IPF) patients treated with pirfenidone. Data are expressed as mean±SD or median (interquartile range), unless otherwise stated. Only statistically significant p-values (<0.05) reported. CT: computed tomography; PPI: proton pump inhibitor; BMI: body mass index; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; GI: gastrointestinal; FEV_1: forced expiratory volume in 1 s; CPI: Composite Physiologic Index (extent of disease on CT = 91.0 − (0.65 × *D*LCO % pred) − (0.53 × FVC % pred) + (0.34 × FEV_1 % pred)). **: p=0.01; *: p=0.049.

hazard model, adjusted for PPI use, age, gender and Composite Physiologic Index (CPI), the hazard ratio for HH and transplant-free survival was 1.74 (95% CI 0.95–3.2; p=0.07). Patients with HH were no more likely to discontinue pirfenidone. Patients with positive acid reflux studies demonstrated no difference in FVC decline or survival (figure 1).

Acid reflux and HH are both common in IPF. However, in these IPF cohorts, only the presence of HH was associated with disease progression and mortality. Although the association between HH and worse outcomes in IPF has been previously described [8], this is the first study to reveal an association with annual FVC decline and to demonstrate this in the context of anti-fibrotic therapy.

Despite similar baseline disease severity, patients with HH were younger, suggesting that HH may be a co-factor in the pathogenesis of IPF, potentially driving earlier presentation and worse outcomes. It might be considered that GOR symptoms associated with HH, such as cough, may result in earlier diagnosis; however, lead-time bias does not explain the more rapid decline and increased mortality observed. As a positive pH impedance study did not identify patients at risk of disease progression, HH may exert a pathogenic role through a combination of both acid and non-acid reflux. An alternative explanation is that

HH occurs due to the effects of progressive fibrosis on thoracic biomechanics, developing because of progressively more negative intrathoracic pressures. However, patients with HH did not have more advanced disease as defined by FVC or CPI and we found no suggestion that HH enlarged over time. This study was not designed to address this "cause or effect" question, which could be evaluated by assessing the presence and impact of HH in interstitial lung abnormality cohorts.

If HH is indeed pathogenically linked to IPF progression, it is tempting to postulate that surgical correction of HH in early or even subclinical disease might modulate the natural history of IPF. Surgical management of reflux in the post-transplant setting has proven prognostic benefits [12]. Definitively addressing reflux before lung transplantation and at an early stage of disease in younger IPF patients may be appropriate, particularly in the setting of a HH [13]. Patients randomised to surgery in WRAP-IPF experienced an FVC decline at 48 weeks of 50 mL, far less than was observed in the phase 3 trials of anti-fibrotic therapy [14, 15]. A positive DeMeester score was the primary inclusion criteria in WRAP-IPF [9]. Our results suggest that this criterion does not identify IPF patients at risk of more rapid disease progression. A HH was present in 85% of the WRAP-IPF participants randomised to surgery, as compared to 55% of the control group. Based on our findings and those of others [8], had WRAP-IPF been targeted to those with HH, a larger effect may have been observed in terms of lung function stabilisation and potentially survival.

A limitation of our study is that the cohort of patients undergoing pH impedance was small and measures of non-acid reflux were not available. Patients with positive impedance studies received lifestyle advice alongside pharmacological therapy to address acid and non-acid reflux. We are therefore not able to definitively exclude the role of acid reflux in IPF progression. Our data suggest that HH is associated with IPF disease progression and while the pathogenic mechanism may be through combined acid and non-acid reflux, prospective studies exploring upper gastrointestinal physiology are required to allow definitive conclusions. A multi-dimensional approach to GOR assessment, incorporating measures of acid and non-acid impedance, manometry and the presence of HH, similar to that recently proposed by Jones *et al.* [16] deserves prospective evaluation. The majority of participants (80%) were prescribed a PPI and therefore our data cannot be utilised to corroborate results of previous studies suggesting PPI therapy might be harmful in IPF [4]. When controlling for PPI use, however, the association between HH and mortality remained. Finally, CT is not the gold standard test for HH, but while CT may miss small HH, this should not negate the associations observed for those with HH large enough to be detected noninvasively.

We have demonstrated that HH is associated with disease progression and increased mortality in IPF patients treated with antifibrotic therapy. A mechanical rather than pathogenic explanation remains possible and further research is required to explore these associations. If confirmed in subsequent studies, identification of HH as a poor prognostic indicator in IPF should prompt clinicians to stratify these patients as being at higher risk for disease progression. Early treatment of acid and non-acid reflux alongside IPF therapy may improve outcomes. As PPIs only address one component of GOR, measures such as pro-kinetics and fundoplication may be effective alternative and/or adjunctive therapeutic strategies. It may be that the most effective strategy for reflux intervention in IPF utilises a personalised approach, based on multiple factors, including HH.

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