Combination of multigene profiles and clinical factors improves prediction of short-term outcomes in idiopathic pulmonary fibrosis

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INTRODUCTION

- IPF is a progressive fibrosing interstitial lung disease with high mortality and a variable clinical course.
- Potential biomarkers of IPF progression have been identified, including circulating proteins and transcripts, but their predictive value beyond clinical risk factors remains uncertain.

AIMS

- To derive gene-inclusive profiles that discriminate risk of short-term disease progression in patients with IPF.
- To identify molecular pathways that are enriched in patients who experience short-term disease progression.
- To compare the performance of gene-inclusive predictors with models that consider clinical factors alone.

METHODS

Analysis cohort

- The cohort was drawn from the IPF-PRO Registry, a multicenter US registry of patients with IPF.[1]
- Patients were included if they had clinical data and whole blood totalRNA sequencing that met quality control parameters (>45 million input reads; intragenic mapping rate >0.7; uniquely mapping reads >50%; rRNA mapping rate <0.05; number of detected genes >10000).

Clinical outcomes and differential gene expression

- Outcomes assessed at 12 months post-enrollment were death and IPF progression (≥10% decline in FVC % predicted, death, or lung transplant).
- Differentially expressed genes between patients with versus without each outcome were identified using DESeq2. For each outcome, genes were filtered to include only those with median counts per million ≥0.125, overall and in those with and without an event (20,623 genes for death; 20,799 genes for IPF progression).
  - The Benjamini-Hochberg procedure controlled the false discovery rate (FDR) at 5%.
  - Enriched pathways were detected by performing overrepresentation analysis at gene level with clusterProfiler and canonical pathways from Reactome.

Predictive models for clinical outcomes

- Elastic net logistic regression was used to derive predictive models for each outcome using the following potential predictors:
  - Differentially expressed genes with FDR-adjusted p≤0.05 and $\log_2$fold-change (FC) ≥1.
  - Demographic/clinical factors at enrollment: FVC % predicted, DLco % predicted, oxygen use, age, sex.
- The variable importance of the selected predictors was plotted.
- Models including only clinical factors were also constructed.
- Model performance was assessed using the raw C-index and optimism-corrected C-index.

CONCLUSIONS

- In patients with IPF, a combination of circulating gene expression profiles and clinical measures accurately predicted the risk of short-term mortality.
- Models that included both gene expression and clinical measures had better discriminatory ability for short-term risk of death or IPF progression than models considering only clinical factors.
- Long non-coding RNAs were important in outcome discrimination, warranting further evaluation of their regulatory functions in IPF.

RESULTS

Cohort characteristics at enrollment (n=259)

Age (years)	70 (65, 75)
Male	195 (75%)
White	248 (96%)
Past/current smoker	176 (67%)
FVC % predicted	70.5 (61.2, 80.2)
DLco % predicted	41.0 (32.5, 49.8)
Oxygen use at rest	47 (18%)
Oxygen use with activity	86 (33%)
Antifibrotic drug use	125 (48%)

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

Number of genes with differential expression in patients with versus without a clinical event

Outcome	$\lvert\log_2FC\rvert \geq 0.58^*$ and corrected p<0.05	$\lvert\log_2FC\rvert \geq 1^\dagger$ and corrected p<0.05
Death (n=27, 10%)	427	94
Progression (n=66, 25%)	40	15

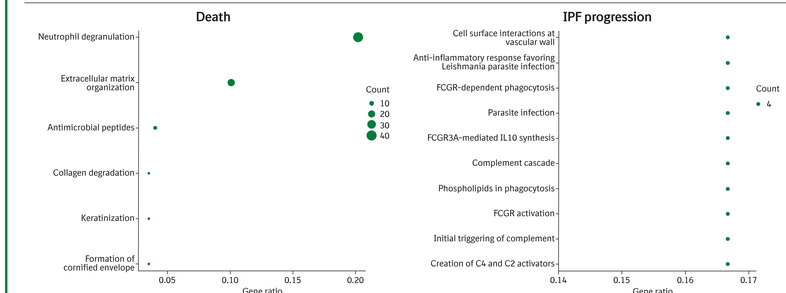
*Absolute fold change >50% in patients with event vs without event.
†Absolute fold change >200% in patients with event vs without event.

Associations between genes and clinical outcomes

Multivariable prediction models

Model	Raw C-index	Optimism-corrected C-index
Death		
Genes alone: • 31 genes selected	0.97	0.90
Genes and clinical factors: • 29 genes and 3 clinical factors selected	0.98	0.92
Clinical factors alone	0.75	0.51
IPF progression		
Genes alone: • 4 genes selected	0.70	0.63
Genes and clinical factors: • 15 genes and 6 clinical factors selected	0.75	0.67
Clinical factors alone	0.63	0.49

Enriched canonical pathways identified by differentially expressed genes related to innate immune system



Only genes with FDR-corrected p<0.05 and $\lvert\log_2FC\rvert$>0.58 were considered. Pathways with adjusted p<0.01 are shown. For IPF progression, only pathways with gene ratio ≥0.13 are shown. FCGR, Fc-gamma receptor.

Variables selected by models, ordered by importance

Variable importance measures were calculated as the absolute value of scaled regression coefficients divided by the largest coefficient in absolute value.
*Long non-coding RNAs.

REFERENCE
1. O'Brien EC et al. BMJ Open Respir Res 2016;3:e000108.

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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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