Gene profile in blood predicts risk of poor outcomes, death for patients with COVID-19

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The study's principal investigator was Jose Herazo-Maya, MD, associate professor of medicine and associate division chief of USF Health Pulmonary, Critical Care and Sleep Medicine. Credit: USF Health/University of South Florida

A blood gene profile associated with a high risk of dying from a severe

lung disease can also predict poor outcomes in patients with COVID-19, a multicenter retrospective study led by the University of South Florida Health (USF Health) demonstrated. The risk profile based on 50 genes could help customize how COVID-19 is treated, improve allocation of limited health care resources such as intensive care beds and ventilators, and potentially save lives.

Idiopathic pulmonary fibrosis (IPF), a disease of unknown cause, affects the lung interstitium or the space between the lung sacs and the bloodstream, leading to severe lung scarring. Severe COVID-19 can also damage the lung interstitium leading to severe lung scarring.

"Our study identified at the molecular level, a gene risk profile that predicts worse COVID-19 outcomes before the patient becomes severely ill," said principal investigator Jose Herazo-Maya, MD, an associate professor and associate chief of pulmonary, critical care and sleep medicine at the USF Health Morsani College of Medicine. "That means every patient with COVID-19 could potentially get a blood test that could tell us if they are at high or low risk of dying... And if we know in advance who will likely end up in the ICU and who will likely do well recovering at home with appropriate monitoring, we can tailor our interventions to individual patients based on their level of risk."

The USF Health study appeared online June 20 in *EBioMedicine*, a publication of *The Lancet*. It builds upon previous genomic research by Dr. Herazo-Maya and colleagues at Yale School of Medicine. In 2017, they led an international team that studied and validated a gene expression signature in the blood that reliably forecasts the likelihood of IPF mortality. (Certain patients with lung scarring can live well for years, while others develop worsening disease and die quickly from IPF.)

As the COVID-19 pandemic unfolded, "the basic question we had was 'Can we repurpose the gene signature known to predict mortality in a

fibrotic lung disease to predict mortality in those infected with a new coronavirus that can cause lung fibrosis as well?'" said the *EBioMedicine* paper lead author Brenda Juan-Guardela, MD, assistant professor of medicine at the USF Health Morsani College of Medicine and medical director of Respiratory Care Services at Tampa General Hospital (TGH). "To the best of our knowledge, this study is the first to compare overlapping immune gene profiles in COVID-19 and IPF, which were remarkably similar."

The USF Health-led team analyzed gene expression patterns of 50 genes known to predict IPF mortality in three COVID-19 cohorts and two IPF cohorts. The researchers used a molecular scoring system to distinguish between high versus low-risk gene profiles in all five cohorts.

Among their findings:

- In the COVID-19 validation cohorts, a 50-gene high risk profile was linked to greater risk of ICU admission, mechanical ventilation, and in-hospital death.
- The researchers also performed single-cell, gene expression analyses and identified specific immune cells—monocytes, neutrophils, and dendritic cells—as the primary source of gene expression changes in the high-risk, COVID-19 gene profile. This finding suggests COVID-19 and IPF may share common innate and adaptive immune responses that trigger lung scarring.
- The 50-gene risk profile in COVID-19 can also predicts mortality in IPF at the exact same threshold.

At TGH, Dr. Herazo-Maya treats previously hospitalized COVID-19 patients who come to the Center for Advanced Lung Disease with severe lung fibrosis; some are being evaluated for lung transplantation. "Even though coronavirus cases are dropping, that doesn't mean all the patients will recover without complications," he said. "We're starting to see the

damaging, long-term effects in the lungs of some COVID-19 survivors."

While more studies are needed, researchers and clinicians may soon be able to apply the gene risk profiles to help advance the care of both COVID-19 and IPF patients, Dr. Herazo-Maya said. His laboratory is currently developing a blood test, based on these genes, that can be easily applied in clinical practice to predict poor disease outcomes.

Besides outcome prediction, the identification of 50-gene risk profiles may also have significant therapeutic potentials. For example, a 10-day regimen of the steroid dexamethasone, a drug that suppresses the immune system, has been shown to increase survival of patients hospitalized with COVID-19.

Immunosuppressant drugs have been essentially discontinued for IPF treatment because they increase mortality when given at high doses and in combination over long periods, Dr. Herazo-Maya said. "But perhaps we could investigate the use of dexamethasone or a similar steroid treatment for a short period of time in a subgroup of IPF patients with a 50-gene high risk profile, using the principle of precision or personalized medicine."

The 50-gene high risk profile may also support the rationale to investigate the use of targeted IPF antifibrotic medications, which slow the rate of lung scarring, to prevent short and long-term sequelae of COVID-19, he added.

USF Health's Gaetane Michaud, MD, professor of medicine and chief of pulmonary, critical care and sleep medicine, was a paper coauthor. The research was supported by the Ubben Pulmonary Fibrosis Fund-USF Foundation, National Institute for Health Clinician Scientist Fellowship, Action for Pulmonary Fibrosis Mike Bray Fellowship, and the National Heart, Lung, and Blood Institute.

More information: Brenda M. Juan Guardela et al, 50-gene risk profiles in peripheral blood predict COVID-19 outcomes: A retrospective, multicenter cohort study, *EBioMedicine* (2021). DOI: 10.1016/j.ebiom.2021.103439