

Phenotypic Clusters Predict Outcomes in a Longitudinal Interstitial Lung Disease Cohort

Ayodeji Adegunsoye, MD; Justin M. Oldham, MD; Jonathan H. Chung, MD; Steven M. Montner, MD; Cathryn Lee, MD; Leah J. Witt, MD; Danielle Stahlbaum, MD; Rene S. Bermea, MD; Lena W. Chen, BS; Scully Hsu, BS; Aliya N. Husain, MD; Imre Noth, MD; Rekha Vij, MD; Mary E. Streck, MD; and Matthew Churpek, MD, MPH, PhD

CHEST 2018; 153(2):349-360

Online supplements are not copyedited prior to posting and the author(s) take full responsibility for the accuracy of all data.

© 2017 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details. DOI: 10.1016/j.chest.2017.09.026

e-Table 1. Baseline Characteristics of Patients With Chronic ILD Stratified by Phenotypic Clusters.

Characteristics	All patients (n=770)	Cluster 1 (n=210)	Cluster 2 (n=114)	Cluster 3 (n=276)	Cluster 4 (n=170)	p-value*
Age, mean (±SD)	64.5 (11.6)	62.6 (11.4)	56.8 (13.4)	66.8 (10.4)	68.4 (9.1)	<0.0001
Female gender, n (%)	369 (47.9)	170 (81.0)	108 (94.7)	57 (20.7)	34 (20.0)	<0.0001
African American race/ethnicity, n (%)	127 (16.5)	13 (6.2)	90 (78.9)	13 (4.7)	11 (6.5)	<0.0001
BMI, mean (±SD)	30.1 (6.8)	31.9 (7.3)	29.3 (7.2)	29.6 (6.2)	29.3 (6.5)	0.0001
Tobacco pack years, mean (±SD)	17.7 (23.9)	13.7 (21.8)	8.6 (15.1)	20.4 (25.8)	24.4 (25.3)	<0.0001
Gastroesophageal reflux, n (%)	394 (51.2)	173 (82.4)	44 (38.6)	51 (18.5)	126 (74.1)	<0.0001
Crackles, n (%)	675 (87.7)	185 (88.1)	90 (78.9)	244 (88.4)	156 (91.8)	0.013
Clubbing, n (%)	111 (14.4)	25 (11.9)	10 (8.8)	41 (14.9)	35 (20.6)	0.025
FVC (% predicted) (±SD)	64.5 (18.1)	69.7 (18.0)	57.1 (17.8)	65.2 (17.8)	62.0 (16.8)	<0.0001
FEV1 (% predicted) (±SD)	76.2 (20.6)	80.5 (20.9)	65.3 (20.7)	78.1 (20.6)	75.3 (17.8)	<0.0001
FEV1/FVC (% predicted) (±SD)	83.7 (8.2)	83.7 (7.7)	85.4 (8.4)	83.3 (8.1)	83.1 (9.0)	0.083
SpO ₂ :FiO ₂ ratio (±SD)	409.7 (75.7)	411.6 (74.1)	423.8 (70.4)	409.9 (75.5)	397.3 (80.1)	0.0344
DLCO (% predicted) (±SD)	49.5 (21.0)	56.4 (22.6)	45.2 (19.6)	48.8 (20.4)	45.0 (18.7)	<0.0001
Gamma gap (mg/dl) (±SD)	3.4 (0.6)	3.2 (0.6)	3.8 (0.7)	3.3 (0.6)	3.5 (0.6)	<0.0001
ANA titer, median (mean)	320 (643)	160 (455)	1280 (1455)	160 (452)	320 (639)	<0.0001
Positive RF, n (%)	86 (11.2)	16 (7.6)	20 (17.5)	32 (11.6)	18 (10.6)	0.059
Other positive serologies**, n (%)	73 (9.5)	16 (7.6)	18 (15.8)	14 (5.1)	25 (14.7)	<0.0001
Radiographic honeycombing, n (%)	266 (34.5)	30 (14.3)	19 (16.7)	68 (24.6)	149 (87.6)	<0.0001
Radiographic emphysema, n (%)	180 (23.4)	31 (14.8)	24 (21.1)	84 (30.4)	41 (24.1)	0.001
Hypothyroidism, n (%)	129 (16.8)	52 (24.8)	15 (13.2)	35 (12.7)	27 (15.9)	0.003
Organic environmental exposure, n (%)	342 (44.4)	152 (72.4)	14 (12.3)	54 (19.6)	122 (71.8)	<0.0001
Inorganic environmental exposure, n (%)	137 (17.8)	24 (11.4)	3 (2.6)	58 (21.0)	52 (30.6)	<0.0001
PA diameter, mean (±SD)	29.9 (4.9)	28.6 (4.2)	30.3 (5.3)	30.2 (5.1)	30.9 (4.6)	<0.0001
Aorta diameter, mean (±SD)	33.8 (4.2)	32.6 (3.9)	31.5 (4.1)	34.8 (4.1)	35.0 (3.9)	<0.0001

*comparing clusters 1, 2, 3, and 4. ILD = Interstitial Lung Disease; BMI=body mass index; FVC=forced vital capacity; FEV1=forced expiratory volume in first second; SpO₂=oxygen saturation by pulse oximetry; FiO₂=fraction of inspired oxygen; DLCO=diffusion capacity of the lungs for carbon monoxide; ANA=antinuclear antibody; RF=rheumatoid factor; PA=pulmonary artery;

**Anti-cyclic citrullinated peptide, Anti-double stranded DNA, Anti-Ro(SSA), Anti-La (SSB), Anti-ribonucleoprotein, Anti-Smith, Anti-topoisomerase (Scl-70), Anti-tRNA synthetase.

e-Table 2. Mixed Regression Model for Monthly FVC and DLCO Change in Chronic ILD.

	ILD Diagnosis Classification					
	CHP	IPF	p-value	CTD-ILD	IPAF	p-value
FVC decline, % (SE)	-0.16 (0.06)	-0.25 (0.07)	0.215	-0.10 (0.07)	-0.09 (0.05)	0.953
DLCO decline, % (SE)	-0.16 (0.07)	-0.31 (0.09)	0.101	-0.10 (0.05)	-0.20 (0.08)	0.233
	Phenotypic Clusters					
	Cluster 1	Cluster 3	p-value	Cluster 2	Cluster 4	p-value
FVC decline, % (SE)	-0.16 (0.04)	-0.17 (0.04)	0.852	+0.01 (0.05)	-0.30 (0.05)	<0.001
DLCO decline, % (SE)	-0.23 (0.07)	-0.14 (0.05)	0.223	+0.01 (0.09)	-0.48 (0.06)	<0.001

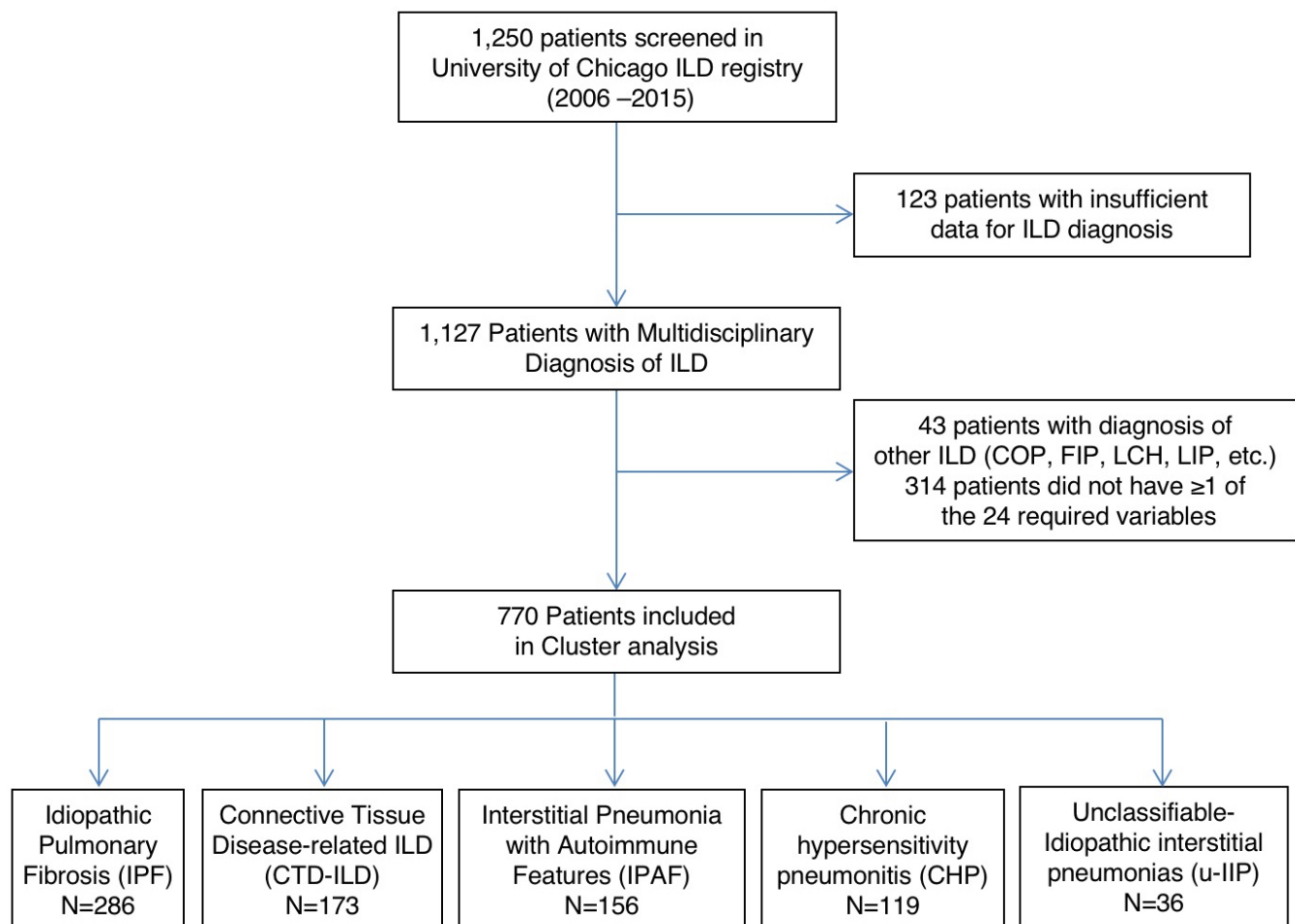
ILD = interstitial lung disease; FVC = forced vital capacity; DLCO = diffusing capacity of the lung for carbon monoxide; SE = standard error; CHP = chronic hypersensitivity pneumonitis; IPF = idiopathic pulmonary fibrosis; CTD-ILD = connective tissue disease-associated ILD

e-Table 3. Prediction of Survival by Clusters in Patients With Chronic Interstitial Lung Disease (ILD) After Adjustment for IPF Classification.

Characteristic	Progression-free survival (within 1 st year of diagnosis)			Transplant-free survival (within 10 years of diagnosis)		
	HR	95% CI	p-value	HR	95% CI	p-value
Multivariable Cox Regression*#						
Phenotypic Cluster						
Cluster 1	2.68	1.44 – 4.96	0.002	1.79	1.09 – 2.93	0.021
Cluster 3	1.95	1.05 – 3.63	0.035	2.46	1.56 – 3.87	<0.001
Cluster 4	3.27	1.77 – 6.03	<0.001	3.01	1.88 – 4.80	<0.001

IPF = idiopathic pulmonary fibrosis; *reference category: Cluster 2; #n=727; adjusted for phenotypic cluster, IPF classification, gender, age, forced vital capacity, diffusing capacity of the lungs for carbon monoxide, ILD subtype and immunosuppressive therapy.

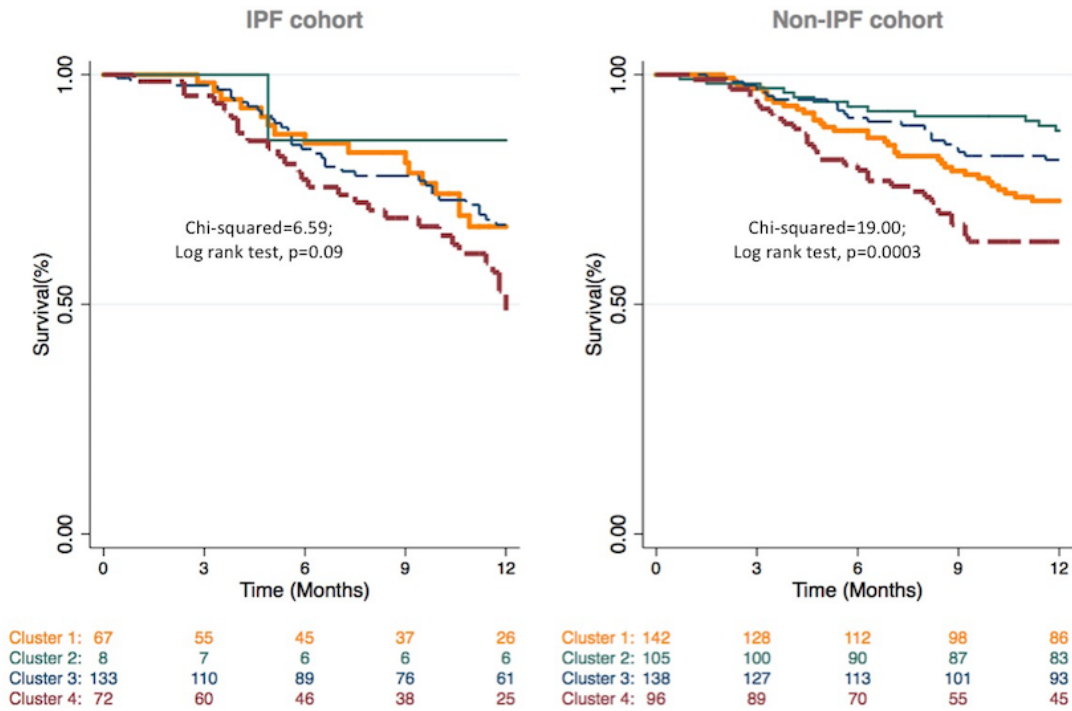
e-Figure 1. CONSORT Diagram.



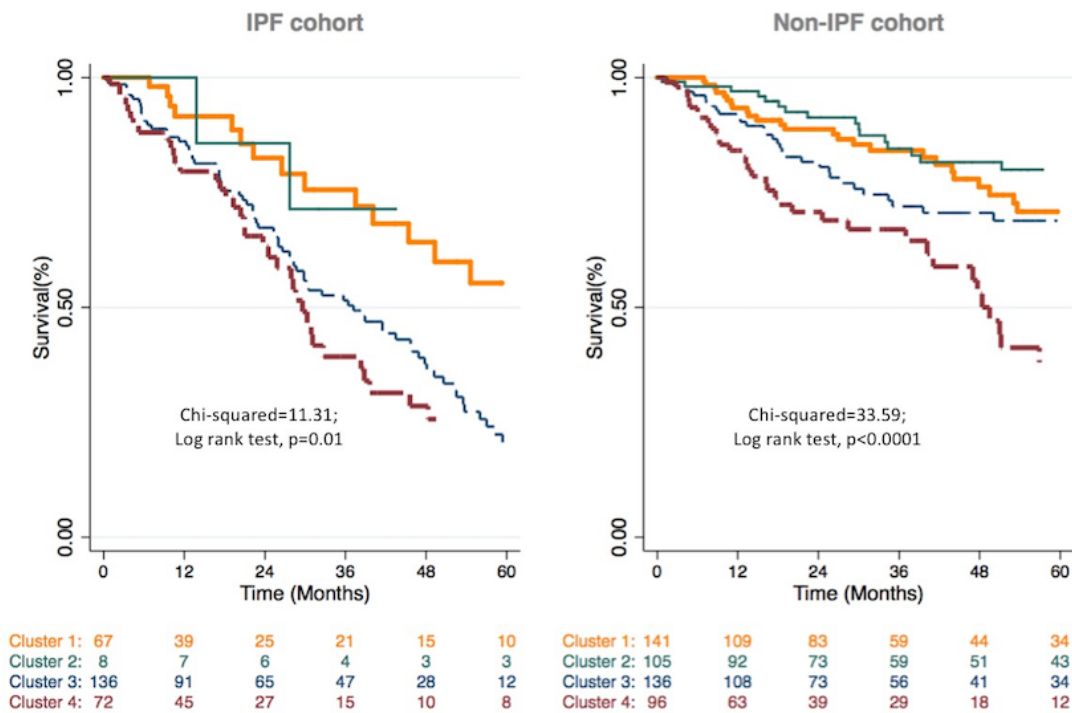
ILD= interstitial lung disease; COP = cryptogenic organizing pneumonia; FIP = familial interstitial pneumonia; LCH = Langerhans cell histiocytosis; LIP – lymphoid interstitial pneumonia.

e-Figure 2. (A) Progression-Free Survival (PFS) in Chronic Interstitial Lung Disease (ILD) After Substratification Into Idiopathic Pulmonary Fibrosis (IPF) and Non-IPF Cohorts; (B) 10-Year Transplant-Free Survival in Chronic ILD After Substratification Into IPF and Non-IPF Cohorts.

PFS in Chronic Interstitial Lung Disease Stratified by ILD subtype



TFS in Chronic Interstitial Lung Disease Stratified by ILD subtype



e-Figure 3. 10-Year Transplant-Free Survival in Chronic ILD (Excluding All Out-of-State Referrals); n = 585.

