Associations between circulating microRNAs and clinical outcomes in patients with IPF: data from the IPF-PRO™ Registry

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on behalf of the IPF-PRO Registry investigators

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INTRODUCTION

- IPF is a progressive fibrosing interstitial lung disease with an unpredictable clinical course.
- MicroRNAs are small non-coding RNA molecules with functions in gene silencing or post-transcriptional gene regulation. Altered expression of microRNAs has been implicated in the pathogenesis of IPF.[1,2]

AIM

- To examine associations between microRNAs 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 283 patients enrolled between March 2016 and February 2017 who had enrollment plasma microRNA sequencing data that met quality control filters. Outcomes were ascertained from enrollment to June 2019.

Analyses

- MicroRNA transcripts with median counts per million ≥1 were analysed. Normalization factors for library sizes were calculated using the Trimmed Means of M values method and an effective elibrary size used to normalize microRNA read counts. Counts were $\log_2$ transformed prior to analysis.
- Univariable associations between microRNA expression at baseline and clinical outcomes were determined using Cox proportional hazards regression analyses.
- 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 microRNAs with non-linear relationships with outcomes, piece-wise linear splines with a single knot were used, resulting in two hazard ratios.
- P-values were corrected for multiple comparisons using the Benjamini-Hochberg method to control the false discovery rate (FDR) at 5%. MicroRNAs were considered to be significantly associated with the outcome if both the FDR-adjusted p-value for the overall association was <0.05 and ≥1 of the two hazard ratios was >2 or <0.5.

CONCLUSIONS

- We identified several microRNAs that were associated with clinically relevant outcomes in patients with IPF after adjustment for demographic/clinical factors known to influence outcomes.
- These microRNAs require further study as candidate biomarkers in patients with IPF.

RESULTS

Patient characteristics at enrollment (n=283)

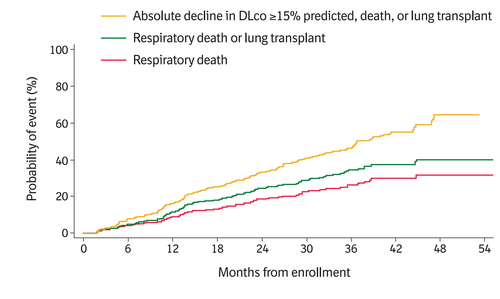
Age, years	70 (65, 75)
Male	209 (74%)
White	264 (93%)
Smoking	
Past	188 (66%)
Never	93 (33%)
Current	2 (1%)
FVC % predicted	69.8 (60.9, 80.3)
DLco % predicted	40.1 (30.7, 49.2)
Composite physiologic index (CPI)	54.0 (46.5, 60.9)
Antifibrotic drug use	
Pirfenidone	96 (34%)
Nintedanib	55 (19%)

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

Associations between circulating microRNAs at baseline and clinical outcomes

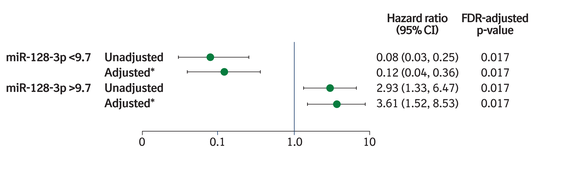
- A total of 472 microRNA transcripts were included in the analysis.
- The median (Q1, Q3) follow-up time was 30.4 (20.0, 41.1) months.
- In adjusted analyses, significant associations were observed between microRNAs and three clinical outcomes:
  - Respiratory death (occurred in 69 patients)
  - Composite of respiratory death or lung transplant (occurred in 93 patients)
  - Composite of absolute decline in DLco ≥15% predicted, death, or lung transplant (occurred in 141 patients).
- No significant associations were observed between microRNAs and the other outcomes investigated: death; death or lung transplant; respiratory hospitalization; absolute decline in FVC ≥10% predicted, death, or lung transplant; ≥5-point increase in CPI, death, or lung transplant; ≥10-point increase in CPI, death, or lung transplant.

Kaplan-Meier curves for clinical outcomes



- In both unadjusted and adjusted analyses, one microRNA was significantly associated with respiratory death.

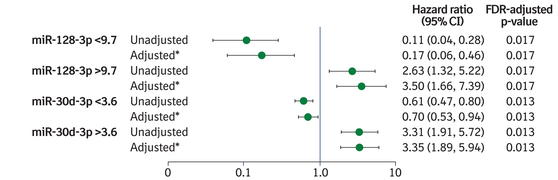
Associations between circulating microRNAs at baseline and respiratory death that were significant in unadjusted and adjusted analyses



There was a non-linear relationship between miR-128-3p and respiratory death so a linear spline with a single knot was used, resulting in two hazard ratios.
*Adjusted models were adjusted for age, sex, FVC % predicted, DLco % predicted, oxygen use at rest, and oxygen use with exertion at enrollment.

- In both unadjusted and adjusted analyses, two microRNAs were significantly associated with the composite of respiratory death or lung transplant.

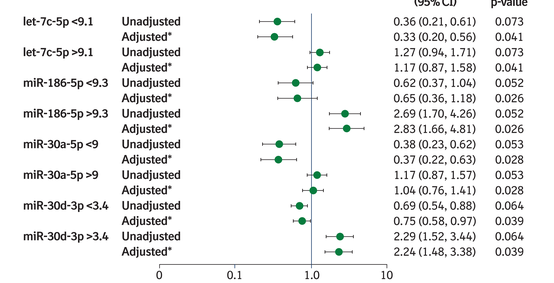
Associations between circulating microRNAs at baseline and composite of respiratory death or lung transplant that were significant in unadjusted and adjusted analyses



There were non-linear relationships between microRNAs and outcomes so linear splines with a single knot were used, resulting in two hazard ratios for each microRNA-outcome combination.
*Adjusted models were adjusted for age, sex, FVC % predicted, DLco % predicted, oxygen use at rest, and oxygen use with exertion at enrollment.

- In adjusted analyses, four microRNAs were associated with the composite of absolute decline in DLco ≥15% predicted, death, or lung transplant.

Associations between circulating microRNAs at baseline and composite of absolute decline in DLco ≥15% predicted, death, or lung transplant that were significant in adjusted analyses



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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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