Circulating prostasin: an independent risk marker in idiopathic pulmonary fibrosis (IPF)

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INTRODUCTION

- Identifying prognostic biomarkers in patients with IPF remains an unmet need.
- Prostasin is a serine protease expressed in alveolar epithelial cells where it regulates fluid and electrolyte balance via sodium channel proteolysis.[1]
- Circulating prostasin level may be predictive of disease progression in patients with interstitial lung diseases.[2,3]

AIM

- To examine associations between prostasin at enrollment and changes in prostasin over 6 months and the risk of respiratory death in patients in the IPF-PRO Registry.

METHODS

- The IPF-PRO Registry is a multicenter US registry of patients with IPF that was diagnosed or confirmed at the enrolling center in the past 6 months.[4]
- Prostasin levels were quantified in plasma samples taken at enrollment (n=624) and at 6 ± 3 months post-enrollment (n=292) using immunoassay (Myriad RBM).
- The cumulative incidence of respiratory death stratified by prostasin level above or below the median at enrollment was described in the overall cohort and in subsets by use of antifibrotic therapy at enrollment.
- Cox proportional hazards models, unadjusted and adjusted for age, sex, FVC % predicted, and DLco % predicted at enrollment, were used to test the association between prostasin level at enrollment and respiratory death.
- Associations between absolute change in prostasin from enrollment to 6 months and subsequent respiratory death were analyzed using Cox proportional hazards models, landmarked at the follow-up (6 ± 3 months post-enrollment) sample collection date. The model was minimally adjusted (for prostasin at enrollment) or fully adjusted (for prostasin, age, sex, FVC % predicted, and DLco % predicted at enrollment).
- Two-step iterative resampling was used to test the internal validity of the associations seen in the Cox proportional hazards models. The analysis cohort was randomly split into discovery and replication cohorts in a 7:3 ratio and 100 random splits were taken. Findings were to be considered internally robust if the association was validated in ≥20% of the 100 random splits.[5]

CONCLUSIONS

- In a real-world cohort of patients with IPF, circulating prostasin level at baseline, and absolute change in prostasin level over 6 months, were associated with the risk of respiratory death after adjusting for demographic and clinical factors known to be associated with disease progression.
- These findings supports the potential value of prostasin as a prognostic biomarker in patients with IPF.

RESULTS

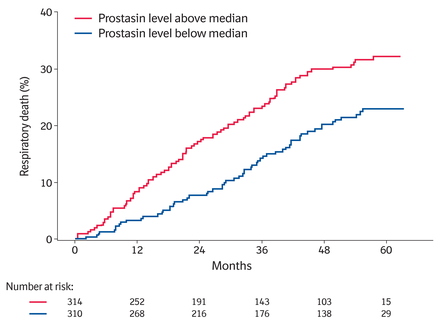
Characteristics at enrollment (N=624)

Age (years)	69.8 (7.8)
Male	464 (74.4)
White*	500 (91.1)
Ever smoker†	416 (66.8)
FVC % predicted	72.5 (18.5)
DLco % predicted	43.6 (15.1)
Taking antifibrotic therapy	302 (48.4)
Nintedanib	157 (25.2)
Pirfenidone	145 (23.2)
Prostasin level (ug/L)	466 (159)

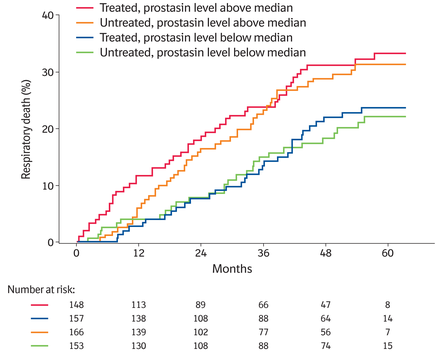
Data are mean (SD) or n (%). *N=549 analyzed. †N=623 analyzed.

Prostasin level at enrollment and risk of respiratory death

Cumulative incidence of respiratory death stratified by prostasin level at enrollment

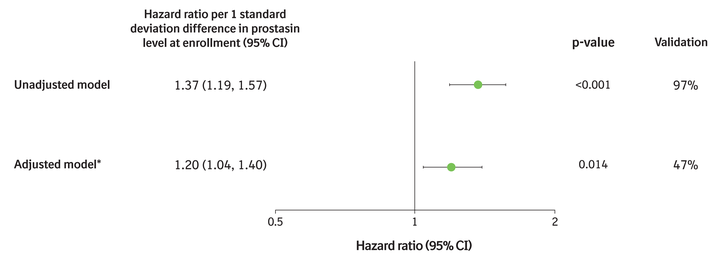


Cumulative incidence of respiratory death stratified by prostasin level and antifibrotic therapy at enrollment



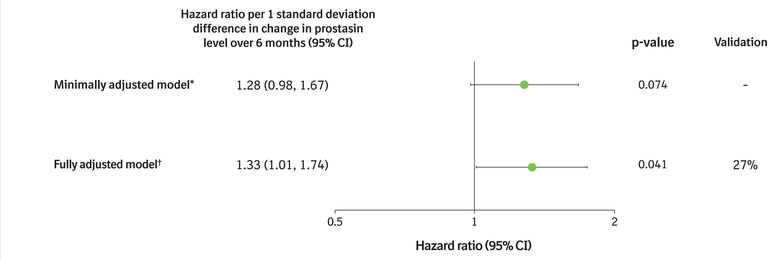
Median follow-up: 37.2 months.

Associations between prostasin level at enrollment and respiratory death in unadjusted and adjusted models



*Adjusted for age, sex, FVC % predicted, and DLco % predicted at enrollment.

Associations between change in prostasin level from enrollment to 6 months and subsequent respiratory death in adjusted models



*Adjusted for prostasin at enrollment. †Adjusted for prostasin, age, sex, FVC % predicted, and DLco % predicted at enrollment.

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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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