High-density lipoproteins, disease severity and clinical outcomes in idiopathic pulmonary fibrosis

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INTRODUCTION

- Apolipoprotein A-1 (ApoA1) and paraoxonase-1 (PON-1) are components of high-density lipoprotein (HDL) with anti-inflammatory and antioxidant properties.[1]
- In animal models, administration of ApoA1 attenuates lung fibrosis.[2]
- Patients with IPF have lower levels of ApoA1 in bronchoalveolar lavage fluid.[2]
- Relationships between ApoA1 and PON-1 and disease severity and outcomes in patients with IPF have not been established.

AIM

- To assess associations between circulating levels of HDL-cholesterol (HDL-C), ApoA1 and PON-1 and outcomes in patients with IPF.

METHODS

The IPF-PRO Registry

- Patients with IPF that was diagnosed or confirmed at the enrolling center in the prior 6 months were enrolled into the IPF-PRO Registry at 46 US sites.[3]
- Blood samples and clinical data were collected at enrollment. Patients were followed prospectively, with follow-up data collected as part of routine clinical care until death, lung transplant, or withdrawal.

Analyses

- HDL-C was measured by standard clinical assay at a single laboratory. ApoA1 and PON-1 were measured using an aptamer-based platform (SOMAscan, SOMALogic, Inc). Values were $\log_2$ transformed before analysis.
- Associations between HDL-C, ApoA1 and PON-1 levels and measures of disease severity (FVC % predicted, DLco % predicted, composite physiologic index [CPI][4]) at enrollment were assessed using linear regression models.
- Associations between HDL-C, ApoA1 and PON-1 levels at enrollment and time to clinically relevant outcomes were assessed using Cox proportional hazards regression models.
- Models were unadjusted or adjusted for age, sex, race (white vs non-white), smoking status, body mass index (BMI), C-reactive protein, triglycerides, low-density lipoprotein (LDL), coronary artery disease, diabetes, heart failure, and use of statins, antifibrotic drugs, and oral corticosteroids at enrollment. FVC (L) at enrollment was included as a covariate in the Cox proportional hazards regression models.

CONCLUSIONS

- Among patients in the IPF-PRO Registry, a higher circulating level of ApoA1 was associated with higher FVC % predicted at enrollment in unadjusted models, with a similar effect size in models adjusted for demographic and clinical variables. A higher circulating level of PON-1 was associated with lower FVC % predicted at enrollment in unadjusted and adjusted models.
- In adjusted models, a higher circulating level of ApoA1 at enrollment was associated with a lower risk of respiratory hospitalization, but not with a lower risk of FVC decline. There were no significant associations between PON-1 levels and clinical outcomes.

RESULTS

Characteristics of analysis cohort at enrollment (n=284)

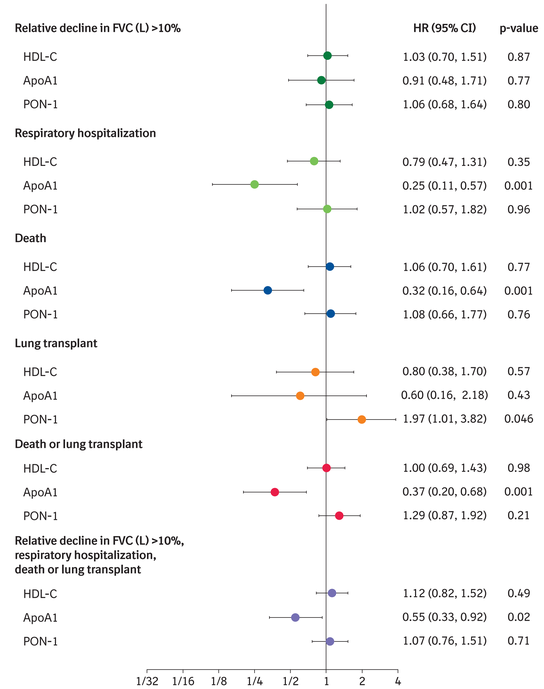
Male	213 (75.0)
Age, years	70 (65, 75)
Ever smoker	193 (68.0)
BMI, kg/m²	29.4 (26.3, 32.8)
FVC % predicted	70.0 (61.2, 80.2)
DLco % predicted	40.8 (31.8, 49.5)
CPI	53.3 (46.2, 60.4)
Antifibrotic drug use	133 (46.8)
Oxygen use at rest	56 (19.8)
Oxygen use with activity	44 (15.5)
HDL-C, mg/dL	48.9 (40.4, 61.0)
ApoA1, RFU	15,284 (13,377, 16,811)
PON-1, RFU	214 (193, 244)

The analysis cohort included all patients active in the registry as of February 2017, with data on HDL-C , ApoA1 and PON-1 levels, and height, sex, age, FEV_1, FVC and DLco at enrollment. Data are median (Q1, Q3) or n (%) of patients. Not all patients provided data for all variables. RFU, relative fluorescent units.

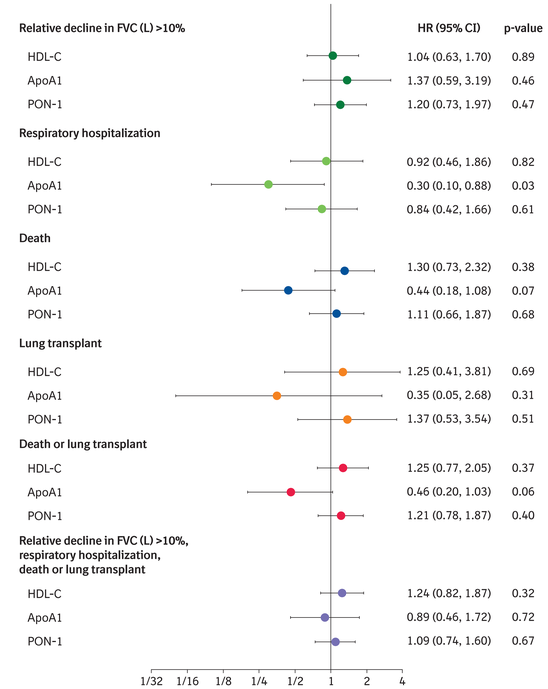
Associations between HDL-C , ApoA1 and PON-1 and disease severity at enrollment

	Unadjusted change in disease severity measure per unit higher $\log_2$ concentration (95% CI)	P-value	Adjusted change in disease severity measure per unit higher $\log_2$ concentration (95% CI)	P-value
FVC % predicted				
HDL-C	3.4 (−1.3, 8.0)	0.15	2.3 (−3.7, 8.3)	0.45
ApoA1	7.4 (0.0, 14.9)	0.049	6.9 (−2.7, 16.5)	0.16
PON-1	−6.9 (−11.9, −1.8)	0.008	−6.5 (−11.5, −1.5)	0.01
DLco % predicted				
HDL-C	−2.1 (−6.0, 1.8)	0.29	0.7 (−4.2, 5.5)	0.79
ApoA1	6.1 (−0.1, 12.3)	0.053	4.3 (−3.5, 12.0)	0.28
PON-1	−1.3 (−5.6, 3.0)	0.56	−1.1 (−5.2, 3.0)	0.59
CPI				
HDL-C	0.4 (−2.7, 3.5)	0.78	−1.7 (−5.6, 2.2)	0.40
ApoA1	−5.5 (−10.4, −0.5)	0.03	−4.5 (−10.8, 1.8)	0.16
PON-1	2.1 (−1.3, 5.5)	0.23	2.1 (−1.3, 5.4)	0.23

Unadjusted associations between HDL-C, ApoA1 and PON-1 and clinical outcomes



Adjusted associations between HDL-C, ApoA1 and PON-1 and clinical outcomes



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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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