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

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**Rationale:** High-density lipoprotein-cholesterol (HDL-C) and its components, apolipoprotein A-1 (ApoA1) and paraoxonase-1 (PON-1), have anti-inflammatory and antioxidant properties, which may protect against the development and progression of pulmonary fibrosis. We hypothesized that higher levels of ApoA1 and PON-1 would be associated with better clinical outcomes in adults with idiopathic pulmonary fibrosis (IPF).

**Methods:** We used baseline and follow-up data collected in the observational IPF-PRO Registry. The cohort included 284 participants with IPF that was diagnosed or confirmed at one of 14 enrolling centers in the US in the prior 6 months, who had a plasma HDL measurement at the time of enrollment. HDL was measured by standard clinical assay. ApoA1 and PON-1 were measured in plasma using an aptamer-based proteomic platform (SOMAscan, SOMALogic Inc., Boulder, CO). Participants were followed for 3-5 years and received local standard of care. Linear regression was used to examine associations between biomarkers and measures of disease severity. Cox models were used to examine associations between biomarkers and time to 10% relative decline in forced vital capacity (FVC) (L), respiratory hospitalization, lung transplantation, and death. Models were adjusted for baseline demographic and clinical variables (**Table**).

**Results:** Mean (SD) age was 69.5 (7.8) years, 75% were male, 94% were white, 3% were Hispanic, 68% were ever-smokers; mean (SD) body mass index was 29.7 (4.9); mean (SD) FVC was 71% (16.6) predicted. Greater ApoA1 was associated with significantly higher FVC % predicted (mean difference 7.4 [95% CI 0.025, 14.9] per unit increase in log2-transformed ApoA1, p=0.049) and numerically higher DLCO % predicted (mean difference 6.1 [95% CI -

0.08, 2.3] per unit increase in log2-transformed ApoA1, p=0.053) Greater PON-1 was associated with lower FVC % predicted in unadjusted and adjusted models [mean adjusted difference -6.5 (95% CI -11.5, -1.5, p=0.12)]. In fully adjusted models, greater ApoA1 was associated with a lower hazard for respiratory hospitalization, but not with the composite outcome of time to 10% relative decline in FVC (L), respiratory hospitalization, lung transplantation, or death (**Table**). There were no significant associations between PON-1 and the outcomes.

**Conclusion:** Among individuals with IPF, greater plasma ApoA1 was associated with better baseline lung function and lower hazard for respiratory hospitalizations, but not FVC decline. Further studies are needed to define the role of ApoA1 and other high-density lipoproteins in the development and progression of pulmonary fibrosis.

**Table.** Associations of HDL-C, ApoA1 and PON-1 with clinical outcomes.

| | Unadjusted | | Adjusted* | |
|---|---|---|---|---|
| | Hazard ratio per unit increase in log2-concentration (95% CI) | P-value | Hazard ratio per unit increase in log2-concentration (95% CI) | P-value |
| **10% relative decline in FVC (L), respiratory hospitalization, lung transplant, or death** | | | | |
| HDL | 1.12 (0.82 - 1.52) | 0.489 | 1.24 (0.82 - 1.87) | 0.315 |
| ApoA-1 | 0.55 (0.33 - 0.92) | 0.023 | 0.89 (0.46 - 1.72) | 0.724 |
| PON-1 | 1.07 (0.76 - 1.51) | 0.705 | 1.09 (0.74 - 1.60) | 0.668 |
| **10% relative decline in FVC (L)** | | | | |
| HDL | 1.03 (0.70 - 1.51) | 0.870 | 1.04 (0.63 - 1.70) | 0.886 |
| ApoA-1 | 0.91 (0.48 - 1.71) | 0.771 | 1.37 (0.59 - 3.19) | 0.461 |
| PON-1 | 1.06 (0.68 - 1.64) | 0.796 | 1.20 (0.73 - 1.97) | 0.472 |
| **Respiratory hospitalization** | | | | |
| HDL | 0.79 (0.47 - 1.31) | 0.353 | 0.92 (0.46 - 1.86) | 0.818 |
| ApoA-1 | 0.25 (0.11 - 0.57) | 0.001 | 0.30 (0.10 - 0.88) | 0.029 |
| PON-1 | 1.02 (0.57 - 1.82) | 0.959 | 0.84 (0.42 - 1.66) | 0.613 |
| **All-cause death** | | | | |
| HDL | 1.06 (0.70 - 1.61) | 0.768 | 1.30 (0.73 - 2.32) | 0.375 |
| ApoA-1 | 0.32 (0.16 - 0.64) | 0.001 | 0.44 (0.18 - 1.08) | 0.074 |
| PON-1 | 1.08 (0.66 - 1.77) | 0.755 | 1.11 (0.66 - 1.87) | 0.683 |
| **All-cause death or lung transplant** | | | | |
| HDL | 1.00 (0.69 - 1.43) | 0.984 | 1.25 (0.77 - 2.05) | 0.368 |
| ApoA-1 | 0.37 (0.20 - 0.68) | 0.001 | 0.46 (0.20 - 1.03) | 0.057 |
| PON-1 | 1.29 (0.87 - 1.92) | 0.209 | 1.21 (0.78 - 1.87) | 0.396 |

*Adjusted for age, sex, race (white vs non-white), smoking status, BMI, baseline FVC (L), antifibrotic drug use, statin use, corticosteroid use, triglycerides, LDL, CRP, CAD, diabetes, heart failure. Continuous adjustment variables were included as natural cubic splines to account for potential non-linear relationships.

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