Association of neoepitopes with disease severity and respiratory hospitalization in patients with IPF

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INTRODUCTION

- IPF is characterized by parenchymal accumulation of collagen-rich extracellular matrix.
- When the extracellular matrix is degraded by matrix metalloproteinases (MMPs), circulating protein fragments known as neoepitopes are generated.[1]
- Higher baseline levels and increases over time in levels of certain neoepitopes have been associated with progression of IPF.[2,3]

AIM

- To determine whether serum concentrations of neoepitopes at baseline associate with measures of disease severity at baseline and clinically relevant outcomes over follow-up in 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 has enrolled patients with IPF that was diagnosed or confirmed at the enrolling center in the past 6 months.[4]
- These analyses were based on data from 300 patients enrolled between March 2016 and February 2017.

Assays

- Serum concentrations of 7 neoepitopes at enrollment were determined using ELISA-based assays:

Neoepitope	Abbreviation
Biglycan degraded by MMP-2/9	BGM
Collagen 3 degraded by ADAMTS-1/4/8	C3A
Collagen 3 degraded by MMP-9	C3M
Collagen 5 degraded by MMP-2/9	C5M
Collagen 6 degraded by MMP-2/9	C6M
C-reactive protein degraded by MMP-1/8	CRPM
Citrullinated vimentin degraded by MMP-2/8	VICM

ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; MMP, matrix metalloproteinase.

- Analytes were $\log_2$ transformed before analysis.

Analyses

- We used generalized linear models to test for associations between levels of these neoepitopes and three disease severity measures at enrollment: the composite physiologic index (CPI), which correlates with the extent of fibrosis on radiography,[5] DLco % predicted, FVC % predicted.
  - Models were then adjusted for use of anti-fibrotic therapy (nintedanib or pirfenidone) at enrollment.
- We used Cox proportional hazards regression models to test for associations between levels of these neoepitopes at enrollment and the following outcomes: death, respiratory death, death or lung transplant, respiratory death or lung transplant, respiratory hospitalization.
  - Models were then adjusted for these variables, all assessed at enrollment: age, sex, oxygen use at rest, oxygen use with activity, DLco % predicted, FVC % predicted, and GAP (gender, age, lung physiology) score.[6]
- P-values were adjusted to control the false discovery rate (FDR) at 5%.

CONCLUSIONS

- In 300 patients with IPF, serum levels of select neoepitopes were associated with measures of disease severity at baseline and the risk of respiratory hospitalization over follow-up.
- Further research is needed to assess the utility of neoepitopes in stratifying risk in patients with IPF.

RESULTS

Patient characteristics at enrollment (n=300)

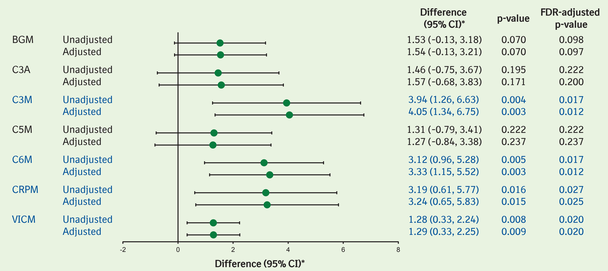
Age, years	70 (65, 75)
Male	223 (74%)
White	281 (94%)
Smoking	
Past	202 (67%)
Never	96 (32%)
Current	2 (1%)
FVC % predicted	69.7 (61.0, 80.2)
DLco % predicted	40.5 (31.1, 49.3)
Antifibrotic drug use	
Pirfenidone	106 (35%)
Nintedanib	56 (19%)
Neither	138 (46%)

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

Associations between neoepitopes and disease severity measures at enrollment

- Circulating levels of C3M, C6M, CRPM and VICM were associated with CPI at enrollment (FDR-adjusted p<0.05). Adjusting for anti-fibrotic drug use did not influence these associations (Figure 1).

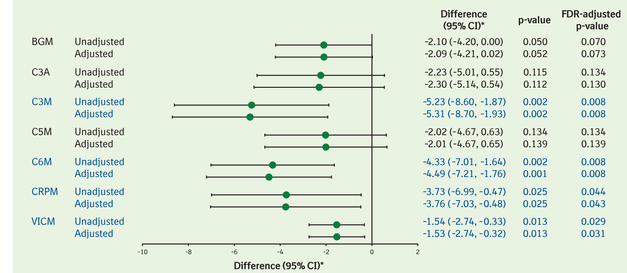
Figure 1. Associations between neoepitopes and CPI at enrollment



*Difference in CPI per doubling of neoepitope concentration.
Adjusted models were adjusted for anti-fibrotic drug use at enrollment.

- C3M, C6M, CRPM and VICM were also associated with DLco % predicted at enrollment (Figure 2).
- No neoepitopes were associated with FVC % predicted at enrollment.

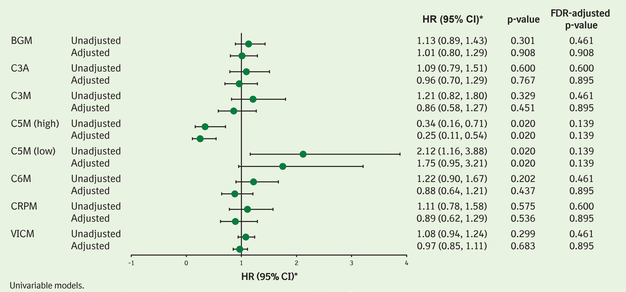
Figure 2. Associations between neoepitopes and DLco % predicted at enrollment



*Difference in DLco % predicted per doubling of neoepitope concentration.
Adjusted models were adjusted for anti-fibrotic drug use at enrollment.

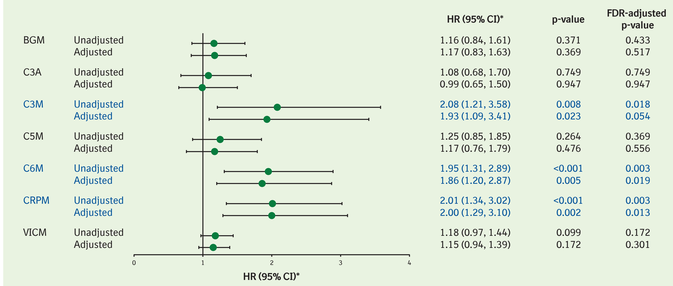
- None of the associations between the level of a neoepitope and the risk of death or lung transplant (Figure 4) or the other outcomes studied had an FDR-adjusted p<0.05.

Figure 4. Associations between neoepitopes at enrollment and risk of death or lung transplant



Univariable models.
*Indicates risk of death or lung transplant per unit increase in baseline $\log_2$ concentration of each neoepitope.
C5M did not meet linearity assumption; piece-wise linear (PWL) spline was used to characterize non-linearity and two components are shown.
Adjusted models were adjusted for age, sex, oxygen use at rest, oxygen use with activity, DLco % predicted, FVC % predicted, and GAP score at enrollment.

Figure 3. Associations between neoepitopes at enrollment and risk of respiratory hospitalization



Univariable models.
*Indicates risk of respiratory hospitalization per unit increase in baseline $\log_2$ concentration of each neoepitope.
Adjusted models were adjusted for age, sex, oxygen use at rest, oxygen use with activity, DLco % predicted, FVC % predicted, and GAP score at enrollment.

Associations between neoepitopes at enrollment and outcomes

- A one-unit increase in the $\log_2$ concentration of C3M, C6M, or CRPM at baseline was associated with an approximately two-fold increase in the risk of respiratory hospitalization (FDR-adjusted p<0.05) over a median follow-up of 30 months (Figure 3).
- C6M and CRPM maintained their associations after adjusting for clinical factors (Figure 3).

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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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