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Original article

Measurement of circulating viral antigens post-SARS-CoV-2 infection in a multicohort study

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'Measurement of circulating viral antigens post-SARS-CoV-2 infection in a multicohort study' – Author's reply

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Abstract

Objectives

To determine the proportion of individuals with detectable antigen in plasma or serum after SARS-CoV-2 infection and the association of antigen detection with postacute sequelae of COVID-19 (PASC) symptoms.

Methods

Plasma and serum samples were collected from adults participating in four independent studies at different time points, ranging from several days up to 14 months post-SARS-CoV-2 infection. The primary outcome measure was to quantify SARS-CoV-2 antigens, including the S1 subunit of spike, full-length spike, and nucleocapsid, in participant samples. The presence of 34 commonly reported PASC symptoms during the postacute period was determined from participant surveys or chart reviews of electronic health records.

Results

Of the 1569 samples analysed from 706 individuals infected with SARS-CoV-2, 21% (95% CI, 18–24%) were positive for either S1, spike, or nucleocapsid. Spike was predominantly detected, and the highest proportion of samples was spike positive (20%; 95% CI, 18–22%) between 4 and 7 months postinfection. In total, 578 participants (82%) reported at least one of the 34 PASC symptoms included in our analysis ≥1 month postinfection. Cardiopulmonary, musculoskeletal, and neurologic symptoms had the highest reported prevalence in over half of all participants, and among those participants, 43% (95% CI, 40–45%) on average were antigen-positive. Among the participants who reported no ongoing symptoms (128, 18%), antigen was detected in 28 participants (21%). The presence of antigen was associated with the presence of one or more PASC symptoms, adjusting for sex, age, time postinfection, and cohort (OR, 1.8; 95% CI, 1.4–2.2).

Discussion

The findings of this multicohort study indicate that SARS-CoV-2 antigens can be detected in the blood of a substantial proportion of individuals up to 14 months after infection. While approximately one in five asymptomatic individuals was antigen-positive, roughly half of all individuals reporting ongoing cardiopulmonary, musculoskeletal, and neurologic symptoms were antigen-positive.

Introduction

Persistent symptoms following the acute phase of COVID-19, termed postacute sequelae of COVID-19 (PASC), or long COVID-19, is a multisystemic condition affecting an estimated 10% of individuals following SARS-CoV-2 infection [1]. PASC is associated with a wide array of symptoms representing most organ systems, encompasses a heterogeneous set of pathophysiological processes, and can substantially affect the quality of life [[2], [3], [4]]. With no effective diagnostic and treatment options available, PASC poses a significant public health burden as SARS-CoV-2 continues to spread.

While the underlying mechanisms of PASC remain incompletely understood, viral persistence, reactivation of latent viruses, autoimmune response, and chronic immunologic dysfunction are among the proposed hypotheses [5,6]. In particular, mounting evidence suggests that some individuals may not fully clear SARS-CoV-2 after acute infection and that residual virus or viral RNA and protein persist in tissue reservoirs [7]. Several autopsy and tissue biopsy studies have detected SARS-CoV-2 RNA and protein in multiple anatomical sites weeks to months after initial infection [[8], [9], [10], [11], [12], [13], [14], [15], [16]]. Additionally, we identified circulating SARS-CoV-2 antigens, which could be derived from tissue reservoirs, in plasma up to a year after acute infection, and others have corroborated our work [[17], [18], [19], [20]]. In our preliminary study, we measured S1, full-length spike, and nucleocapsid (N) antigens in plasma samples collected from individuals infected with SARS-CoV-2. We found that ~65% of those individuals diagnosed with PASC were antigen-positive during at least one time point [17]. Most PASC patients were positive for spike, whereas none of the individuals who experienced only acute COVID-19 were spike positive, suggesting that spike present in the postacute phase could potentially serve as a biomarker for PASC. Additionally, the presence of circulating spike was not attributed to mRNA vaccination, where predominantly S1 was detected within a few days of the first dose [21]. In our pilot study, we analysed many samples up to 1-year postinfection for PASC patients, but very few longer-term time points for individuals who reported recovery after acute COVID-19. Furthermore, this preliminary study consisted only of samples from individuals who were infected early in the pandemic.

Thus, we sought to quantify the prevalence of postacute antigenemia in a larger cohort by measuring the levels of SARS-CoV-2 antigens in plasma and serum samples collected from 706 individuals over 2 years of the COVID-19 pandemic at multiple healthcare sites in the United States. We hypothesized that a subset of individuals would test positive for circulating antigen, representing the group of individuals harbouring a persistent viral reservoir, and those individuals would suffer from one or more common PASC symptoms.

Section snippets

Study cohort

This retrospective longitudinal study included samples collected from adult participants already enrolled in the following studies: Long-term Impact of Infection with Novel Coronavirus at the University of California, San Francisco (LIINC, n=171) [22], Mass General Brigham in Boston (MGB, n=63), Seattle COVID-19 Cohort Study to Evaluate Immune Responses in Persons at Risk and with SARS-CoV-2 Infection at the Allen Institute for Immunology (Allen, n=80), and Researching COVID-19 to Enhance …

Participant characteristics

This study encompassed four independent sample cohorts that included samples collected at one or more time points from a given individual spanning both the acute and postacute phases of COVID-19 during different pandemic waves (Fig.1). The median (interquartile range) age of all participants was 46years (35–58), 263 of 706 (37%) were male, 369 (52%) were fully vaccinated before SARS-CoV-2 infection, and 51 (7%) had been hospitalized with acute COVID-19. Demographic characteristics for each of …

Discussion

We analysed over one thousand plasma and serum samples from four independent cohorts from participants infected with SARS-CoV-2 and detected circulating SARS-CoV-2 antigens up to 14months postinfection, confirming our earlier findings. Overall, 21% of the samples analysed were positive for either spike, S1, or N during the postacute phase. Though we cannot rule out re-infection, the frequency of antigen detection is much greater than the estimated 2.5% incidence of re-infection per year [26]. …

Author contributions

Z.S., E.B., E.W.K., and D.R..W. participated in conceptualization of the project. Z.S. and E.B. contributed equally in this work and participated in writing the manuscript. E.W.K. and D.R.W. equally contributed in the supervision of this work and revision of the manuscript. Z.S., E.B., Y.S., and S.C. participated in processing the patient samples and

performing experiments to measure SARS-CoV-2 antigens. Z.S., E.B., and Y.C. participated in performing the data analysis. Z.M.-H., J.Z.L., G.A., …

Potential conflict of interest

J.Z.L. has consulted for Abbvie and received research funding from Merck. S.G.D. reports consulting for Enanta Pharmaceuticals and Pfizer and research support from Aerium Therapeutics, outside the submitted work. M.J.P. reports consulting fees from Gilead Sciences and AstraZeneca, and research support from Aerium Therapeutics, outside the submitted work. D.R.W. has a financial interest in Quanterix Corporation, a company that develops an ultra-sensitive digital immunoassay platform; is an …

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References (30)

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