Several reports have described the persistence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA and/or antigen(s) in tissues of patients with long COVID syndrome who often tested negative on reverse transcription polymerase chain reaction (rt-PCR) of nasopharyngeal swabs for SARS-CoV-2, especially in gastrointestinal tissues and fecal samples. Numerous scientists have, therefore, proposed a pathophysiological model for long COVID, based on the persistence of SARS-CoV-2, as an infection-associated chronic disease that affects every organ system and leads to multisystem injury in both adults and children. In this study, the authors from the United States investigated whether SARS-CoV-2 antigens persist in once-thawed plasma samples for 14 months after confirmed SARS-CoV-2 infection.

postmortem study of the replication, persistence, and evolution of SARS-CoV-2 in infected human tissues showed a widespread distribution of SARS-CoV-2 RNA in 84 distinct anatomic locations up to 230 days after infection. The virus was not found in the plasma, however, high-sensitivity droplet digital PCR (ddPCR) detected the virus in multiple tissue samples from all deceased individuals. Also, the detection of subgenomic RNA, a marker for recent viral replication, and the isolation of replication-competent viruses from respiratory and non-respiratory tissues indicated that viral replication may continue for several months after initial infection. (Yang C et al. Association of SARS-CoV-2 infection and persistence with long COVID. Lancet Respir Med 2023.)

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Similarly, residual viral protein and RNA were detected in the appendix, skin, and breast tissue of two individuals who developed long COVID syndrome 163 and 426 days after the onset of symptoms, respectively. https://discovermednews.com/sars-cov-2-rna-and-antigens-appendix-skin-breast-patients-long-covid/ Also, a recent ddPCR study demonstrated the presence of viral nucleic acid in solid tissue samples from various organs, including the lung, liver, kidney, stomach, intestine, brain, breast, thyroid, blood vessels, and skin, in patients who had recovered from mild COVID-19 at one month, two months, and four months after the infection. Interestingly, viral nucleic acids were detected in a proportion of plasma samples, granulocytes, and peripheral blood mononuclear cells from immunocompromised patients two months after SARS-CoV-2 infection, but not in immunocompetent individuals. https://discovermednews.com/the-persistence-of-residual-sarscov2-four-months-after-infection/

The persistence of SARS-CoV-2 triggers a dysregulation of the immune system, followed by increased release of inflammatory cytokines and abnormal endothelial damage. This results in chronic inflammation, vascular damage, hypercoagulability, microthrombosis, and multiorgan symptoms. The SARS-CoV-2 spike (S) protein alone has different pathological effects causing damage to various cells and organs.

The authors noted that studies on SARS-CoV-2 persistence have been limited by small and non-representative study populations, unclear documentation of vaccination and reinfection histories, and the absence of a true negative comparator group to assess assay specificity.

About the Study and Results

The authors evaluated the presence of SARS-CoV-2 antigens in once-thawed plasma from 171 adults at several time points during 14 months after RNA-confirmed SARS-CoV-2 infection. To avoid concerns that vaccination against SARS-CoV-2 or recent reinfections could affect the interpretation of positive results, they studied specimens collected before the emergence of the Delta and Omicron SARS-CoV-2 variants and before vaccination (pandemic-era participants). Their results were compared to those of 250 adults who had not been infected with SARS-CoV-2, as their plasma samples were collected before 2020 (pre-pandemic era participants).

The diagnostic used to measure the SARS-CoV-2 S protein, the S1 subunit of the S protein,

and the nucleocapsid (N) antigen was the Simoa single molecule array detection platform.

Of the 660 pandemic-era specimens tested, 9·2% (61) specimens from 42 participants (25% of the group), contained one or more detectable SARS-CoV-2 antigens. The most frequently detected antigen was S protein, followed by S1 and N antigens.

Analysis of temporal antigen profiles, performed by collecting blood samples at multiple time points, revealed that the prevalence of SARS-CoV-2 plasma antigens was 10.6% 3-6 months after the onset of COVID-19, 8.7% after 6-10 months and 5.4% after 10-14 months.

Participants who required hospitalization for acute COVID-19 were nearly twice as likely to have SARS-CoV-2 antigens detected in their plasma than those who had not been hospitalized. These findings suggest that the acute phase of infection influences the establishment of a persistent SARS-CoV-2 reservoir. Interestingly, among participants who were not hospitalized, greater post-acute antigen detection was found in those with worse self-reported health during acute COVID-19.

Conclusion

This study has shown that SARS-CoV-2 antigens can persist in plasma for up to 14 months after the acute SARS-CoV-2 infection. The acute infection influenced this persistence. These findings are consistent with a study that found that approximately 60% of patients with post-acute sequelae of coronavirus disease had circulating SARS-CoV-2 S protein up to 12 months after diagnosis. (Swank Z et al. Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae. CID 2023:76 (1 February) • e487.) https://doi.org/10.1093/cid/ciac722

This study suggests that SARS-CoV-2 may seed distal sites through the bloodstream and establish protected reservoirs. Therefore, the researchers have suggested that these findings should motivate further research regarding the clinical manifestations of SARS-CoV-2 persistence.

Journal Reference

Peluso, Michael J et al. Plasma-based antigen persistence in the post-acute phase of COVID-19. The Lancet Infectious Diseases, Volume 24, Issue 6, e345 – e347. (Open Access)

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