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THE EFFECT OF VACCINES AND BOOSTER DOSES ON DISEASE PROGRESSION AND MORTALITY IN COVID-19

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Abstract

Aim: Since the first months of 2020, vaccination has become the most effective method to combat the COVID-19 pandemic. This study aims to describe the vaccination status of inpatients, the effectiveness of booster vaccine protocols, and the risk factors for intensive care unit (ICU) and mortality of COVID-19 patients.

Methods: The study included 247 hospitalized patients in a tertiary care hospital due to COVID-19. Data of the participants were recorded using the hospital database and a questionnaire. Patients were divided into groups as mild-moderate-severe disease in terms of disease severity, ward and ICU in terms of hospitalization clinic. According to vaccination status, they were categorized as unvaccinated, Sinovac-based protocols, BioNTech-based protocols and others.

Results: Of the 247 patients, 55.1% were male and the mean age was 60 ± 17.26 years. 38.5% of the patients were admitted to ICU and 9.3% died. It was observed that 38.8% of those admitted to ICU and 56.5% of those who died were not vaccinated. Being over 65 years (p=0.008), being hospitalized for over 7 days (p=0.003), having a severe illness (p=0.002), having a nervous system disease (p=0.005) and having other comorbidities (p=0.000) were significant risk factors for ICU admission, whereas disease severity (p=0.000) and comorbidities such as hypertension (p=0.000), diabetes mellitus (p=0.020) and cardiovascular diseases (p=0.000) were found to be risk factors for mortality. Vaccination generally decreased ICU admission and mortality, and rapel dose were found to reduce mortality, but the different was not statistically significant.

Conclusions: Complete vaccination in COVID-19 is beneficial in preventing ICU admission and especially mortality.

Keywords: *COVID-19, ICU, mortality, vaccines, BioNTech, Sinovac*

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected approximately 644 million people worldwide and caused more than 6.6 million deaths as of December 12, 2022 [1]. To end this pandemic, effective immunization against the virus is necessary, and the safest way to do this is through vaccination. Vaccines are safe technology products that humanity has often relied on in the past to reduce the mortality rate of infectious diseases. In the 12 months following the outbreak, several research teams have risen to the challenge and developed vaccines that protect against SARS-CoV-2. Another major challenge after the vaccines were available was to make them available to people around the world.

Countries have different vaccines and vaccination protocols for COVID-19 vaccines. In general, several types of vaccines have been developed, including messenger ribonucleic acid (mRNA), vector and inactivated vaccines, and their efficacy has been demonstrated in population studies in different regions [2, 3]. Estimates of vaccine efficacy among people vaccinated as part of national vaccine rollouts have been similar to efficacy results in the first few months after vaccine inoculation [4]. However, vaccination rates, especially booster vaccination rates, remain below the targeted level in most countries [5]. In Turkey, according to data from the Ministry of Health, a total of 152.6 million doses of vaccine were administered as of January 6, 2023, resulting in 85.6% of the population being immunized with at least 2 doses of vaccine.

Despite the availability of effective vaccines today, cases and hospitalizations still continue. Knowing whether and to what extent vaccine efficacy is declining is crucial for vaccine policy decisions, such as the need for booster doses, timing and target populations [6,7]. There has been uncertainty about the duration of protection from the outset, especially in subjects in whom an adequate antibody response to vaccines has not been detected, and so an additional dose has been needed in some population groups, striking a speculative balance between risks and benefits [2, 6]. With the exception of one of the vaccines (Ad26.COV2.S, Johnson & Johnson-Janssen), all vaccination protocols require two injections at 1-2 month intervals [8]. The limited number of systematic reviews published for COVID-19 efficacy did not provide clear information on the duration of protection of COVID-19 vaccines [6-10]. Declining immunity over time after vaccination, impaired response to vaccines in high-risk patients, and new virus variants have necessitated protocol modifications and replacement of booster vaccines. A pandemic is a dynamic period when our knowledge increases and new mutations emerge; therefore, data sharing is critical. The aim of this study was to assess the vaccination status of hospitalized patients, compare the effectiveness of booster vaccine protocols, and identify risk factors for intensive care unit (ICU) and mortality in hospitalized COVID-19 patients.

Materials and Methods

Study design

Data in this retrospective cross-sectional study were collected from a tertiary university hospital over a five-month period from September 2021 to February 2022.

Inclusion criteria

Hospitalized patients older than 18 years of age with radiologic lung involvement and definitive diagnosis of COVID-19 by nasopharyngeal PCR test.

Exclusion criteria

Age younger than 18 years, hospitalized for other systemic diseases or social indications rather than COVID-19 itself.

Participants were included in the study after ethical approval (114/2021) was obtained

from Cukurova University Non-Interventional Clinical Research Ethics Committee.

Participants and Data Sources/Measurement

Age, gender, vaccination status and comorbidities (diabetes mellitus (DM), hypertension (HT), cardiovascular diseases, chronic obstructive pulmonary disease (COPD), neurological diseases, cancer, chronic kidney disease (CKD), solid organ transplantation and pregnancy) were recorded by a questionnaire administered by the attending physician. Comorbidities were categorized using the Charlson comorbidity index as 0 (no comorbidity, low risk), 1 (1-2 points, moderate risk), 2 (3-4 points, high risk), 3 (5 or more points, very high risk). COVID-19 disease was categorized into 3 groups according to the percentage of thoracic computed tomography (CT) involvement and oxygen saturation (SaO2) status of the patients: mild (less than 25% involvement on CT and SaO2 above 92%), moderate (25-50% involvement on CT and SaO2 between 88-92%) and severe disease (more than 50% involvement on CT and SaO2 below 88%). To determine the vaccination status and dates of the patients in the current cases, the Republic of Turkey Ministry of Health vaccine tracking system and hospital data processing database were used. Sinovac (inactivated), BioNTech (mRNA) and Turkovac (inactivated) vaccines currently used in Turkey and their combinations were evaluated for the study.

Patients were divided into four groups according to their vaccination status

1. Unvaccinated
2. Sinovac-based protocols (two doses of Sinovac, three doses of Sinovac, two doses of Sinovac plus one dose of BioNTech or two doses of Sinovac plus two doses of BioNTech)
3. BioNTech-based protocols (two doses of BioNTech or three doses of BioNTech)
4. Others (one dose of Sinovac plus one dose of BioNTech, four doses of Sinovac, three doses of Sinovac plus one dose of BioNTech, or the last dose of any protocol performed less than 14 days after the last dose).

Primary outcome

Determine the effectiveness of COVID-19 vaccines (especially boosters) by comparing the vaccination status of hospitalized patients and to determine the risk factors of ICU and mortality.

Secondary outcomes

-To identify vaccination schemes for COVID-19 patients admitted to clinics or intensive care units
-To criticize the impact of the fourth dose of COVID-19 vaccines

Influencing factors

Different vaccines, need for ward/ICU admission, comorbidities, gender, age.

Sample size and selection

We collected the data of all consecutive hospitalized COVID-19 patients between September 2021 to January 2022. We analyzed data from a total of 247 patients admitted to hospital with a diagnosis of COVID-19 and followed in the ward or ICU. All other hospitalized COVID-19 patients were included in the study, except for patients hospitalized for other non-COVID-19 systemic diseases, social reasons or isolation.

Statistical methods

Statistical analysis was performed with IBM SPSS for Windows version 25. Normality of numerical variables was assessed by Shapiro-Wilk test. For non-normal numerical variables, the Mann-Whitney U test was performed to compare patients with and without long-term symptoms. In multivariate

analysis, variables were selected according to significance in univariate analysis. Binary logistic regression analyses were performed to estimate the risk of ICU admission and calculate odds ratios (aOR) and 95% confidence intervals (CI). p value <0.05 was considered statistically significant.

Results

In the study that is conducted in a tertiary care university hospital with a total of 247 patients, 55.1% of the participants were male and the mean age was 60 ± 17.26 years (min 18-max 94). Ninety-nine (40.1%) of the participants had a mild illness and the mean duration of hospitalization was 8 ± 5.37 days. Ninety-five patients (38.5%) were admitted to intensive care units and 23 patients (9.3%) died. Sociodemographic and diagnostic characteristics of the participants are shown in Table 1.

In the analyses, being over 65 years of age (p=0.008), being hospitalized for more than 7 days (p=0.003), presence of severe disease (p=0.002), presence of neurological diseases (p=0.005) and presence of other comorbidities (p=0.000) were statistically significant risk factors for ICU admission, whereas disease severity (p=0.000) and comorbidities HT (p=0.000), DM (p=0.020) and cardiovascular diseases (p=0.000) were statistically significant risk factors for mortality. The findings regarding the effects of demographic-clinical characteristics and comorbidities on ICU admission and mortality are presented in detail in Table 2.

Approximately one-third of the patients (35.6%) were unvaccinated, and the next largest groups were the two-dose and three-dose Sinovac vaccine groups administered to the same number of people (14.6%). We observed that 38.8% of patients admitted to the ICU and 56.5% of those who died were unvaccinated. These rates were higher for both the different vaccination groups and the number of vaccine doses. Single Sinovac-based vaccines had lower ICU admission and mortality rates compared to non-vaccinated patients, and this was also observed with rapel doses. It was observed that ICU admission and mortality rates were lower in BioNTech-based vaccines compared to Sinovac-based vaccines, but no statistical significance was found for both conditions. It was observed that ICU admission and mortality were lower in single-dose and 4-dose vaccinees compared to 2-dose and 3-dose vaccinees, and single or combined administration of Sinovac or Biontech vaccine subgroups did not make a significant difference on ICU admission and mortality.

Table 1. Sociodemographic and Diagnostic Characteristics of the Patients

Characteristics	n (%) or X±S.D. (min–max)
Age (years)	60 ± 17.26 (18–94)
Sex (male / female)	136 (55.1) / 111 (44.9)
Charlson Comorbidity Index (0 / 1 / 2 / 3)	64 (25.9) / 158 (64) / 21 (8.5) / 4 (1.6)
Length of hospitalization (day)	8 ± 5.37 (1-27)
Disease severity (mild / medium / severe)	99 (40.1) / 73 (29.6) / 75 (30.4)
Intensive care unit follow-up (no / yes)	95 (38.5) / 152 (61.5)
Discharge status (recovery / death)	224 (90.7) / 23 (9.3)

Table 2. Relationship of Demographic-Clinical Characteristics and Comorbidities with ICU and Mortality

Characteristics		Total n (%)	Inpatient Service n (%)	ICU n (%)	p	Recovery n (%)	Exitus n (%)	p
Age (years)	<65	136 (55.1)	62 (65.3)	74 (48.7)	0.008	127 (93.4)	9 (6.6)	0.082
	≥65	111 (44.9)	33 (34.7)	78 (51.3)		97 (87.4)	14 (12.6)	
Sex	male	136 (55.1)	56 (58.9)	80 (52.6)	0.201	122 (89.7)	14 (10.3)	0.359
	female	111 (44.9)	39 (41.1)	72 (47.4)		102 (91.9)	9 (8.1)	
BMI (kg/m^2)	<30	221 (89.5)	84 (88.4)	137 (90.1)	0.411	200 (90.5)	21 (9.5)	0.554
	≥30	26 (10.5)	11 (11.6)	15 (9.9)		24 (92.3)	2 (7.7)	
Length of hospitalization (day)	<8 day	112 (45.3)	54 (56.8)	58 (38.2)	0.003	105 (93.8)	7 (6.3)	0.098
	≥8 day	135 (54.7)	41 (43.2)	94 (61.8)		119 (88.1)	16 (11.9)	
Disease severity	Mild	99 (40.1)	42 (44.2)	57 (37.5)	0.002	99 (44.2)	0 (0)	0.000
	Medium	73 (29.6)	36 (37.9)	37 (24.3)		69 (30.8)	4 (17.4)	
	Severe	75 (30.4)	17 (17.9)	58 (38.2)		56 (25)	19 (82.6)	
Charlson Comorbidity Index	0	64 (25.9)	26 (27.4)	38 (25)	0.933	57 (25.4)	7 (30.4)	0.629
	1	158 (64)	59 (62.1)	99 (65.1)		145 (64.7)	13 (56.5)	
	2	21 (8.5)	8 (8.4)	13 (8.6)		18 (8)	3 (13)	
	3	4 (1.6)	2 (2.1)	2 (1.3)		4 (1.8)	0 (0)	
HT		49 (19.8)	14 (14.7)	35 (23)	0.076	37 (75.5)	12 (24.5)	0.000
DM		49 (19.8)	14 (14.7)	35 (23)	0.076	40 (81.6)	9 (18.4)	0.020
Cardiovascular Disease		33 (13.4)	11 (11.6)	22 (14.5)	0.327	21 (63.6)	12 (36.4)	0.000
COPD		19 (7.7)	8 (8.4)	11 (7.2)	0.456	18 (94.7)	1 (5.3)	0.452
Neurological Diseases		50 (20.2)	11 (11.6)	39 (25.7)	0.005	48 (96)	2 (4)	0.115
CKD		13 (5.3)	4 (4.2)	9 (5.9)	0.393	10 (76.9)	3 (23.1)	0.109
Rheumatologic Disease		11 (4.5)	3 (3.2)	8 (5.3)	0.329	11 (100)	0 (0)	0.333
Cancer		22 (8.9)	12 (12.6)	10 (6.6)	0.083	21 (95.5)	1 (4.5)	0.367
Solid Organ Transplant		7 (2.8)	2 (2.1)	5 (3.3)	0.452	6 (85.7)	1 (14.3)	0.500
Obesity		8 (3.2)	5 (5.3)	3 (2)	0.147	8 (100)	0 (0)	0.452
Thyroid Disorders		14 (5.7)	5 (5.3)	9 (5.9)	0.534	13 (92.9)	1 (7.1)	0.618
Other Diseases (hematologic, psychiatric, skin...)		24 (9.7)	0 (0)	24 (100)	0.000	19 (79.2)	5 (20.8)	0.057

Abbreviations; ICU: Intensive care unit, BMI: Body mass index, HT: Hypertension, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease

Table 3. How Patients Left the Hospital According to Vaccination Characteristics

Vaccination Situation	Total n (%)	Inpatient Service n (%)	ICU n (%)	p	Recovery n (%)	Exitus n (%)	p
Participants	247 (100)	95 (100)	152 (100)		224 (100)	23 (100)	
Type of vaccinated							
• Unvaccinated	88 (35.6)	29 (30.5)	59 (38.8)		75 (33.5)	13 (56.5)	
• Single Sinovac Vaccines							
1 dose of Sinovac	8 (3.2)	5 (5.3)	3 (2)		8 (3.6)	0 (0)	
2 dose of Sinovac	36 (14.6)	20 (21.1)	16 (10.5)		33 (14.7)	3 (13)	
3 dose of Sinovac	36 (14.6)	13 (15.1)	23 (13.7)		33 (14.7)	3 (13)	
• Single Biontech Vaccines							0.446
1 dose of Biontech	15 (6.1)	6 (6.3)	9 (5.9)	0,077	15 (6.7)	0 (0)	
2 dose of Biontech	25 (10.1)	8 (8.4)	17 (11.2)		24 (10.7)	1 (4.5)	
• Mixed Vaccines							
1 dose Sinovac + 1 dose Biontech	26 (10.5)	11 (11.6)	15 (9.9)		23 (10.3)	3 (13)	
2 dose Sinovac + 1 dose Biontech	5 (2)	3 (3.2)	2 (1.1)		5 (2.2)	0 (0)	
• Others	8 (3.2)	0 (0)	8 (5.3)		8 (3.6)	0 (0)	
Total vaccination dose							
Unvaccinated	88 (35.6)	29 (30.5)	59 (38.8)		75 (33.5)	13 (56.5)	
1 dose vaccinated	23 (9.3)	11 (11.6)	12 (7.9)	0.356	23 (10.3)	0 (0)	0.179
2 dose vaccinated	66 (26.7)	28 (29.5)	38 (25)		61 (27.2)	5 (21.7)	
3 dose vaccinated	67 (27.1)	27 (28.4)	40 (26.3)		62 (27.7)	5 (21.7)	
4 dose vaccinated	3 (1.2)	0 (0)	3 (2)		3 (1.3)	0 (0)	

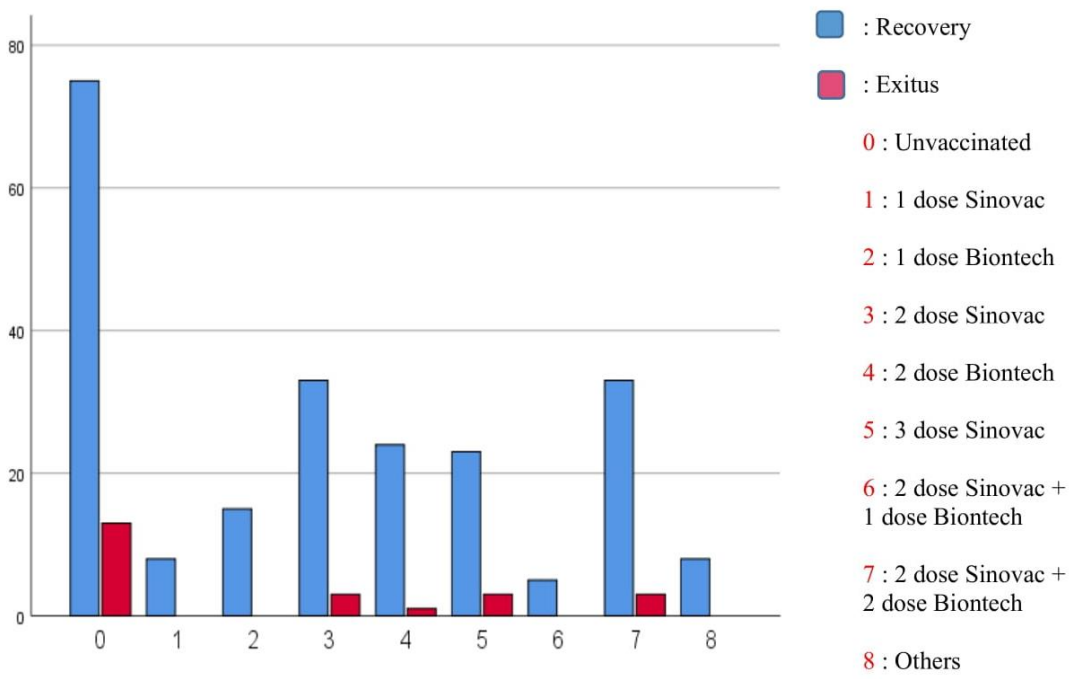

Figure 1. How patients leave the hospital according to vaccination status

Another finding that attracted our attention was that there were no single-dose vaccinated patients as well as 4-dose vaccinated patients among those who died. However, statistical significance was not found in these findings in our study. The vaccination status of the patients and the effects of vaccination on ICU follow-up and mortality are shown in Table 3 and Figure 1.

In the model in which all comorbid conditions, hospitalization day, disease severity and age variables were included, it was found that hospitalization day, disease severity and comorbid conditions such as chronic neurological disease and diabetes made a significant contribution to the model. The risk of ICU hospitalization was found to be 2.12 times higher in patients with a length of stay of more than 7 days, 2.89 times higher in patients with severe disease, 3.88 times higher in patients with chronic neurological disease and 2.18 times higher in patients with diabetes. Table 4 shows the estimated logistic regression analysis for ICU hospitalization.

Discussion

In our study, the rates of ICU admission and mortality were 38.5% and 9.3%, respectively. Of the patients admitted to the ICU, 38.8% and 56.5% of those who died were not vaccinated. Additionally, we discovered that death risk factors included HT, DM, cardiovascular disorders, severe sickness, advanced age, hospitalization for longer than seven days, and severe illness and comorbidities, particularly neurological diseases.

As of January 2023, more than 13 billion doses of COVID-19 vaccines have been administered worldwide [1]. While Turkey primarily used Sinovac (inactivated vaccine) vaccine in the third wave, western countries used mRNA (BioNTech and Moderna) or vector vaccines (AstraZeneca and Johnson & Johnson-Janssen). The effectiveness of mRNA vaccines, which are more widely used in Western countries, has been clearly documented in three doses with studies [11-13].

Table 4. Logistic Regression Analysis for ICU Hospitalization Prediction

	B	p	O.R.	95% C.I. for O.R. Lower	Upper
Length of hospitalization (day)	0.752	0,008	2.122	1.218	3.697
Disease severity		0.001			
Disease severity	-0.294	0.381	0.745	0.386	1.439
Disease severity	1.062	0.004	2.892	1.410	5.929
Neurological Diseases	1.356	0.001	3.882	1.788	8.428
DM	0.779	0.042	2.180	1.027	4.627
Constant	1.184	<0.001	3.267		

In a study of 1222 adolescent patients in the USA on the general effectiveness of COVID-19 vaccines, it was found that the risk of hospitalization due to COVID-19 was nearly 94% and the risk of death was nearly 100% lower in vaccinated children [14]. Sablerolles et al. demonstrated the safety and efficacy of Ad26.COV2.S and mRNA enhancers in healthcare workers who received the first dose of Ad26.COV2.S vaccine [15]. Clemens et al. used four different vaccines (Ad26.COV2-S, Janssen or BNT162b2, Pfizer-BioNTech or AZD1222, AstraZeneca or Sinovac) as repeat doses and measured antibody titers 28 days after reminder doses following two doses of Sinovac. They concluded that heterologous boosters resulted in stronger immune responses than homologous boosters and that heterologous boosters may increase protection [16]. In another study, Cerqueira-Silva et al. reported increased vaccine efficacy against infection and serious outcomes 14-30 days after booster [17]. In our study, 38.8% of patients admitted to the ICU and 56.5% of those who died were not vaccinated. Mortality rates were significantly reduced in the patient groups in which booster doses were administered; we observed that vaccination for COVID-19, regardless of subgroup, reduced ICU admission and mortality, and that repeated doses had positive effects especially on reducing mortality. In general, our results were consistent with the literature.

In different studies conducted in patients hospitalized due to COVID-19, it was determined that the mortality rate ranged from 12 to 78% (mean 25-50%) [18, 19]. In a retrospective observational study conducted in Spain, in which 523 patients were examined, it was determined that 21% of patients developed critical illness, 10.3% were admitted to the ICU and 13.8% of all patients died within 30 days [20]. In a study conducted in China with the participation of 1590 patients from 575 hospitals, the rates of critical illness and mortality were found to be 8.2% and 3.2%, respectively [21]. In our study, we found the rates of ICU admission and mortality to be 38.5% and 9.3%, respectively, and these results were consistent with the literature.

Many studies examining risk factors for critical illness and ICU admission in COVID-19 have reported that parameters such as advanced age, hypertension, DM, cardiovascular disease, comorbidities, especially COPD, elevated levels of CRP, ferritin, procalcitonin and proinflammatory markers such as IL-1, IL-6, progressive decrease in lymphocyte count, respiratory rate, heart rate, peripheral oxygen saturation may be indicators of ICU admission and critical illness [18, 22, 23]. Wu et al.[24] found that older age and more comorbidities were associated with a higher risk of developing ARDS and mortality in COVID-19 patients. Although globally, the consistent major risk factor associated with mortality in patients with COVID-19 is older age (≥64 years), other risk factors associated with mortality in these patients include the development of particularly severe ARDS and the need for mechanical ventilation, comorbidities (e.g., obesity, chronic heart and lung disease, chronic heart and lung disease), and the

need for mechanical ventilation. obesity, chronic heart and lung disease, hypertension, diabetes, chronic kidney disease, renal replacement therapy, cancer), inflammation or coagulation markers (e.g., fever, D-dimer level >1 microg/mL, elevated fibrin degradation products, prolonged activated partial thromboplastin and prothrombin times), laboratory findings (e.g. worsening lymphopenia, neutrophilia, elevated troponin), male gender, severity of organ dysfunction at presentation [25, 26]. In our study, we found that advanced age, hospitalization for more than 7 days, severe illness and comorbidities, especially the presence of nervous system disease, may be risk factors for ICU admission, whereas the presence of HT, DM, cardiovascular disease and severe illness may be risk factors for mortality. We also found that hospitalization for more than 7 days may lead to a 2.12-fold increased risk for ICU admission, severe illness 2.89-fold, chronic neurological disease 3.88-fold and diabetes 2.18-fold. Our current data are consistent with the literature. The presented study also has some limitations. The study includes data from a single city and a tertiary university hospital and does not reflect the entire population. The exact date of the last vaccine administration could not be determined for all participants in the study, which limits the evaluation of vaccine effects. In addition, SARS-CoV-2 mutation data of individuals are unknown, as mutations were not investigated in all samples collected in accordance with national policy. Based on these limitations, we believe that inferences cannot be drawn from our study for the whole population. In order to evaluate vaccine efficacy and the effects of reminder doses on the disease process, multicenter, long-period studies involving many people from different segments of the society are needed.

Conclusion

In conclusion, this study suggests that complete vaccination, even in disadvantaged populations, may be beneficial in preventing the need for intensive care and mortality in COVID-19. Since there is very limited data on this subject in the literature, our data gain value.

Conflict of interest
The authors declare that they have no conflict of interest.

Funding
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Ethical approval
The research protocol was approved by institution's (Cukurova Universty) Ethical Committee.

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