Associations between circulating matrix metalloproteinases and their inhibitors and mortality in patients with IPF: data from the IPF-PRO™ Registry

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INTRODUCTION

- IPF is a progressive fibrosing interstitial lung disease with an unpredictable clinical course.
- Matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of matrix metalloproteinases (TIMPs), are involved in the development and progression of IPF.[1,2]

AIM

- To examine associations between circulating MMPs and TIMPs and clinical outcomes in patients with IPF.

METHODS

Study cohort

- The cohort was drawn from the 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.

Analyses

- Concentrations of 8 MMPs (MMPs 1, 2, 3, 7, 8, 9, 12, 13) and 3 TIMPs (TIMPs 1, 2, 4) in enrollment plasma samples were quantified by ELISA and $\log_2$ transformed prior to analysis.
- Univariable associations between each MMP or TIMP and clinical outcomes were determined using Cox proportional hazards regression analyses. We present results for death and for the composite of absolute decline from baseline in FVC ≥10% predicted, death, or lung transplant.
- Analyses were unadjusted and adjusted for demographic/clinical factors assessed at enrollment (age, sex, FVC % predicted, DLco % predicted, oxygen use at rest, oxygen use with exertion).
- For MMPs/TIMPs that failed proportional hazards assumptions, hazard ratios were computed at 12, 24 and 36 months to describe the non-proportionality over time.
- P-values were corrected for multiple comparisons using the Benjamini-Hochberg method to control the false discovery rate (FDR) at 5%. An MMP or TIMP was considered to be significantly associated with the outcome if the FDR-adjusted p-value was <0.05.

CONCLUSIONS

- In this analysis of 300 patients with IPF with long-term follow-up data, circulating levels of select MMPs or TIMPs identified patients at increased risk of death or disease progression, independent of clinical characteristics known to influence these outcomes.
- Ongoing work includes validation of these findings and assessment of longitudinal changes in these MMPs and TIMPs to clarify their roles as candidate biomarkers for progression of IPF.

RESULTS

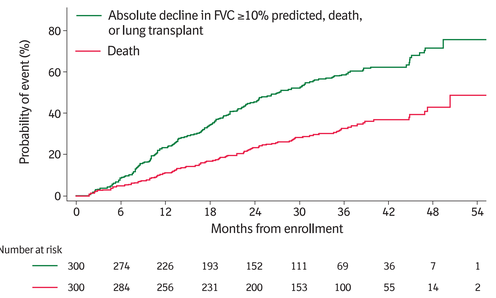
Patient characteristics at enrollment (n=300)

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%)

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

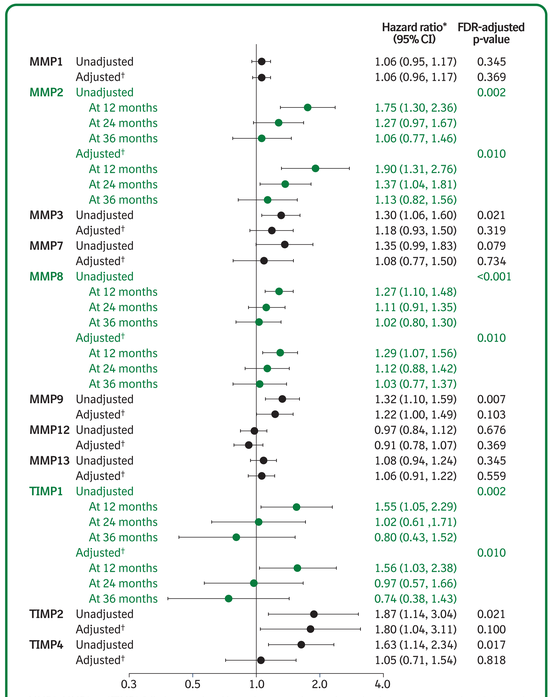
- Over a median (Q1, Q3) follow-up of 30.4 (20.1, 41.1) months:
  - 98 patients died
  - 182 patients met the composite outcome of absolute decline in FVC ≥10% predicted, death, or lung transplant:
    - » Absolute decline in FVC ≥10% predicted: n=110
    - » Death: n=61
    - » Lung transplant: n=11.

Kaplan-Meier curves for death and composite of absolute decline in FVC ≥10% predicted, death, or lung transplant



Associations between circulating MMPs and TIMPs at baseline and death

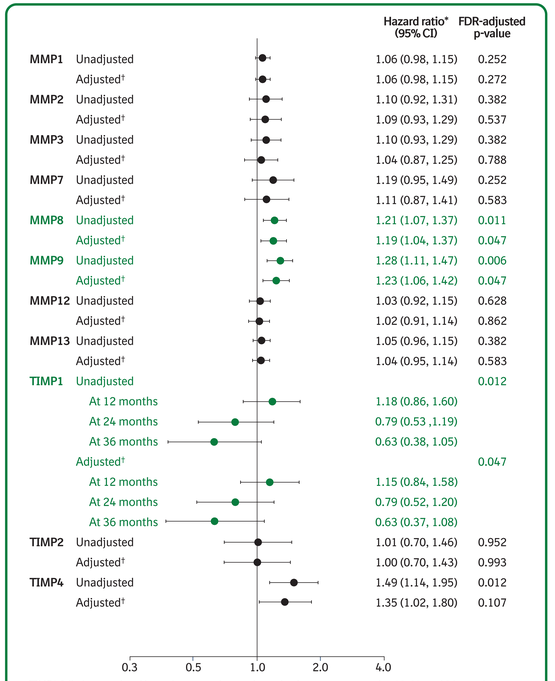
- In unadjusted analyses, higher concentrations of MMPs 2, 3, 8 and 9 and TIMPs 1, 2 and 4 were associated with an increased risk of mortality. MMPs 2 and 8 and TIMP1 remained significantly associated with mortality after adjustment for demographic/clinical factors.



MMP2, MMP8 and TIMP1 failed proportional hazards assumptions so hazard ratios were computed at 12, 24, and 36 months.
*Hazard ratio per unit increase in baseline $\log_2$(concentration) of each MMP/TIMP.
†Adjusted models were adjusted for age, sex, FVC % predicted, DLco % predicted, oxygen use at rest, and oxygen use with exertion at enrollment.

Associations between circulating MMPs and TIMPs at baseline and composite of absolute decline in FVC ≥10% predicted, death, or lung transplant

- In unadjusted analyses, higher concentrations of MMPs 8 and 9 and TIMPs 1 and 4 at baseline were associated with the composite outcome. MMPs 8 and 9 and TIMP1 remained significantly associated with the composite outcome after adjustment for demographic/clinical factors.



TIMP1 failed proportional hazards assumptions so hazard ratios were computed at 12, 24, and 36 months.
*Hazard ratio per unit increase in baseline $\log_2$(concentration) of each MMP/TIMP.
†Adjusted models were adjusted for age, sex, FVC % predicted, DLco % predicted, oxygen use at rest, and oxygen use with exertion 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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