Early changes in serum PRO-C6 predict lung function trajectories in idiopathic pulmonary fibrosis

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BACKGROUND

- Extracellular matrix remodelling is central to idiopathic pulmonary fibrosis (IPF) pathology and progression. Especially remodelling of type VI collagen (COL6) has been linked to disease severity and progression.
- COL6 synthesis releases the neoepitope PRO-C6, which includes the signalling peptide endotrophin, that has pro-fibrotic effects and may bind to and activate platelets.
- Thus, serum PRO-C6 may be a candidate surrogate endpoint in clinical trials of IPF. Currently, there are no reliable tools to predict lung function trajectories.
- The aim of this study was to evaluate the prognostic ability of assessing early changes in serum PRO-C6 for predicting future lung function trajectories in IPF.

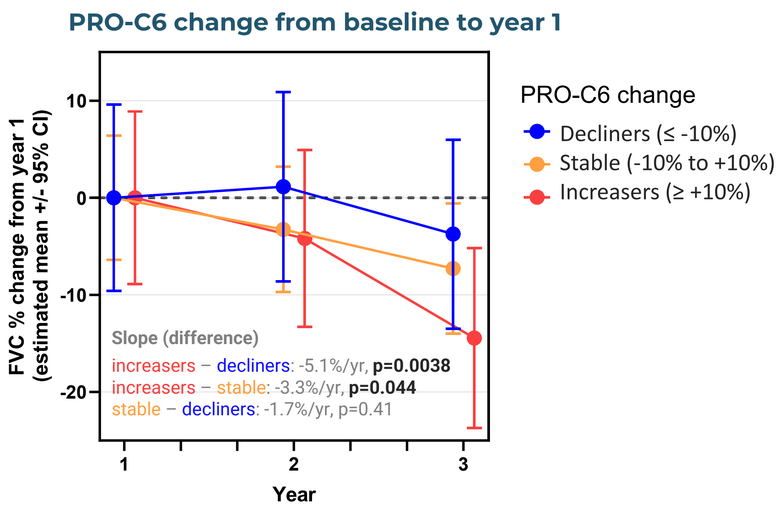
METHODS

- The PFBIO cohort (*NCT02755441*) recruited incident IPF patients prior to commencing anti-fibrotic therapy.
- COL6 synthesis was quantified in serum collected at baseline and year 1 by the biomarker PRO-C6 using the nordicPRO-C6™ ELISA.
- Patients were classified according to their relative serum PRO-C6 change from baseline to year 1 as increasers (≥ +10%, n=23), decliners (≤ -10%, n=20), or stable (-10 to +10%, n=45).
- Additional analyses investigated the predictive value of FVC change within the first year and an alternative definition of PRO-C6 change (increasers: ≥ +10%, n=101; decliners: ≤ -10%, n=30) that included the 6-month PRO-C6 data if 1-year data were unavailable to increase power.
- Trajectories of percent predicted forced vital capacity (FVC %) over three years were analyzed by linear mixed-effects models with random intercepts, stratified by change in serum PRO-C6 from baseline to year 1.

RESULTS

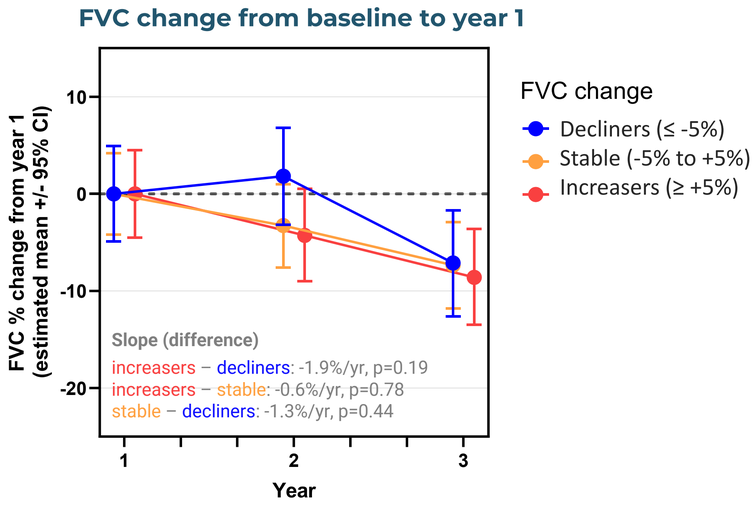
PRO-C6 increase predicted lung function decline better than FVC change

- PRO-C6 increasers had **5.1% more decline in FVC** per year than PRO-C6 decliners (P=0.0038).
- PRO-C6 increasers had a steeper FVC decline than patients with stable PRO-C6 levels (difference in slope -3.3% per year; P=0.044).



FVC change from year 1 by PRO-C6 change in year 1. IPF patients were stratified by serum PRO-C6 change from baseline to year 1 into decliners (≤ -10%), stable (-10 to +10%) and increasers (≥ +10%). The difference in change in FVC % from year 1 to 3 was analyzed by estimated annual change (slope) by group using a linear mixed-effects model.

- FVC trajectories from baseline to year 1 **had no association with FVC trajectories** in years 1-3 (P=0.19-0.78).



FVC change from year 1 by FVC change in year 1. IPF patients were stratified by their relative FVC change from baseline to year 1 into decliners (≤ -5%), stable (-5 to +5%) and increasers (≥ +5%). The difference in change in FVC % from year 1 to 3 was analyzed by estimated annual change (slope) by group using a linear mixed-effects model.

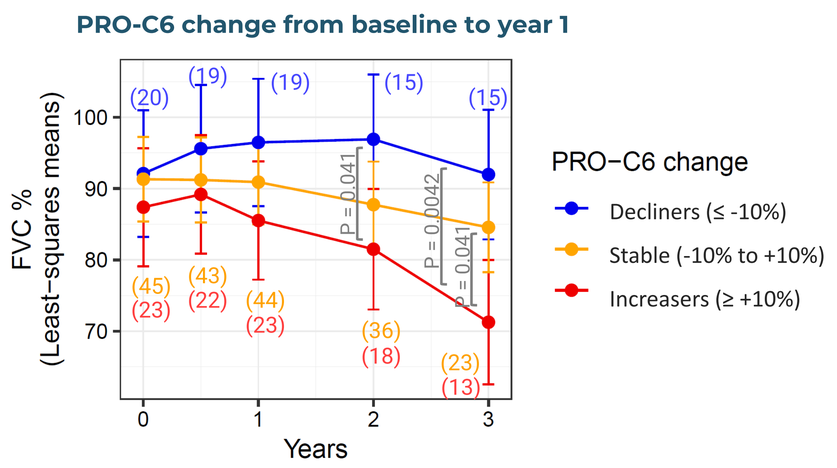
		Decliners	Increasers	Stable	p-value
n		20	23	45	
Age, years		75 [71, 79]	74 [66, 78]	72 [70, 78]	0.8
Male sex		16 (80)	17 (74)	32 (71)	0.8
BMI, m/kg^2		27 [23.8, 29.1]	25.5 [23.9, 32.0]	26.5 [25.1, 28.1]	>0.9
Smoking status	Current	2 (10)	3 (13)	5 (11)	0.5
	Former	10 (50)	16 (70)	31 (69)	
	Never	8 (40)	4 (17)	9 (20)	
Pack-years*		15 [6, 38]	20 [10, 50]	28 [12, 40]	0.7
FVC, % pred		93 [80, 98]	87 [75, 95]	89 [77, 104]	0.7
DLCO, % pred		59 [51, 63]	49 [41, 69]	55 [49, 62]	0.7
Treatment	None	4 (20)	3 (13)	8 (18)	>0.9
	Nintedanib	6 (30)	9 (39)	18 (40)	
	Pirfenidone	10 (50)	11 (48)	19 (42)	
Serum PRO-C6, ng/mL		10.5 [9.5, 12.7]	8.7 [7.4, 11.3]	9.2 [8.0, 10.9]	0.018

Data presented as median [Q_1, Q_3] or n (%). Analysed by Kruskal-Wallis rank sum test, Pearson's Chi-squared test or Fisher's exact test. *Pack-years = (packs smoked per day) × (number of years smoked). BMI: body mass index, %FVC: percent predicted forced vital capacity, %DLCO: percent predicted diffusing capacity of lung for carbon monoxide

3-years FVC trajectories were related to PRO-C6 change in year 1

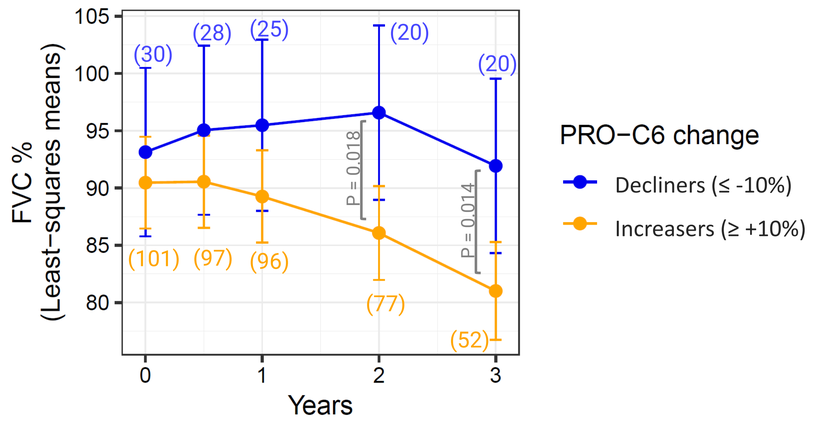
Clinical characteristics of the three PRO-C6 groups were similar at baseline (all p≥0.2). Interestingly, PRO-C6 change in year 1 was not associated with baseline %FVC or anti-fibrotic therapy regime.

PRO-C6 decliners maintained stable %FVC over three years whereas PRO-C6 increasers had lower %FVC at year 2 (mean difference -15.4% [95% CI -30.3 to -0.5]; p=0.041) and year 3 (-20.7% [-35.8 to -5.6]; p=0.0042). Additionally, PRO-C6 increasers had lower %FVC than stable PRO-C6 patients at year 3 (-13.3% [-26.2 to -0.4]; p=0.041).



Lung function trajectories for IPF patients by 1 year change in serum PRO-C6. IPF patients were stratified by serum PRO-C6 change from baseline to year 1 into decliners, stable and increasers. FVC trajectories were determined by linear mixed-effects models and plotted over three years.

PRO-C6 change from baseline to year 1 or month 6



Lung function trajectories for IPF patients with >10% change in serum PRO-C6 within 1 year. IPF patients were stratified by serum PRO-C6 change from baseline to year 1 into decliners and increasers. If 1-year data were unavailable, 6-month data were used instead. FVC trajectories were determined by linear mixed-effects models and plotted over three years.

TAKE HOME MESSAGES

- Changes in serum PRO-C6 over one year were independently associated with distinct lung function trajectories over three years in incident IPF patients.
- An increase in serum PRO-C6 of at least 10% within the first year was prognostic for decline in FVC in the next two years:
  - 5.1% per year steeper decline compared with PRO-C6 decliners
  - 3.3% per year steeper decline compared with patients with stable PRO-C6 levels
- Change in FVC within the first year was not associated with FVC slope in the next two years. Thus, PRO-C6 provided valuable insights into IPF progression beyond spirometry.
- In conclusion, increases in serum PRO-C6 were prognostic for future FVC decline, suggesting that PRO-C6 dynamics may identify high risk patients and could be a surrogate endpoint in clinical trials and a tool to improve patient care.

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Disclosures: JMBS, SHR, FBS, MAK, and DJL are employed at Nordic Bioscience and may be shareholders

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