original article

Sinovac vaccination and the course of COVID-19 disease in hospitalized patients in Turkey

Leman Acun Delen,[a] Mesut Örtekus[b]

From the [a]Department of Anesthesiology and Reanimation, Malatya Education and Research Hospital, Malatya, Turkey; [b]Department of Anesthesiology and Reanimation, Malatya Turgut Özal University, Malatya, Turkey

Correspondence: Dr. Mesut Örtekus · Department of Anesthesiology and Reanimation, Malatya Turgut Özal University, Battalgazi 44210, Turkey · mesutoterkus@hotmail.com · ORCID: https://orcid.org/0000-0003-1025-7662

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BACKGROUND: The Alpha variant of SARS-CoV-2 has a higher transmission rate than the first variant identified. The efficacy of vaccines is affected by the characteristics of SARS-CoV-2 variants.

OBJECTIVE: Investigate the relationship of vaccination and virus variant on the course of the disease in patients who were hospitalized with a diagnosis of COVID-19.

DESIGN: Retrospective, cohort study

SETTING: Tertiary health institution

PATIENTS AND METHODS: The study included patients older than the age of 18 years who were hospitalized in a COVID-19 service or the intensive care unit with a diagnosis of COVID-19 between 1 January 2021 and 30 April 2021. Demographic characteristics, vaccination and the Alpha virus variant status, comorbidities, and information about hospitalization were obtained from the hospital automation system and patient files.

MAIN OUTCOME MEASURES: Vaccination rate and relationship with course of disease.

SAMPLE SIZE: 608

RESULTS: Most of the patients (n=482, 79.3%) were admitted to the COVID-19 service. More of the COVID-19 service patients had the Alpha variant than the patients admitted to ICU ($P<.009$). The Alpha variant was also more common in younger patients ($P<.001$). There was no relationship between the Alpha virus and comorbid diseases such as diabetes mellitus and hypertension. Mortality was lower in the patients who had received a second dose of the Sinovac vaccine ($P=.004$) compared with unvaccinated patients.

CONCLUSION: Although the Alpha variant spreads faster, it has a milder course. If only the Sinovac vaccine is available, we recommend that the two doses of the Sinovac vaccine be administered.

LIMITATIONS: Our study is single-center and did not include pregnant and pediatric patients.

CONFLICT OF INTEREST: None.

The coronavirus disease 2019 (COVID-19) pandemic began in December 2019. Presentation ranges from a severe course such as acute respiratory distress syndrome to clinically asymptomatic cases. It is usually asymptomatic or mild in the young.[1] Fever and cough are the most common symptoms.[2] Headache, weakness and fatigue, nausea-vomiting, taste disorders, diarrhea, shortness of breath are other symptoms.[2,3] In moderate and severe cases, lymphopenia, eosinopenia, increased D-dimer, C-reactive protein and procalcitonin levels can be seen.[4] The COVID-19 outbreak affected nearly 500 million people and killed more than 6 million people as of March 2022.[5] In Turkey, as of November 2021, it had affected more than 8.1 million people and killed approximately 72000 people.[6] In addition to isolation measures such as masks, social distancing, and curfews as preventive health measures in the fight against COVID-19, vaccination also has an important role. Many countries today use Sinovac, which is an inactivated virus vaccine made in China, and two mRNA-based vaccines, Pfizer/BioNtech made in Germany and Sputnik V made in Russia. Moreover, phase III studies have started on TURKOVAC (*https://clinicaltrials.gov/ct2/show/NCT04942405*), which is an inactivated virus vaccine developed in Turkey. As a result of vaccination, the number of cases, including severe cases of COVID-19, are decreasing.

Because new variants may become resistant to the vaccine, the biggest concern in vaccination is the impact of virus mutations. The COVID-19 virus, SARS-CoV-2, is an enveloped RNA virus from strain B of the beta-coronaviruses of the coronavirus family.[7] RNA viruses mutate frequently, and several variants of COVID-19 viruses (Alpha variant, Delta variant, and others.) have been detected. The Alpha variant, designated a variant of concern (VOC) 202012/01 mutation, is highly contagious, but severe lung and respiratory tract involvement is less compared with other variants.[8] In this study, we aimed to compare the effects of vaccination and the variant on the course of the disease in patients who were hospitalized with a diagnosis of COVID-19.

PATIENTS AND METHODS

The case definition for COVID-19 in our study was the presence symptoms (fever, respiratory distress, cough, etc.) and/or a ground glass image in the thorax CT and a positive PCR test performed in our hospital. Since mild cases were treated as outpatients, our patient population consisted of moderate and severe COVID-19 patients. Our study was a retrospective cohort study, which was approved by the Malatya Turgut Özal University Faculty of Medicine Clinical Research Ethics Committee (date: 08.03.2021; no: 2021/50). The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patients aged 18 years and older who were being treated for a diagnosis of COVID-19 in Malatya Training and Research Hospital between 1 January 2021 and 30 April 2021 were included in the study. Patients younger than the age of 18 years, patients who were pregnant, and patients who were diagnosed with COVID-19 after hospitalization were excluded from the study.

The real-time reverse transcriptase polymerase chain reaction (RT-PCR) test is routinely performed on patients with COVID-19 symptoms and/or a ground glass appearance in the thorax imaging. In addition, PCR testing is applied to people who have a history of contact with people diagnosed with COVID-19. We retrieved the data on patient age, gender, symptoms present during hospitalization (fever, cough, and respiratory distress), comorbidities (hypertension, diabetes mellitus, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, malignancy), days in intensive care and/or the COVID-19 service, oxygen support on the day of hospitalization (oxygen support with a nasal prong and/or a reservoir mask), respiratory support (intubation and/or continuous positive airway pressure) status, discharge status (discharge, mortality), virus variant, and vaccine status. We analyzed relationships between the COVID-19 Alpha variant (testing was only available for the Alpha variant as it was the dominant variant at the time. Sinovac vaccination, comorbidities and mortality. Resources for our research were published in the last 5 years and in internationally published indexing services such as Google Science, PubMed, Index Copernicus, Scopus, and Web of Science. Studies in non-international journals and non-peer-reviewed journals were excluded.

IBM SPSS Statistics version 21.0 (IBM Corp, Armonk, NY, USA.) was used for the statistical analysis. The Shapiro-Wilk test was used to evaluate the normal distribution. Age and total hospitalization days are given as the median (minimum, maximum). Other data are given as the number of cases (n) and percentages (%). The Mann-Whitney U test was used in the analysis of age and hospitalization days. The Pearson chi-square test was used for the analysis of the categorical variables. Multiple logistic regression analysis was performed to evaluate the relationship of hospitalization in the COVID-19 service or intensive care unit, gender, comorbidities, symptoms, vaccination status, and mutation on mortality (dependent variable). $P<.05$ was considered statistically significant.

RESULTS

Of the 608 patients hospitalized with a diagnosis of COVID-19, 244 (40.1%) were vaccinated with either one or two doses of the Sinovac vaccine (**Table 1**). The COVID-19 variant known as the Alpha variant (VOC 202012/01; B.1.1.7) was detected in 270 (44.4%) patients. No other variants were detected. The Alpha variant was detected more frequently in younger patients (**Figure 1**) (*P*<.001).

While 4 (0.8%) patients who were followed up in the service died, 71 (56.3%) patients died in the ICU (*P*<.001). In the analysis of comorbid diseases, chronic obstructive pulmonary disease was more frequent in patients hospitalized in the COVID-19 service (*P*=.001). Otherwise, comorbidities were similar. Fever and cough were higher in the COVID-19 service patients, while respiratory distress was higher in the patients in intensive care. In the unvaccinated patients, 75% had the Alpha variant, while in the vaccinated patients fewer patients had the Alpha variant (*P*<.001) (**Table 2**). The number of hospitalization days and mortality rates were

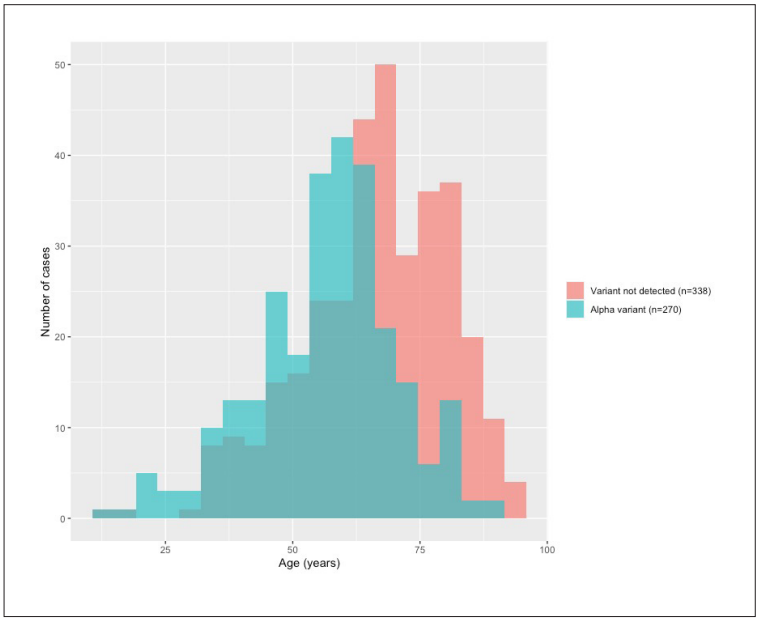

Figure 1. Alpha variant mutation (VOC 202012/01; B.1.1.7) of SARS-CoV-2 in COVID-19 positive patients by age (*P*<.001, Mann-Whitney U test).

Table 1. Analysis according to service and intensive care follow-up (n=608).

	COVID-19 service (n=482, 79.3%)	Intensive care (n=126, 20.7%)	*P* value
Male	257 (53.3)	77 (61.1)	.118
Age (years)[a]	61 (13-94)	69 (43-94)	**<.001**
Alpha variant	227 (47.1)	43 (34.1)	**.009**
Vaccination status	285 (59.1)	78 (62.4)	.164
No vaccine	80 (16.6)	26 (20.8)	
Single dose			
Two doses	117 (24.3)	21 (16.8)	
Mortality	4 (0.8)	71 (56.3)	**<.001**
Hypertension	167 (34.6)	55 (43.7)	.062
Diabetes mellitus	83 (17.2)	13 (10.3)	.059
Cerebrovascular disease	26 (5.4)	8 (6.3)	.678
Chronic obstructive pulmonary disease	442 (91.7)	103 (81.7)	**<.001**
Congestive heart failure	35 (7.3)	16 (12.7)	.050
Malignancy	3 (0.6)	3 (2.4)	.075
Symptoms	194 (40.2)	37 (29.4)	**.025**
Fever			
Cough	200 (41.5)	38 (30.2)	**.020**
Respiratory distress	227 (47.1)	122 (96.8)	**<.001**

Data are n (%) unless noted otherwise. [a]Median (minimum-maximum).

Table 2. Analysis according to the SARS-CoV-2 variant status.

	No variant detected (n=338)	Alpha variant (n=270)	*P* value
Male	185 (54.7)	149 (55.2)	.911
Age (years)[a]	68 (14-94)	58 (13-90)	**<.001**
Length of stay (days)[a]	8 (1-52)	7 (1-72)	**.004**
Vaccine			
No vaccine	160 (47.5)	203 (75.2)	
Single dose	69 (20.5)	37 (13.7)	**<.001**
Two doses	108 (32.0)	30 (11.1)	
Mortality	51 (15.1)	24 (8.9)	**.021**
Hypertension	133 (39.3)	89 (33.0)	.104
Diabetes mellitus	57 (16.9)	39 (14.4)	.416
Cerebrovascular disease	21 (6.2)	13 (4.8)	.456
Chronic obstructive pulmonary disease	38 (11.2)	25 (9.3)	.425
Congestive heart failure	34 (10.1)	17 (6.3)	.096
Malignancy	3 (0.9)	3 (1.1)	.782
Symptoms			
Fever	127 (37.6)	104 (38.5)	.812
Cough	125 (37.0)	113 (41.9)	.222
Respiratory distress	192 (56.8)	157 (58.1)	.739

Data are n (%) unless noted otherwise. [a]Median (minimum-maximum)

Table 3. Association of vaccination status and mortality.

	Mortality (n)	*P* value	Total number of cases
Vaccination status			
No vaccine	51 (14.1%)	.011 vs vaccination	363
Single dose	17 (16.0%)	.609 vs no vaccine	106
Two dose	7 (5.1%)	.004 vs no vaccine	138

lower in the patients infected with the Alpha variant of the virus. Oxygen support was provided to 223 (36.67%) patients nasally, to 315 (52.06%) patients by reservoir mask, and to 7 (1.15%) nasally and with a reservoir mask. Continuous positive airway pressure support was given to 16 (2.63%) patients, and 11 (1.8%) patients were intubated. Mortality was lower in patients who received two vaccine doses compared to the patients who received a single vaccine dose (*P*=.004) (**Table 3**).

In the analysis of the relationship between comorbidity and vaccination, mortality was higher in patients with comorbidity and unvaccinated patients hospitalized in the intensive care unit (**Table 4**).In the multivariant analysis, hospital unit (COVID-19 service or ICU), COPD, and vaccination were significantly associated with mortality (**Table 5**).

DISCUSSION

The COVID-19 virus directly or indirectly affects many tissues and systems, especially the respiratory system.

Table 4. Associations between vaccination status in COVID-19 patients with comorbid disease.

	Comorbidity	Vaccination status	Mortality	Discharged from Hospital	*P* value
Intensive care unit	No	No vaccine	15	17	**.011**
		Single dose	4	2	
		Two dose	3	7	
	Yes	No vaccine	34	22	**.023**
		Single dose	13	7	
		Two dose	2	9	
COVID-19 service unit	No	No vaccine	0	148	.100
		Single dose	0	31	
		Two dose	1	38	
	Yes	No vaccine	2	148	.703
		Single dose	0	31	
		Two dose	1	38	

Statistical analyses by chi-square test.

Table 5. Multiple logistic regression analysis with discharge alive or not as dependent variable.

	B	SE	β	t	*P*
Constant	0.045	0.025		1.791	.074
Hospital stay unit	0.545	0.027	0.67	20.163	**<.001**
Gender	-0.014	0.02	-0.021	-0.706	.480
Hypertension	0.008	0.03	0.011	0.262	.794
Diabetes mellitus	0.043	0.031	0.047	1.384	.167
Cardiovascular disease	0.013	0.046	0.009	0.288	.773
Chronic obstructive pulmonary disease	0.08	0.036	0.074	2.189	**.029**
Congestive heart failure	0.067	0.038	0.056	1.76	.079
Fever	-0.011	0.02	-0.016	-0.55	.583
Respiratory disease	0.003	0.022	0.004	0.138	.891
Comorbidity	-0.036	0.035	-0.053	-1.002	.317
Vaccination	-0.026	0.012	-0.066	-2.104	**.036**
Alpha variant	-0.028	0.021	-0.042	-1.354	.176

R^2: 0.487, Overall test: *P*<.001

Although the infection is usually asymptomatic or mild, severe pulmonary involvement can occur. The main natural reserve of the SARS-CoV virus is thought to be a certain bat species in the Yunnan province of China. The virus is thought to be transmitted to humans by ingestion of the infected animal.[9] The virus variant obtained from bats shows 79.5%–96.2% similarity to SARS-CoV-2.[9,10]

The SARS-CoV-2 virus has a high mutation rate. After the first virus was isolated, many variants have

been described as a result of mutations. Vang et al found mutations in 13 402 of 31 421 genome isolates.[11] With the emergence of variant viruses, variant analysis was started in cases with positive polymerase chain reaction (PCR) tests. The Alpha variant identified as VOC 202012/01 (B.1.1.7) is one variant that became dominant in 2021.[12] Studies show that this variant spreads faster than the original virus, and it is spreading rapidly in Turkey.[13,14] It has been shown that the N501Y mutation seen in the spike protein in the VOC 202012/01 variant increases viral affinity for angiotensin converting enzyme receptors.[13,15] Some researchers state that increased affinity may aggravate the course of the disease.[16,17] However, despite the increase in the severity of the disease, it is unclear whether the increase in number is a consequence or is due to increased pathogenicity. Conversely, the VOC 202012/01 variant is a subtype of the D614G variant,[18] and some studies have shown that although the transmission capacity of the D614G variant is high, it has a milder course.[19,20] In our study, 44.4% (n=270) of our patients were infected with the Alpha virus, which shows that the infection rate of this variant is high. Only the Alpha variant was detected in patients during the study period. Our study showed that the patients infected with the Alpha mutation had a lower follow-up rate in the ICU; in other words, it caused acute respiratory distress syndrome at a lower rate. In addition, the number of patients with the Alpha variant was significantly lower than the original variant. However, in the literature, some researchers have argued that there is no significant relationship between the VOC 202012/01 variant and the clinical course.[21,22]

In our study, no relationship was found between gender and the VOC 202012/01 variant. However, the VOC 202012/01 variant was more common in the younger population. Other studies have also shown that it is more prevalent in the young population.[23] It can be seen as natural that the young population is infected with the Alpha variant, which shows a higher spread rate due to the more active work and social lives of younger people. This result also provides clues about the clinical course of the patient population. The increase in comorbid diseases, such as diabetes mellitus and hypertension, which cause an increase in the mortality of COVID-19 in the elderly population, causes a more severe clinical course and thus increases mortality.[15] Therefore, the fact that the Alpha variant is more common in the young population appears to be a factor that reduces mortality. In our study, chronic obstructive pulmonary disease (COPD), one of the comorbid diseases, affected the course of the disease and was significantly higher in intensive care patients. Studies in the literature support this finding.[24,25] However, when we examined the patients with COPD in relation to the course of the disease, no significant relationship was found between the virus variant and COPD. İn addition no association was found between other comorbid diseases (malignancy, hypertension, diabetes mellitus, cerebrovascular diseases, cardiac disease, and heart failure) and the Alpha variant.

Perhaps the most important element in the fight against the pandemic is vaccination. From the first days of the epidemic, many countries, including Turkey, started work to produce a vaccine. In addition to traditional vaccines (e.g., Sinovac and Turkovac) in parallel with the developing technology, studies are continuing to produce new-generation vaccines, including mRNA (CureVac BioNTtech), DNA (INO-4800), and protein-based vaccines (Ad5-nCoV, NVX-CoV2373).[26] While some of these vaccines are in phase 1 and phase 2 studies, many countries have started to use some of the phase 3 vaccines (Sinovac, BioNTech, for example) with emergency use approval. At the time of our study, the patients who had been vaccinated had all received the inactive virus vaccine, Sinovac. We found no relationship between vaccinated vs non-vaccinated patients and the course of the disease, but the Alpha variant was more common in the vaccinated group. This result indicates that the Sinovac vaccine was less effective against the Alpha variant. Conti et al stated that the reason for this is that the antibodies formed by the vaccine may be less effective against this variant.[27] Along with vaccination, the number of severely ill patients has decreased worldwide. The isolation, travel restrictions, and filiation studies implemented in Turkey have attempted to bring the pandemic under control. With the administration of the Sinovac and later the BioNTec vaccines, the incidence and death rates have decreased significantly. However, it is open to debate whether this decrease is due to a decrease in the number of patients or whether the vaccine is effective in affecting the course of the disease.

Another problem in vaccine studies is the duration of the antibody response created by the vaccine.[28] Re-infection of patients already infected or vaccinated is common. It is unclear whether the person is unable to produce an adequate antibody response or whether there is a decrease in the level of antibodies formed. Also, the fact that COVID-19 mutates quite frequently is a separate problem. In our study, the mortality of

those who received two doses of the Sinovac vaccine was lower than those who were not vaccinated and those who received a single vaccine dose. However, there was no difference in mortality between those who were not vaccinated and those who received a single dose. Therefore, two doses of the Sinovac vaccine reduced mortality. We think that a single dose of vaccine does not produce sufficient antibody levels clinically. However, studies on this subject in larger patient groups are needed. As in our study, other researchers on vaccine efficacy have found that a single vaccine dose may not provide sufficient protection.[29,30]

Since our study was single-centered and did not include pediatric or pregant patients, our data may be considered insufficient and results and conclusions should be interpreted with caution. Since only the Sinovac vaccine was used in our country at the time of the study, only the efficacy of that vaccine could be evaluated. In our study, the previous COVID-19 history of the patients, vaccination immunity and the history of re-infection (normal variant, Alpha variant) in the treated patients were not in the hospital data. Therefore, it was not possible to evaluate the mortality and course of the disease in patients with recurrent COVID diseases. In conclusion, COVID-19 virus variants are a determining factor in the spread and course of the disease. As a result of our study, we suggest that although the Alpha variant spreads rapidly, it has a milder course. We also recommend that the Sinovac vaccine be administered in two doses to provide adequate clinical protection.

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