Supplementary material

Title: Diagnostic delay in IPF impacts progression-free survival, quality of life and hospitalisation rates

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Symptom	Diagnostic delay < 1 year (N=78)	Diagnostic delay > 1 year (N=186)	Total (N=264)	p value
Dry cough	24 (30.8%)	57 (30.6%)	81 (30.7%)	0.98
Productive cough	23 (29.5%)	52 (28.0%)	75 (28.4%)	0.80
Coughing up blood	1 (1.3%)	7 (3.8%)	8 (3.0%)	0.28
Shortness of breath	43 (55.1%)	110 (59.1%)	153 (58.0%)	0.55
Chest pain	10 (12.8%)	19 (10.2%)	29 (11.0%)	0.54
Chest discomfort	6 (7.7%)	23 (12.4%)	29 (11.0%)	0.27
Changed breath sounds	13 (16.7%)	21 (11.3%)	34 (12.9%)	0.23
Fever	6 (7.7%)	6 (3.2%)	12 (4.5%)	0.11
Fatigue	20 (25.6%)	46 (24.7%)	66 (25.0%)	0.88
Weight loss	6 (7.7%)	18 (9.7%)	24 (9.1%)	0.61
Other	14 (17.9%)	28 (15.1%)	42 (15.9%)	0.56

Table E1: First IPF-related symptom, as reported by patients stratified according to diagnostic delay below or above 1 year. Patients could report multiple symptoms. P-value based on chi-squared test.

	FVC ≤ 80% predicted	FVC > 80% predicted	Total	p value
Total diagnostic delay	1.4 (0.7-5.6)	2.2 (0.9-4.9)	2.0 (0.9-5.0)	0.40
Emphysema at baseline, n (%)	8 (9.2%)	17 (9.8%)	25 (9.6%)	0.87

Table E2: Total diagnostic delay and emphysema in patients stratified according to forced vital capacity (FVC) at the time of diagnosis.

	Diagnostic delay < 1 year (N=78)	**Diagnostic delay > 1 year (N=186)**	**Total (N=264)**	**p value**
Antifibrotic treatment				0.41
- Nintedanib	23 (29.5%)	69 (37.1%)	92 (34.8%)	
- Pirfenidone	43 (55.1%)	96 (51.6%)	139 (52.7%)	
- No treatment	12 (15.4%)	21 (11.3%)	33 (12.5%)	

Table E3: Antifibrotic treatment in patients with a short (< 1 year) or long (> 1 year) diagnostic delay. Patients not eligible for antifibrotic treatment according no national guidelines (FVC < 50% or DLCO < 30% predicted) did not receive specific antifibrotic therapy are included in the "No treatment" group.

	Diagnostic delay < 1 year (N=70)	**Diagnostic delay > 1 year (N=168)**	**Total (N=238)**	**p value**
Antifibrotic treatment				0.39
- Nintedanib	22 (31.4%)	67 (39.9%)	89 (37.4%)	
- Pirfenidone	38 (54.3%)	84 (50.0%)	122 (51.3%)	
- No treatment	10 (14.3%)	17 (10.1%)	27 (11.3%)	

Table E4: Antifibrotic treatment in patients with a short (< 1 year) or long (> 1 year) diagnostic delay in patients eligible for antifibrotic treatment according to national guidelines. Patients not eligible (FVC < 50% or DLCO < 30% predicted) did not receive antifibrotic therapy.

	All patients				FVC ≤ 80% predicted at diagnosis				FVC > 80% predicted at diagnosis			
	< 1 year (N = 76)	> 1 year (N = 186)	Unadjusted p value	Adjusted p value	< 1 year (N = 28)	> 1 year (N = 58)	Unadjusted p value	Adjusted p value	< 1 year (N = 47)	> 1 year (N = 126)	Unadjusted p value	Adjusted p value
SGRQ total score deterioration [1]	15 (19.7%)	45 (24.2%)	0.44	0.52	2 (7.1%)	12 (20.7%)	0.11	0.11	13 (27.7%)	33 (26.2%)	0.85	0.88
SGRQ-$I_{derived}$ total score deterioration [2]	17 (22.4%)	59 (31.7%)	0.13	0.13	5 (17.9%)	16 (27.6%)	0.33	0.15	12 (25.5%)	43 (34.1%)	0.28	0.28
CAT total score deterioration [3]	21 (27.6%)	72 (38.7%)	0.09	0.12	7 (25.0%)	23 (39.7%)	0.18	0.19	14 (29.8%)	49 (38.9%)	0.27	0.31
Relative decrease in FVC > 10%	10 (13.2%)	31 (16.7%)	0.48	0.51	3 (10.7%)	12 (20.7%)	0.25	0.30	7 (14.9%)	19 (15.1%)	0.98	0.97
Relative decrease in DLCO > 15%	17 (22.4%)	63 (33.9%)	0.07	0.06	9 (32.1%)	16 (27.6%)	0.66	0.40	8 (17.0%)	47 (37.3%)	0.01	0.008
Death within 12 months	6 (7.9%)	17 (9.1%)	0.75	0.37	4 (14.3%)	7 (12.1%)	0.77	0.96	2 (4.3%)	10 (7.9%)	0.40	0.35
Fulfils definition of progressive ILD [4]	29 (38.2%)	92 (49.5%)	0.10	0.05	14 (50.0%)	29 (50.0%)	1.0	0.95	15 (31.9%)	63 (50.0%)	0.03	0.03

Table E5: Proportion of patients with progression within the first year from diagnosis of quality of life scores, lung function measurements, death and a compound definition of progressive fibrotic interstitial lung disease (ILD). [1] Increase of St. George's respiratory questionnaire (SGRQ) total score of at least 4 points, previously reported as the minimal clinically important difference (MCID)[1] [2] Increase of the IPF-specific version of the SGRQ, derived from the original SGRQ (SGRQ-$I_{derived}$) total score of at least 4 points. [3] Increase of the COPD assessment test (CAT) total score of at least 2, previously reported as the MCID[2] [4] Compound definition of progressive fibrotic ILD, based on forced vital capacity (FVC), diffusing capacity of carbon monoxide (DLCO), symptoms and progression of fibrosis on high resolution CT (HRCT) within 2 years, as previously described[3] Unadjusted p values based on chi-squared test. Adjusted p values based on logistic regression models, adjusted for age, sex, antifibrotic treatment, FVC at baseline and DLCO at baseline.

	HR (95% CI)	**p-value**
Entire cohort		
- Model A	1.70 (1.18–2.46)	0.004
- Model B	1.62 (1.13–2.33)	0.009
FVC > 80% at baseline		
- Model A	2.43 (1.45–4.01)	< 0.001
- Model B	2.47 (1.47–4.14)	< 0.001
FVC ≤ 80% at baseline		
- Model A	0.91 (0.51–1.62)	0.76
- Model B	0.85 (0.48–1.51)	0.57

Table E6: Sensitivity analysis of the multivariate cox proportional hazards analysis for the association between diagnostic delay (< 1 year or > 1 year) and progression-free survival.

Model A (presented in the main manuscript): adjusted for age, sex, FVC % predicted at baseline, DLCO % predicted at baseline and antifibrotic treatment.

Model B: adjusted for age, sex, FVC % predicted at baseline, DLCO % predicted at baseline, antifibrotic treatment and emphysema (yes/no)

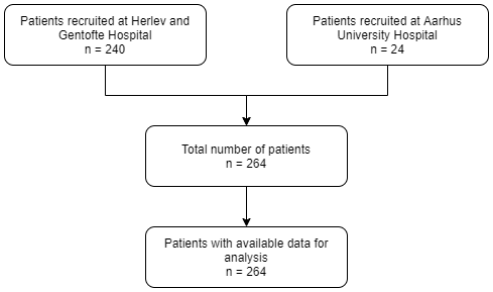

Figure E1: Flowchart of recruitment and follow-up of patients

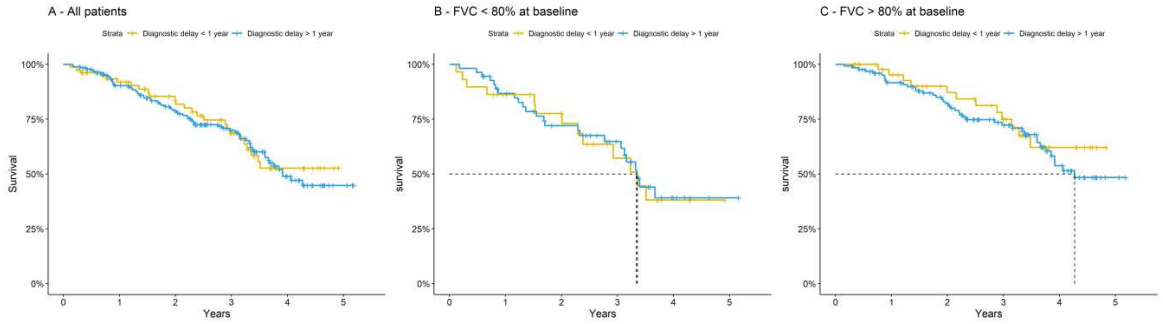

Figure E2: All-cause survival in patients with a short or long diagnostic delay in patients in subgroups based on FVC % of predicted at the time of diagnosis

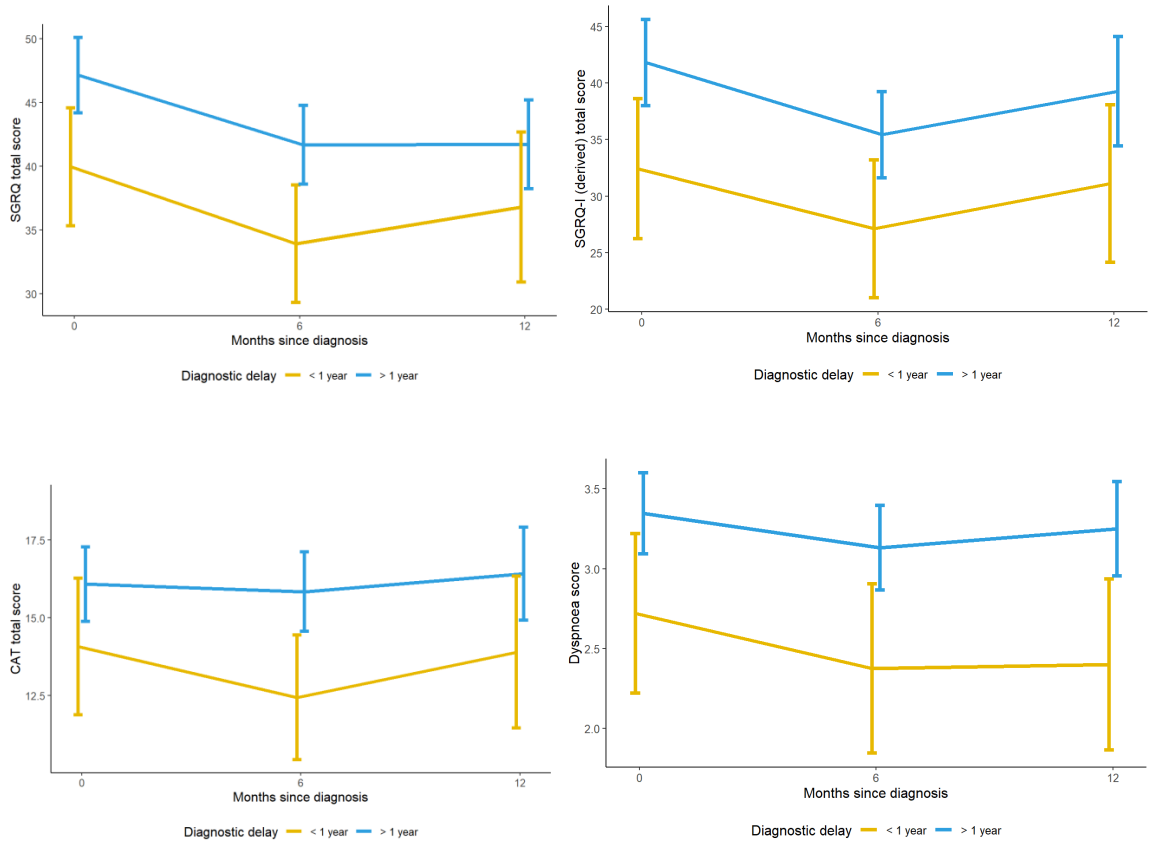

Figure E3: Change in Quality of life scores for patients with a short or long diagnostic delay and FVC>80% predicted at baseline.

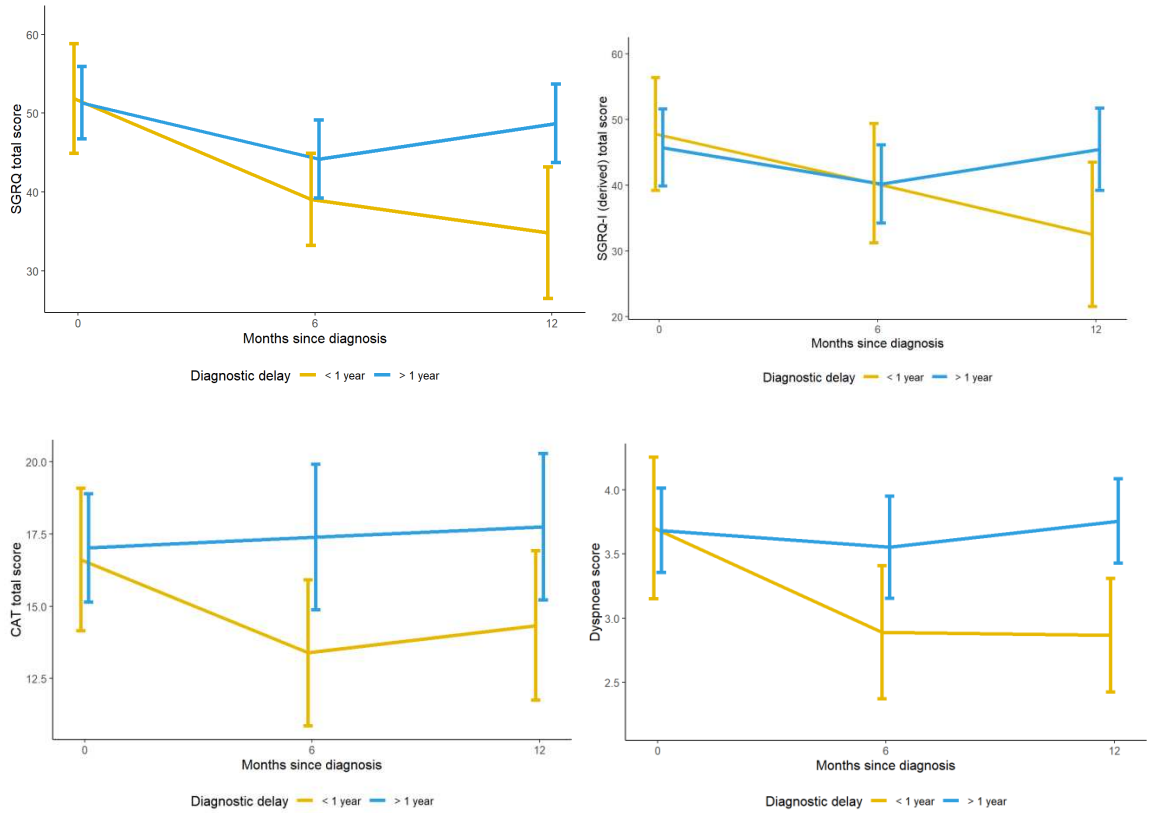

Figure E4: Quality of life scores for patients with a short or long diagnostic delay and FVC≤80% predicted at baseline.

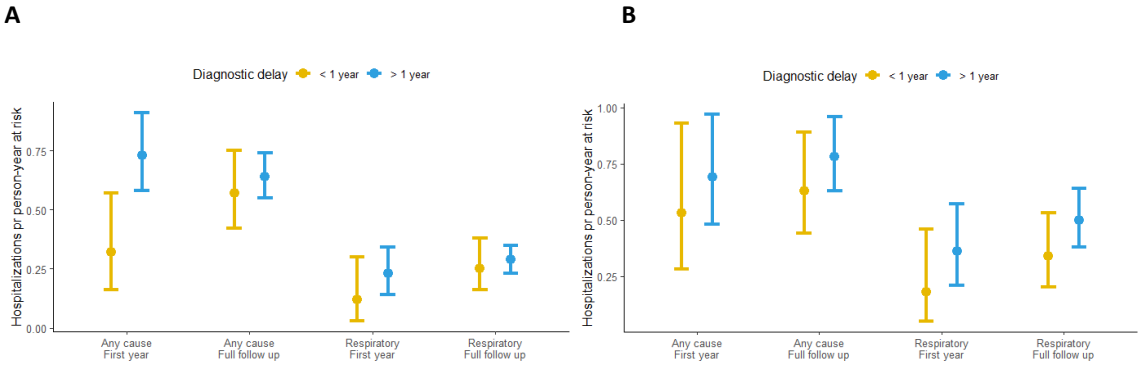

Figure E5: Hospitalisation rates in subgroups with baseline FVC > 80% predicted (A) and ≤ 80% predicted (B)

1. Jones Paul W. St. George's respiratory questionnaire: MCID. *COPD J. Chronic Obstr. Pulm. Dis.* 2005; 2: 75–79.
2. Kon Samantha SC, Canavan Jane L, Jones Sarah E, et al. Minimum clinically important difference for the COPD Assessment Test: A prospective analysis. *Lancet Respir. Med.* [Internet] Elsevier Ltd; 2014; 2: 195–203Available from: http://dx.doi.org/10.1016/S2213-2600(14)70001-3.
3. George Peter M, Spagnolo Paolo, Kreuter Michael, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. *Lancet Respir. Med.* [Internet] Elsevier Ltd; 2020; 8: 925–934 Available from: http://dx.doi.org/10.1016/S2213-2600(20)30355-6.