A COVID-19 biomarker: Low blood levels of sphingosine predict symptomatic infections

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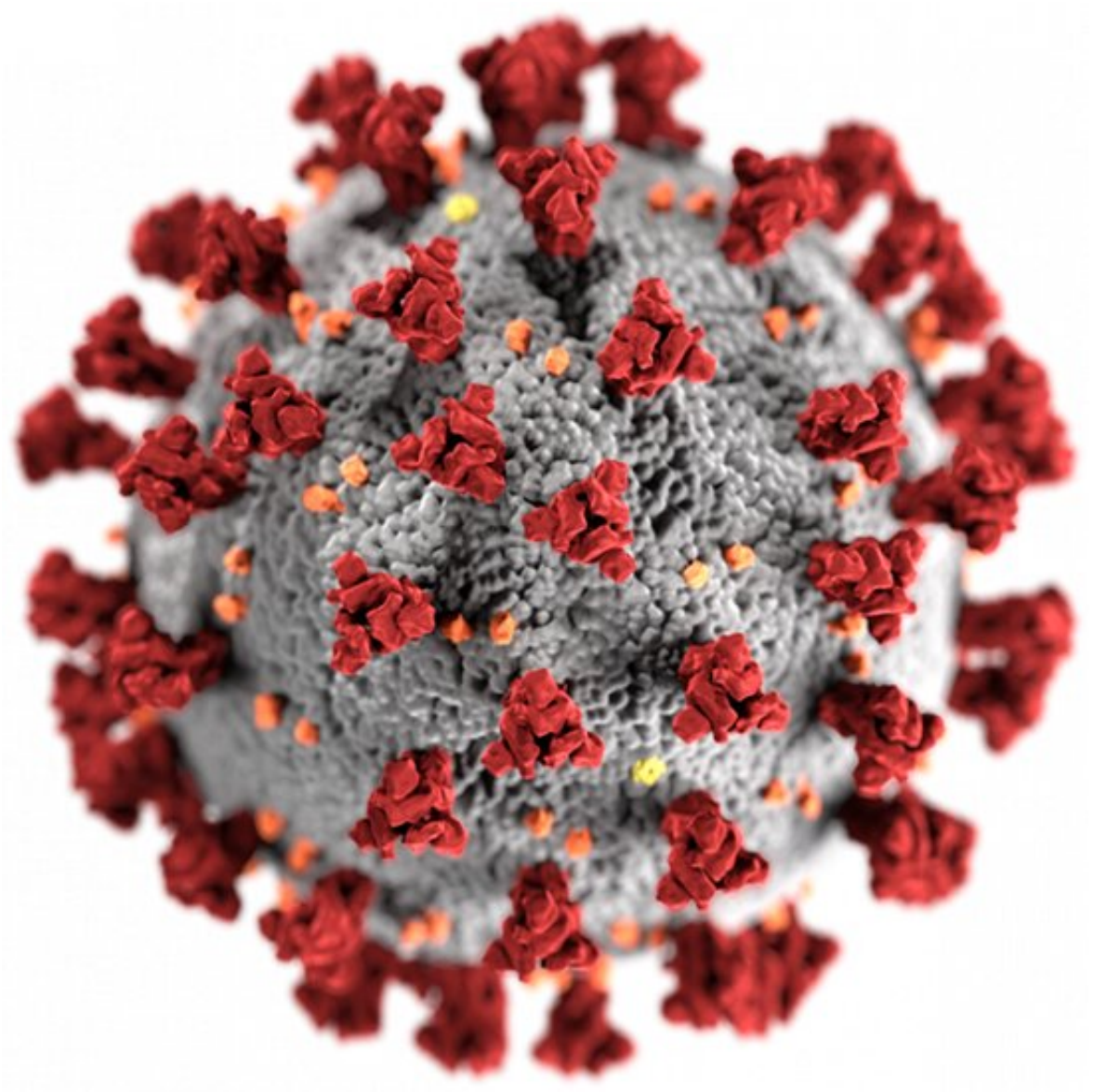

Image of the ultrastructural morphology exhibited by the 2019 Novel Coronavirus (2019-nCoV). Credit: CDC

Researchers remain perplexed as to why some patients infected with SARS-CoV-2, the virus responsible for COVID-19, remain asymptomatic while other patients develop severe disease symptoms. This question is once again at the front of mind as the Delta variant spreads across the country. In a new retrospective study, researchers at the Medical University of South Carolina (MUSC) discovered a specific and sensitive biomarker in blood samples that predicts which patients will develop COVID-19 symptoms. Their results, published online on July 9 in *Scientific Reports*, show that reduced levels of a specific lipid, sphingosine, are significantly associated with developing COVID-19 symptoms. Conversely, elevated levels of sphingosine, as well as a protein involved in its production, acid ceramidase (AC), are associated with asymptomatic infections.

"We developed this project at a time when there wasn't a successful vaccine," said Besim Ogretmen, Ph.D., director of the Lipidomics Shared Resource at Hollings Cancer Center and leader of the Hollings Developmental Cancer Therapeutics Research Program. "We wanted to contribute to the field and know which patients who were exposed to this virus would be symptomatic versus asymptomatic."

Over the past 16 months several waves of SARS-CoV-2 infections in the U.S. have resulted in more than 35 million cases and almost 630,000 deaths. Despite the development of multiple safe and effective vaccines, we are currently experiencing another wave of infections.

The mortality of COVID-19 is thought to result from an overactive immune response to the virus in the lungs of infected patients that causes severe respiratory distress. However, symptoms vary widely, and scientists and clinicians don't understand why some patients develop severe symptoms while others remain asymptomatic.

It is known that sphingolipids, a class of molecules that are important for the integrity of the cell membrane and communication between cells, can regulate inflammation and the immune system in response to various infections. The Ogretmen laboratory has decades of expertise in analyzing the production and processing of different lipids, including sphingolipids, using a global measurement method called lipidomics.

Using this expertise, the Ogretmen lab undertook an unbiased analysis of COVID-19 patient serum samples from the MUSC COVID-19 Biorepository to look for changes in sphingolipid levels.

The results were striking.

Dr. Besim Ogretmen and Alhaji Janneh from the Medical University of South Carolina. Credit: Sarah Pack of the Medical University of South Carolina

"Just by looking at the data, you can clearly separate the different patient groups, even without doing technical statistical analyses," said Alhaji Janneh, lead author and graduate student in the Department of Biochemistry and Molecular Biology.

In asymptomatic patients who tested positive for a SARS-CoV-2 antibody, the researchers found a slight increase in serum sphingosine levels—and only sphingosine—compared to patients who tested negative. Remarkably, in patients who developed COVID-19 symptoms, there was a 15-fold reduction in sphingosine levels. Conversely, almost 75% of asymptomatic patients had elevated AC levels while most symptomatic patients had no detectable AC. The presence of serum AC correlates with the increased levels of sphingosine.

"Can this be an alternative way to predict which patients are the most vulnerable to severe disease?" asked Ogretmen, who is also a professor in the Department of Biochemistry and Molecular Biology and the SmartState Endowed Chair in Lipidomics and Drug Discovery. "If we can separate asymptomatic patients from symptomatic patients, we can use limited remedies and resources for patients who are more vulnerable."

Overall, there is a 99% probability of correctly determining which patients, who have tested positive for SARS-CoV-2 antibodies, will develop disease symptoms versus remain asymptomatic, using blood levels of sphingosine.

These striking results would not have been possible without the MUSC COVID-19 Biorepository and collaboration with the South Carolina Clinical & Translational Research Institute (SCTR). SCTR set up the biorepository to serve as a resource for COVID-19 research, and SCTR

co-principal investigator Patrick Flume, M.D. is its director and one of the authors of the article.

Analyzing levels of various lipids from patient samples is expensive and requires sophisticated equipment, making this type of analysis prohibitive under most circumstances. However, the development of an ELISA-based assay—like those used to diagnose HIV infection—to detect levels of AC could provide a cost-effective alternative that could be widely implemented.

There are several outstanding questions remaining. How does vaccination impact sphingosine levels? How do sphingosine levels change with the introduction of more variants? Nevertheless, the ability to identify at-risk patients quickly could vastly improve treatment of COVID-19 and allow for effective distribution of scarce resources.

More information: Alhaji H. Janneh et al, Alterations of lipid metabolism provide serologic biomarkers for the detection of asymptomatic versus symptomatic COVID-19 patients, *Scientific Reports* (2021). DOI: 10.1038/s41598-021-93857-7

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