A high-throughput cell- and virus-free assay shows reduced neutralization of SARS-CoV-2 variants by COVID-19 convalescent plasma

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The detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific antibodies in the serum of an individual indicates prior infection or vaccination. However, it provides limited insight into the protective nature of this immune response. Neutralizing antibodies recognizing the viral spike protein are more revealing, yet their measurement traditionally requires virus- and cell-based systems that are costly, time-consuming, inflexible, and potentially biohazardous. Here, we present a cell-free quantitative neutralization assay based on the competitive inhibition of trimeric SARS-CoV-2 spike protein binding to the angiotensin converting enzyme 2 (ACE2) receptor. This high-throughput method matches the performance of the gold standard live virus infection assay, as verified with a panel of 206 seropositive donors with varying degrees of infection severity and virus-specific IgG titers, achieving 96.7% sensitivity and 100% specificity. Furthermore, it allows for the parallel assessment of neutralizing activities against multiple SARS-CoV-2 spike protein variants of concern. We used our assay to profile serum samples from 59 patients hospitalized with coronavirus disease 2019 (COVID-19). We found that, although most sera had high activity against the 2019-nCoV parental spike protein and, to a lesser extent, the alpha (B.1.1.7) variant, only 58% of serum samples could efficiently neutralize a spike protein derivative containing mutations present in the beta (B.1.351) variant. Thus, we have developed an assay that can evaluate effective neutralizing antibody responses to SARS-CoV-2 spike protein variants of concern after natural infection and that can be applied to characterize vaccine-induced antibody responses or to assess the potency of monoclonal antibodies.
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