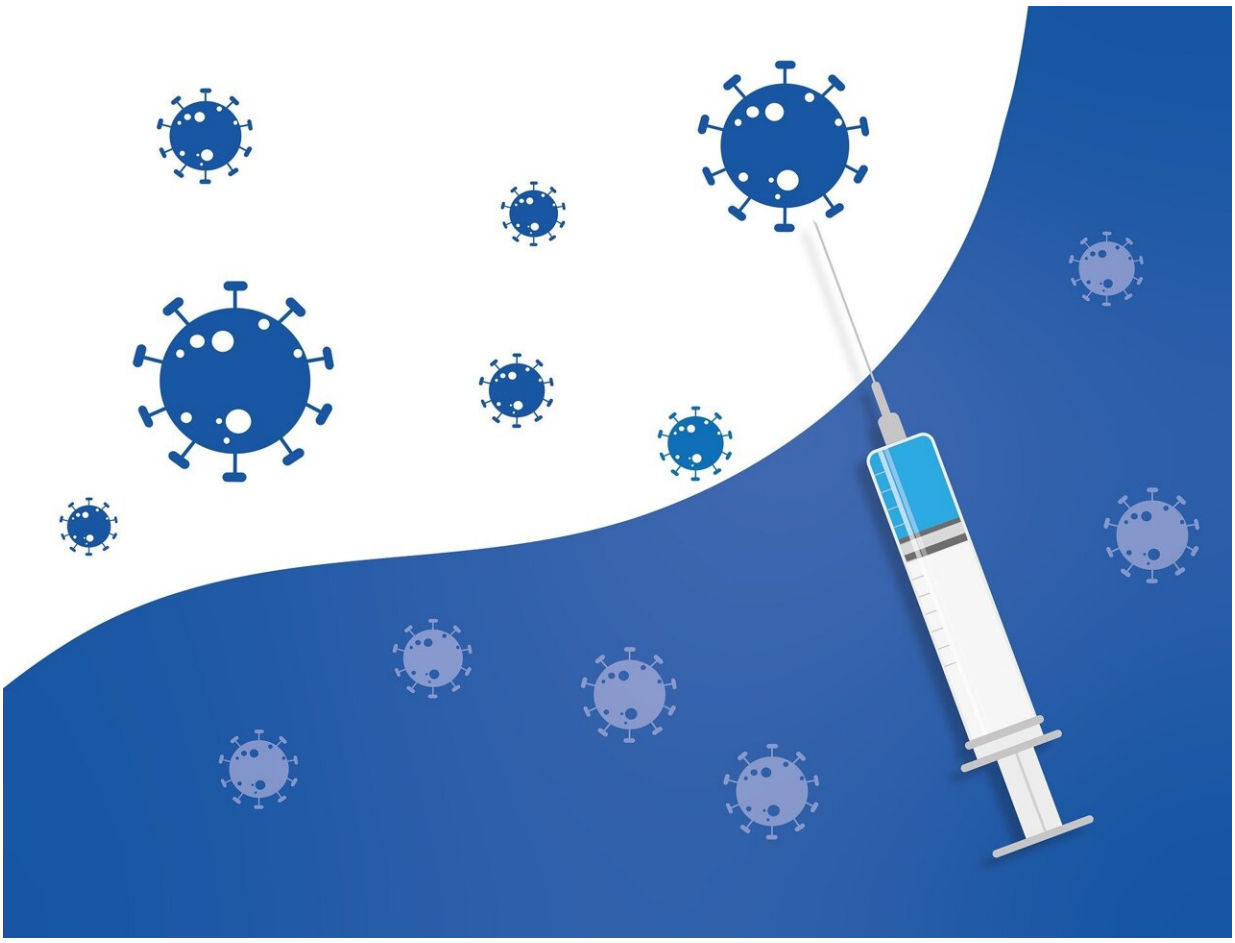
Mathematical model may help improve treatments and clinical trials of patients with COVID-19 and other illnesses

January 14 2022



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Investigators who recently developed a mathematical model that indicated why treatment responses vary widely among individuals with COVID-19 have now used the model to identify biological markers related to these different responses. The team, which was led by scientists at Massachusetts General Hospital (MGH) and the University of Cyprus, notes that the model can be used to provide a better understanding of the complex interactions between illness and response and can help clinicians provide optimal care for diverse patients.

The work, which is published in *EBioMedicine*, was initiated because COVID-19 is extremely heterogeneous, meaning that illness following SARS-CoV-2 infection ranges from asymptomatic to life-threatening conditions such as respiratory failure or acute respiratory distress syndrome (ARDS), in which fluid collects in the lungs. "Even within the subset of critically ill COVID-19 patients who develop ARDS, there exists substantial heterogeneity. Significant efforts have been made to identify subtypes of ARDS defined by clinical features or biomarkers," explains co–senior author Rakesh K. Jain, Ph.D., director of the E.L. Steele Laboratories for Tumor Biology at MGH and the Andrew Werk Cook Professor of Radiation Oncology at Harvard Medical School (HMS). "To predict disease progression and personalize treatment, it is necessary to determine the associations among clinical features, biomarkers and underlying biology. Although this can be achieved over the course of numerous clinical trials, this process is time-consuming and extremely expensive."

As an alternative, Jain and his colleagues used their model to analyze the effects that different patient characteristics yield on outcomes following treatment with different therapies. This allowed the team to determine the optimal treatment for distinct categories of patients, reveal biologic pathways responsible for different clinical responses, and identify markers of these pathways.

The researchers simulated six patient types (defined by the presence or absence of different comorbidities) and three types of therapies that modulate the immune system. "Using a novel treatment efficacy scoring system, we found that older and hyperinflamed patients respond better to immunomodulation therapy than obese and diabetic patients," says co–senior and corresponding author Lance Munn, Ph.D., who is the deputy director of the Steele Labs and an associate professor at HMS. "We also found that the optimal time to initiate immunomodulation therapy differs between patients and also depends on the drug itself." Certain biological markers that differed based on patient characteristics determined optimal treatment initiation time, and these markers pointed to particular biologic programs or mechanisms that impacted a patient's outcome. The markers also matched clinically identified markers of disease severity.

For COVID-19 as well as other conditions, the team's approach could enable investigators to enrich a clinical trial with patients most likely to respond to a given drug. "Such enrichment based on prospectively predicted biomarkers is a potential strategy for increasing precision of clinical trials and accelerating therapy development," says co–senior author Triantafyllos Stylianopoulos, Ph.D., an associate professor at the University of Cyprus.

More information: Sonu Subudhi et al, Strategies to minimize heterogeneity and optimize clinical trials in Acute Respiratory Distress Syndrome (ARDS): Insights from mathematical modelling, *eBioMedicine* (2022). DOI: 10.1016/j.ebiom.2021.103809

Provided by Massachusetts General Hospital