Association of circulating proteins with death or lung transplant in the IPF-PRO™ Registry cohort

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INTRODUCTION

- Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease with an unpredictable clinical course.
- Biomarkers that predict clinically relevant outcomes remain an unmet need.
- Prior work has demonstrated that patients with IPF have a unique peripheral blood proteome,[1,2] thus proteomic profiling may identify targets for development of prognostic biomarkers.

AIM

- To examine the association between circulating proteins and the composite outcome of respiratory death or lung transplant in 300 patients with IPF.

METHODS

Study cohort

- The cohort was drawn from the Idiopathic Pulmonary Fibrosis Prospective Outcomes (IPF-PRO) Registry, a multicenter US registry that enrolled patients with IPF that was diagnosed or confirmed at the enrolling center in the past 6 months.[3]
- These analyses were based on data from 300 patients enrolled between March 2016 and February 2017.
- Outcomes were ascertained from enrollment to June 2019.

Proteomic assays

- Plasma samples taken at enrollment were assayed using an aptamer-based platform encompassing 1305 proteins.
- Protein data were $\log_2$ transformed prior to analysis.

Analyses

- The univariable association between each protein and the composite outcome of respiratory death or lung transplant was determined using Cox proportional hazards modelling.
  - Linearity and proportional hazards assumptions associated with the unadjusted model were assessed prior to fitting each model.
  - Analyses were adjusted for sex, age, FVC % predicted, DLco % predicted, oxygen use at rest, oxygen use with activity (all assessed at enrollment).
  - P-values were corrected for multiple comparisons using the Benjamini-Hochberg method to control the false discovery rate (FDR) at 5%.
- Multivariable analyses were performed to determine a set of candidate predictors for the composite outcome of respiratory death or lung transplant, using Cox regression modelling with the elastic net penalty considering:
  1. proteins only
  2. proteins and clinical factors (sex, age, FVC % predicted, DLco % predicted, oxygen use at rest, oxygen use with activity [all assessed at enrollment]).
- Model performance was assessed by Harrell's C-index, corrected for optimism.

CONCLUSIONS

- In a cross-sectional analysis of 300 patients with IPF, select circulating proteins strongly associated with respiratory death or lung transplant, even after considering clinical factors known to influence outcomes.
- We report a protein signature for predicting respiratory death or lung transplant in patients with IPF that can be evaluated in a validation cohort.
- Important considerations for validation studies will include the method of protein measurement (aptamer vs ELISA) and exposure to antifibrotic drugs.

RESULTS

Patient characteristics at enrollment (n=300).

Age, years	70 (65, 75)
Male	223 (74%)
White	281 (94%)
Smoking	
Past	202 (67%)
Never	96 (32%)
Current	2 (1%)
FVC % predicted	69.7 (61.0, 80.2)
DLco % predicted	40.5 (31.1, 49.3)
Antifibrotic drug use	
Pirfenidone	106 (35%)
Nintedanib	56 (19%)
Neither	138 (46%)

Values are median (Q1, Q3) or n (%).

Figure 1: Kaplan-Meier curve for the composite of respiratory death or lung transplant.

- Median (Q1, Q3) follow-up was 30.4 (20.1, 41.1) months
- 76 respiratory deaths and 26 lung transplants occurred during follow-up

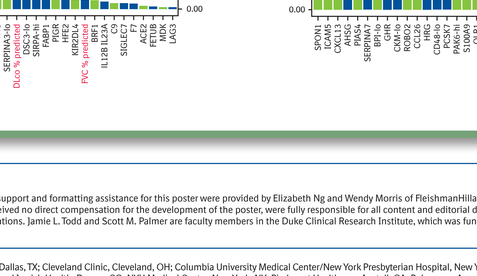
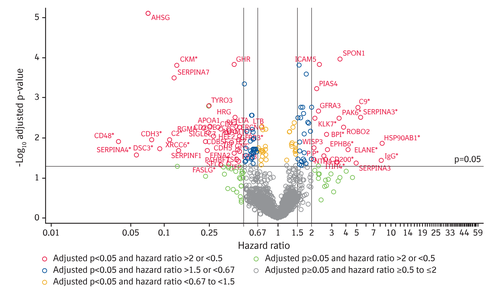


Figure 2: Unadjusted analyses of associations between each protein and composite of respiratory death or lung transplant.



*Analyte failed linearity or proportional hazards assumption. For analytes that failed the linearity assumption, the hazard ratio associated with the maximum relative effect from 2-3 piece-wise linear (PWL) components used to represent this analyte is shown. For analytes that failed the proportional hazards assumption, the time-dependent hazard ratio associated with the maximum relative effect at 12, 24, or 36 months is shown. For analytes that failed both, the maximum hazard ratio associated with PWL components at 12, 24, or 36 months is shown.

In unadjusted analyses, **61 proteins** were significantly associated* with the composite of respiratory death or lung transplant

After adjustment for clinical factors, **22 proteins** were significantly associated* with the composite of respiratory death or lung transplant

*Hazard ratio >2 or <0.5 and adjusted p<0.05.

Variable importance of predictors of respiratory death or lung transplant

Figure 4: Model considering proteins and clinical factors as predictors of respiratory death or lung transplant.

Selected clinical factors were oxygen use at rest, oxygen use with activity, DLco % predicted, FVC % predicted

Only oxygen use had greater importance than proteins in predicting the composite outcome

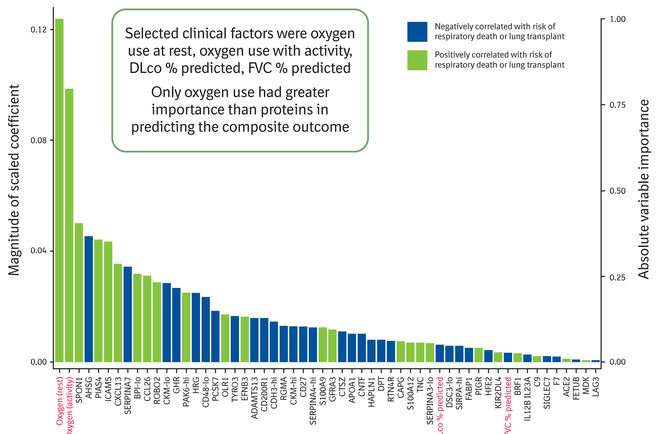
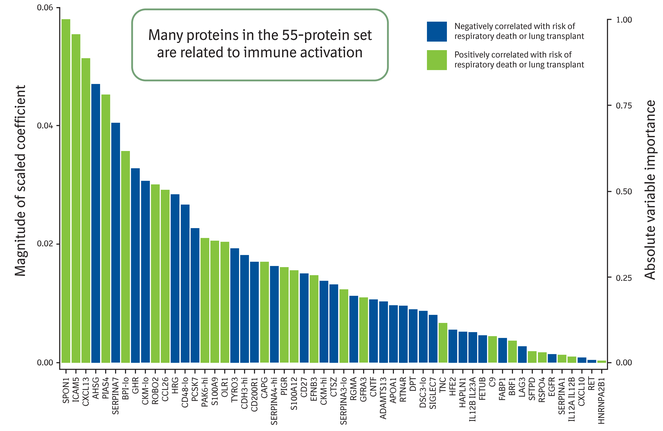


Figure 3: Model considering proteins only as predictors of respiratory death or lung transplant.

Many proteins in the 55-protein set are related to immune activation



Multivariable analyses of predictors of respiratory death or lung transplant: model performance metrics

In analyses considering proteins only, a set of **55 proteins** predicted the probability of respiratory death or lung transplant with a C-index* of 0.76

In analyses considering proteins and clinical factors†, a set of **56 predictors (52 proteins, 4 clinical)** were selected with a C-index* of 0.77

*Corrected for optimism.
†Sex, age, FVC % predicted, DLco % predicted, oxygen use at rest, oxygen use with activity (all assessed at enrollment).

REFERENCES
1. O'Dwyer DN, et al. Sci Rep 2017;7:46560.
2. Todd JL, et al. Respir Res 2019;20:227.
3. O'Brien EC, et al. BMJ Open Respir Res 2016;3:e000108.

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INTERACTIVE

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IPF-PRO™ Registry enrolling centers: Albany Medical Center, Albany, NY; Baylor College of Medicine, Houston, TX; Baylor University Medical Center at Dallas, Dallas, TX; Cleveland Clinic, Cleveland, OH; Columbia University Medical Center/New York Presbyterian Hospital, New York, NY; Duke University Medical Center, Durham, NC; Froedtert & The Medical College of Wisconsin Community Physicians, Milwaukee, WI; Houston Methodist Lung Center, Houston, TX; Lahey Clinic, Burlington, MA; Loyola University Health System, Maywood, IL; Lynchburg Pulmonary Associates, Lynchburg, VA; Medical University of South Carolina, Charleston, SC; National Jewish Health, Denver, CO; NYU Medical Center, New York, NY; Piedmont Healthcare, Austell, GA; Pulmonary Associates of Stamford, Stamford, CT; PulmonIx LLC, Greensboro, NC; Renovatio Clinical, The Woodlands, TX; Salem Chest and Southeastern Clinical Research Center, Winston Salem, NC; South Miami Hospital, South Miami, FL; St. Joseph's Hospital, Phoenix, AZ; Stanford University, Stanford, CA; Temple University, Philadelphia, PA; The Oregon Clinic, Portland, OR; Tulane University, New Orleans, LA; UNC Chapel Hill, Chapel Hill, NC; University of Alabama at Birmingham, Birmingham, AL; University of California, Davis, Sacramento, CA; University of California Los Angeles, Los Angeles, CA; University of Chicago, Chicago, IL; University of Cincinnati Medical Center, Cincinnati, OH; University of Louisville, Louisville, KY; University of Miami, Miami, FL; University of Michigan, Ann Arbor, MI; University of Minnesota, Minneapolis, MN; University of Pennsylvania, Philadelphia, PA; University of Pittsburgh, Pittsburgh, PA; University of Virginia, Charlottesville, VA; UT Southwestern Medical Center, Dallas, TX; Vanderbilt University Medical Center, Nashville, TN; Vermont Lung Center, Colchester, VT; Wake Forest University, Winston Salem, NC; Washington University, St. Louis, MO; Weill Cornell Medical College, New York, NY; Wilmington Health and PMG Research, Wilmington, NC; Yale School of Medicine, New Haven, CT.

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