HEALTH SCIENCES **MEDICINE**

Correlation between antibody levels and long-term symptoms in survivors of COVID-19: health outcomes and societal implications

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ABSTRACT

Aims: It was aimed to evaluate the relationship between antibody levels, demographic characteristics, and ongoing symptoms of people who have positive COVID-19 real-time PCR (RT-PCR) tests and donated plasma after the disease.

Methods: Patients who voluntarily donated plasma were called by phone, and 105 patients who wanted to participate in the survey were included in the study. Ongoing symptoms, antibody test results, demographic characteristics, and other data of the participants were recorded.

Results: IgM was high in patients whose first complaint was fever and muscle pain at the onset of the disease and who used favipiravir for treatment (p=0.030, p=0.035, p=0.007). In those who survived the disease, it was determined that the IgM level decreased after the peak in the first month and the IgG level in the third month; the results were statistically significant. The IgG level decreased with the elapsed time and smoking, and the IgG level was found to be high in those who used favipiravir, hydroxychloroquine, or both during the disease and those in the AB blood type.

Conclusion: Some symptoms may persist even after the COVID-19 infection has been overcome. This study will contribute to a better understanding of this disease and the process after it.

Keywords: COVID-19, IgM and IgG antibodies, post-COVID symptoms, cigarette, blood type

INTRODUCTION

COVID-19 disease caused by the SARS-CoV-2 virus, which affected the whole world in late December 2019, was first identified in Wuhan, Hubei Province, China.¹ The disease can be recovered from with no or mild symptoms, or it can result in severe illness and death. Common symptoms are cough, fever, shortness of breath, weakness, fatigue, muscle pain, loss of taste and/or smell.²⁻⁶

The disease is diagnosed with clinical symptoms, serological tests, and lung imaging.^{7,8} The sensitivity of ELISA-based IgM and IgG-detecting antibody tests used in the diagnosis of COVID-19 is 77-83%, and the specificity is >95%. When a serum sample taken two weeks after the first positive RT-PCR test is studied, the accuracy of serological tests increases even further.⁹

COVID-19 antibody level is used epidemiologically to determine those who have recovered from the disease. As a result of the follow-ups, it has been shown that some complaints persist even months after the illness. 10,11

This study aimed to evaluate the correlation between antibody levels, demographic characteristics, and ongoing symptoms in healthy volunteers who tested positive for an RT-PCR test diagnosed with COVID-19. Then, the PCR test turned negative, and they wanted to donate Convalescent plasma (CP). Patients who volunteered to donate CP were contacted by phone, and those who agreed to participate in the survey were included in the study.

METHODS

The study was carried out with the permission of Adıyaman University Non-interventional Clinical Researches Ethics Committee (Date: 19.01.2021, Decision No: 2021/01-4). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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In this retrospective descriptive type study, those who applied to the Adıyaman University Training and Research Hospital blood center, who had a positive COVID-19 RT-PCR test before, whose PCR test was negative in their follow-up, who voluntarily donated CP, and whose IgG antibodies turned positive, were called by phone. Those who accepted to participate in the survey were included in the study.

The study participants' symptoms, antibody test results, epidemiological characteristics, and other data were registered between the time the first PCR test was positive and the time they donated. In the antibody study, 5 cc blood taken from volunteer CP donors into a biochemistry tube was centrifuged and quantitatively studied using the micro-ELISA method with the GRIFOLS brand TIRITURUS model device.

In the survey, 105 people participated. The participants were asked about their blood group, the date on which they were PCR positive, IgM and IgG levels, time of illness, first seen complaints, hospitalization or outpatient treatment, how many days they received treatment, drugs used in the treatment of COVID-19 disease, presence of ongoing complaints, if complaints not continued, what and when the last complaint was, smoking, whether there is any other person (spouse, children, mother, father, siblings) who had COVID-19 disease in the family, whether there is a person (spouse, children, mother, father, siblings) who died due to COVID-19 disease in the family.

Statistical Analysis

Predictive Analytics Software (PASW) 18 (2009) program was used for statistical analysis. The cases where the Type-1 error level is below 5% were interpreted as statistically significant. The conformity of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilkt tests).

Descriptive statistics were presented as numbers and percentages for categorical variables, median, percentile 25, and percentile 75 for numerical variables. The Kruskal Wallis test was used as the normal distribution condition was not met in the multi-group comparison analysis in numerical variables, and the Mann Whitney U test was used as the normal distribution condition was not met in the paired group comparison analysis.

Mann-Whitney U test with Bonferroni correction was used for post hoc analysis. Spearman's rho test was used to examine the correlation between numerical variables. Patient characteristics are summarized in Table 1.

Table 1. Demographic characteristics	(continued)	
Complaint continuation status, n (%)	105	15 (14.3)
Time of the last complaint, n (%)	105	
10 Days ago		5 (4.8)
20 Days ago		11 (10.5)
1 Month ago		5 (4.8)
Over 1 month		69 (65.7)
My complaint continues		15 (14.3)
Latest resolved complaint, n (%)		
Weakness		14 (13.3)
Muscle pain		7 (6.7)
Muscle pain+other complaints		1 (1)
Muscle pain+weakness		1 (1)
Muscle pain+fatigue		1 (1)
Shortness of breath		4 (3.8)
Fatigue		14 (13.3)
Fatigue+other complaints		2 (1.9)
Fatigue+shortness of breath		1(1)
Other complaints	105	60 (57.1)
Latest resolved complaint, n (%)		
Muscle pain	105	10 (9.5)
Weakness	105	15 (14.3)
Fatigue	105	18 (17.1)
Shortness of breath	105	5 (4.8)
Other complaints	105	63 (60)
Smoking status, n (%)	105	14 (13.3)
Presence of another person who had COVID-19 disease in the family, n (%) 105	41 (39)
Presence of a person who died due to COVID-19 disease in the family, n (%) 105	5 (4.8)

RESULTS

A total of 105 people participated in our study. We found that females were 16 (15.2%), males were 89 (84.8%), and the mean age was 37 (29-47). It was determined that 44 (41.9%) people had A blood group, 30 (28.6%) people had O blood group, 24 (22.9%) people had B blood group, and 7 (6.7%) people had AB blood group. It was observed that 32 (30.5%) people had illness two months ago, 31 (29.5%) people three months ago, 19 (18.1%) people one month ago, 12 (11.4%) people five months ago, 6 (5.7%) people six months ago and 5 (4.8%) people four months ago. We found 28 (26.7%) people whose first complaint was weakness and fatigue, 17 (16.2%) with other complaints (other than weakness, fatigue, muscle pain, fever, cough, and shortness of breath), 14 (13%) people with muscle pain, 14 (13.3%) people with fever and fatigue complaints, 8 (7.6%) people with complaints of weakness and muscle pain, 8 (7.6%) people with only fever. It was found that 98 (93.3%) people survived the disease at home, and 7 (6.7%) people were hospitalized. During the illness, 80 (76.2%) people received treatment for five days, 11 (10.5%) people for ten days, 1 (1%) person for one day, and 13 (12.4%) people recovered without treatment. While 56 people (53.3%) were found to use favipiravir and hydroxychloroquine together in the treatment of the disease, 35 people (33.3%) were found to use favipiravir, only one person (1%) was found to use hydroxychloroquine,13 (12.4%) were found not to receive any medical treatment.

It was observed that the complaints of the disease continued in 15 (14.3%) people after surviving the disease. For those who did not have a complaint, the most recent complaints were seen more than a month ago in 69 (65.7%) people, 20 days ago in 11 (10.5%) people, one month ago in 5 (4.8%) people, and ten days ago in 5 (4.8%) people. The most recently recovered complaints were found to include fatigue in 18 people (17.1%), weakness in 15 people (14.3%), muscle pain in 10 people (9.5%), shortness of breath in 5 people (4.8%), other complaints (other than fatigue, weakness, muscle pain, and shortness of breath) in 63 people (60%).

There were 14 smokers (13.3%) and 91 non-smokers (86.7%). It was found that 41 (39%) people had a person in their family (spouse, children, mother, father, siblings) other than themselves with COVID-19 disease. It was observed that 5 (4.8%) people died in the family due to COVID-19 disease (Table 1).

In our survey study, 105 healthy volunteers who previously had a positive COVID-19 PCR test and had a negative COVID-19 PCR test in their follow-up and who donated CP participated. The difference between the antibody levels between the time of illness and the time of the last complaint was statistically significant.

IgM levels were higher in those who had the disease one month ago, and IgG levels were higher in those who had the disease three months ago (p=0.040, p<0.001, respectively). IgM and IgG levels were higher in those whose last complaint was ten days ago (p=0.030, p<0.001, respectively). The difference between the treatment received groups and antibody level was found to be statistically significant. Higher IgM level was found to be statistically significant in patients using favipiravir or favipiravir and Plaquenil compared to those not receiving treatment (p=0.011, p=0.007). The IgM level was higher in patients whose first complaint was fever and muscle pain and who used favipiravir for treatment (p=0.030, p=0.035, respectively). The IgM level was found to be low in patients whose last recovered complaints were not weakness, fatigue, or shortness of breath (p=0.011), and the results were found to be statistically significant.

The risk of SARS-CoV-2 infection was the highest in people with A blood group (44 people 41.9%), and the risk of SARS-CoV-2 infection was the lowest in people with AB blood group (7 people 6.7%). Although the antibody level was high in the AB blood group, it was observed that there was no statistically significant difference between the other groups.

Antibody levels were found to be higher in hospitalized patients. There was no statistically significant difference between those who were not hospitalized. The IgM level was high in those treated for ten days during the disease, and the IgG level was high in those treated for five days. The results were not found to be statistically significant between the treatment periods.

Patients whose complaints did not continue after recovering from the disease were found to have high IgG levels; there was no statistically significant difference in antibody levels between those who continued their complaints after recovering from the disease and those who did not. IgG levels were found to be high in non-smokers. No statistically significant difference was found between smoker and non-smoker antibody levels.

There was no statistically significant difference in antibody levels between those with family members other than themselves (spouse, children, mother, father, siblings) with COVID-19 disease and those who do not. IgM was higher in those with family members (spouse, children, mother, father, siblings) who died due to COVID-19 disease; no statistically significant difference was found between the results (Table 2).

Table 2. Comparison of various findi	ngs wi	th antibody lev	rel					
	IgM Level						IgG Level	
	N	Mean±SD	Median (Q1-Q3)	p	N	Mean±SD	Median (Q1-Q3)	р
Blood group				0.640*				0.080*
A	44	7.57±4.91	5.5 (4.05-11)		44	33.43±15.12	34.6 (21.35-41.75)	
В	24	10.74±9.35	7.15 (4.9-13.85)		24	42.3±19	41.9 (34.5-45.2)	
AB	7	7.01±2.38	7.2 (5-9)		7	52.31±31.16	59 (17-63.6)	
0	30	8.67±6.94	6.45 (3.4-12)		30	42.87±36.12	45.65 (17.6-48.3)	
Time of illness				0.004*				< 0.001*
1 month ago	19	11.62±9.36	11 (4.3-17)		19	39.34±33.05	37.7 (23.7-42)	
2 months ago	32	7.11±4.81	5 (3.8-9.55)		32	36.45±25.7	40.5 (18.85-44.45)	
3 months ago	31	10.75±7.01	9 (6-12.7)		31	53.95±17.75	53 (42-62)	
4 months ago	5	4.94±3.05	4.2 (2.5-6)		5	26.94±10.08	23 (19.9-32.2)	
5 months ago	12	5.03±1.39	5.1 (3.65-6.15)		12	24.7±12.68	22 (15-35.6)	
6 months ago	6	5.55 ± 5.63	3.24 (2.9-4.1)		6	20.17±13.48	13.5 (11.5-32)	
First complaint								
Fever				0.030**				0.879**
No	77	7.87±6.16	5.6 (3.6-10.4)		77	39.03±24.53	41.2 (20.7-48)	
Yes	28	10.5±7.75	9.1 (5.35-13.35)		28	40.45±26.76	40.8 (26.85-45.65)	
Cough				0.643**				0.152**
No	96	8.73±6.84	6.1 (4.05-11.65)		96	40.48±25.51	41.45 (23.5-48)	
Yes	9	6.87±4.65	6 (3.7-6.6)		9	27.96±15.86	18 (17-42)	
Shortness of breath				-				-
No	104	8.61±6.71	6.1 (4-11.4)		104	39.43±25.14	41.2 (20.9-48)	
Yes	1	4.9±0	4.9 (4.9-4.9)		1	37.7±0	37.7 (37.7-37.7)	
Muscle pain				0.035**				0.062**
No	79	7.88 ± 6.08	6 (3.5-11)		79	36.3±21.93	37.7 (17.6-48)	
Yes	26	10.67 ± 8.05	9.05 (4.9-13.4)		26	48.87±31.31	41.8 (32.4-48)	
Weakness				0.447**				0.649**
No	50	9.19±7.5	6.3 (4.2-11.6)		50	39.24±27.04	37.85 (19.9-48)	
Yes	55	8.01±5.87	6 (3.6-11.2)		55	39.57±23.29	41.7 (26-48)	
Other complaints				0.651**				0.386**
No	83	8.3±6.51	6 (4-11.2)		83	40.94±26.81	41.7 (23-48)	
Yes	22	9.58±7.38	7 (3.5-13.5)		22	33.65±15.82	32.1 (19.7-46)	
Hospitalization status				0.576**				0.714**
Yes	7	11.46 ± 13.27	6.3 (4.9-11)		7	36.11±17.74	41.2 (14.2-46)	
No	98	8.37±6.03	6 (4-11.6)		98	39.65±25.51	41.1 (21-48)	
Day of treatment received				0.646*				0.379*
5 Days	80	9.31±7.24	6.4 (4.15-12.35)		80	41.87±26.77	41.7 (23.85-48.15)	
7 Days	1	4.2±0	4.2 (4.2-4.2)		1	32.2±0	32.2 (32.2-32.2)	
10 Days	11	8.51±3.91	7.2 (6.3-11)		11	31.31±19.23	26 (14.2-46)	
Over 10 days	0	0±0	0 (0-0)		0	0±0	0 (0-0)	
I did not receive any treatment	13	4.45±2.37	3.6 (2.9-5.2)		13	31.72±15.18	24.2 (20.7-42)	

		dings with antibody level (continued) IgM Level IgG Level						
	N	Mean±SD	Median (Q1-Q3)	p	N	Mean±SD	Median (Q1-Q3)	р
Treatment used		intenni±012		Y		interni 2010		P
Favipiravir				0.007**				0.089**
No	14	4.94±3.23	3.85 (2.9-5.6)		14	29.25±16.28	23.95 (19.7-42)	
Yes	91	9.13±6.91	6.6 (4.2-12)		91	40.97±25.82	41.7 (23.3-48)	
Plaquenil	71	9.15±0.91	0.0 (1.2 12)	0.082**	71	10.97 ±23.02	11.7 (20.0 10)	0.108**
No	48	7.96±7.48	5.45 (3.5-10)	0.002	48	33.51±17.72	31.35 (18.35-47.5)	0.100
Yes	40 57	9.09±5.96	8 (4.6-12)		40 57	44.38±29.05	41.7 (28-48)	
Treatment used	57	J.0J±3.J0	0 (4.0-12)	0.011*	57	44.30±27.03	11.7 (20-40)	0.146*
Favipiravir	35	9.22±8.25	6.3 (3.7-11.7)	0.011	35	35.31±17.95	40.4 (17-48.3)	0.140
Favipiravir+plaquenil	56	9.07±6.01	7.6 (4.6-12.35)		56	44.52±29.3	41.7 (27.1-48)	
I did not use any drugs	13	9.07±0.01 4.55±3	3.5 (2.9-5,2)		13	44.32±29.3 28.68±16.8	23.7 (19.7-42)	
			5.5 (2.9-5,2)				23.7 (19.7-42)	
Plaquenil	1	10		0.21.455	1	36.6		0.4025
Complaint continuation status	15	0 (5, 10,00	E (2 E 11)	0.314**	15	22.02.16.42		0.492**
Yes	15	8.67±10.09	5 (3.5-11)		15	33.82±16.43	37 (20.7-45.3)	
No	90	8.56±6.02	6.3 (4.1-11.6)		90	40.34±26.13	41.2 (21-48)	
Time of last complaint				0.030*				< 0.001
10 days ago	5	13.74±6.04	13 (10.4-17)		5	108.2 ± 60.46	107 (105-159)	
20 days ago	11	8.25±3.26	8 (6-9)		11	57.04±15.7	62 (61-62)	
1 Month ago	5	6.82±3.67	5 (4.9-8)		5	55.34±2.74	55 (53-58)	
Over 1 month	69	8.7±6.42	6 (4-11.6)		69	33.63±12.9	38 (21-42)	
My complaint continues	15	7.07±9.85	4.2 (2.9-5.4)		15	24.83±14.22	23.7 (10.2-41.7)	
Latest resolved complaint								
Muscle pain				0.290**				0.172**
No	95	8.42±6.75	6 (3.7-11.2)		95	38.58 ± 24.88	40.4 (20.7-48)	
Yes	10	10.02 ± 6.23	8.5 (5-17)		10	47.26±26.3	43.9 (26-62)	
Weakness				0.425**				0.826**
No	90	8.5±6.93	6 (4-11.2)		90	38.9 ± 22.98	41.2 (23-48)	
Yes	15	8.99±5.17	8 (4.1-13)		15	42.46±35.78	37.7 (17-48)	
Fatigue				0.109**				0.936**
No	87	7.79±5.35	6 (3.6-11)		87	39.94±26.96	41.2 (19.7-48.3)	
Yes	18	12.34±10.51	9 (4.3-17)		18	36.86±12.03	37.5 (28-45.1)	
Shortness of breath				0.077**				0.320**
No	100	8.4±6.73	6 (3.85-11.1)		100	39.22±25.46	40.7 (20.9-47.5)	
Yes	5	12.04±5	11.6 (9-17)		5	43.28±14.58	48 (41.7-48)	
Other complaints				0.011**				0.351**
No	42	10.08±6.35	9 (4.9-15)		42	41.9±25.46	41.7 (26.2-48)	
Yes	63	7.57±6.77	5.9 (3.5-9.7)		63	37.75±24.78	41 (17.6-48)	
Smoking status	00	// ±0.//	0.0 (0.0))	0.720**	00	07.00121.00	11 (17.0 10)	0.685**
Yes	14	8.4±4.99	7.5 (4.2-12.7)	0.720	14	44.67±37.48	36.4 (23-58.3)	0.005
No	91	8.6±6.93	6 (4-11.2)		91	38.6±22.7	41.2 (20.8-47)	
Presence of another person who ha				0.380**	71	50.0122.7	41.2 (20.0-47)	0.430**
			•	0.380	41	36 11+10 EF	10 1 (20 7 45 2)	0.430
Yes	41	7.78±5.82	5.6 (4-11)		41	36.44±19.55	40.4 (20.7-45.3)	
No	64	9.08±7.18	6.45 (3.95-11.8)	0.05011	64	41.31±27.95	41.45 (22-48)	0.0101
Presence of a person who died due			•	0.059**	-	26.02.5.00		0.910**
Yes	5	13.26±5.34	14.8 (13.4-17)		5	36.82±7.02	41.7 (32-41.8)	
No * Kruskal Wallis, ** Mann-Whitney U	100	8.34±6.68	6 (3.85-11)		100	39.54±25.6	41.1 (20.75-48)	

DISCUSSION

Research is ongoing on the COVID-19 disease that affects the world. Uncertainties in the symptoms, diagnosis, and treatment of the disease continue. In addition, it has been observed that there are ongoing symptoms even if the disease is recovered. PCR is still used in the foreground in diagnosing the disease, and antibody level is checked in epidemiological examinations.

The duration and nature of the immunity that occurs in response to the infection caused by SARS-CoV-2 are unknown. The duration of immunity will determine the overall course of the pandemic and the post-pandemic dynamics. Therefore, understanding the temporal dynamics of protective immunity is critical.¹¹ In the study conducted by Yang et al.¹² the data of 67 patients have been analyzed. In the first month, higher positive IgM rates have been found against SARS than IgG. The proportion of patients who performed seroconversion for IgM peaked 30 days after onset. Subsequently, it has been shown that a gradual decrease was observed in IgM levels, and IgG levels peaked in the 25th week. In our study, similar to the study of Yang et al., we found that IgM peaked in the first month in survivors, and differently, IgG peaked earlier (3rd month).

Even if the COVID-19 disease process is recovered, ongoing symptoms can be seen. In a study by Carfi et al.¹³ it has been reported that patients continued Post COVID Syndrome (PCS) after an average of 60 days (72.7% of hospitalized participants had an additional disease, interstitial pneumonia), the most frequently reported symptoms were fatigue 53.1%, shortness of breath 43.4%, joint pain 27.3%, and chest pain 21.7%. On the other hand, in a study by Garrigues et al.¹⁴ it has been reported that patients who were hospitalized due to COVID-19 had PCS for more than 100 days after discharge, the most frequently reported symptoms were fatigue 55%, dyspnea 42%, and in addition, memory loss 34%, concentration and sleep disturbances 28% and 30.8%, respectively.

In our study, PCS continued after an average of 28 days in 15 people; among those with symptoms, only one person (1%) was hospitalized, and no additional disease was found in any of the participants. The most common PCS was similar to the studies of Carfi and Garrigues; as a proportion, the symptoms were weakness and fatigue at 26.6%; differently, muscle pain was at 13.3%, fever at 7.6%, cough at 3.8%, dyspnea at 0.9%, and memory loss, concentration, and sleep disturbances were seen as other symptoms at a rate of 6.1%. Again, differently, it was found that two or more symptoms persisted at a rate of 41.7%. In addition, our study checked the IgG level according to the presence of symptoms. The IgG level was lower in those with symptoms (33.3%) than those without symptoms (40.3%). In our study, the shorter PCS incidence time compared to other studies was attributed to the fact that the participants were healthy volunteers who donated CP, did not have any additional disease, and donated in the early period.

In a study by Li et al.¹⁵ it has been reported that people with A blood group had a significantly higher risk of SARS-CoV-2 infection, while those with O blood group had a significantly lower risk of SARS-CoV-2 infection; in another study conducted by Göker et al.16, it has been reported that while increased susceptibility to COVID-19 infection was detected in those with A blood group, O blood group may be somewhat protective. All participants in our study were followed up on an outpatient basis; similar to Li et al., while people with A blood group 41.9% had the highest risk of having COVID-19 disease, differently, we found that the risk of COVID-19 disease was the lowest in people with AB blood group, 6.7%. The lowest risk in those with the AB blood group was attributed to the lowest number of respondents with the AB blood group (6.7%).

In our study, the blood group mean antibody levels were found to be IgM 5.5 (4.05-11), IgG 34.6 (21.3-41.7) in group A, and IgM 7.2 (5-9), and IgG 59. (17-63.6) in the AB group.

It has been shown by Carlos et al.¹⁷ that being a smoker or a former smoker is a risk factor for the worse progression of COVID-19 infection. Our study found the rate of smokers to be 13.4%. PCS continued in 4 smokers and 11 non-smokers. Among those who continued PCS, the IgG level of smokers (18.4%) was lower than that of nonsmokers (40.3%).

Although many antivirals have been tried for COVID-19 disease, an effective treatment still needs to be found. In a study by Jean SS et al.¹⁸, favipiravir, hydroxychloroquine, and azithromycin co-treatment are acceptable alternatives for treating COVID-19 patients. In the study conducted by Zarir F et al.¹⁹ it has been determined that treatment with favipiravir may be beneficial in the clinical recovery period in patients admitted to hospital with mild (including asymptomatic) and moderate COVID-19. In another study with hydroxychloroquine, it has been mentioned that it can contribute to palliate the inflammatory response in COVID-19 patients and effectively inhibit SARS-CoV-2 infection in vitro.²⁰

Participants in our study were people between the ages of 20-60 without any comorbidities. 87.62% of the participants received treatment during the illness period, and 12.4% did not. Those who received treatment were found to use favipiravir, hydroxychloroquine, or favipiravir and hydroxychloroquine together. It was observed that the level of IgG (40.3%) in those who received treatment was higher than those who did not (22.4%).

CONCLUSION

On the one hand, while the diagnosis, treatment, protection time of antibodies, and vaccination studies of COVID-19 disease continue, studies on PCS also continue in the post-disease period. Even if the disease was recovered, some symptoms continued at varying rates, and IgG levels decreased with the elapsed time and smoking. IgG levels were high in those who used favipiravir, hydroxychloroquine, or both during the treatment and those with AB blood group. Providing a framework for the possible physical symptoms of the disease after recovery in patients with COVID-19

and the results obtained when studies are conducted to determine the factors that contribute to or reduce protection will contribute to a better understanding of this disease and the subsequent process. Continuing such studies is essential to reveal the need to open a clinic for these patients in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Adıyaman University Non-interventional Clinical Researches Ethics Committee (Date: 19.01.2021, Decision No: 2021/01-4).

Informed Consent

Written informed consent was obtained from all participants in this study.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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