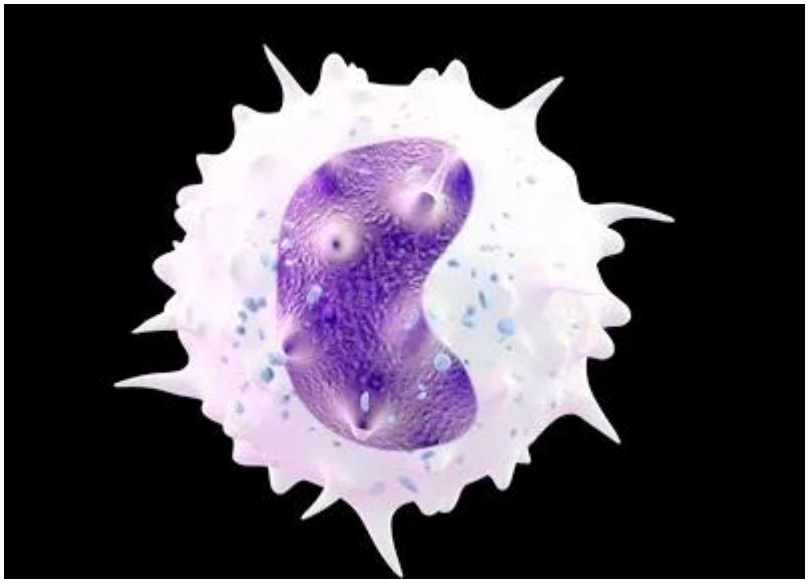
The persistent post-vaccination symptoms, commonly referred to as post-COVID-19 vaccination syndrome (PCVS), include new-onset cardiac, vascular, and neurological symptoms that manifest within minutes to hours of vaccination and, in many cases, last for months or even years. The symptomatology of PCVS closely mirrors that of post-acute sequelae of COVID-19 (PASC or Long COVID), suggesting that their pathophysiological mechanisms may be similar. In their earlier studies, the American research team demonstrated that the S1 subunit of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein persists in non-classical and intermediate monocytes for months to years after an acute infection, which may have contributed to PASC. Since approved COVID-19 vaccines (Pfizer, Moderna, Janssen, AstraZeneca) deliver synthetic S1 to elicit immunity, this study, conducted by the same research team, investigated whether the persistence of vaccine-derived S1 protein in CD16+ monocytes maintains inflammation and contributes to post-COVID-19 vaccination syndrome.



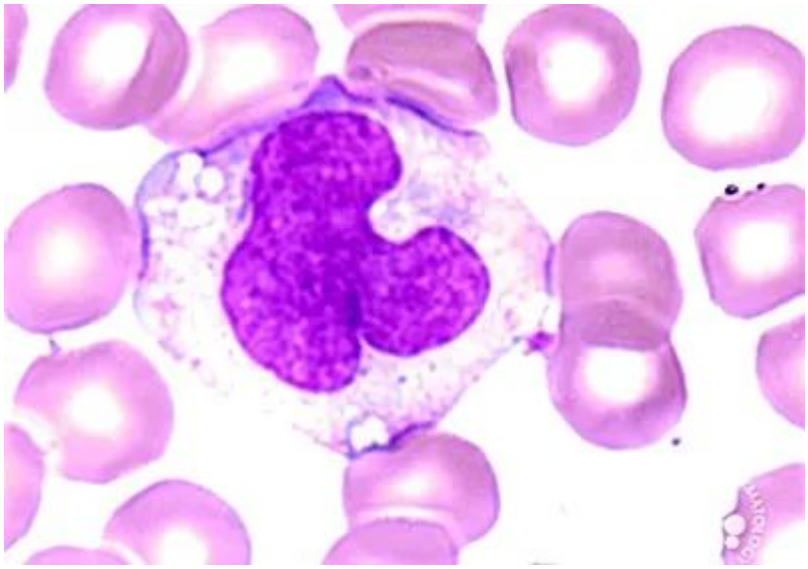
About the study

The study included participants who had received at least one dose of an approved SARS-CoV-2 vaccine, BNT162b2 (Pfizer), mRNA-1273 (Moderna), Janssen (Johnson & Johnson), or ChAdOx1 nCoV-19 (AstraZeneca), and reported new-onset symptoms lasting more than 30 days after COVID-19 vaccination, as well as asymptomatic vaccinated controls.

Exclusion criteria were a prior history of seizures, migraines, neuropathy, inflammatory bowel disease, depression, anxiety disorders, chronic fatigue syndrome, Lyme disease, fibromyalgia, arthritis, chronic obstructive pulmonary disease, asthma, diabetes, chronic

kidney disease, chronic heart failure, arrhythmias, bleeding disorders, or if the participants were on anticoagulation therapy. Those with a documented history of positive polymerase chain reaction (PCR) tests for SARS-CoV-2, positive tests for anti-SARS-CoV-2 nucleocapsid antibodies (indicating past natural infection), or positive T-Detect tests (indicating SARS-CoV-2-specific T-cell responses) were also excluded. These criteria were assessed through the patient's clinical history and laboratory tests conducted before enrollment.

Blood specimens were taken between 38 and 245 days from the last COVID-19 vaccination (mean: 105 days for the study group and 97 days for the control group). Three analytical approaches were employed: machine learning-based immune profiling to compare cytokine signatures of PCVS with those of PASC, flow cytometry to detect the persistence of the S1 in CD16+ monocyte subsets, and liquid chromatography-mass spectrometry to confirm the presence of the S1 subunit of the SARS-CoV-2 S protein and related peptides in individuals vaccinated with different vaccine types. The researchers also explored possible correlations between the persistence of S1 protein, symptoms of post-COVID-19 vaccination syndrome, and inflammatory markers.



Results

50 symptomatic individuals (mean age 42 years, ranging from 13 to 65 years, 36 females and 14 males) and 26 asymptomatic vaccinated controls (mean age 40 years, ranging from 20 to 70 years, 16 females and 10 males) were included in this study. Previous SARS-CoV-2 infection was excluded by clinical history, anti-nucleocapsid antibody tests, and T-Detect assays.

In individuals with symptoms after COVID-19 vaccination, 32/50 patients received one dose of the vaccine, and 18/50 patients received two doses. Most of them were vaccinated with BNT162b2, Pfizer (27 patients), followed by mRNA-1273, Moderna (15 patients), Janssen, Johnson & Johnson (7 patients), or ChAdOx1 nCoV-19, AstraZeneca (1 patient). The predominant post-vaccination symptoms were fatigue (27/50), neuropathy (27/50), brain fog (22/50), and headache (23/50), with variations in symptom presentation according to vaccine type. In the control group, 23/26 individuals received two doses of either BNT162b2, Pfizer, or mRNA-1273, Moderna, and the remaining three controls received one dose of the Janssen vaccine.

Given the symptomatic overlap between PCVS and PASC, and the absence of an ongoing replication-competent virus, researchers explored a cytokine panel in 50 symptomatic individuals. The symptomatic vaccinated group had significantly increased levels of interleukin (IL)-4, C-C motif chemokine ligand (CCL)3, CCL5 (RANTES), soluble CD40 ligand (sCD40L), vascular endothelial growth factor (VEGF), and IL-8, and downregulated tumor necrosis factor (TNF)-alpha and granulocyte-macrophage-colony-stimulating factor (GM-CSF) compared to asymptomatic vaccinated controls.

Most inflammatory cells can express CCL5; among them, T cells and monocytes are the most common. CCL5 has the highest affinity for CCR5, a G-protein-coupled receptor expressed on T cells, smooth muscle endothelial cells, epithelial cells, and even parenchymal cells. On the other hand, GM-CSF plays a role in promoting monocyte maturation into macrophages and dendritic cells; thus, a decrease of GM-CSF, as observed in this study, could limit this process, potentially favoring the persistence of less differentiated monocytes, such as non-classical monocytes. According to the authors, these profiles aligned with PASC-like features, except for IL-8.

Interestingly, a correlation analysis showed a link between these cytokines and specific symptoms. IL-2, CCL3, and VEGF correlated positively with shortness of breath, and sCD40L with twitching, tremors, fatigue, and brain fog. Fatigue correlated negatively with IL-10, GM-CSF, TNF-alpha, and VEGF.

To explore the cellular basis, researchers examined the presence of vaccine-derived S1 protein in monocyte subsets of 12 symptomatic vaccinated patients and 10 asymptomatic vaccinated controls. Up to 245 days after vaccination, 92% (11/12) of symptomatic patients had significantly elevated S1 levels in non-classical monocytes, and 67% (8/12) in intermediate monocytes. The vaccine-derived S1 protein was also detected in intermediate monocytes of one control subject (1/10).

Importantly, the persistence of vaccine-derived S1 protein in classical monocytes correlated with menstrual irregularities, sensory hypersensitivity, tachycardia, joint pain, and headaches. The S1 persistence in intermediate monocytes correlated with sensory hypersensitivity, tinnitus, tachycardia, postural orthostatic tachycardia syndrome (POTS), and headaches. The S1 persistence in non-classical monocytes correlated with vision disturbances, POTS, fatigue, and headaches.

Conclusion

These findings suggest that the persistence of vaccine-derived S1 protein in CD16+ monocytes and PASC-like cytokine profile may contribute to post-COVID-19 vaccination syndrome. The authors stated that although S1 was detected, causality remains unproven due to the limited sample size and variable presence of the S1 protein. However, these findings raise questions about vaccine-specific effects and their unclear clinical roles. Additionally, the detection of S1 in one control subject suggests that it may not be exclusive to symptomatic post-COVID-19 vaccination syndrome.

The authors concluded that larger, longitudinal studies with advanced infection screening are needed to confirm these associations and test interventions targeting CCR5 or VEGF signaling pathways.

This article was published in Human Vaccines & Immunotherapeutics.

Journal Reference

Patterson BK, Yogendra R, Francisco EB, et al. Detection of S1 spike protein in CD16+ monocytes up to 245 days in SARS-CoV-2-negative post-COVID-19 vaccine syndrome (PCVS) individuals, Human Vaccines & Immunotherapeutics, 2025; 21:1, 2494934 (Open Access). https://doi.org/10.1080/21645515.2025.2494934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