Oskar Szymański, Magdalena Grzesiak

University Medical Hospital in Wroclaw, Poland

Investigating biomarkers: a path to understanding long-COVID?

Dear Editor,

I recently reviewed the study by Smykiewicz et al. [1], published in the *Medical Research Journal*, which focuses on potential biomarkers for COVID-19 outcomes. The search for potential markers of disease progression is closely tied to addressing questions related to complications, risk stratification in patients, and the selection of therapeutic options. It also allows for a deeper understanding of the pathophysiological processes occurring in the acute phase of the disease. The complex interplay of cytokines and chemokines requires further research and clinical evaluation. Recent articles, however, highlight the importance of pro-inflammatory cytokines such as IL-6, which was investigated in the article [2]. Similar searches for laboratory parameters with diagnostic or prognostic significance extend beyond the acute phase of COVID-19.

As the COVID-19 pandemic continues, our understanding of the disease and its long-term consequences is evolving. While public attention may be shifting, the scientific community is increasingly focusing on the complications and persistent issues that follow the acute phase of infection, underscoring the importance of long-term research efforts. Long COVID, also known as Postacute Sequelae of SARS-CoV-2 Infection (PASC), encompasses a wide range of symptoms, including respiratory, cardiovascular, neurological, and psychiatric manifestations, typically persisting for at least four weeks after the initial illness. The prevalence of long COVID, estimated to affect around 10% of COVID-19 infections, poses a significant challenge to global healthcare systems [3].

Given the diversity of long COVID symptoms and their involvement of multiple organ systems, it seems reasonable to consider long COVID more as a syndrome rather than a specific disease entity. The significant variety of symptoms aligns with the observation of different long COVID phenotypes [4]. Although detailed characterization of these phenotypes remains inconsistent, continued research into cytokine and chemokine interactions may be essential. For example, recent literature has increasingly focused on the phenotype and pathophysiology of the vascular form of long COVID. Damage to the vascular endothelium during the acute phase, progressing to endothelitis and complement-mediated thromboinflammation triggered by tissue damage and the presence of the virus, can lead to microvascular thrombosis and increased atherosclerosis [5, 6].

In contrast to potential biomarkers in the acute phase of COVID-19, where pro-inflammatory cytokines like IL-6 were predominant — resulting in elevated levels of acute-phase proteins such as CRP and procalcitonin — the dominant feature in long COVID has been changes in complement proteins and the persistent thromboinflammation they mediate. Patients with Long COVID exhibited dysregulated terminal complement complex (TCC) formation, characterized by elevated levels of soluble C5b-9 complexes and reduced levels of C7-containing TCCs capable of membrane insertion. This imbalance suggests an increased propensity for

Corresponding author:

Oskar Szymański, University Medical Hospital in Wroclaw, 6/1 Prudnicka St., 50-503 Wroclaw, Poland; e-mail: osgiliat@wp.pl

Medical Research Journal 2024; DOI: 10.5603/mrj.102231, Copyright © 2024 Via Medica, ISSN 2451-2591, e-ISSN 2451-4101

TCC membrane insertion in Long COVID patients, potentially contributing to ongoing tissue damage. A deeper understanding of this pathophysiology, facilitated by blood sample analyses, has led to the identification of potential biomarkers for long COVID. Through the analysis of over 7.000 proteins, it has been observed that complement and thromboinflammatory proteins may serve as biomarkers for diagnostic and therapeutic purposes [5]. These findings suggest that by integrating clinical and laboratory data with phenotyping efforts, we can make significant strides in understanding long COVID and translating this knowledge into clinical practice.

Article information

Acknowledgments: *None.*
Conflict of interest: The authors declare no conflicts of interest.
Funding: *None.*
Supplementary material: *None.*

References

1. Smykiewicz J, Wiacek M, Buczkowski J, et al. Markers of the outcome of COVID-19. Med Res J. 2024, doi: 10.5603/mrj.100590.
2. Ranjbar M, Cusack RP, Whetstone CE, et al. Immune Response Dynamics and Biomarkers in COVID-19 Patients. Int J Mol Sci. 2024; 25(12), doi: 10.3390/ijms25126427, indexed in Pubmed: 38928133.
3. Ballering AV, van Zon SKR, Olde Hartman TC, et al. Lifelines Corona Research Initiative. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. Lancet. 2022; 400(10350): 452–461, doi: 10.1016/S0140-6736(22)01214-4, indexed in Pubmed: 35934007.
4. Thaweethai T, Jolley SE, Karlson EW, et al. RECOVER Consortium. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. JAMA. 2023; 329(22): 1934–1946, doi: 10.1001/jama.2023.8823, indexed in Pubmed: 37278994.
5. Zanini G, Selleri V, Roncati L, et al. Vascular "Long COVID": A New Vessel Disease? Angiology. 2024; 75(1): 8–14, doi: 10.1177/00033197231153204, indexed in Pubmed: 36652923.
6. Cervia-Hasler C, Brüningk SC, Hoch T, et al. Persistent complement dysregulation with signs of thromboinflammation in active Long Covid. Science. 2024; 383(6680): eadg7942, doi: 10.1126/science.adg7942, indexed in Pubmed: 38236961.