Antibody response three months after SARS-CoV-2 infection

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Abstract
The coronavirus disease-19 (COVID-19) pandemic became the greatest public health challenge globally. In our study, it was aimed to determine the antibody levels in the third month after the COVID-19 infection and the symptoms that continued until the third month from the onset of the infection. One hundred people who applied to Tarsus State Hospital with the suspicion of COVID-19 and were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by real-time reverse transcriptase-polymerase chain reaction were included. We collected serum samples from individuals, who were 3 months postinfection, and tested them in anti-SARS-CoV-2 Quanti-Vac ELISA IgG kit coated with recombinant S1 antigen for testing SARS-CoV-2 antibodies. Antibody levels were found to be higher in those aged ≥55 years, nonsmokers, those with comorbidities, and those who were hospitalized. The four most common symptoms that individuals initially encounter; are weakness, muscle and joint pain, loss of taste and smell, and cough. In 3 months after COVID-19 infection, the most common four symptoms are; muscle and joint pain, insomnia, fatigue, and other problems were determined. In conclusion; more research is needed to determine threshold levels of serum antibodies that could prevent reinfection of SARS-CoV-2.

KEYWORDS
immunoglobulin, immune responses, infection, SARS coronavirus, virus classification

1 | INTRODUCTION
Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, was first detected in Wuhan, China in December 2019 and has since become a global epidemic. As of December 19, 2020, 349 641 119 cases of COVID-19 have been confirmed and 5 592 266 related deaths have been reported. These cases have posed significant challenges for health systems.1 According to recent reports, most patients with COVID-19 have an incubation period of 3–7 days. Fever, cough, and fatigue are the most common symptoms, while nasal congestion, runny nose, and diarrhea occur in only a minority of patients. Severe cases can progress rapidly to acute respiratory distress syndrome (ARDS), septic shock, difficult-to-treat metabolic acidosis, and bleeding and coagulation dysfunction. Some patients with COVID-19 have been reported to have only mild atypical symptoms initially, even in severe and critical cases. Chest computed tomography (CT) scans of COVID-19 patients are characterized by ground-glass opacity and bilateral patchy shading. For laboratory testing, most patients have been reported to have lymphopenia and elevated C-reactive protein. However, the clinical and laboratory features mentioned above are not easily distinguishable from pneumonia caused by other common respiratory pathogens.2

Understanding the long-term immunological memory response to SARS-CoV-2 after infection is critical for the development and administration of a SARS-CoV-2 vaccine. Recent studies have shown that most patients continue to have virus-specific antibody response 6–8 months after infection, but there is a tendency for patients to decline in humoral immunity over time. In studies, memory CD8+ and CD4+ T cells specific to SARS-CoV-2 were detected in most patients,
but decreased with a half-life of 3–5 months, while virus-specific memory B cells (MBCs) increased or remained unchanged 5–6 months after infection reported to persist.\(^3\)

In our study, it was aimed to determine the antibody levels in the third month after the COVID-19 infection and the symptoms that continued until the third month from the onset of the infection.

2 | MATERIALS AND METHODS

This study was approved by the TR Ministry of Health COVID-19 Scientific Research Evaluation Commission (Date: 04.03.2021 and Decision No: 2021-03-02T16_08_22) and Toros University Scientific Research and Publication Ethics Committee approval (Date: 26.03.2021 and Decision No: It was carried out by taking 2021/33).

2.1 | Working group and examples

Hundred patients who applied to Tarsus State Hospital Infectious Diseases and Clinical Microbiology with the suspicion of COVID-19 and whose diagnosis of COVID-19 was confirmed by reverse transcriptase-polymerase chain reaction were included in the study. Three months after the diagnosis, blood samples were taken from the patients.

Age, gender, height, weight, smoking, and COVID-19 infection status were recorded to determine the factors that may affect the SARS-CoV-2 antibody response. 4–5 ml blood samples from the healthcare workers included in the study were taken into tubes with ethylenediaminetetraacetic acid (EDTA) and centrifuged at 3500 rpm for 10 min and serum samples were separated. The obtained serum samples were stored at −80°C until the study.

2.2 | Enzyme-linked assay (ELISA) test

For the quantitative determination of SARS-CoV-2 IgG class antibodies, the Anti-SARS-CoV-2 QuantiVac ELISA IgG (Euroimmun) kit coated with recombinant S1 antigen of SARS-CoV-2 S protein including receptor-binding domain (RBD) was used. Serum samples were diluted 1:101 with sample buffer and tested according to the manufacturer’s instructions. At the end of the study, the absorbance of each well was determined spectrophotometrically at 450 nm. Results were calculated by plotting a point calibration curve to the units corresponding to the measured optical density values for six calibrators with concentrations ranging from 1 to 120 relative units (RU/ml). Antibody concentrations were determined in RU/ml by linear regression. Quantitative results obtained in RU/ml were converted to BAU/ml by multiplying by 3.2 by WHO specifications. Samples with antibody concentration <25.6 BAU/ml were considered negative, samples with ≥25.6 BAU/ml <35.2 BAU/ml were considered borderline positive, and samples ≥35.2 BAU/ml were considered positive. If the optical density of the samples was above calibrator 1 (120 RU/ml), the serum samples were diluted 1/400 and re-run and the results were multiplied by four.

2.3 | Statistical analysis

Statistical analyzes were performed using a package program called SPSS (IBM SPSS Statistics 24). Frequency tables and descriptive statistics were used to interpret the findings. Parametric methods were used for measurement values suitable for normal distribution. By parametric methods, the Independent Sample-t test (t-table value) method was used to compare the measurement values of two independent groups. Nonparametric methods were used for the measurement values that did not conform to the normal distribution. By nonparametric methods, the Mann–Whitney U test (Z-table value) was used to compare the measurement values of two independent groups, and the Kruskal–Wallis H test (χ²-table value) method was used to compare the measurement values of three or more independent groups. Bonferroni correction was applied for pairwise comparisons of variables with a significant difference for three or more groups.

3 | RESULTS

It was determined that the mean age of 100 people with COVID-19 infection included in the study was 44.65 ± 12.15 (years) and 42 (42%) were in the 45–54 age group. It was determined that 54 (54%) women were women, 38 (38%) were overweight, and 58 (58%) were not working. It was determined that 86 people (86%) did not smoke, 59 (59%) did not have a comorbidity, 64 (64%) did not have hospitalization, and 24 (66.7%) had a hospitalization period of 10–15 days (Table 1).

The four most common symptoms that individuals initially encounter; are weakness, muscle and joint pain, loss of taste and smell, and cough. In the 3rd month, the most common four symptoms are; muscle and joint pain, insomnia, fatigue, and other problems (hair loss, diabetes due to COVID-19 infection) were determined (Table 2).

It was determined that only 11% of the 100 patients included in the study had an asymptomatic infection. Their mean age was 46 (31–65), 63.6% of them were male and nonsmokers. Mean antibody levels were found to be 129.67232 BAU/ml in these individuals in the third month of infection.

According to the data collected to determine the factors affecting the antibody response in the body 3 months after the infection, there was no statistically significant difference in antibody levels according to gender, body mass index (BMI), employment status, and length of hospital stay (p > 0.05). A statistically significant difference was found in terms of antibody levels according to age classes (χ² = 24.680; p = 0.000). Antibody levels in the ≥55 age group were significantly higher than those in the <35 and 35–44 age group. A statistically significant difference was found in terms of antibody levels according to smoking status (Z = −3.509; p = 0.000). Antibody
levels of nonsmokers were found to be higher than those of smokers. A statistically significant difference was found in antibody levels according to the accompanying disease ($Z = -4.732; p = 0.000$). Antibody levels of those with comorbidities were found to be significantly higher than those without comorbidities.

A statistically significant difference was found in terms of antibody levels according to hospitalization status ($Z = -5.180; p = 0.000$). The antibody levels of those who were hospitalized were found to be significantly higher than those who were not hospitalized (Table 3). A statistically significant difference was found in terms of hospitalization time according to the initial symptoms of anorexia ($Z = -2.030; p = 0.042$). The length of stay of patients with anorexia symptoms is significantly higher than those without anorexia symptoms. The comparison of hospitalization times according to initial symptom findings is shown in Table 4.

### Table 1: Sociodemographic characteristics of the patients

| Variable (N = 100) | n | % |
|--------------------|---|---|
| Age $[\bar{X} \pm S.S. \rightarrow 44.65 \pm 12.15]$ (year) | | |
| <35 | 24 | 24.0 |
| 35-44 | 15 | 15.0 |
| 45-54 | 42 | 42.0 |
| ≥55 | 19 | 19.0 |
| Sex | | |
| Female | 54 | 54.0 |
| Male | 46 | 46.0 |
| BMI $[\bar{X} \pm S.S. \rightarrow 27.72 \pm 4.96]$ (kg/m²) | | |
| Weak | 1 | 1.0 |
| Normal | 31 | 31.0 |
| Overweight | 38 | 38.0 |
| Obese | 30 | 30.0 |
| Working status | | |
| Working | 42 | 42.0 |
| Not working | 58 | 58.0 |
| Smoking | | |
| Yes | 14 | 14.0 |
| No | 86 | 86.0 |
| Comorbidities | | |
| Yes | 41 | 41.0 |
| No | 59 | 59.0 |
| Hospitalization | | |
| Yes | 36 | 36.0 |
| No | 64 | 64.0 |
| Length of stay $[\bar{X} \pm S.S. \rightarrow 13.73 \pm 5.57]$ (day) | | |
| <10 day | 4 | 11.1 |
| 10-15 day | 24 | 66.7 |
| >15 day | 8 | 22.2 |

Abbreviation: BMI, body mass index.

### Table 2: Distribution of symptom findings at the beginning and third month of infection

| Variable | Beginning | Third month |
|----------|-----------|-------------|
| Fever | 43 | 43.0 | - |
| Cough | 45 | 45.0 | 2 | 2.0 |
| Sore throat | 30 | 30.0 | 2 | 2.0 |
| Shortness of breath | 31 | 31.0 | 5 | 5.0 |
| Headache | 39 | 39.0 | 3 | 3.0 |
| Loss of taste/smell | 45 | 45.0 | 4 | 4.0 |
| Joint/Muscle pain | 55 | 55.0 | 15 | 15.0 |
| Chest pain | 24 | 24.0 | 4 | 4.0 |
| Back pain | 44 | 44.0 | 9 | 9.0 |
| Diarrhea | 10 | 10.0 | 2 | 2.0 |
| Nausea/Vomiting | 11 | 11.0 | 3 | 3.0 |
| Anorexia | 41 | 41.0 | 2 | 2.0 |
| Fatigue | 63 | 63.0 | 9 | 9.0 |
| Skin rash | 2 | 2.0 | 1 | 1.0 |
| Psychological disorder | 12 | 12.0 | 3 | 3.0 |
| Palpitation | 14 | 14.0 | 8 | 8.0 |
| Loss of memory and concentration | 3 | 3.0 | 1 | 1.0 |
| Insomnia | 22 | 22.0 | 10 | 10.0 |
| Other | 15 | 15.0 | 10 | 10.0 |

Abbreviation: BMI, body mass index.

### Table 3

| Variable | n | % |
|----------|---|---|
| Working | 42 | 42.0 |
| Not working | 58 | 58.0 |
| Smoking | | |
| Yes | 14 | 14.0 |
| No | 86 | 86.0 |
| Comorbidities | | |
| Yes | 41 | 41.0 |
| No | 59 | 59.0 |
| Hospitalization | | |
| Yes | 36 | 36.0 |
| No | 64 | 64.0 |
| Length of stay | | |
| <10 day | 4 | 11.1 |
| 10-15 day | 24 | 66.7 |
| >15 day | 8 | 22.2 |

4 | DISCUSSION

SARS-CoV-2 infection can lead to asymptomatic or symptomatic infection, ranging from mild to severe illness and even death. In our study, 89% of the participants were found to be symptomatic, while this data was found to be quite opposite to the symptom situation of the general population, where most of the individuals (91%) were reported as asymptomatic. A statistically significant difference was found in terms of hospitalization status ($Z = -5.180; p = 0.000$). According to our results, some symptoms were found to persist in 46% of patients after SARS-CoV-2 infection, and the most common symptoms were fatigue (53.1%) and dyspnea (43.4%), and a decrease in weight and appetite was also noted.
TABLE 3 Comparison of antibody levels according to sociodemographic characteristics of patients

| Variable                  | n   | Antibody level | Statistical analysis* |
|---------------------------|-----|----------------|-----------------------|
|                           |     | X ± S. S.      | Median [Min.–Max.]    | Possibility   |
| Age [X ± S. S. → 44.65±12.15(yıll)] | 24  | 40.29 ± 28.13  | 37.7 [12.1–120.0]     | χ² = 24.680   |
| <35                       | 15  | 63.76 ± 43.36  | 66.1 [7.0–120.0]      | p = 0.000     |
| 35–44                     | 42  | 81.72 ± 39.48  | 88.9 [9.1–120.0]      | [1.2–4] [1–3] |
| 45–54                     | 19  | 103.57 ± 33.48 | 120.0 [21.6–120.0]    |               |
| ≥55                       |     |                |                       |               |
| Sex                       |     |                |                       |               |
| Female                    | 54  | 69.94 ± 44.25  | 65.8 [7.0–120.0]      | Z = -0.866    |
| Male                      | 46  | 77.40 ± 41.71  | 75.1 [9.1–120.0]      | p = 0.387     |
| BMI [X ± S. S. → 27.72±4.96[kg/m²]] |     |                |                       |               |
| Weak                      | 32  | 68.56 ± 45.95  | 63.8 [7.0–120.0]      | χ² = 0.639    |
| Normal                    | 38  | 74.22 ± 42.91  | 74.9 [9.1–120.0]      | p = 0.727     |
| Overweight obese          | 30  | 77.61 ± 40.85  | 75.1 [9.1–120.0]      |               |
| Working status            |     |                |                       |               |
| Working                   | 42  | 76.51 ± 40.17  | 75.9 [9.1–120.0]      | Z = -0.612    |
| Not working               | 58  | 71.23 ± 45.16  | 65.4 [7.0–120.0]      | p = 0.540     |
| Smoking                   |     |                |                       |               |
| Yes                       | 14  | 33.48 ± 23.58  | 28.3 [7.0–69.0]       | Z = -3.509    |
| No                        | 86  | 79.04 ± 42.23  | 88.5 [9.1–120.0]      | p = 0.000     |
| Comorbidities             |     |                |                       |               |
| Yes                       | 41  | 98.19 ± 31.73  | 120.0 [15.6–120.0]    | Z = -4.732    |
| No                        | 59  | 56.73 ± 41.76  | 45.2 [7.0–120.0]      | p = 0.000     |
| Hospitalization           |     |                |                       |               |
| Yes                       | 36  | 103.78 ± 27.08 | 120.0 [32.6–120.0]    | Z = -5.180    |
| No                        | 64  | 56.25 ± 40.95  | 50.5 [7.0–120.0]      | p = 0.000     |
| Length of stay [X ± S. S. → 13.73±5.57(gün)] |     |                |                       |               |
| <10 day                   | 28  | 103.43 ± 28.39 | 120.0 [32.6–120.0]    | Z = -0.375    |
| 10–15 day                 | 8   | 100.80 ± 26.69 | 120.0 [63.3–120.0]    | p = 0.707     |
| >15 day                   |     |                |                       |               |

*Mann–Whitney U test (Z-table value) for comparison of measurement values of two independent groups in non-normally distributed data; Kruskal–Wallis H test (χ²-table value) statistics were used to compare the measurement values of three or more independent groups.

in quality of life as measured by the EuroQol visual analog scale was reported in 44.1% of patients in this study.⁷ According to five articles that determined the frequency of symptoms among individuals with a positive COVID 19 test; We found a lower prevalence (45%) for fever (combined prevalence ranging from 78.4% to 92.8%) and cough (47.7% vs. a combined prevalence ranging from 58.3% to 72.2%).

Our estimates for body aches (44.1%) and breathing difficulties (23.1%) were within the ranges reported in the studies (29.4%–51.0% and 20.6%–45.6%, respectively). Finally, the prevalence of headaches in our study (39%) was considerably higher than in the reviews (8.0%–14.0%).⁸⁻¹² Changes in smell or taste were not investigated in these studies. In our study, we found the prevalence of loss of taste and smell to be 45%, and this data reported a prevalence ranging from 5.1% to 85.6%, which is consistent with other studies.¹³⁻¹⁶

In a study by Xiong et al.; in a 3-month follow-up survey of 538 COVID-19 patients, they found that physical regression or fatigue, post-activity polypnea, and hair loss were more common in women than in men.¹⁷ Among other symptoms in our study; Diabetes and hair loss associated with COVID-19 infection have been reported, and it is more common in men than in women.

At 6 months after the onset of symptoms, fatigue or muscle weakness and sleep difficulties were the main symptoms of patients
recovery from COVID-19. The risk of anxiety or depression as a major psychological complication and impaired pulmonary diffusion capacities were higher in patients with more severe diseases. These results support the need for post-discharge care for those with severe illnesses. Longer follow-up studies in a larger population are needed to understand the full spectrum of health outcomes from COVID-19.18

Asymptomatic individuals are potential sources of SARS-CoV-2 infection, which exhibits strong infectivity and rapid transmission during the incubation period. Therefore, a much larger portion of the population may have been exposed to much more viruses than has been documented. Therefore, estimating the prevalence of these unreported infections is critical to understanding the overall

| Table 4 | Comparison of hospitalization times according to the initial symptom findings of the patients |
|-----------------|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Initial symptoms | Symptom (+) | Median | Symptom (-) | Median | Statistical analysis* |
|                 | X ± S. S. [Min.-Max.] |          | X ± S. S. [Min.-Max.] |          | Possibility |
| Fever           | 15.19 ± 7.17 [7.0-30.0] | 14.0 | 12.35 ± 3.12 [6.0-18.0] | 13.0 | Z = -0.985, p = 0.325 |
| Cough           | 13.57 ± 5.26 [7.0-30.0] | 14.0 | 14.00 ± 6.31 [6.0-30.0] | 13.0 | Z = -0.095, p = 0.925 |
| Sore throat     | 14.53 ± 5.79 [7.0-30.0] | 15.0 | 13.20 ± 5.50 [6.0-30.0] | 12.0 | Z = -0.970, p = 0.332 |
| Shortness of breath | 14.89 ± 6.68 [6.0-30.0] | 14.0 | 12.14 ± 3.13 [7.0-17.0] | 10.5 | Z = -0.978, p = 0.328 |
| Headache        | 14.14 ± 6.21 [7.0-30.0] | 14.5 | 13.42 ± 5.19 [6.0-30.0] | 13.0 | Z = -0.240, p = 0.811 |
| Loss of taste/smell | 15.67 ± 7.23 [6.0-30.0] | 15.0 | 12.11 ± 3.05 [7.0-19.0] | 11.0 | t = 1.778, p = 0.092 |
| Joint/Muscle pain | 13.43 ± 5.26 [6.0-30.0] | 14.0 | 14.40 ± 6.48 [9.0-30.0] | 12.0 | Z = -0.999, p = 0.921 |
| Chest pain      | 14.85 ± 5.38 [10.0-30.0] | 14.0 | 13.00 ± 5.70 [6.0-30.0] | 11.0 | Z = -1.194, p = 0.232 |
| Back pain       | 14.47 ± 5.34 [7.0-30.0] | 14.0 | 12.71 ± 5.92 [6.0-30.0] | 10.0 | Z = -1.457, p = 0.145 |
| Nausea/Vomiting | 15.00 ± 9.11 [6.0-30.0] | 14.0 | 13.50 ± 4.91 [7.0-30.0] | 13.0 | Z = -0.025, p = 0.980 |
| Anorexia        | 14.86 ± 6.07 [6.0-30.0] | 15.0 | 11.45±3.64 [9.0-22.0] | 10.0 | Z = -2.030, p = 0.042 |
| Fatigue         | 14.24 ± 6.07 [6.0-30.0] | 14.0 | 12.12±3.39 [9.0-19.0] | 10.5 | Z = -0.893, p = 0.372 |
| Psychological disorder | 15.80 ± 8.61 [10.0-30.0] | 11.0 | 13.35±4.98 [6.0-30.0] | 13.5 | Z = -0.458, p = 0.647 |
| Palpitation     | 16.00 ± 7.13 [7.0-30.0] | 15.0 | 13.00±4.92 [6.0-30.0] | 11.0 | Z = -1.149, p = 0.251 |
| Insomnia        | 16.82 ± 7.70 [7.0-30.0] | 15.0 | 12.18±3.39 [6.0-19.0] | 10.5 | Z = -1.818, p = 0.069 |

*Mann–Whitney U test (Z-table value) for comparison of measurement values of two independent groups in non-normally distributed data; Kruskal–Wallis H test (χ²-table value) statistics were used to compare the measurement values of three or more independent groups.
prevalence and pandemic potential of this disease.\textsuperscript{18} In asymptomatic cases, the prevalence ranges from 4% to 75% in the literature.\textsuperscript{8,9,19-23} in our study, it was 11%.

Titers of anti-Spike (S) antibodies targeting the RBD (associated with cell entry) are widely thought to be associated with protection from re-infection. In persons with strong neutralizing antibody titers, these can be maintained for at least 6 months. In our study, it was aimed to determine the antibody titers and ongoing symptoms in the third month after the COVID 19 infection. In our study, IgG antibody levels against N-protein were still found to be high in the serum samples of patients with COVID-19 after 3 months, while a study conducted in India reported that 40% of them were negative for IgG antibodies against N-protein.\textsuperscript{24} Almost all confirmed patients achieve IgG or IgM seroconversion within 20 days of symptom onset, as evidenced by both the cross-sectional analysis and the follow-up study. This finding suggests that SARS-CoV-2 infection can be ruled out if antibodies to SARS-CoV-2 are still not detectable 20 days after onset of symptoms or 23 days after exposure.

Our study found that after 3 months, approximately 3% of serum samples were negative for IgG against S protein, whereas a similar study in the United States detected SARS-CoV-2 IgG negative in only 7.7% 3-6 months after symptom. Although the difference was statistically insignificant, males had higher titers than females at the end of 12 weeks. Twenty-one of these male patients were hospitalized and the mean antibody level was determined as 73.4166 RU/ml.\textsuperscript{25} A study in Brazil (initial investigation) and Spain reported similar elevations of antibodies across age groups, with seroprevalence among adults older than 65 years lower than those in Santa Clara County, CA, USA, and between 5 and 65 years of age, and in Greece and Iceland.\textsuperscript{26} It has been reported to be higher in older adults according to the data we obtained from other studies, it was determined that the antibody levels were higher in those aged ≥55 years. In our study, no significant correlation was found between the height of antibodies and gender, in a study conducted in Switzerland; A higher seroprevalence was found in men.\textsuperscript{27}

It has been reported that chronic diseases such as hypertension, diabetes, respiratory system disease, and cardiovascular disease may be associated with your COVID-19 pathogenesis. It shares several features with infectious diseases, such as a proinflammatory state and weakening of the innate immune response. For example, diabetes occurs in part because the accumulation of activated innate immune cells in metabolic tissues leads to the release of inflammatory mediators, particularly IL-1β and TNF-α, which promote systemic insulin resistance and β-cell damage.\textsuperscript{10} Studies\textsuperscript{5,10} have generally revealed that patients treated in intensive care units and undergoing invasive mechanical ventilation are predominantly male, elderly, and have various comorbidities. It has been reported that approximately 32% of COVID-19 patients admitted to hospitals in Wuhan have underlying diseases such as diabetes, hypertension, and cardiovascular disease.\textsuperscript{5} Yang et al.\textsuperscript{10} evaluated the prevalence of comorbidity in COVID-19 patients in seven different studies in the Chinese population, and consistent with our study, common comorbidities were found to be hypertension. and found that he had diabetes. Similarly, our findings suggest that IgG antibody is higher in people with underlying diseases.

The most important limitation of this study is that we planned a longitudinal follow-up cohort study of patients in our study. Antibody levels would be monitored by taking blood samples from the patients at 3, 6, 9, and 12 months after the onset of COVID 19 symptoms. However, since the vaccination policy has changed in our country, we could only measure antibody levels in the third month after infection.

As a result, we report the results of a comprehensive health assessment of patients 3 months after infection with COVID-19. Our results determined that 3 months after COVID-19, a significant proportion of patients continued to have symptoms, such as mild. Threshold levels of serum antibodies that could prevent reinfection of SARS-CoV-2 are still unknown and further research is needed. It is currently unclear why some patients experience long-term symptoms after COVID-19. Potential causes for different outcomes of infection are thought to be viral dose as well as host-dependent factors such as genetic susceptibility or induction of anti-inflammatory cells and proteins.

**AUTHOR CONTRIBUTIONS**

Dr. Öğr. Üyesi Efdal Oktay Gültekin: Conception, design, supervision, materials, data collection and/or processing, analysis and/or interpretation. literature review, writing, critical review. Dr. Onur Gültekin: Conception, design, supervision, materials, data collection and/or processing, critical review. Arzu Coskun: Materials, data collection and/or processing, literature review. Tiince Aksak: Literature review, critical review.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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