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Editorial

# An Editorial on Distinct Early Serological Signatures with SARS-CoV-2 Survival

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As SARS-CoV-2 infections and death counts continue to rise, it remains unclear why some individuals recover from infection, whereas others rapidly progress and die. Although the immunological mechanisms that underlie different clinical trajectories remain poorly defined, pathogen-specific antibodies often point to immunological mechanisms of protection. Here, we profiled SARS-CoV-2-specific humoral responses in a cohort of 22 hospitalized individuals. Despite inter-individual heterogeneity, distinct antibody signatures resolved individuals with different outcomes. Although no differences in SARS-CoV-2-specific IgG levels were observed, spike-specific humoral responses were enriched among convalescent individuals, whereas functional antibody responses to the nucleocapsid were elevated in deceased individuals. Furthermore, this enriched immunodominant spike-specific antibody profile in convalescents was confirmed in a larger validation cohort. These results demonstrate that early antigen-specific and qualitative features of SARS-CoV-2-specific antibodies point to differences in disease trajectory, highlighting the potential importance of functional antigen-specific humoral immunity to guide patient care and vaccine development.

SARS-CoV-2 is the newest coronavirus to cross into the human population. Millions of infections have been diagnosed; however, the number of asymptomatic carriers is likely to far exceed these numbers. Although the rapid spread of SARS-CoV-2, even during the asymptomatic phase of this infection, is alarming, more harrowing is our inability to predict disease trajectories among symptomatic individuals. In the absence of therapeutic agents and vaccines as countermeasures for this infection, there is an urgent need to begin to map the evolution of immunity to the pathogen to guide patient care and future immune interventions.

Although antibody responses and T cells have been linked to disease resolution, and neutralizing antibodies have been demonstrated to block infection in small-animal models, little is known about the antibody features that are important for protection. Neutralizing antibodies develop in the majority of SARS- and MERS-infected individuals; however, the virus can mutate to overcome these antibody responses. Passive immunization studies with neutralizing and poorly neutralizing antibodies have shown protection in lethal MERS infection in mice suggesting that the neutralizing and extra-neutralizing functions of antibodies may play a critical role in control and resolution of disease. Moreover, recent studies have found lower neutralization titers in younger individuals and higher neutralization among individuals with severe disease, suggesting that antibodies may depend on additional mechanisms to clear the virus.

Antibody dynamics during the acute window of infection have been linked to differential outcomes across infections, including HIV, influenza, and Ebola virus infection. Specifically, selection of specific antibody subclasses and functional profiles is heavily influenced by inflammatory cascades and may not only forecast disease outcomes but also point to antibody mechanisms of action vital in early pathogen control and clearance.

However, whether identifiable antibody functional profiles across SARS-CoV-2 antigen specificities evolve early following infection and track differentially with disease outcome is unknown. In this study, we assembled two cross-sectional sample sets of SARS-CoV-2-infected individuals at the time of hospital admission to begin to comprehensively profile the evolution of the early SARS-CoV-2 S-specific response and to define antibody features that are predictive of disease outcome.

Through this analysis, we found that deceased and convalescent individuals present different humoral profiles, with a more spike (S)-focused response in individuals who convalesced and a stronger nucleocapsid (N)-specific response in individuals who succumbed to disease.

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