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RESEARCH ARTICLE

LONG-COVID: WHAT AWAITS US AFTER CORONA INFECTION?

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ABSTRACT

Purpose: In this study, it was aimed to investigate the symptoms (Long-Covid) that continue after 28 days and the factors affecting its formation in patients who had a mild course of Covid-19 and recovered.
Material and Methods: Until July 2021, 64 thousand Covid-19 patients were diagnosed in Kütahya. A questionnaire was conducted by contacting 659 people, who did not have hospitalization indications, either face-to-face or by telephone and 635 people completed it.
Results: The mean age of the patients, 50.10% of whom were women and 43.50% were university graduates, was 44.26±15.69 years. It was determined that an average of 6.39±2.61 months (min:2; max:14) had passed since the patients were diagnosed with Covid-19. The most common symptoms was fatigue followed by muscle pain, memory problems, joint pain, and loss of smell, respectively. It was found that there was a significant relationship between the presence of prolonged symptoms and the observation of symptoms at the beginning of the disease, the presence of lung involvement, the status of taking anticoagulants, and the prolongation of the recovery time of active symptoms ($p<0.05$). Female gender, presence of chronic disease and non-vaccination were observed at higher rates in Long-Covid patients.
Conclusion: Prolonged symptoms are more common in patients with a severe clinical course of Covid-19 disease. As vaccination rates increase, the rate of observing prolonged symptoms decreases. There is a need for new research on this subject with more vaccinated individuals.

Keywords: covid-19, long-covid, persistent symptoms

INTRODUCTION

For nearly two years, the whole world has been struggling with a new epidemic, which we know to have started in Whuan, China in November 2019 and then spread to the whole World as a viral epidemic caused by SARS-Cov2 and called Covid-19 disease (1-3). According to the reports of the World Health Organization (WHO), Covid-19 has caused the death of approximately 4.5 million people (4). While this disease may progress asymptomatically, it may progress with symptoms such as fever, dry cough, joint and muscle aches, pain and pressure in the chest, fatigue, shortness of breath, myocarditis, and elevated liver function tests (5-7).

Vaccines have been developed to protect against Covid-19. Vaccination studies, which started with a single dose, are currently continuing with 3 or even 4 doses in some countries. However, due to evolving mutations, it is not possible to completely prevent this epidemic with vaccination. Still, it is reported that it is possible to overcome the disease mildly with vaccination. Despite the scientific stage that the world has come to today, an effective treatment for Covid-19 has not been found yet (8-11). At this point, the question of whether the Covid-19 disease has left some sequelae in our body has come to mind. Studies show that the effects of this disease sometimes last for months. In fact, new terminologies such as Post-acute Covid=Ongoing Symptomatic Covid-19, Chronic Covid=Post-Covid-19 Syndrome have started to be used for cases where some symptoms continue after Covid-19 (12). The condition

Table 1. Demographic characteristics of the Covid 19 patients

	Number (n)	Percentage (%)
Gender		
Female	318	50,10
Male	317	49,90
Education		
No education	16	2,50
Primary school	136	21,40
Secondary school	38	6,00
High school	169	26,60
University	276	43,50
Occupation		
Civil servant	120	18,90
Worker	164	25,80
Tradesman	44	6,90
Retired	83	13,10
Housewife	165	26,00
Not working	25	3,90
Student	34	5,40
Blood type (A,B,AB and O)		
A	267	42,00
B	87	13,70
AB	52	8,20
O	177	27,90
Not known	52	8,20
Rh Factor		
(+) Positive	525	82,70
(-) Negative	58	9,10
Not known	52	8,20
Total	**635**	**100,00**

of observing the symptoms that continue 28 days after the Covid-19 disease is called “Long-Corona Syndrome” (13-17). According to some studies, it has been determined that a series of symptoms such as fatigue, muscle-joint pains, forgetfulness, difficulty concentrating, smell-taste loss and mood changes continue (18-20). Abnormal cellular or humoral immune responses are also held responsible for the etiopathogenesis of this condition (21).

This study was carried out to determine the presence, frequency and affecting factors of symptoms that continue after 28 days in patients who had a mild course of Covid-19 and recovered.

MATERIAL AND METHODS

Study Design

This descriptive cross-sectional study was conducted on patients who had Covid19 disease in the province of Kütahya.

Study Population

This study was carried out in accordance with the Declaration of Helsinki, with the approval of the Non-Interventional Ethics Committee of Kütahya Health Sciences University with the decision number 2021/11-27 dated 30.06.2021. As of July 2021, there are approximately 64 thousand diagnosed Covid-19 patients in Kütahya and these patients constitute the population of our study. The sampling was calculated as 631 with 99% confidence level, 40% prevalence and 5% margin of error. We reached 659 people who had Covid 19 disease at least 1 month ago. Children who couldn’t express themselves, mentally ill, patients with speech disorders, and those less than 1 month after the illness were not included in our study. Thus, the study was performed on 635 patients. Those who experienced the disease at least 28 days ago were included in the study, and those who had a shorter period of time were excluded.

Data Collection

A questionnaire- consisting of 17 items that examine demographic characteristics, the method of diagnosis, the course of the disease, how long it took to heal, the drugs used, whether treatment was received in the intensive care unit, whether there were serious symptoms related to lungs, how long it had been since recovery, whether there were any ongoing symptoms, and if there was any, how long the symptom persisted- was conducted by contacting these people face to face or by telephone.

Statistical Analysis

Data were recorded in the SSPS 20.0 (Statistical Package for the Social Science, Inc.; Chicago, IL, USA) package program and statistical analysis was performed. Numerical variables were shown as mean±standard deviation and median (minimum, maximum), while categorical variables were shown as number (n) and percentage (%). Chi-square significance test was used to compare the categorical variables of the patient and control groups, while t test

Table 2. Diagnosis method, symptom status, vaccination status, smoking status, drug treatment and anticoagulant treatment status of Covid-19 patients

	Number (n)	Percentage (%)
Diagnosis method		
RT-PCR	567	89.30
CT Thorax	16	2.50
PCR+CT	52	8.20
Symptom status at the time of diagnosis		
Exists	592	93.02
None	43	6.80
Lung involvement		
Exists	140	22.00
None	495	78.00
Vaccination status		
Not vaccinated	609	95.09
Inactivated virus vaccine	23	3.60
m-RNA vaccine	3	0.50
Chronic disease		
Exists	187	29.40
None	448	70.60
Smoking		
Yes	429	67.60
No	127	20.00
Quitted	79	12.40
The effect of Covid-19 on smoking habit		
Non-smoker	429	67.60
Negative effect (started smoking)	1	0.20
No effect (smoker as before)	194	30.60
Quitted and started again	11	1.70
Total	635	100.00

was used to compare the numerical variables. For statistical differences, $p<0.05$ was considered statistically significant.

RESULTS

The mean time passed since the diagnosis of Covid-19 patients participating in our study was 6.39±2.61 months (min:2; max:14). Of the patients, 318 (50.10%) were female and 317 (49.90%) were male. The mean age was 44.26±15.69 years (min:18, max:88) and 43.50% of the participants were university graduates (Table 1).

It was observed that the diagnosis of Covid-19 was made by RT-PCR in 567 (89.30%) patients. At the time of diagnosis, 592 patients (93.02%) had one or more symptoms. When the patients were asked whether their lungs were affected at the time of diagnosis, 140 (22%) patients stated that they were affected, while 495 (78%) patients stated that they were not affected or that no clear information was given to them. In terms of the vaccination level, it was observed that 26 (4.10%) people were vaccinated, 23 (3.6%) with inactivated virus vaccine and 3 (0.50%) with m-RNA vaccine. It was observed that 448 (70.60%) of the patients did not have a chronic disease. Diabetes and hypertension (n:187, 29.40%) were the most common diseases in patients with chronic disease. While 127 (20%) of the patients stated that they smoked and the Covid-19 disease had no effect on their smoking habit, one patient stated that they started smoking, and 11 patients stated that they quitted smoking and then started again (Table 2).

In the study group, it was observed that 539 people (84.90%) used favipiravir. Of those who did not use it, 63 (65.62%) stated that it was because they thought it might be harmful. 314 (49.40%) of the patients used an anticoagulant, either low molecular weight heparin (LMWH) or acetylsalicylic acid (ASA). Most of those who used anticoagulant said it was recommended by

Table 3. Getting treatment, taking anticoagulants, needing hospitalization and treatment periods in Covid disease

	Number (n)	Percentage (%)
Status of receiving Covid-19 Treatment		
Received	539	84.90
Not received	96	15.10
Reason for not receiving treatment		
Received regularly	539	84.90
Allergy	4	0.60
Detrimental	63	9.90
Pregnant	8	1.30
Below 18 years of age	1	0.20
Not given	5	0.80
No symptoms	10	1.60
Lactating	5	0.80
Taking anticoagulant (AC)		
Yes	314	49.40
No	321	50.60
Type of anticoagulant taken		
Not taken	321	50.60
Acetylsalicylic Acid (ASA)	89	14.00
Low Molecular Weight Heparin (LMWH)	225	35.4
Person(s) who recommended taking AC		
Not used	321	50.6
Doctor	231	36.4
Folks	66	10.4
Using for a long time	17	2.7
Recovery time of active symptoms		
0-7 days	316	49.80
8-14 days	243	38.30
15-29 days	63	9.90
30 days or over	13	2.00
Symptom resuming 28 days after recovery		
None	401	63.10
Exists	234	36.90
Total	635	100.00

a physician. While 316 (49.80%) of the patients stated that their active symptoms disappeared in 0-7 days, 243 (38.30%) said they disappeared in 7-14 days and 234 (36.90%) stated that one or more symptoms persisted after 28 days (Table 3).

When all of the patients were examined, it was found that the most common ongoing symptom was fatigue (n: 95, 40.60% among ongoing symptoms) persisting for an average of 4.67±2.25 months (min:2-max:9), followed by muscle pains (n:61, 26.06%; mean: 5.07±2.35 months; min:2-max:10), memory problems (n:57, 24.36%; mean:6.35±2.109 months; min:2-max:10), joint pains (n:48, 20.51%; mean:4.67±2.253 months; min:2-max:9), and loss of smell (n:41, 17.52%; mean :4.90±2.596 months; min:2-max:10) respectively. The minimum and maximum duration of symptoms persisting after 28 days and the average duration in months are shown in Figure 1 and Table 4.

It was found that the prolongation of symptoms (Long-Covid) was associated with the presence of symptoms during the diagnosis of Covid-19, the presence of pulmonary involvement at the beginning, the status of taking anticoagulants, and the prolongation of the recovery times of active symptoms ($p<0.05$), but had no significant association with gender, blood type, Rh factor, vaccination, chronic disease, smoking, treatment (favipiravir), and anticoagulant type (ASA, LMWH) ($p>0.05$). Although no statistical relationship was

Table 4. Analysis of symptoms persisting for more than 28 days and their duration*

Ongoing Symptoms And Their Duration	N (Number of People Observed)	% (Ratio in ongoing symptoms)	Minimum (month)	Maximum (month)	Mean (month)	SD Deviation
Fatigue	95	40.60	2	10	5,49	2,342
Muscle pain	61	26.06	2	10	5,07	2,358
Memory problems	57	24.36	2	10	6,35	2,109
Joint pain	48	20.51	2	9	4,67	2,253
Smell loss	41	17.52	2	10	4,90	2,596
Hair loss	34	14.53	2	6	3,00	1,073
Dyspnea	32	13.68	2	9	4,16	2,065
Sleep problems	24	10.25	2	12	5,37	2,533
Taste loss	23	9.82	2	8	3,74	1,888
Difficulty thinking	23	9.82	2	12	5,91	2,448
Feeling of pressure in the chest	22	9.40	2	10	4,59	2,239
Coughing	22	9.40	2	4	2,64	0,581
Palpitation	19	8.12	2	9	5,32	2,540
Headache	17	7.26	2	9	4,71	2,365
Anxiety	15	6.41	2	7	4,53	1,598
Chest pain	15	6.41	3	9	5,00	1,890
Mood changes	14	5.98	2	13	5,64	2,951
Dizziness (vertigo)	10	4.27	2	10	4,30	2,584
Desquamation	9	3.84	2	6	2,78	1,302
Skin rash	5	2.14	3	4	3,20	0,447
D-dimer elevation	5	2.13	2	4	3,00	0,707
Numbness in fingers	5	2.13	2	9	5,20	3,114
Hoarseness	4	1.71	2	6	3,00	2,000
Dysfunction of the lungs	4	1.71	2	8	5,25	3,202
Sweating	4	1.71	2	7	5,25	2,217
Hearing loss	4	1.71	4	7	5,50	1,291
Liver dysfunction	3	1.28	2	4	3,00	1,000
Depression	2	0.85	2	6	4,00	2,828
Tinnitus	2	0.85	5	6	5,50	0,707
Intermittent fever	1	0.43	7	7	7,00	.
Nasal congestion	1	0.43	7	7	7,00	.
Nail disorders	1	0.43	6	6	6,00	
Urticaria	1	0.43	2	4	3,00	.

* More than one answer given.

found between the status of being vaccinated and the incidence of Long-Covid, when analysed proportionally, it was found that the frequency of ongoing symptoms decreased with the number of vaccinations (37.30% in non-vaccinated patients; 28.60% in those who had been vaccinated for 1 dose; 26.30% in those who had been vaccinated for 2 doses) (Table 5).

DISCUSSION

During the current pandemic period, some of the patients who were thought to have recovered realized that some symptoms continued (19). WHO accepted such ongoing complaints as a health problem (20). Studies have reported that prolonged Corona symptoms can be seen at a rate of 30.3% to 53.1% (23,24,25). In our study, it was found that the symptoms continued after Corona disease at a rate of 36.90% with one prolonged symptom in some patients while multiple in others; that is, 101 (43.16%) of the patients with prolonged symptoms had one symptom, while 55 (23.5%) had two prolonged symptoms. Besides, 11.111% (n:26) of the patients had three, 5.98% (n:14) had four, 5.56% (n:13) had

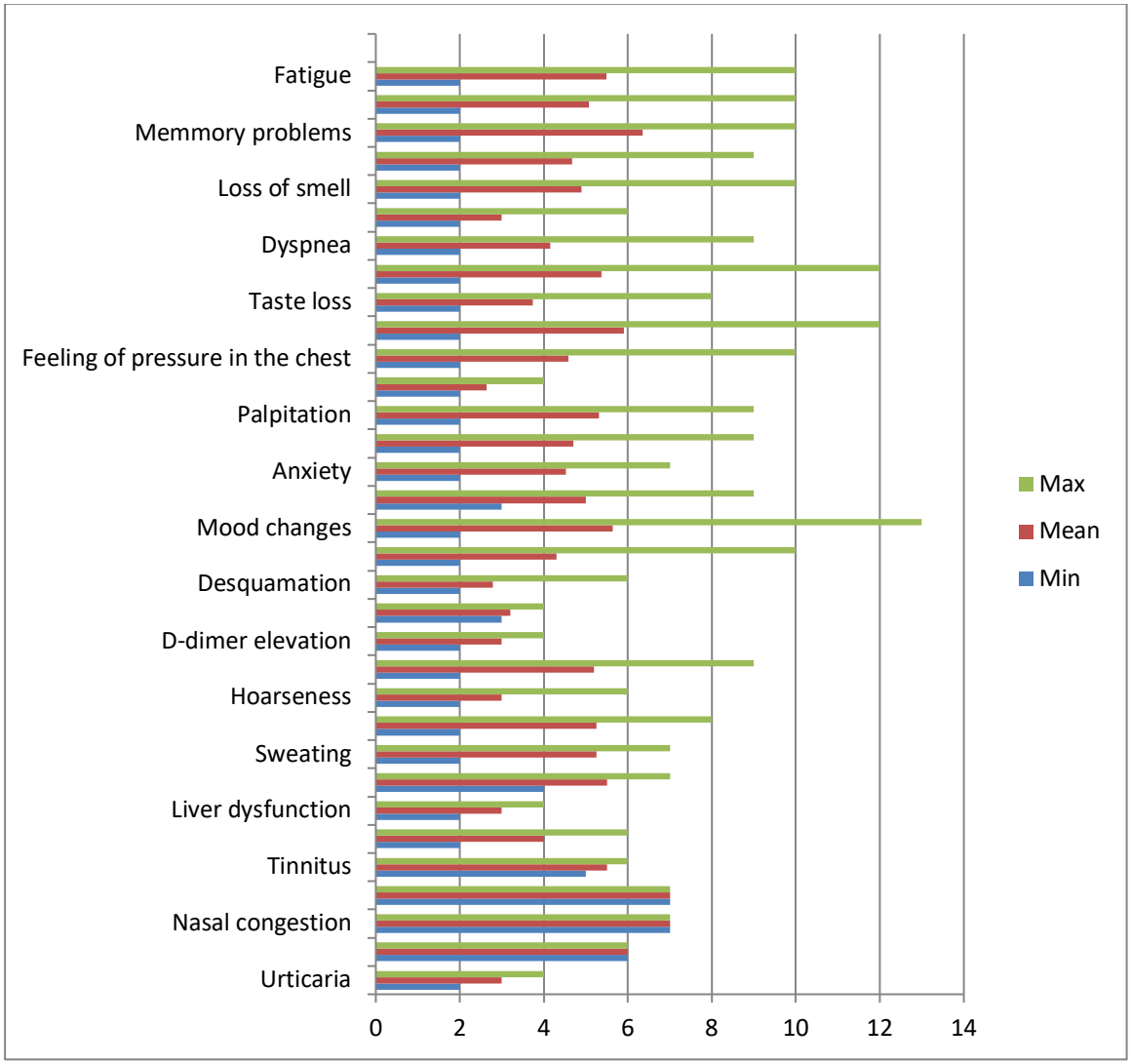

Figure 1. Maximum, mean, and minimum time of prolonged symptoms (month)

five, 4.28% (n:10) had six, 1.28% (n:3) had seven, 2.14% (n: 5) had eight, 0.85% (n: 2) had nine, 0.43% (n: 1) had ten, 0.85% (n: 2) had eleven, 0.43% (n:1) had 14, and 0.43% (n:1) had fifteen prolonged symptoms. In the study of Carfi et al. on patients experiencing Covid disease 60 days ago, 3 or more ongoing symptoms were found to be 68%. In our study, the rate of patients with one or two prolonged symptoms was higher, but the rate of patients with three or more prolonged symptoms was almost half that of Carfi et al. In their study, Carfi et al. included Covid-19 patients who were treated and recovered in the hospital. In our study, however, mostly recovered outpatients were included. Compared to outpatients, patients with indications for hospitalization may have experienced a greater variety of long-covid symptoms due to the diversity of sequelae (26).

Most patients who have had Covid-19 say that their quality of life has deteriorated after Covid-19. El Sayed et al. found that the prevalence of fatigue and anhedonia was high in patients after Covid-19 (27). In our study, we found that the most commonly observed symptom was fatigue (40.60%). Similarly, in other studies, fatigue was reported to be the most commonly observed symptom (71.8%) (26,27,28). The difference on a percentage basis may also be due to the fact that our study was conducted over a wider period of time. In addition, dyspnea, joint pain, cough, and loss of smell were among the other symptoms that persisted most frequently after 28 days of recovery (27). In a study conducted by Willi et al. based on 31 studies, fatigue (39-73%) was the most common symptom, followed by decreased lung function (39-85%), neurological and functional brain disorders (55%), increase in psychiatric symptoms

Table 5. Comparison of Long-Covid with gender, drug or anticoagulant use, smoking, recovery times, diagnosis method, vaccination status

	Ongoing symptoms exist		No ongoing symptoms		
	n	%	n	%	p
Gender					
Female	127	39.90	191	60.10	
Male	107	33.80	210	66.20	0,106
Blood type					
A	99	37.10	168	62.90	
B	26	29.90	61	70.10	
AB	22	42.30	30	57.70	0,445
O	68	38.40	109	61.60	
Rh Factor					
(+) positive	195	37.10	330	62.90	
(-) negative	20	34.50	38	65.50	0,690
Vaccination status					
None	227	37.30	382	62.70	
With 1 dose	2	28.60	5	71.40	0,560
With 2 doses	5	26.30	14	73.70	
Having a chronic disease					
Exists	78	41.70	109	58.30	
None	156	34.80	292	65.20	0,101
Smoking					
Yes	44	34.60	83	65.40	
No	157	36.60	272	63.40	0,577
Quitted	33	41.80	46	58.20	
Symptoms at the time of diagnosis					
Exists	228	38.50	364	61.50	
None	6	14.00	37	86.00	**0,001**
Lung involvement					
Exists	69	49.30	71	50.70	
None	165	33.30	330	66.70	**0,001**
Receiving treatment					
Yes	204	37.80	335	62.20	
No	30	31.20	66	68.80	0,217
Taking anticoagulants					
Yes	134	42.70	180	57.30	
No	100	31.20	221	68.80	**0,003**
Anticoagulant type taken					
Acetyl salicylic acid	34	38.20	55	61.80	
Low-molecular-weight heparins	100	44.40	125	55.60	0,314
Recovery time					
0-7 days	83	26.30	233	73.70	
8-14 days	99	40.70	144	59.30	**<0,001**
15-29 days	42	66.70	21	33.30	
30 days or over	10	76.90	3	23.10	
Total		**100.00**		**100.00**	

(5.8%), loss of smell and taste (33-36%) (28). Karaaslan et al. reported observing fatigue (44.3%), arthralgia (22.0%), myalgia (21.0%), shortness of breath (26.3%), loss of taste (15.0%), cough (14.0%), loss of smell (12.3%), anorexia (% 10.10), headache (8.7%), sore throat (3.0%), diarrhea (1.3%), dizziness (1.3%), and fever (0.3%) (29), which are close to the rates found in our study. In the study conducted by Bakılan et al. on 280 post-acute Corona patients who applied to the Physiotherapy outpatient clinic between December 2020 and May 2021 (a 6-month period), they reported that musculoskeletal pain was the most common symptom after fatigue. They added that the most common pain area was the back (30%).

In our study, joint and muscle pain symptoms were observed in 46.57% of the patients. They were especially localized in the back and waist. Bakılan et al. reported that cough, dyspnea and chest pain symptoms were also observed frequently. In our study, these symptoms were at lower rates, which might be due to the long time-interval of our study (30).

Long-covid was found to be associated with the presence of symptoms and lung involvement at the onset of the disease, the status of taking anticoagulants, and prolongation of recovery time. These factors suggest that Long-Covid may be encountered more frequently, especially if the active disease progresses more severely.

In our study, it was found that 29.40% of the patients had at least one chronic disease. Hypertension (45.98%) and diabetes (35.29%) were the most common. However, when we investigated the presence of chronic disease and long-covid, we did not find a statistically significant relationship (p=0.101). Still, we observed more prolonged symptoms in cases with chronic disease in percentage (41.70%). In a study by Logue et al. on 177 patients, hypertension and diabetes were observed the most often, and 35.50% of patients with these chronic diseases were found to have prolonged symptoms. Since we included other chronic diseases such as thyroid, multiple sclerosis, and asthma in our study, prolonged symptoms were observed in 41.70% of the patients (25).

No statistically significant correlation was found between the rates of Long-Covid observation and vaccinated and unvaccinated patients. However, as vaccination and dose increased, Long-Covid incidence decreased. It was determined that prolonged symptoms were observed at decreasing rates as 37.30% Long-Covid in those who were not vaccinated, 28.60% in those who received the 1st dose of vaccine and 26.30% in those who were vaccinated for the 2nd dose. Nevertheless, since the number of cases is insufficient in this regard, new studies with larger case numbers are needed.

In our study, we found that Long-Covid incidence rates were unrelated to gender, blood type, chronic disease, smoking and the type of anticoagulant taken. Sigalin stated in his study that prolonged corona symptoms were observed more frequently in women and the elderly. In our study, we also found that Long-Covid was observed more frequently in women as a percentage. In addition, we found that Long-Covid was observed more frequently in middle-aged people, which can be explained by the fact that vaccination studies started in the elderly population in our country and the incidence of Long-Covid symptoms in vaccinated individuals decreased as the vaccine dose increased. In addition, Sigal reported that Long-Covid was observed more frequently in cases where the onset of Covid-19 disease was severe. Similarly, we found that Long-Covid would be observed more in cases with the presence of symptoms and lung involvement at the onset of the disease (31).

Having being treated with Favipiravir in the early stages of the disease may have an impact on other complications that could have developed and the length of hospital stay. In a meta-analysis study conducted by Manabe et al., it was determined that Favipiravir had a positive effect on recovery times (32). However, Almoosa et al., in another study, found that Favipiravir had no effect on clinical improvement and mortality (33). In our study, we found that there was no relationship between the incidence of Long-Covid development and Favipiravir treatment (p=0.217). Still, new studies are needed to have clearer information on this subject.

In the study by Klein et al., fatigue (21%), changes in smell (14%) and shortness of breath (9%) were the most common symptoms that persisted in the 6th months. In our study, fatigue (40.6%), loss of smell (17.52%) and dyspnea (13.68%) were observed at the end of fourteen months. In terms of the average observation time of these symptoms, in our study, it was found that the fatigue symptom improved in an average of 5.49 months in patients with Covid-19, sometimes extending up to 10 months. In addition, muscle pain (26.06%), memory problems (24.36%), joint pain (20.51%) and loss of smell (17.52%) were the longest-persisting symptoms. The mean time of observation of symptoms was determined to be close to the rates found by Klein et al. In addition, similar to the result of Klein et al., we also found that loss of smell improved later than loss of taste. The former showed fluctuations in some patients, increasing and decreasing from time to time. Some patients said that they smelled of burnt molasses, burned rubber, or an odour that they could not describe. Some of the patients stated that they had no taste at all or that they had a different taste with garlic (34).

In our study, some patients reported that they developed concentration impairment (9.82%) and memory problems (24.6%). Besides, some patients reported that their current forgetfulness increased

even more. Non-immunogenic and autoimmunity such as septic encephalopathy, vascular thrombosis, blood pressure changes caused by the virus, immunological mechanisms such as activation in microglia cells and cytokines were held responsible for this event (35). In addition, although it has been reported that the hippocampus region is particularly vulnerable to Corona infection, the exact mechanism has not been explained. All of these increase the possibility of post-infection memory impairment and the acceleration of neurodegenerative disorders such as Alzheimer's disease. In our study, prolonged symptoms such as anxiety (6.41%), mood changes (5.98%), depression (0.85%) were also observed (36). It was known that the participants had a mild course. On the other hand, it is expected that these symptoms will continue to be higher in Covid patients who are more severely intubated and have long hospital stays, considering the rate of sequelae.

Garrigues et al. found that 30.8% of the patients who had been discharged from the hospital had sleep disturbances after 100 days. We observed that sleep disturbance persisted at a rate of 10.25% and for 5.37±2.533 months (min:2, max:12) in the 14-month follow-up. Most of the patients complained of trouble falling asleep (37).

In their study on hospitalized Covid-19 patients, Wambier et al. reported that the incidence of both androgenic hair loss and grey hair increased, with a higher incidence in males, compared to the expected prevalence for an age-matched population (38). Patients reported that they experienced intense hair loss, especially in the first 2 months. Vitamin B12 levels turned out to be significantly lower in most patients who were invited to the outpatient clinic. However, it was not known exactly whether it was a pre-existing vitamin deficiency or a vitamin deficiency due to Covid-19 infection. Therefore, new research is needed on this subject.

D-dimer elevation (2.13%) and liver enzyme elevations (1.28%) were other Long-Covid symptoms. These patients had had to use LMWH for 4 months. We determined that Covid-19 patients did not have D-dimer and other tests after their active symptoms had passed. If tests such as blood tests, pulmonary function tests and echocardiography had been performed regularly in Covid-19 patients after the active symptoms had passed and the quarantine period had ended, more clear information about the sequelae due to Covid-19 could have been obtained. However, in this devastating pandemic, such examinations could not be carried out to avoid extra workload and congestion in hospitals. Therefore, it can be thought that the information about the sequelae that could be detected with laboratory tests is insufficient, especially in patients who recover without the need for hospitalization and intensive unit care.

CONCLUSION

All in all, we live in a pandemic where we gain new information every day and we still cannot predict the outcome. It seems that the effects of Covid-19 continue even after recovery. But a promising hypothesis can be drawn from this study, which is that the rates of prolonged symptoms decrease with vaccination. After all, it is known that vaccination reduces the indication for hospitalization, which, in turn, can reduce prolonged symptom diversity. In order to reveal the importance of Covid-19 vaccination for long-covid, new studies with a larger number of cases are needed.

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