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How does comorbidity influence survival in idiopathic pulmonary fibrosis?

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Summary
Introduction: Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. It is a serious and progressive lung disease with a median survival of three years. The role of comorbidities in the prognosis of IPF is not clear.
Objectives: To describe comorbidity and co-medication in a Danish IPF cohort and the association between clinically important comorbidities and survival.
Methods: The study cohort included all patients diagnosed with IPF at Aarhus University Hospital, Denmark between April 2003 and April 2009. Details on diagnostic examinations, pulmonary function, medication and comorbidities were registered based on medical records.
Results: A total of 121 patients were included. The most frequently observed comorbidities were cardiovascular disease (20%), arterial hypertension (15%) and diabetes mellitus (11%). Cardiovascular disease diagnosed during follow-up significantly increased mortality (HR 4.7, 95% CI 2.0–11.1). No difference was found based on cardiovascular disease already present at the time of IPF diagnosis. Diabetes (HR 2.5, 95% CI 1.04–5.9) and anticoagulant treatment (HR 3.3, 95% CI 1.5–7.2) were also factors associated with a significantly higher mortality in this population-based cohort.
Conclusion: These findings emphasize the need of careful diagnosis and treatment of comorbidities and their risk factors in patients with IPF. In the absence of efficient treatment options for the majority of patients diagnosed with IPF, this may play a role in the effort to optimize the survival of IPF patients. Further studies are needed to fully clarify the impact of comorbidities on prognosis in patients diagnosed with IPF.

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Background

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. It is a serious and progressive disease with a median survival of 2–3 years. In many cases, IPF is not diagnosed until pulmonary function is severely impaired. Comorbid diseases like lung cancer and cardiovascular disease may affect the prognosis of patients with IPF. However, the reported prevalence of comorbidity is variable and little is known about the impact of concomitant diseases on survival in patients with IPF. Corticosteroid therapy was widely used in IPF until recently, and may have had a negative influence on some comorbid diseases such as diabetes and osteoporosis. The aim of this study was to describe important comorbid conditions and to assess their impact on outcome in a well-characterized cohort of Danish IPF patients.

Methods

Study patients

IPF patients were identified in the Interstitial Lung Disease (ILD) Registry at Aarhus University Hospital, a retrospective cohort including all incident patients diagnosed with ILD at the Department of Respiratory Diseases, Aarhus University Hospital, between 1 April 2003 and 1 April 2009. ILD diagnoses in the International Classification of Diseases, version 10 (ICD-10) and lists of HRCT scans performed at the hospital were used to identify ILD patients in the hospital's administration system. All ILD diagnoses were re-evaluated according to standard diagnostic criteria by two ILD specialist pulmonologists. All available HRCT scans were re-evaluated by expert thoracic radiologists, and all biopsies had been evaluated by expert pathologists at our institution [1].

IPF was diagnosed according to the 2011 ATS/ERS/JRS/ALAT criteria [2]. Eligible patients were followed from the time of first hospital visit with suspected ILD to the last visit, death or transplantation. Follow-up ended 15 November 2009.

The study was approved by the Danish Data Protection Agency and The Danish National Board of Health.

Data collection and assessments

All comorbidities were registered based on information from medical records. A diagnosis of diabetes was registered if the patient received antidiabetic therapy. Osteoporosis was registered in the presence of a DXA-scan with *T*-score below −2.5 or a history of fragility fracture. Cardiovascular disease was defined as one or more of the following: ischaemic heart disease, cerebral infarction or peripheral arterial disease based on patients' medical records.

Pulmonary hypertension (PH) was diagnosed in the presence of a tricuspid pressure regurgitation gradient ≥40 mmHg, a tricuspid annular plane systolic excursion <1.8 cm or right ventricular dilatation on echocardiography and/or mean pulmonary artery pressure ≥25 mmHg on right heart catheterization (RHC). Mild PH was defined as tricuspid regurgitation gradient ≤60 mmHg or mean pulmonary artery pressure ≤35 mmHg, and severe PH was defined as tricuspid regurgitation gradient >60 mmHg or mean pulmonary artery pressure >35 mmHg. PH was considered present at the time of diagnosis when the diagnosis was made within 90 days of the first visit to the department. When PH was diagnosed later than 90 days after first visit to the department it was considered as diagnosed during follow-up. Echocardiography was used as a screening tool for PH prior to referral for RHC.

Treatment for comorbid conditions was registered when the patient received the treatment at any time during the study period.

Severity of IPF was assessed on the basis of the GAP prognostic model [3] that incorporates gender, age, diffusion capacity of carbon monoxide (DLco) and forced vital capacity (FVC), and allows a separation of patients into disease categories with significantly different prognosis. Causes of death were registered based on the information from medical records. Follow-up with respect to mortality was based on information from the hospital's currently updated patient administration system and was complete.

Statistical analysis

Data are presented as means ± SD if continuous or as frequencies if categorical. Unless otherwise specified, the number of patients with available data (*n*) was used in the calculation of summary statistics. Survival was evaluated using the Kaplan–Meier method, and the log-rank test was used to determine statistical significance. Differences in hazard ratio (HR) for death were evaluated using Cox proportional hazards analysis. Unadjusted and adjusted Cox proportional hazards regression analyses were performed, and HR are presented along with 95% confidence intervals. Comorbidities diagnosed during follow-up were assessed as time dependent covariates.

Adjustment was performed using age and FVC as continuous variables and gender as categorical variable. Based on the number of events in the survival analysis, the number of variables in the adjusted analysis had to be limited to the clinically most important and robust parameters, but the inclusion of DLco in the model did not change the results. Differences in the use of antidepressants were assessed using a logistic regression model. All analyses were performed using STATA statistical software (version 12.1; StataCorp, College Station, Texas, USA).

Results

Comorbid conditions in IPF

A total of 121 IPF patients were included. IPF was the most frequent diagnosis in the 2003–2009 ILD cohort and constituted 28% of the diagnoses. Ninety-seven patients were diagnosed with definite IPF and one patient with possible IPF. Furthermore, 23 patients were classified as having IPF based on a probable UIP pattern on HRCT and clinical features typical of IPF, although no histopathological diagnosis was made because a surgical lung biopsy

entailed too high a risk. Mean follow-up time in IPF was 23.6 months (SD = 19.2). One-year survival was 73% and 5-year survival was 34%. Smoking was not associated with poorer survival (HR $p = 0.19$). Demographics and clinical characteristics are shown in Table 1.

Sixty-one deaths occurred during the study period. Forty-one patients were still under follow-up at our institution at the end of the study period, while 15 patients had been discharged for further follow-up at their local hospitals. Four patients underwent a lung transplant.

The most frequent comorbidities among IPF patients are listed in Table 2. Osteoporosis was diagnosed in ten patients (8%) during follow-up; eight of these patients had received steroid therapy during follow-up. Antidepressant therapy, either selective serotonin re-uptake inhibitors or tricyclic antidepressants, was used by a total of 25 patients (21%). At the time of IPF diagnosis, only eight of them had a diagnosis of depression and received antidepressant therapy. No difference in the frequency of antidepressant therapy was observed in patients with mild, moderate or severe IPF; with severity assessment based on the GAP staging system [3].

Lung cancer was diagnosed in seven patients (6%). The follow-up time was 197 person-years, equivalent to an incidence rate of 3.6%/year. The incidence of lung cancer in the general Danish population was 83/100,000/year for men (0.083%/year) and 64/100,000/year for women (0.064%/year) in 2010 [4]. A review of medical records of the patients alive at the end of follow-up, revealed no additional lung cancer cases up to January 2013. No difference in survival from the time of IPF diagnosis was seen between lung cancer patients and patients without lung cancer. Survival from the cancer diagnosis ranged from one to fifteen months. The available data on cancer stage and therapy were incomplete, but none of the patients underwent surgical therapy or other intendedly curative therapy.

The presence of diabetes at inclusion was associated with a statistically significant decrease in survival (Fig. 1). The difference persisted after adjustment for age, gender and FVC (HR 2.47, 95% CI 1.04–5.88, $p = 0.041$). Seven out of nine deaths in diabetic IPF patients were fibrosis-related, one was cancer-related and one was of unknown cause. The percentage of fibrosis-related deaths was the same among diabetics and non-diabetics. Diabetes diagnosed during follow-up did not affect survival (Tables 3 and 4). All patients with diabetes diagnosed during follow-up ($n = 10$) received corticosteroid therapy. Of the patients who had diabetes at the time of IPF diagnosis, eight out of eleven patients (73%) received corticosteroids.

No survival difference was seen based on the presence of cardiovascular disease prior to IPF diagnosis, $p = 0.17$ (crude) and $p = 0.27$ (adjusted for age, gender and FVC), but cardiovascular disease diagnosed during the follow-up period significantly increased mortality (HR 4.7, 95% CI 2.0; 11.1, $p < 0.001$). Four patients died of their lung disease, two patients died of combined pulmonary and cardiac cause. One death was caused by intracerebral haemorrhage and one was of unknown cause. One patient was still alive at the end of the follow-up period.

Half of the patients (61/121) received medical therapy for gastro-oesophageal reflux, either because of symptomatic gastro-oesophageal reflux or prophylactically

Table 1 Demographics and clinical characteristics in the Danish IPF cohort.

n	121
Male:female	93:28
% male	77
Age (SD)	67.4 (8.4)
Smoking % (current or previous)	81
Number of pack years	29
Clinical-radiological diagnosis %	57
Histological diagnosis %	43
FVC % predicted (SD)	72.0 (20.7)
DLCO % predicted (SD)	42.3 (16.4)

FVC: forced vital capacity, DLCO: diffusion capacity of carbon monoxide.

Table 2 Comorbid diseases in the Danish IPF cohort.

Comorbid diagnosis	At time of inclusion *n* (%)	Diagnosed during follow-up *n* (%)	Total *n* (%)
Cardiovascular disease[a]	24 (20%)	9 (7%)	33 (27%)
Arterial hypertension	18 (15%)	4 (3%)	22 (18%)
Ischaemic heart disease	16 (13%)	6 (5%)	22 (18%)
Pulmonary hypertension	12 (10%)	14 (11%)	26 (21%)
Diabetes	11 (9%)	10 (8%)	21 (17%)
Gastro-oesophageal reflux	10 (8%)	0	10 (8%)
Depression	8 (7%)	20 (17%)	25 (21%)
Osteoporosis	8 (7%)	10 (8%)	18 (15%)
Cerebral infarction	8 (7%)	3 (2%)	11 (9%)
Atrial fibrillation	5 (4%)	6 (5%)	11 (9%)
Lung cancer	0	7 (6%)	7 (6%)
Other cancers[b]	0	4 (3%)	4 (3%)

[a] Ischaemic heart disease, cerebral infarction, peripheral arteriosclerosis. Some patients had more than one diagnosis.
[b] Bladder ($n = 1$), rectum ($n = 1$), prostate ($n = 2$).

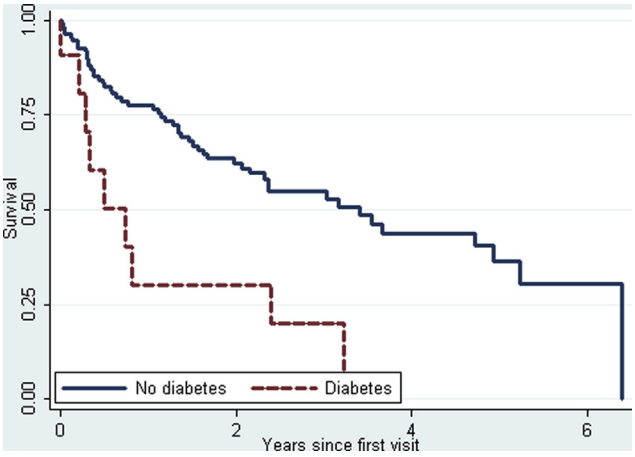

Figure 1 Survival time estimates based on presence or absence of diabetes. HR = 3.1, $p = 0.002$ (unadjusted).

Table 3 Therapy given for IPF 2003–2009.

	n	%
Prednisolone	91	75
High-dose methylprednisolone courses	64	53
Both Prednisolone and high-dose methylprednisolone courses	52	43
Azathioprine	75	62
N-acetylcysteine[a]	69	57
Triple therapy[b]	58	48
Cyclophosphamide	8	7
Oxygen therapy	67	55

[a] N-acetylcysteine (NAC) was only used as part of combination therapy, none of the patients received NAC alone.
[b] N-acetylcysteine, prednisolone, azathioprine.

because of concomitant corticosteroid therapy. No difference in survival was seen between the treated and non-treated groups ($p = 0.74$). Symptomatic gastro-oesophageal reflux did not impact on survival (HR 1.6, 95% CI (0.60; 4.4)) (Table 3).

IPF therapy

The treatment options used in IPF at the time of the study are listed in Table 5. Comparison of treated and untreated groups in adjusted analysis revealed no significant positive or negative influence on survival (data not shown).

Anticoagulant therapy

Sixteen patients received anticoagulant treatment with either warfarin ($n = 15$) or phenprocoumon ($n = 1$). Clinical indications for anticoagulant treatment were deep venous thrombosis ($n = 3$), pulmonary embolism ($n = 4$), artificial heart valve ($n = 2$), atrial fibrillation ($n = 3$), transitory cerebral ischaemia ($n = 1$), and pulmonary hypertension ($n = 3$). A pronounced statistically significant survival difference was seen in favour of the non-treated group ($p < 0.001$) (Fig. 2). The difference persisted after adjustment for age, gender and FVC (HR 3.3, 95% CI 1.55–7.21, $p = 0.002$).

The results were unchanged when we excluded three patients receiving anticoagulants due to PH (adjusted HR 3.49, 95% CI 1.56–7.81, $p = 0.002$).

Table 4 Comorbidity present at first hospital visit for IPF and its association to survival (adjusted for age, gender and FVC).

	n	HR (95% CI)	*p*
Cardiovascular disease	24	0.66 (0.32; 1.37)	0.27
Diabetes	11	2.5 (1.04; 5.9)	0.041
Pulmonary hypertension	12	2.2 (0.94; 5.2)	0.068
Gastro-oesophageal reflux	10	1.6 (0.60; 4.4)	0.34
GER medication	61	1.0 (0.58; 1.8)	0.95
Anticoagulant treatment (Non-PH indication)	13	3.3 (1.5; 7.2)	0.002

GER: gastro-oesophageal reflux, PH: pulmonary hypertension.

Pulmonary hypertension

A total of 26 patients were diagnosed with PH. In 12 patients (10%), the lung disease was complicated by PH at the time of IPF diagnosis, seven patients had mild PH and five had severe PH. In these patients with PH, unadjusted mortality was significantly higher than in patients without pulmonary hypertension ($p = 0.048$), but the difference did not persist after adjustment for age, gender and FVC (HR 2.2, 95% CI 0.94–5.2, $p = 0.068$). During follow-up, 14 additional patients were diagnosed with PH, twelve of those had mild PH and two patients had severe PH. The development of PH caused no difference in survival when compared to non-PH patients in the cohort.

In eight patients, PH was diagnosed based on RHC and in 18 patients, the primary diagnosis was based on echocardiography. Four of those patients had RHC performed later in the course of disease. Three patients had severe PH (mPAP >35 mmHg) at the time of IPF diagnosis, and one patient diagnosed during follow-up had severe PH. Two patients were diagnosed with severe PH based on echocardiography (tricuspid regurgitation gradient >60 mmHg).

Twenty-three patients with PH (88%) required long-term oxygen treatment, and six patients (23%) received medical therapy for out-of-proportion PH. Survival range in out-of proportion PH was 4 months to 2.4 years.

Discussion

Main results

The most frequently observed comorbidities were cardiovascular disease (20%), arterial hypertension (15%) and diabetes mellitus (11%). Cardiovascular disease diagnosed during follow-up significantly increased mortality (HR 4.7, 95% CI 2.0–11.1). No difference was found based on cardiovascular disease already present at the time of IPF diagnosis. Diabetes (HR 2.5, 95% CI 1.04–5.9) and anticoagulant treatment (HR 3.3, 95% CI 1.5–7.2) were also factors associated with a significantly higher mortality in this population-based cohort.

The impact of comorbidity on survival in IPF is not well characterized, and studies are few. This study describes the frequency of comorbidities in a Danish IPF cohort with typical demographic and clinical characteristics. Prevalence data on comorbidity in IPF are sparse. In a large cohort of American IPF patients identified from medical claims databases, 25% of the patients were diabetics and 25% had coronary artery disease [5]. In a small, population-based cohort from Minnesota, USA that included 47 patients with IPF [6], coronary artery disease was present in 45% of patients, diabetes in 17% and depression in 11%. The Minnesota patients' higher age, higher DLCO and longer survival may explain the higher frequency of comorbidities compared to our cohort. BMI and smoking status were comparable between the two cohorts. To our knowledge, this is the only study of comorbidity in a comparable cohort that has been published.

Diabetes was a significant prognostic determinant in the present study. A higher prevalence of diabetes in IPF patients compared with the background population has

Table 5 Comorbidity diagnosed during IPF follow-up and its association to survival (adjusted for age, gender and FVC).

	n	Mean follow-up time to comorbid diagnosis Days (range)	HR (95% CI)	*p*
Cardiovascular disease	9	516 (118; 986)	4.7 (2.0; 11.1)	<0.001
Diabetes	10	597 (78; 1464)	1.1 (0.33; 3,8)	0.85
Pulmonary hypertension	14	620 (192; 1213)	2.2 (0.82; 6.0)	0.12

previously been reported [7,8], but to our knowledge, the survival implication of diabetes in IPF has not previously been addressed. There is no evidence that corticosteroid therapy modifies the natural history of the disease, and recommendations against its use are strong [2,9]. We have no data to assess the degree of diabetes control or compliance to antidiabetic therapy in this cohort. The reasons for the observed difference in survival are not clear, but poor diabetes control due to steroid treatment is likely to have played a role. The change in treatment recommendations for IPF may in itself improve outcome in diabetic IPD patients, but the possible impact of diabetes on prognosis in IPF remains an important focus for further investigations in larger IPF cohorts.

Cardiovascular disease diagnosed during the course of IPF resulted in a highly significant decrease in survival. On the other hand, cardiovascular disease already present at the time of IPF diagnosis, did not impact on survival. A British case–control study showed that ischaemic heart disease was four times more frequent in IPF patients than in age- and gender-matched controls [10], but the study did not assess survival implications in IPF. Cardiovascular disease was also investigated as one of several potential predictors of mortality in a prognostic model developed in a large IPF cohort from two clinical trials [11]. Similar to our study, cardiovascular disease was present at baseline in 27% of the patients, and no significant difference in all-cause mortality was found based on the presence of cardiovascular disease. These results based on a large group of participants in a clinical trial corroborate our findings in a cohort of unselected patients in a population-based study. It contrasts with findings in COPD where cardiovascular disease is known to be an important prognostic factor [12,13]. However, Nathan et al. [14] showed that a subgroup of IPF patients who were transplant candidates had a higher prevalence of coronary artery disease than transplant candidates with COPD, and found that mortality was significantly higher among IPF patients.

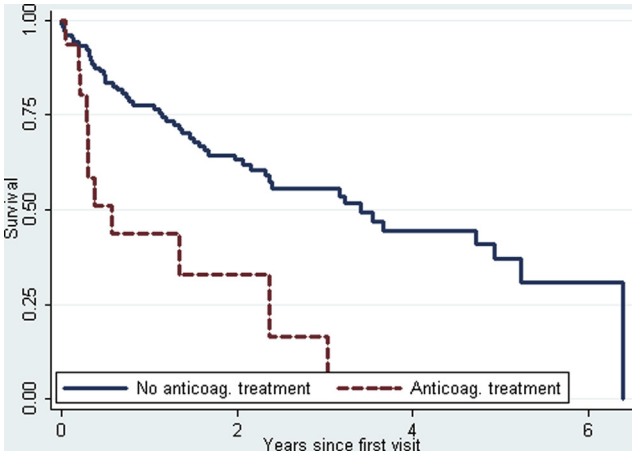

Figure 2 Survival time estimates based on anticoagulant treatment. HR = 3.4, $p < 0.001$ (unadjusted).

The occurrence of lung cancer is low in the Danish IPF cohort compared with previous studies. Ozawa et al. [15] reported a lung cancer incidence of 20% in a Japanese cohort. Earlier IPF diagnosis and longer observation time owing to long survival seemed to account for the difference in the occurrence of lung cancer between the Japanese and the Danish cohort. In another Japanese study, 17% (9/52) of IPF deaths were ascribed to lung cancer [16], and in the Minnesota cohort [6], 17% (8/47) of the patients developed lung cancer.

A large, population-based study from Britain [17] compared IPF patients with age- and gender-matched controls, and found a lung cancer rate of 122 per 10,000 person-years among IPF patients and 22.9 per 10,000 person-years among controls. The rate of 3.6% per year found in our study was three times higher than in the British study. In another British study, Harris et al. [18] showed that lung cancer caused 9% of deaths in patients with CFA/IPF. Different methods and study populations complicates a direct comparison, but our results corroborate other studies showing a considerably increased risk of lung cancer in IPF compared with the background population.

The frequency of depression was 21% in the Danish cohort, based on registered antidepressant use. A previous study reported a diagnosis of depression in 11% of IPF patients [6], while the screening for depression in a mixed ILD cohort [19,20] revealed clinically relevant depression in 24% of the IPF patients. Depression score was found to be related to dyspnoea and functional status in the same cohort. Another study focused on the quality of life of IPF patients [21] and showed that subjective breathlessness is related to depressive symptoms and to quality of life, and a score indicative of significant depression was found in 23.5% of the patients. It has also been shown that the scores on the Saint George Respiratory Questionnaire (SGRQ) and the Hospital Anxiety and Depression Questionnaire are correlated with the severity of IPF based on pulmonary function parameters [22]. The high frequency of antidepressant therapy among patients in our cohort suggests that the recognition of depressive symptoms is coming more into focus. However, the optimal way to address depressive symptoms in IPF and the role of physical impairment, medical therapy and pulmonary rehabilitation needs further investigation.

Pulmonary hypertension is a serious complication in ILD and was seen in 21% of our patients; almost half of them

had PH at the time of IPF diagnosis. A cross-sectional study of a mixed ILD population from our centre [23] showed a prevalence of PH of 14% in all ILDs and 24% in IPF, a prevalence level that corroborates our findings. We found no survival effect of the presence of PH at the time of IPF diagnosis when adjustment was made for age, gender and FVC. The number of patients with PH in this cohort was not large enough to allow stratification based on severity of PH. The presence of mild PH does not seem to influence survival, and the number of patients with severe PH in this study is too low to show a survival difference. Parallel to our findings, the study by Hamada et al. [16] estimated pulmonary arterial pressure as part of the initial diagnostic work up, and showed that the presence of PH provided no independent prognostic information in a multivariate regression analysis. In later stages of IPF, PH has been shown to be an important prognostic determinant [24].

Only one patient was diagnosed with sleep apnoea. The condition may have been underdiagnosed, but is seeing an increased focus as overweight is becoming more common in the Danish population. None of our patients had concomitant COPD based on FEV1/FVC on spirometry. Some patients had significant emphysema on HRCT-scan, but radiological emphysema quantification was not performed systematically.

Patients receiving anticoagulant treatment for clinical indications had a significantly higher mortality. The impact of warfarin treatment on IPF outcome when warfarin is given on clinical indication has only been briefly addressed in previous studies. The issue of warfarin in IPF has attracted focus in the light of the recently published results of the ACE-IPF trial [25] that showed no clinical benefit of warfarin treatment. The trial was stopped early, because treatment with warfarin was associated with an increased risk of mortality in an IPF population who lacked other indications for anticoagulation. The small group of patient on anticoagulant therapy in our study did not allow stratification based on indication for warfarin therapy, and it is difficult to exclude that the concomitant disease itself may affect survival. Warfarin treatment as a possible predictor of survival was investigated in the study of the association of gastro-oesophageal reflux therapy with survival in IPF [26]. Four percent of the patients received anticoagulant treatment, and the association with survival was not significant. However, a recent study by Tomassetti et al. [27] also showed increased mortality in warfarin-treated patients. Further studies in larger patient cohorts are needed to address the question of a connection between concomitant vitamin K antagonists and disease outcome in IPF. Whether new oral anticoagulants such as Factor Xa inhibitors should be preferred over warfarin for anticoagulant therapy in patients with IPF is another issue that needs further investigation.

The role of gastro-oesophageal reflux in IPF is still debated. In the Danish cohort, PPI treatment was used by half of the patients as prophylaxis during corticosteroid treatment or for symptomatic GER, and symptomatic GER may have been underreported. Previous studies have demonstrated differences in outcome based on GER medication use. One study has shown improved survival in patients treated with PPI [26], but this finding was not retrieved in our smaller cohort, perhaps because proton pump inhibitor therapy was given prophylactically in many cases. The study by Lee et al. that was based on patients in the placebo arms of three clinical trials in IPF [28], showed a small, but statistically significant difference in FVC decline at 30 weeks in favour of PPI treatment.

Prognostic models in IPF, such as the GAP score [3] or the Composite Physiology Index (CPI) [29], focus on factors directly related to IPF and are strong prognostic determinants. However, none of these models have incorporated the impact of comorbidities, and the role of comorbidity in IPF prognosis is still not clear. In COPD, a newly introduced comorbidity index, the COTE index [30], identified 12 comorbidities that confer an independent risk of death in COPD patients and complements the BODE index [31] in prediction of survival. For each BODE score quartile, the characterization of patients by the level of COTE score provides additional prognostic information when added to the BODE score. This model may inspire the incorporation of concomitant diseases into prognostic models in IPF.

Our study is limited by its small size and limited number of patients with comorbidities. However, it provides valuable information of the occurrence and impact of common comorbid conditions in a population-based cohort of IPF patients.

Conclusion

The present study suggests an increased mortality in diabetics and in patients experiencing cardiovascular events in the course of their fibrotic disease. These findings emphasize the need of careful diagnosis and treatment of comorbidities and their risk factors in patients with IPF. In the absence of efficient treatment options for the majority of patients diagnosed with IPF, this may play a role in the effort to optimize the survival of IPF patients. The findings in this study also suggest that anticoagulant treatment with vitamin K antagonists may be associated with a more serious outcome, but further studies of the role of comorbidities and concomitant medication in IPF are needed.

Conflicts of interest

The authors CH, OH and EB declare no conflicts of interest.

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