The infection with severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) can lead to a new disease called long COVID or post-acute COVID-19 syndrome (PACS). This syndrome can occur in various populations, including children and young adults, and those who had only mild COVID-19. Although they are still under debate, the pathophysiological mechanisms of post-COVID syndrome are thought to involve autoimmune reactions, continuous inflammation, or immunological responses to the persistent SARS-CoV-2 infection. In this study, Finnish authors investigated the gene transcriptomics of peripheral blood cells in vaccinated patients with post-COVID syndrome, as well as specific gene signatures in various clinical groups.

Transcriptomics (sometimes referred to as gene expression profiling) is the quantitative study of all genes expressed in a given biological state. Transcriptomics is commonly applied to compare gene expression in diseased and non-diseased tissues to provide a catalogue of genes that show altered expression in disease. These data can be utilized to identify individual genes that show large changes in disease or to create a global profile or "signature" comprised of multiple expression changes associated with disease. Such findings advance understanding of disease pathogenesis and reveal transcripts that can be quantitatively assessed as new biomarkers. (Pedrotty DM *et al*. Transcriptomic Biomarkers of Cardiovascular Disease. Prog Cardiovasc Dis. 2012 Jul-Aug;55(1):64–69.)

According to the authors of this study, earlier research revealed impaired erythrocyte function in individuals with PACS. A previous study showed increased deformation of red blood cells (RBCs) in children and adolescents infected with SARS-CoV-2 or vaccinated against COVID-19. The researchers discussed possible mechanisms that caused a loss of membrane integrity and increased deformation of RBCs.
https://discovermednews.com/increased-median-deformation-of-red-blood-cells-in-children-and-adolescents-following-sars-cov-2-infection-vaccination/

About the Study and Results

The study included 54 cases with PACS and previously laboratory-confirmed SARS-CoV-2 infection (positive nucleic acid amplification test), aged 18-65 years. They were recruited approximately 11-12 months after a positive SARS-CoV-2 test. None of the patients with PACS were hospitalized during the acute COVID-19 infection. Patients with PACS more often had comorbidities, like nervous system disorders, circulatory disorders, respiratory disorders (asthma), and musculoskeletal diseases, compared to recovered COVID-19 patients or controls.

The authors defined PACS as the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, lasting for at least two months and for which no other explanation exists. The cases with PACS received at least two COVID vaccines, either the Comirnaty mRNA vaccine (Pfizer) or the Vaxzevria adenoviral vector (Oxford–AstraZeneca). The study also included 57 convalescents from COVID-19 and 63 healthy controls not infected with SARS-CoV-2. Among recovered and control volunteers, individuals with diseases that strongly affect the immune system were excluded.

All participants provided blood samples. All patients with PACS completed questionnaires on lifestyle factors and quality of life. Physical function testing included assessments of dominant hand grip strength (HGST) in kilograms using a Jamar/Saehan dynamometer and a 6-minute walking test (6MWT) in meters. The patients with post-COVID syndrome had significantly reduced functional capacity (self-reported), lower quality of life, and lower

6MWT distance.

Laboratory findings

33% of convalescents from COVID-19 and 21% of healthy controls had antibodies against the SARS-CoV-2 nucleocapsid protein, indicating that at least one-fifth of the control group also had asymptomatic COVID-19. Antibody concentrations to nucleocapsid and spike-1 proteins were lower in healthy controls than in convalescents from COVID-19 or patients with PACS.

Only small differences were found in the transcriptome of peripheral blood mononuclear cells between patients with PACS, convalescents from COVID-19, and healthy controls, with only 3–6 differentially expressed genes (DEGs) identified in all comparisons. Despite this low number of DEGs, further analysis revealed changes in immune-related signaling pathways in patients with PACS.

Compared to healthy controls, patients with PACS and convalescents from COVID-19 showed significant changes in the expression of variable immunoglobulin light or heavy chain genes (IGKV2D-29 and IGHV1-2), which play a role in the antigen-binding activity of antibodies and B cell receptors.

Sex-specific differences in the transcriptome of peripheral blood cells

Further analysis revealed significant differences in some other immunoglobulin genes (IGHV3-53, IGKV6-21, and IGLV2-18) between women with PACS, women who had recovered from COVID-19, and healthy control women.

The gene expression analysis also revealed that 399 DEGs differed between men with PACS, men convalescents from COVID-19, and healthy control men. These DEGs showed high enrichment in genes related to RBC development, RBC differentiation, and heme metabolism. According to the authors, these findings observed in a subgroup of men with PACS may indicate a compensatory mechanism to overcome the effects of low iron concentration or dysfunctional erythroblasts.

Conclusion

This study, which investigated the gene transcriptomics of peripheral blood cells, found minor changes in convalescents from COVID-19 or patients with current post-COVID syndrome compared to each other or the healthy controls. However, distinct changes in genes related to RBC development, RBC differentiation, and heme metabolism in a subset of men with PACS indicate a condition-specific effect rather than incidental findings. In addition, significant differences in some immunoglobulin genes (IGHV3-53, IGKV6-21, and IGLV2-18) between women with PACS, women who had recovered from COVID-19, and healthy control women indicate possible sex-specific differences in the pathophysiology of PACS.

The authors concluded that due to the small sample size in men, further studies with larger cohorts of men and mechanistic studies focusing on RBCs are needed to validate these results.

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Patients with post-COVID-19 condition show minor blood transcriptomic changes, with altered erythrocyte gene expression in a male subgroup. Front. Immunol; 21 March 2025; Volume 16. https://doi.org/10.3389/fimmu.2025.1500997