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

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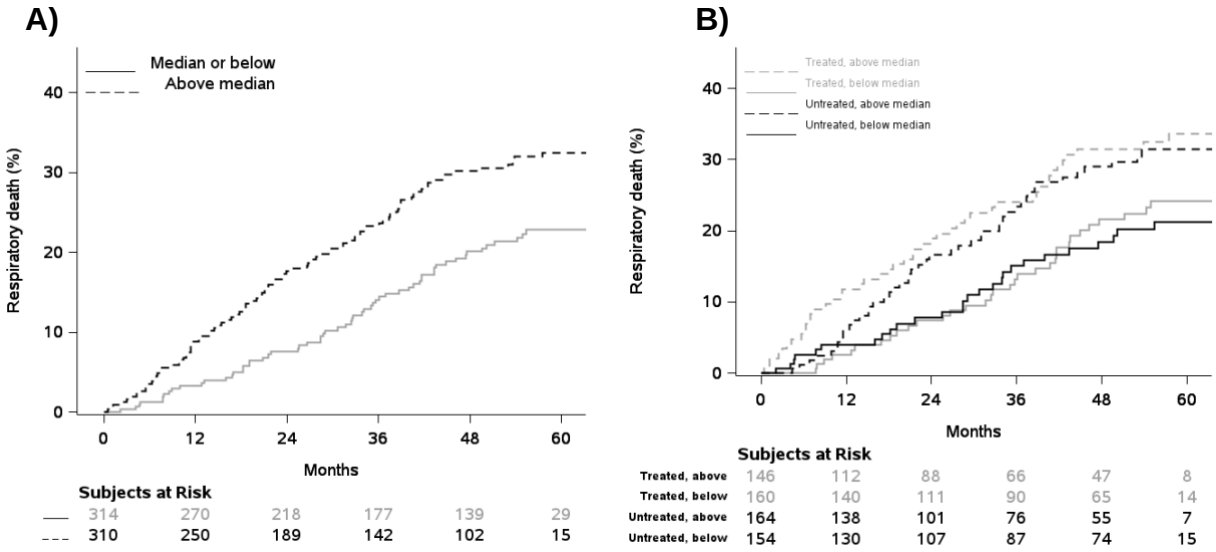
Rationale: Identifying prognostic biomarkers in patients with IPF remains an unmet need. Prostasin is a serine protease expressed in alveolar epithelial cells where it regulates fluid and electrolyte balance via sodium channel proteolysis. Prior analyses of the IPF-PRO Registry demonstrated that circulating prostasin level correlates with the presence and severity of IPF. We examined associations between prostasin at enrollment and changes in prostasin over 6 months and risk of respiratory death.

Methods: The cohort included 627 patients with IPF that was diagnosed or confirmed at the enrolling center in the prior 6 months. Prostasin was quantified by ELISA in plasma collected at enrollment (n=624) and at 6 (+/- 3) months post-enrollment (n=292). The cumulative incidence of respiratory death was described using plots stratified by enrollment prostasin level above or below the median. Cox proportional hazards models tested the associations between a) enrollment prostasin level, b) absolute change in prostasin level over 6 months and respiratory death. Models were adjusted for age, sex, FVC % predicted, DLco % predicted at enrollment. Models evaluating change in prostasin were adjusted for prostasin at enrollment and landmarked at the time of the 6-month sample.

Results: At enrollment, mean (SD) age was 69.8 (7.8) years, 74% were male, 91% were white. Mean FVC % predicted and DLco % predicted were 72.5 (18.5) and 43.6 (15.1), respectively; half of patients were taking antifibrotic therapy (24.8% nintedanib, 23.6% pirfenidone). Prostasin level was similar in patients on vs. not on antifibrotic therapy (median [Q1, Q3] among all patients 445.0 [352.5, 553.5] ug/L). Over a median follow-up of 37.2 (17.2, 59.0) months, the

cumulative incidence of respiratory death was higher among patients with an enrollment prostasin level above than below the median; this finding was consistent between untreated and treated patients (Figure). In multivariable analyses, enrollment prostasin level was associated with respiratory death, with a 12% increase in HR with every 100-unit higher prostasin level (adjusted HR 1.12; 95% CI 1.02, 1.23; p=0.014). Increases in prostasin over 6 months were associated with an increased risk of subsequent respiratory death, with an 8% increase in HR for every 30-unit increase in prostasin (adjusted HR 1.08; 95% CI 1.00, 1.17; p=0.041).
Conclusions: These results suggest that prostasin is an independent risk marker for mortality in patients with IPF, including those receiving antifibrotic therapy. Dynamic changes in prostasin may provide useful information about mortality risk beyond that provided by a single measurement.

Figure: A) Cumulative incidence of respiratory death among patients stratified by enrollment prostasin level above the median vs. at or below the median. **B)** Cumulative incidence of respiratory death among patients not taking antifibrotic therapy and taking antifibrotic therapy stratified by enrollment prostasin level above the median vs. at or below the median.



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