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Coronavirus Pandemic

Impact of vaccination on ICU admissions of hospitalized COVID-19 patients in a country with a heterologous vaccine policy

Süleyman Yıldırım[1], Cenk Kirakli[1], Yeliz Özdemir[2], Selma Tosun[2], Sinem Ermin[3], Gülru Polat[3], Celalettin Yılmaz[3], Semra Bilaçeroğlu[3], Bilge Salık[3], Berna Kömürcüoğlu[3], İlker Ödemiş[4], Şükran Köse[4], Uğur Uzun[5], Gaye Aydın[5], Enver İlhan[6]

[1] University of Health Sciences Turkey, Izmir School of Medicine, Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital, Intensive Care Unit, Izmir, Turkey
[2] University of Health Sciences Turkey, Izmir School of Medicine, Bozyaka Training and Research Hospital, Department of Infectious Disease and Clinical Microbiology, Izmir, Turkey
[3] University of Health Sciences Turkey, Izmir School of Medicine, Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital, Department of Pulmonology, Izmir, Turkey
[4] University of Health Sciences Turkey, Izmir Faculty of Medicine, Izmir Tepecik Training and Research Hospital, Department of Infectious Disease and Clinical Microbiology, Izmir, Turkey
[5] University of Health Sciences Turkey, Izmir Faculty of Medicine, Izmir Tepecik Training and Research Hospital, Department of Anesthesiology and Reanimation, Izmir, Turkey
[6] University of Health Sciences Turkey, Izmir Faculty of Medicine, Bozyaka Research and Training Hospital, Izmir, Turkey

Abstract

Introduction: Vaccination against coronavirus disease-19 (COVID-19) is highly effective in preventing severe disease and mortality. Adenoviral vector and mRNA vaccines were effective against intensive care unit (ICU) admission, but the effectiveness of inactivated vaccine on ICU admission was unclear. We aimed to evaluate the effect of vaccination status on ICU admission in hospitalized COVID-19 patients in a country with heterologous vaccination policy.

Methodology: This is a retrospective multicenter study conducted in three hospitals in Izmir, Turkey between 1 January 2021 and 31 March 2022. Patients aged ≥ 18 years and hospitalized due to COVID-19 were included in the study. Patients who had never been vaccinated and patients who had been vaccinated with a single dose were considered unvaccinated. A logistic regression analysis was performed for evaluating risk factors for ICU admission.

Results: A total of 2,110 patients were included in the final analysis. The median age was 66 years (IQR, 53-76 years) and 54% of the patients were vaccinated. During the study period, 407 patients (19.3%) were transferred to the ICU due to disease severity. Patients who were admitted to the ICU were older (median age 68 vs. 65 years, $p < 0.001$); and the number of unvaccinated individuals was higher among ICU patients (57% vs. 45%, $p < 0.001$). In multivariate regression analysis, being unvaccinated was found to be the most important independent risk factor for ICU admission with an OR of 2.06 (95% CI, 1.64-2.59).

Conclusions: Vaccination against COVID-19 is effective against ICU admission and hospital mortality.

Key words: COVID-19; vaccination; hospitalization; intensive care unit.

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Introduction

Vaccination against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been shown to be effective in preventing the development of severe disease [1,2]. Gracelli *et al.* reported that vaccination significantly decreased admission to the intensive care unit (ICU) with an unadjusted relative risk of 0.15 [3]. Hilty *et al*. reported that, less than 4% of coronavirus disease-19 (COVID-19) patients who were admitted to the ICU were vaccinated in the first nine months of the vaccination program in Switzerland [4]. However, the effectiveness of vaccines against ICU admission waned over time, especially in the case of inactivated vaccines [5]. A booster dose was recommended in many countries.

Two vaccine forms (inactivated SARS-CoV-2 vaccine, such as the Sinovac-CoronaVac; and the BNT162b2 mRNA vaccine developed by Pfizer–BioNTech) have been available since the beginning of 2021. Both vaccines have been shown to be safe and

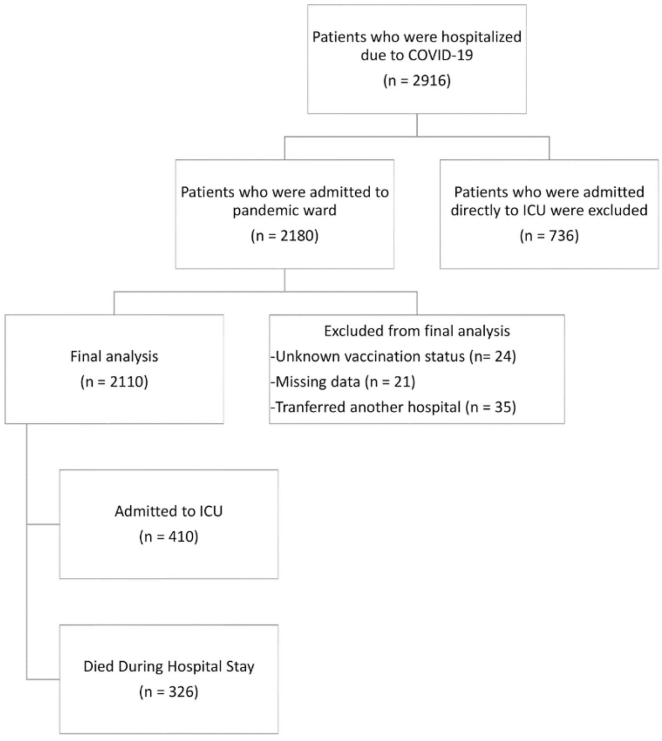
provide protection against severe disease [6,7]. The vaccination program was successfully implemented throughout Turkey, and more than 85% of the population aged ≥ 18 years had been vaccinated with at least two doses at the end of 2021 [8]. A booster dose was available at least three months after the second dose of any vaccine, and there were no restrictions on vaccination or booster preference in Turkey. Cerqueira-Silva *et al.* reported that a booster dose of mRNA vaccine six months after a second dose of inactivated vaccine improved vaccine effectiveness against severe outcomes [9]. However, the effectiveness of a booster dose of inactivated vaccine on ICU admission in hospitalized COVID-19 patients remains unclear.

We aimed to evaluate the effect of vaccination status on ICU admission in hospitalized COVID-19 patients in a country with a heterologous vaccination policy.

Methodology

This is a retrospective study conducted in three training and research hospitals (Dr. Suat Seren Chest Disease and Surgery Hospital, Bozyaka Hospital, and Tepecik Hospital) of the University of Health Sciences, Turkey, between 1 January 2021 and 31 March 2022, in Izmir. Izmir is the third biggest city in Turkey, and the vaccination rate in Izmir was similar to the vaccination rate in Turkey for individuals ≥ 18 years of age. This study was conducted after receiving approval from the Ethical Committee of University of Health Sciences Turkey, Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital (ethical approval number 2022/37-39). The study was performed in accordance with the principles of the Declaration of Helsinki.

Figure 1. Status of hospitalized COVID-19 patients over the study period.



COVID-19: coronavirus disease 2019; ICU: intensive care unit.

Participants

Patients who were ≥ 18 years of age and followed up in pandemic wards due to COVID-19 between 1 January 2021, and 31 March 2022, were included in the study. The diagnosis of COVID-19 was confirmed by a real-time reverse transcriptase polymerase chain reaction (RT-PCR), clinical assessment, and radiological findings. Patients who were directly admitted to the ICU and patients who were infected for the second time with SARS-CoV-2 were excluded from the study. Patients with unknown vaccination status, missing data, or those who were transferred to another hospital were also excluded from the final analysis (Figure 1). Patients' demographic features and vaccination status were obtained from medical records. The vaccination status of patients was obtained from the Vaccine Tracking System of the Turkish Health Ministry. The decisions regarding ICU admission were made by an intensivist according to the COVID-19 Guidelines of Turkish Health Ministry [10]. The criteria for ICU admission were tachypnea (respiratory rate > 35 breaths/min), refractory hypoxemia, requirement of mechanical ventilation support (invasive or non-invasive), unstable hemodynamic condition, impaired consciousness, and cardiopulmonary arrest.

Definitions

The inactivated vaccine (Sinovac-CoronaVac) was available from January 2021, and the mRNA vaccine (BNT162b2, Pfizer–BioNTech) was available from April 2021. After April 2021, both vaccines were available during the study period. There were no restrictions on vaccination preference, and a booster dose was available at least 3 months after the second dose of any vaccine. In this study, a patient was considered as vaccinated if there were at least 14 days after the second dose of any vaccine. If a patient was not vaccinated or had less than 14 days after the second dose, she/he was defined as unvaccinated. Booster vaccinations were divided into two groups 1) heterologous booster, if an individual was initially vaccinated with the inactivated vaccine and had a

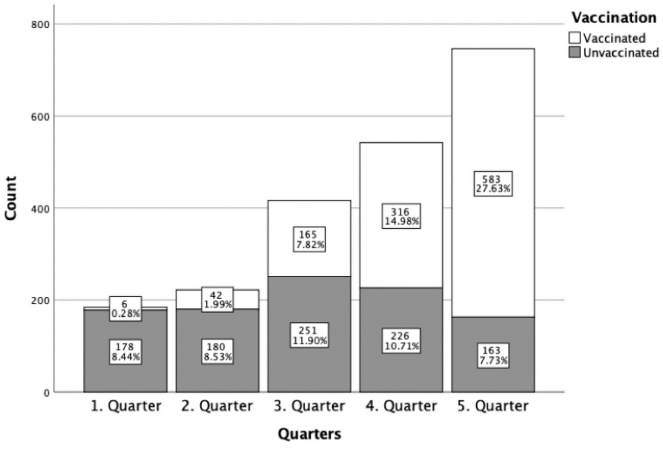
booster dose was with mRNA vaccine or vice versa; 2) homologous booster, if an individual had the booster vaccine which was the same as the initial vaccine.

Our main focus was the comparison of vaccinated and unvaccinated patients in terms of ICU admission. We also compared the effectiveness of vaccination with mRNA, inactivated plus mRNA vaccine, and vaccination with solely inactivated vaccine against ICU admission.

Statistical analysis

Normality of continuous data were tested with the Kolmogorov-Smirnov test, and continuous data were reported as median (IQR, interquartile range). Categorical variables were reported as numbers (%). Mann-Whitney U test was used for comparison of continuous variables, and Chi-square test was used for comparison of categorical variables. A univariate regression analysis was performed to define the factors associated with ICU admission. A multivariate regression analysis was performed to the evaluate risk factors for ICU admission using variables that were found to be associated with ICU admission in the univariate regression analysis. The model included age, having at least one comorbid disease, and vaccination status. Type of comorbid disease associated with ICU admission such as malignancy and chronic kidney failure, were not included in the model to avoid multicollinearity. A p value < 0.05 was considered statistically significant.

Figure 2. Proportion of vaccinated patients among the COVID-19 patients followed up in the hospital.



Results

A total of 2,110 patients were included in the final analysis. The median age of the patients was 66 years (IQR, 53–76 years), and 1,245 patients (59%) were male. A total of 1,112 patients (52.7%) were vaccinated, and 600 patients (28.4%) received at least one booster dose. 673 (60%) of the vaccinated patients were immunized with only the inactivated vaccine. Patients who received only inactivated vaccines were older than those who received the mRNA vaccine (median age 72 vs. 66 years, $p < 0.001$) and had more comorbidities (median number of comorbidities 2 vs.1, $p = 0.009$). The proportion of vaccinated patients among the COVID-19 patients followed up in the hospital increased over time (Figure 2). Vaccinated patients were older (median age 70 years vs. 60 years, $p < 0.001$) and had more comorbidities (median number of comorbidities 2 vs. 1, $p < 0.001$) than unvaccinated

Table 1. Demographic and clinical characteristics of patients.

	All Patients (n = 2110)	**Unvaccinated (n = 998)**	**Vaccinated (n = 1112)**	***p* value**
Age, years, median (IQR)	66 (53 – 76)	60 (58 – 80)	70 (46 – 73)	< 0.001
Gender, male, n (%)	1245 (59.0)	557 (57.8)	668 (60.1)	0.29
Comorbidity, n (%)				
Hypertension	863 (40.9)	343 (34.4)	520 (46.8)	< 0.001
Diabetes Mellitus	640 (30.3)	214 (21.4)	426 (38.3)	< 0.001
COPD	230 (10.9)	135 (13.5)	85 (8.3)	< 0.001
CAD	310 (14.7)	94 (9.4)	216 (19.4)	< 0.001
CHF	172 (8.2)	49 (4.9)	123 (11.1)	< 0.001
Malignancy	251 (11.9)	74 (6.1)	177 (15.9)	< 0.001
CVD	100 (4.7)	31 (3.1)	69 (6.2)	0.001
Alzheimer	117 (5.5)	39 (3.9)	78 (7.0)	0.002
CKF	172 (8.2)	51 (5.1)	121 (10.9)	< 0.001
At least one comorbidity, n (%)	1556 (73.7)	605 (60.6)	951 (85.5)	< 0.001
Number of comorbidities, median (IQR)	1 (0 – 2)	1 (0 – 2)	2 (1 – 2)	< 0.001
ICU admission, n (%)	407 (19.3)	233 (23.3)	174 (15.6)	< 0.001
Time from hospital admission to ICU admission days, median (IQR)	4 (2 – 8)	4 (2 – 8)	5 (2 – 9)	0.042
Non-survivor, n (%)	326 (15.5)	168 (17.4)	158 (14.8)	0.11
LOS in ICU, days, median (IQR)	7 (3 – 14)	7 (4 – 14)	6 (2 – 13)	
LOS in hospital, days, median (IQR)	7 (5 – 12)	8 (5 – 13)	7 (4 – 12)	< 0.001

CAD: coronary artery disease; CHF: chronic heart failure; CKF: chronic kidney injury; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay. Data are shown as median (IQR) or n (%).

patients. The most common comorbidities in vaccinated patients were hypertension in 520 patients (46.8%) and diabetes mellitus in 426 patients (38.3%); and 951 (85.5%) vaccinated patients had at least one comorbidity (Table 1).

ICU admission

During the study period, 407 patients (19.3%) were transferred to the ICU due to disease severity. Patients who were admitted to ICU were older (median age 68 vs. 65 years, $p < 0.001$) and had a higher proportion of unvaccinated patients (57% vs. 43%, $p < 0.001$) (Table 2). The rate of ICU admission was lower among patients who were vaccinated with the mRNA vaccine than among patients who were vaccinated with only inactivated vaccine (9.2% vs. 18.1%, $p = 0.002$) (Table 3).

Advanced age, having at least one comorbid disease, and being unvaccinated were found to be associated with ICU admission in univariate analysis. In a univariate analysis, having a booster dose of vaccination and vaccination with mRNA vaccine were found to be associated with a decreased risk of ICU admission (Table 4). In multivariate regression analysis, being unvaccinated was found to be the most important independent risk factor for ICU admission, with an odds ratio (OR) of 2.06 (95% CI, 1.64–2.59). Other independent risk factors for ICU admission were advanced age with an OR of 1.02 (95% CI, 1.01–1.02) and having at least one comorbid disease with an OR of 1.56 (95% CI, 1.15–2.11) (Table 5). Vaccination only with the inactivated vaccine increased the risk of ICU admission with an OR of 1.56 (95% CI, 1.08–2.24) when adjusted for age and number of comorbid diseases in multivariate regression analysis, compared to vaccination with mRNA or inactivated plus mRNA vaccine.

Table 2. Demographic features and clinical characteristics of ICU and non-ICU patients.

	ICU Patients (n = 407)	Non-ICU Patients (n = 1703)	*p* value
Age, years, median (IQR)	68 (58 – 80)	65 (52 – 76)	< 0.001
Gender, male, n (%)	254 (62.4)	991 (58.2)	0.12
Comorbid disease, n (%)			
Hypertension	162 (39.8)	701 (41.2)	0.61
Diabetes Mellitus	110 (27.0)	530 (31.1)	0.10
COPD	47 (11.5)	183 (10.7)	0.64
CAD	65 (16.0)	245 (14.4)	0.41
CHF	33 (8.1)	139 (8.2)	0.97
Malignancy	61 (15.0)	190 (11.2)	0.032
CVD	19 (4.7)	81 (4.8)	0.94
Alzheimer	34 (8.4)	83 (4.9)	0.006
CKF	43 (10.6)	129 (7.6)	0.048
At least one comorbidity, n (%)	329 (80.8)	1227 (72.0)	< 0.001
Number of comorbidities	1 (1 – 2)	1 (0 – 2)	0.20
Vaccination status, n (%)			
Unvaccinated	233 (57.2)	765 (44.9)	< 0.001
Vaccinated	174 (42.8)	938 (55.1)	
Only inactivated vaccine	122 (70.1)	551 (58.7)	0.005
Inactivated plus mRNA or only mRNA vaccine	52 (29.9)	387 (41.3)	
Booster, n (%)	89 (21.9)	511 (30.0)	0.001
Heterologous	33 (8.1)	205 (12.4)	0.60
Homologues	56 (13.8)	308 (18.9)	

CAD: coronary artery disease; CHF: chronic heart failure; CKF: chronic kidney injury; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay.Data are shown median (IQR) or n (%).

Table 4. Risk factors for ICU admission in univariate analysis.

	OR	CI	*p* value
Age	1.02	1.01–1.02	< 0.001
Malignancy	1.40	1.03–1.91	0.033
Chronic kidney failure	1.44	1.01–2.07	0.049
At least one comorbidity	1.63	1.24–2.14	< 0.001
Being unvaccinated	1.64	1.30–2.04	< 0.001
Being vaccinated with only inactive vaccine	0.89	0.70–1.13	0.33
Being vaccinated with both inactive and mRNA vaccine	0.66	0.45–0.97	0.037
Being vaccinated with only mRNA vaccine	0.39	0.24–0.64	< 0.001
Having a booster	0.65	0.50–0.84	< 0.001

CI: confidence interval; ICU: intensive care unit; OR: odds ratio.

Mortality

During the study period, 326 (15.5%) patients died during their hospital stay. Mortality rate was lower among vaccinated patients than unvaccinated patients, but the difference was not statistically significant (14.8% vs. 17.4%, $p = 0.11$). Advanced age and having at least one comorbid disease were found to be independent risk factors for mortality in multivariate analysis. Being unvaccinated was an independent risk factor for mortality when adjusted for age and having comorbid diseases (Table 5). The mortality rate was lower among patients who were vaccinated with the mRNA vaccine, than among patients who were vaccinated with only inactivated vaccine (5.8% vs. 17.5%, $p = 0.002$) (Table 3).

Discussion

Our study shows that vaccination decreased the risk of ICU admission in hospitalized COVID-19 patients. Unvaccinated patients had a two-times higher risk of

Table 3. Comparison of inactivated and mRNA vaccines' effectiveness on ICU admission and hospital mortality in vaccinated patients.

	ICU admission	*p* value	Mortality	*p* value
Only inactivated vaccine vs hybrid vaccine*	18.1% vs.14.2%	0.174	17.5% vs.12.1%	0.039
Only inactivated vaccine vs only mRNA vaccine	18.1% vs. 9.2%	0.002	17.5% vs. 5.8%	< 0.001
Hybrid vaccine vs only mRNA vaccine	14.2% vs. 9.2%	0.102	12.1% vs. 5.8%	0.019

ICU: intensive care unit. *Hybrid vaccine: patients who were vaccinated with both inactivated and mRNA vaccine.

Table 5. Risk factors for ICU admission and mortality in multiple regression analysis.

	ICU Admission			Mortality		
	OR	**CI**	***p* value**	**OR**	**CI**	***p* value**
Age	1.02	1.01–1.02	< 0.001	1.02	1.01 – 1.03	< 0.001
Having at least one comorbid disease	1.56	1.15–2.11	0.004	2.55	1.75 – 3.73	< 0.001
Being unvaccinated*	2.06	1.64–2.59	< 0.001	1.68	1.31 – 2.15	< 0.001

CI: confidence interval; ICU: intensive care unit; OR: odds ratio. *When adjusted for age and having at least one comorbidity.

ICU admission than vaccinated patients. Advanced age and having at least one comorbid disease were also found to be independent risk factors for ICU admission among hospitalized COVID-19 patients. Vaccination status, advanced age, and having at least one comorbid disease were also found to be associated with in-hospital mortality.

During the study period, most (52.7%) hospitalized COVID-19 patients were vaccinated. Previous studies have shown that vaccination reduces hospitalizations due to COVID-19 [1,2]. However, with the increase in the rate of vaccination, the rate of vaccinated patients increased among hospitalized COVID-19 patients over time. Globally, the rate of vaccination varied from 1.3% to 11.9% in the first half of 2021, when the rate of vaccination was relatively lower [11–13]. In our study, a small proportion of the hospitalized COVID-19 patients were vaccinated in the first half of 2021, similar to previous studies [11–13]. The proportion of vaccinated people hospitalized for COVID-19 increased in the second half of 2021 and 2022 [12,14,15]. The increase in vaccination rate over time, newly emerging variants, a lack of booster doses, and the waning effectiveness of vaccination over time may be the primary reasons for this situation [5,16].

Previous studies have shown that vaccination reduces ICU admissions [1,17]. Grasselli *et al*. reported that unvaccinated patients had a seven-times higher risk for ICU admission [3]. We also found that vaccination with inactivated vaccine did not affect ICU admission, and vaccination with mRNA or inactivated plus mRNA vaccine reduced ICU admission. mRNA and adenoviral vector vaccines were found to be highly effective against ICU admission in previous studies [3,4,18]. Cerqueira-Silva *et al.* compared adenoviral vector vaccine and inactivated vaccine, and they reported that both vaccines were effective against ICU admission, but the effectiveness of the inactivated vaccine was less than that of adenoviral vector vaccine (72% vs. 91%) [17]. In our study, patients who received only inactivated vaccine were older, had more comorbid diseases, and the time from the last vaccine to hospitalization was longer, than patients who received mRNA or inactivated plus mRNA vaccine. A previous study showed that age-related vaccine effectiveness reduced in inactivated vaccines in Brazil [19]. In addition, it has been shown that effectiveness against ICU admission wanes over time in the case of inactivated vaccines [5]. The vaccination program in Turkey was started with the inactivated vaccine, and only inactivated vaccine was available in the first quarter of 2021. Individuals who were older and had more comorbid diseases were given priority in the vaccination program. This caused individuals who received inactivated vaccines to be older and have more comorbidities.

Our results have also shown that a booster dose (homogenous or heterogenous) reduced the risk of ICU admission. Vaccine effectiveness has been shown to wane over time, and several countries have recommended a booster dose [20–22]. Cerqueira-Silva *et al.* reported that the effectiveness of the inactivated vaccine against severe outcomes decreased over 180 days after the second dose, and a booster with mRNA vaccine increased effectiveness against severe outcomes from 72% to 97% [9]. Jara *et al.* reported that a booster dose of inactivated, mRNA, or adenoviral vaccine after the second dose of inactivated vaccine provided a high level of protection against ICU admission. They reported that adjusted vaccine effectiveness against ICU admission was 92% for homologous boosters with inactivated vaccine, 96% for boosters with mRNA vaccine, and 98% for boosters with adenoviral vector vaccine [23]. Similar to previous studies, other risk factors for ICU admission in our study were advanced age and having at least one comorbid disease [3,15].

Vaccination favored better outcomes; unvaccinated patients had a longer hospital stay and shorter pre-ICU hospital stay than vaccinated patients. However, vaccination status did not affect the duration of ICU stay. In previous studies, the association between vaccination status and length of hospital stay and ICU stay was controversial. Grasselli *et al.* reported that vaccinated and unvaccinated patients had similar hospital and ICU stays [3]. On the contrary Hilty *et al.* reported that vaccination reduced ICU stays and Korishettar *et al.* reported that unvaccinated patients had longer hospital stays than vaccinated patients [4,11]. The length of stay in the hospital may be associated not only with vaccination, which helps in

faster recovery, but also with decreasing the hospital occupancy rate.

Unadjusted mortality was similar in vaccinated and unvaccinated patients. After adjustment for age and comorbid conditions, being unvaccinated increased mortality by 1.6 times. Vaccination reduced mortality in community-based studies [1,2]. However, vaccination status did not affect survival in patients who were admitted to the ICU due to COVID-19 [3,24]. Vaccinated patients were older and had more comorbid diseases, and these factors were considered to be the main reason for this situation. There are several confounders that are associated with mortality such as sepsis or acute kidney injury after ICU admission.

Our study has some limitations. First, our study is a retrospective study and has the all limitations of retrospective studies. Second, although more than 2,000 patients were included in the study, a larger sample is needed to generalize the results. Third, we focused on the effectiveness of vaccination on ICU admission after hospitalization; however, approximately one-fourth of the patients were admitted directly to the ICU. Since the vaccination status of these patients was unknown, it may have affected the results of our study. Further studies are needed to determine the efficacy of vaccination in this patient group. Fourth, we could not focus on treatments for COVID-19 or complications such as secondary bacterial infection or cause of death due to the retrospective nature of the study and lack of data. Finally, we did not include information about the variants of SARS-CoV-2 in the analysis, and they may have influenced the effectiveness of the vaccine.

Conclusions

Vaccination was effective against ICU admission and hospital mortality. The effectiveness of vaccination may wane over time, but a booster dose can increase the efficacy of the vaccine. After two doses of inactivated vaccine, a booster dose administered with the mRNA vaccine was more effective than an inactivated vaccine.

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Corresponding author

Süleyman Yıldırım, MD.
University of Health Sciences Turkey, Izmir School of Medicine, Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital, Intensive Care Unit, Yenişehir, Gaziler Cd No:331 D:28, 35170 Konak/İzmir, Turkey.
Tel: +902324333333
Email: deu.syldrm@gmail.com

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