Clinical Significance of Monitoring IgG and IgM Antibodies and the D-dimer in the Diagnosis and Therapy of Long Covid: Experiences from Practice

Muharem Zidzic[1,2], Nizama Salihefendic[1,3]

[1]*Polyclinic "Medicus A" Gracanica, Gracanica, Bosnia and Herzegovina*

[2]*Academy of Medical Sciences of Bosnia and Herzegovina, Sarajevo, Bosnia and Herzegovina*

[3]*Bosnian Academy of Sciences and Arts "BANUK", Sarajevo, Sarajevo, Bosnia and Herzegovina*

Corresponding author: Muharem Zildzic, MD, PhD. Academy of Medical Sciences of Bosnia and Herzegovina, Sarajevo, Bosnia and Herzegovina. E-mail: zildzic@yahoo.com.
ORCID ID: http://www.orcid.org/0000-0001-5418-2274

Background: Antibodies are key elements in the fight against diseases, including Covid-19. The pandemic is still ongoing, and Long Covid is a challenge due to the unclear chronic course of the disease. **Objective:** To analyze the antibody profile and coagulation status in patients who recovered from Covid-19 and developed symptoms of Long Covid, with a focus on D-dimer as an indicator of thromboembolic complications. **Methods:** The subjects are patients of the family medicine clinic who had an acute form of Covid-19 and after 3 months developed symptoms of Long Covid. The level of IgG and IgM antibodies to SARS-CoV-2 was regularly monitored during the acute form of the pandemic, and then also when symptoms of the chronic course appeared. The control group consists of patients who have recovered from the acute form of the disease without symptoms of Long Covid. Antibody analysis will provide insight into the diagnostic, prognostic and therapeutic value of antibody titer determination. **Results:** The occurrence of elevated levels of IGM and D-dimer were significantly increased in patients with various symptoms of Long Covid. Monitoring of IgG and IgM antibodies can be of key importance in the diagnosis, prognosis and therapy of Long Covid, and D-dimer for the diagnosis of vascular disorders and the detection of patients at risk for thromboembolic complications. In the practice of family medicine, but also in many specialist protocols, the importance of assessing the immune response when symptoms of Long Covid appear is neglected. **Conclusion:** Given the complex clinical picture of Long Covid, most doctors, regardless of specialty, must acquire knowledge and skills for diagnosis and treatment of Long Covid symptoms. It is necessary to create guides that can be supplemented with new discoveries, especially in the field of human immune defense against new virus variants and new forms of Long Covid.

Keywords: Long Covid, Antibodies IgG and IgM, D-Dimer.

Dilemma, Received: Octl 14th 2024, Accepted: Nov 10th 2024, doi: 10.5455/ijbh.2024.12.314-318, Int J Biomed Healthc. 2024; 12(4): 314-318

1. BACKGROUND

After the new corona virus SARS-CoV-2 was transmitted from animals to humans and caused the disease COVID-19, the infection spread rapidly throughout the world, causing one of the largest pandemics in the history of mankind (1-3). At the same time, intensive research was started on the properties of the virus, pharmacological and non-pharmacological protection measures, and the creation of a suitable vaccine (4-6). At the beginning, symptoms from the respiratory tract dominated, which were accompanied by high fever and changes in smell and taste. During the last two years of the pandemic, symptoms and signs indicating a multiorgan disorder in the form of general weakness and malaise, muscle pain, diffuse abdominal pain with diarrhea, headache with impaired concentration, insomnia, mental fog, intense sweating, palpitations, dizziness and pronounced decreased exercise tolerance. Gastrointestinal disorders become the first signs of the disease, so there is a possibility that the digestive system is also an entry point for the virus and that it spreads through the feco-oral route ((7-9).

Changes in the clinical picture can also be associated with constant virus mutations. The Sars-CoV-2 virus managed, despite pharmacological and non-pharmacological protection measures, to maintain itself in an active form and to develop lesions of almost all organs and organ systems with clinical manifestations of Long Covid. The human immune system has different levels of defense, where the natural immune response from non-specific cells reacts in the first line. Antibodies, B-cells and T-cells are the most important immune fac-

tors for the specific response to the SARS-CoV-2 virus. The entire immune system, including antibodies, did not succeed in completely eliminating the presence of the SARS-CoV-2 virus, but it was thoroughly changed after overcoming the COVID-19 infection.

The appearance of antibodies from the IgG and IgM group varies from the beginning of the disease, and the corresponding values of the presence and level of antibody production can help in the diagnosis of the course of the acute phase, and especially in the case of clinical signs of Long Covid.

One of the obstacles to the development of clinical guidelines is the lack of research into the occurrence of dysfunction of the Long Covid guidelines is the lack of research into the biological causes of fatigue and autonomic dysfunction - damage to the nervous system that can affect the function of all organ systems

Although the WHO announced the end of the pandemic, epidemiological data indicate that episodes of acute disease continue to occur with a tendency to increase, and that there is undoubtedly a prolonged and chronic course of the disease, which can have the same or greater consequences for the overall health of people. The public media and health systems somehow ignored these epidemiological data from practice about a significant increase in the incidence of diseases that can be related to the chronic course of the COVID-19 disease (10, 11).

WHO has defined Long Covid as the continuation of symptoms of various organ systems of the disease of COVID-19 even after 3 months from the beginning of the acute phase. The definition should include the duration of the symptoms (at least 2 months) and the need to rule out an alternative disease. The frequency of Long Covid is not yet known exactly, but it is believed that almost every fifth patient develops symptoms of Long Covid after the acute form.

Different theories exist about the mechanism of chronic course development, and one of the possible is changes in the immune system. It has been proven that T, B and stem cells, as the main actors of the immune response, have a memory about the nature of the Sars-CoV-2 virus and can even a year after infection retain information about the need to create anti-inflammatory factors, and contribute to the appearance of long-term symptoms. There is also a theory about the long-term presence of viruses in some tissues of the human body, which in the stages of weakening of the immune response can cause a range of different symptoms. Changes in the intestinal microflora and initiation of the autoimmune process during the active phase of the disease are additional important cofactors in the etiopathogenesis of Long Covid. Many symptoms of this disease are a reflection of dysfunction of the autonomic nervous system, which is closely related to immune changes. In the pathogenesis of all symptoms of long-COVID, there may be hematological changes in the coagulation process and inflammatory changes in the endothelium of small vascular structures. Small vessel vasculitis with microthrombi may be a common etiological factor for the different clinical entities of Long Covid.

The symptoms of Long Covid can be classified into several categories according to the affection of individual organs and organ systems. In practice most often occur:

- General fatigue syndrome and muscle pain
- Cardiorespiratory syndrome: pain, cough, difficult breathing, palpitations, decreased exercise tolerance, fever
- Neuropsychiatric syndrome: headache, insomnia, mental fog, cognitive disorders, depression, anxiety, memory loss
- Gastrointestinal syndrome: diffuse abdominal pain, nausea, bloating, diarrhea, vomiting, loss of appetite
- Genitourinary: dysuric disorders, lower abdominal pain
- Neurosensory syndrome: disorder of the sense of smell and taste
- Dermatological syndrome: various skin manifestations with circulatory disorders, hair loss
- Dysautonomia syndrome: (dysregulation of the autonomic nervous system) collapsing states with tachycardia, intense sweating
- Endocrine: occurrence of disturbed functions of endocrine glands, diabetes
- Multisystem syndrome: All symptoms and signs of long Covid can appear simultaneously or in small time intervals and can also mean a multiorgan lesion.

Until now, more than 200 different symptoms have been published that can be associated with the pres-

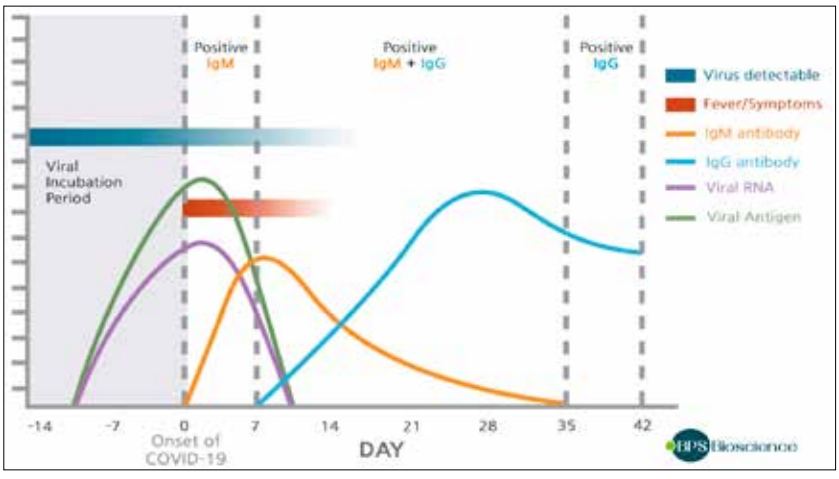

Figure 1. Dynamics of the temporal appearance of viral antigen and antibodies for Covid-19

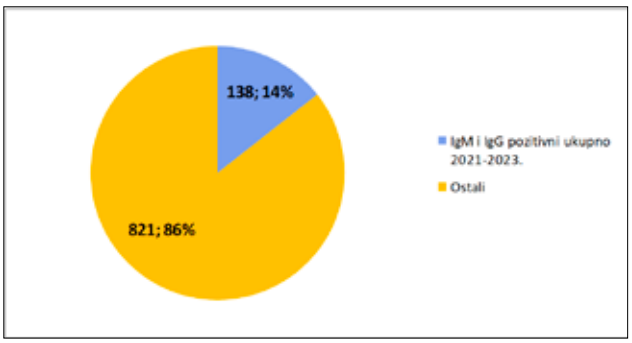

Figure 2. Proven elevated titer values of both antibodies during 3 years.

ence of Long Covid.

There are numerous clinical studies on this disease and the method of diagnosis and treatment, but there is no clearly defined clinical guide for practice, which was applied in primary health care. Doctors in practice are forced to create their own protocols for prevention, diagnosis and therapy of long-term COVID- and with the experience of fighting with the acute form. The assessment of the patient's immune status and data on the active phase of the disease and comorbid conditions, as well as a detailed analysis of the occurrence and duration of symptoms, can direct attention to Long COVID. In addition to routine tests, determining the titer of antibodies for COVID-type IgM and IgG, D-dimer values as a parameter for possible coagulation disorders can provide significant data for the final diagnosis. Figure 1 illustrate the usual appearance of antibodies after the acute phase of the disease

In practice, it has been shown that the monitoring of these antibody dynamics is very important even after the period of acute infection, because symptoms that point to relapses of the disease or Long Covid still appear. These experiences from practice indicate the need to create clinical guides that will use these immunological phenomena for diagnostic and therapeutic purposes

2. OBJECTIVE

The aim of this article is to analyze the antibody profile and coagulation status in patients who recovered from Covid-19 and developed symptoms of Long Covid, with a focus on D-dimer as an indicator of thromboembolic complications.

3. MATERIAL AND METHODS

The subjects were patients of the family medicine clinic who had an acute form of Covid-19 and after 3 months developed symptoms of Long Covid. Control of the level of IgG and IgM antibodies to SARS-CoV-2 was regularly monitored during the pandemic of the acute form, and then also during the emergence symptoms of a chronic course. The control group consists of patients who have recovered from the acute form of the disease without symptoms of Long Covid. Antibody analysis will provide insight into the diagnostic, prognostic and therapeutic value of antibody titer determination.

4. RESULTS

During 3 years period (2021 - 2023), a total of 959 patients were treated in the family medicine clinic in which there was a suspicion of Long Covid after the acute phase had passed. In all patients, the level of antibody values for COVID-19 was determined on several occasions according to the occurrence of symptoms of Long Covid

A total of 138 patients had a positive test for the presence of both forms of antibodies (Figure 2).

Elevated values of both antibody titers were demonstrated in 14% of patients, and they are usually found during the second to seventh week of the acute phase of the disease. Significant fluctuations in the titer of IgG antibodies during 3 years were demonstrated in one patient with various symptoms of Long-Covid (Figure 3).

During 2023, due to the large number of patients

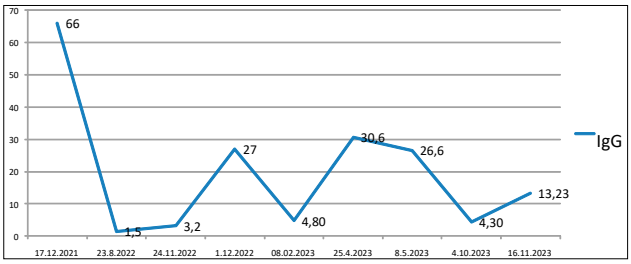

Figure 3. Significant fluctuations of the IgG titer in a patient with various symptoms of Long Covid

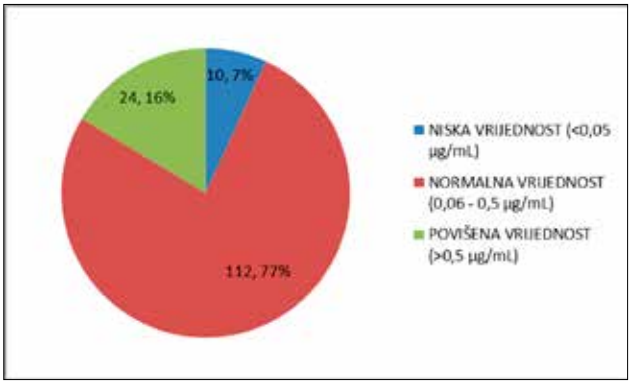

Figure 4. D-Dimer values in 146 patients with Long Covid symptoms

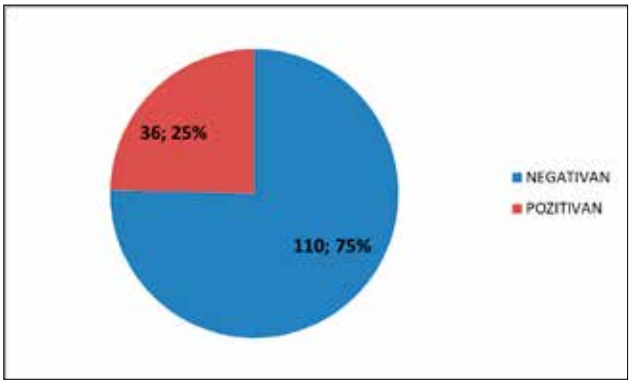

Figure 5 Results of testing 146 patients for IgM antibody to Covid-19

with risk factors for thromboembolic complications, D-Dimer was controlled in 146 patients. Elevated D-dimer values were detected in 24 patients, all of whom received anticoagulant therapy (Figure 4).

In the same group of patients, IgM antibody values were also controlled. Figure 5 shows that the appearance of IgM antibodies appears in a significant percentage, which can be a significant parameter for the verification of clinical suspicion of Long Covid (Figure 5).

5. DISCUSSION

Testing patients in different stages of the Covid-19 disease is gaining importance due to epidemiological data that this disease continues to appear with a significant incidence throughout the world and that it continues to represent an important global health problem for which an adequate answer has not yet been found. Pharmacological and non-pharmacological protection measures did not give the expected results, vaccination did not lead to collective immunity, so there is still a need for intensive research in the field of natural and specific human defense against the SARS-CoV-2 virus before the virus mutates into new types with possible new epidemic clinical manifestations. Experiences from the practice of primary health care can help researchers, but also family doctors in the process of rapid diagnosis and appropriate therapy (11-14).

Testing for the occurrence of immunological phenomena, such as IgM and IgG antibodies in clinical practice are often neglected, especially in the process of demystifying Long Covid and accepting the fact that many uncharacteristic symptoms such as general weakness, headache, insomnia and behavioral disturbances are a consequence of the presence of Long Covid . The relatively frequent reappearance of elevated IgM values during a long period of time after an acute infection and large fluctuations in the titer of IgG antibodies during the same period may justify the suspicion of a high incidence of Long Covid. New research is needed in the field of immunology and the creation of multidisciplinary teams and clinical guidelines for good clinical practice (14).

6. CONCLUSION

Monitoring of IgG and IgM antibodies can be of key importance in the diagnosis, prognosis and therapy of Long Covid, and D-dimer for the diagnosis of vascular disorders and the detection of patients at risk for thromboembolic complications. In the practice of family medicine, but also in many specialist protocols, the importance of assessing the immune response when symptoms of Long Covid appear is neglected. Given the complex clinical picture of Long Covid, most doctors, regardless of specialty, must acquire knowledge and skills for diagnosis and treatment of Long Covid symptoms. It is necessary to create guides that can be supplemented with new discoveries, especially in the field of human immune defense against new variants of the virus and new forms of Long Covid.

- **Author's contribution***: The both authors were involved in all steps of preparation this article. Final proofreading was made by the first author.*
- **Conflict of interest***: None declared.*
- **Financial support and sponsorship***: Nil.*

REFERENCES

1. Salihefendic N, Zildzic M, Masic I. Long Covid: A New Challenge for Healthcare Systems and Family Medicine Practice. Inter J Biomed Healthc. 2023; 11(3): 280-283. doi:10.5455/ijbh.2023.11.280-283.
2. Saliefendic N, Masic I. Public Health Aspect of the Promotional Activities in Defending the Population from theStress Intensified by COVID-19 Pandemic. Inter J Biomed Healthc. 2022; 10(1): 39-49. doi: ijbh.10.5455/ijbh.2022.10.39-49.
3. Masic I, Naser N, Zildzic M. Public Health Aspects of COVID19 Infection with Focus on Cardiovascular Dis -eases. Mater Sociomed. 2020; 32(1): 71-76. doi: 10.5455/msm.2020.32.71-76.
4. Gerc V, Masic I, Salihefendic N, Zildzic M. Cardiovas-cular Diseases (CVDs) in COVID-19 Pandemic Era. Mater Sociomed. 2020; 32(2): 158-164. doi: 10.5455/msm.2020.32.158-164.
5. Wang C, Horby PW, Hayden FG, et al. A novel corona-virus outbreak of global health concern. Lancet. 2020; 395(10223): 470-473.
6. Salihefendic N, Zildzic M, Huseinagic H, Ahmetagic S, Salihefendic Dz, Masic I. Intrafamilial Spread of COVID-19 Infection Within Population in Bosnia and Herzegovina.Mater Sociomed. 2021; 33(1): 4-9. doi: 10.5455/msm.2021.33.4-9.
7. Elisa GentilottI et al., (2023) Clinical phenotypes and quality of life to Research uncovers new insights into post-COVID-19 syndrome (PCS) phenotypes and impact onquality of life Saved from URL: https://www.news-medical.net/news/20230726/Research-uncovers-new-insightsinto-post-COVID-19-syndrome-(PCS)-phenotypes-andimpact-on-quality-of-life.aspx define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort, eClinicalMedicine. doi: 1016/j.eclinm.2023. 102107. https://www.thelancet.com/journals/eclin m/article/PIIS2589-5370(23)00284-5/fulltext#%20
8. Scurati R, Papini N, Giussani P, Alberti G, Tringali C. TheChallenge of Long COVID-19 Management: From Disease.Molecular Hallmarks to the Proposal of Exercise as Ther-apy. Int J Mol Sci. 2022, 23, 12311. https://doi.org/10.3390/ijms232012311 https://www.mdpi.com/journal/ijms
9. Huot N. Planchais C, Rosenbaum P, Contreras V, Jacque-lin B, Petitdemange C. et al. SARS-CoV-2 Viral Persistencein Lung Alveolar Macrophages Is Controlled By IFN- □ andNK Cells. Demystifying Long COVID International Confer-ence 2023. Hybrid Meeting. Madrid Spain.

7-9 December2023. Abstract 001.
10. Mehmedinovic S, Causevic M, Zildzic M, Salihovic R,Avdic A, Sitarevic M, Salihefendic N, Sinanovic. Impactof COVID-19 Pandemic on Perceived Social Support andMental Health of Persons with Disabilities in Bosnia andHerzegovina. Mater Sociomed. 2023; 35(3): 196–200. doi:10.5455/msm.2023.35.196-200.
11. Salihefendic N, Sehanovic A, Cabric E, Zildzic M. The Optic Neuritis Developed During COVID-19 Infection - a Case Report. Int J Biomed Healthc. 2024; 12(1): 74-76. doi: 10.5455/ijbh.2024.12.74-76.
12. Salihefendic N, Zildzic M, Masic I. Pandemic COVID-19: What We Know and What We Expect in 2022?. Int J Biomed Healthc. 2021; 9(3): 159-167. doi: 10.5455/ijbh.2021.9.159-167.
13. Selmanovic S, Beganlic A, Salihefendic N, Ljuca F, Softic A, Smajic. E. Therapeutic Effects of Curcumin on Ultrasonic Morphological Characteristics of Liver in Patients with Metabolic Syndrome. Acta Informatica Medica. 2017; 25(3): 169-174.
14. Zildzic M, Masic I. Relationship Between Education andFamily Medicine Practice. What Did we Learn in Covid-19Pandemic? Int J Biomed Healthc. 2021; 9(4): 282-287. doi:10.5455/ijbh.2021.9282-28.