AKADÉMIAI KIADÓ

Acta Microbiologica et Immunologica Hungarica

69 (2022) 4, 270–276

DOI:
10.1556/030.2022.01860

RESEARCH ARTICLE

Evaluation of clinical outcomes of vaccinated and unvaccinated patients with hospitalization for COVID-19

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Received: August 17, 2022 • Accepted: August 25, 2022
Published online: September 21, 2022

ABSTRACT

We aimed to compare vaccinated and unvaccinated patients hospitalized with COVID-19 in terms of disease severity, need for intensive care unit (ICU) admission, and death. In addition, we determined the factors affecting the COVID-19 severity in vaccinated patients. Patients aged 18–65 years who were hospitalized for COVID-19 between September and December 2021 were retrospectively analyzed in three groups: unvaccinated, partially vaccinated, and fully vaccinated.

A total of 854 patients were included. Mean age was 47.9 ± 10.6 years, 474 patients (55.5%) were male. Of these, 230 patients (26.9%) were fully vaccinated, 97 (11.3%) were partially vaccinated, and 527 (61.7%) were unvaccinated. Of the fully vaccinated patients, 67% (n = 153) were vaccinated with CoronaVac and 33% (n = 77) were vaccinated with Pfizer-BioNTech. All patients (n = 97) with a single dose were vaccinated with Pfizer-BioNTech. One hundred thirteen (13.2%) patients were transferred to ICU. A hundred (11.7%) patients were intubated and 77 (9.0%) patients died. Advanced age (P = 0.028, 95% CI = 1.00–1.07, OR = 1.038) and higher Charlson Comorbidity Index (CCI) (P < 0.001, 95% CI = 1.20–1.69, OR = 1.425) were associated with increased mortality, while being fully vaccinated (P = 0.008, 95% CI = 0.23–0.80, OR = 0.435) was associated with survival in multivariate analysis. Full dose vaccination reduced the need for ICU admission by 49.7% (95% CI = 17–70) and mortality by 56.5% (95% CI = 20–77). When the fully vaccinated group was evaluated, we found that death was observed more frequent in patients with CCI>3 (19.1 vs 5.8%, P < 0.01, OR = 3.7). Therefore, the booster vaccine especially in individuals with comorbidities should not be delayed, since the survival expectation is low in patients with a high comorbidity index.

KEYWORDS

COVID-19, mortality, vaccination, CoronaVac, Pfizer-BioNTech

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INTRODUCTION

As of July 30, 2022, more than 572 million confirmed COVID-19 cases and over 6.3 million COVID-19-related deaths have been reported, worldwide [1]. Since an effective treatment for

COVID-19 has not yet been discovered, disease prevention approaches have gained more importance [2]. However, many COVID-19 vaccines have been rapidly developed in response to the COVID-19 pandemic. These vaccines were administered to the community in mass vaccination programs, with priority given to high-risk individuals [3]. While vaccination rates vary by country, as of July 30, 2022, 61.5% of the world's population had been fully vaccinated against COVID-19, and 5.6% had been partially vaccinated [4].

CoronaVac, an inactivated whole virus vaccine, and Pfizer-BioNTech, an mRNA vaccine, started to be used in community vaccination against COVID-19 in Turkey on January 14, 2021, and April 12, 2021, respectively. The second dose of vaccines were administered 4 weeks after the first dose, and the third dose of booster vaccines were administered 3–6 months after the second dose. As of December 30, 2021, TurkoVac vaccine was also included in the booster dose administration [5].

Over time, many different variants of the SARS-CoV-2 virus have dominated and caused pandemic. Many real-life data have shown that vaccines are effective against these variants [6–7]. Recently, Delta (B.1.617.2) and Omicron (B.1.1.529) variants, which are considered variants of concern (VOCs), are the main cause of the pandemic. Delta variant is more than 2 times more contagious than previous variants and it also causes more severe disease than the original virus and previous variants. The Omicron variant is more contagious than the delta variant and other COVID-19 variants however, it usually causes less severe disease than other variants [8]. As of August 20, 2021, >90% of COVID-19 cases in our country were delta variants. On December 12, 2021, the first omicron variant was detected.

Our center is an emergency pandemic hospital with 1,006 beds, where outpatient or inpatient treatment services are provided for COVID-19 patients during the pandemic period. In this study, we aimed to compare vaccinated and unvaccinated patients hospitalized with COVID-19 in terms of disease severity, need for intensive care unit (ICU) admission and death in the Delta (B.1.617.2) variant dominant period In addition, we aimed to determine the factors affecting the severity of COVID-19 disease in people who were vaccinated before.

MATERIALS AND METHODS

Study design

This is a cross-sectional, and epidemiological study. Patients aged 18–65 years who received inpatient treatment in our hospital due to COVID-19 between September 1, 2021 and December 15, 2021, were included. Patients who received at least 2 doses of vaccine were defined as "fully vaccinated", patients who received a single dose of vaccine were defined as "partially vaccinated", and patients without any vaccine were defined as "unvaccinated".

Inclusion Criteria: In this study, 854 confirmed COVID-19 patients aged 18–65 years who were positive by the SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) test were included.

Exclusion Criteria: Patients whose RT-PCR test was negative and who had COVID-19 within the first 2 weeks after 2 doses of vaccine were excluded in the study.

Independent variables

The independent variables were: sex, age, underlying diseases, previous history of COVID-19, and post-vaccination time period.

The primary outcomes were the effects of COVID-19 vaccines on disease severity, need for ICU admission, need for mechanical ventilation, and death in hospitalized COVID-19 patients.

Secondary outcome was death in vaccinated patients with COVID-19.

Mortality was defined as in-hospital mortality.

The patients' comorbidities were evaluated using the Charlson Comorbidity Index (CCI).

The evaluation of disease severity was based on the recommendations of the WHO severity definitions [9]. The following criteria were used to identify the patient's severity:

- Severe COVID-19: Defined by any of the following: oxygen saturation <90% on room air; or respiratory rate>30 breaths/min; or signs of severe respiratory distress (accessory muscle use, inability to complete full sentences).
- Non-severe COVID-19: Defined as the absence of any criteria for severe or critical COVID-19.
- Critical COVID-19: Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

Statistical analysis

Quantitative variables were expressed as mean and standard deviation when they included continuous data. Categorical data were expressed as percentages (%) and frequencies (n). The normal distribution of the data questioning the necessity of using the parametric test was decided by evaluating Kolmogorov-Smirnov test results, Box plot distributions, median, mean proximity, Skewness, Kurtosis results, and histogram curves altogether. According to the normality of the distribution, appropriate parametric or non-parametric tests were applied.

Univariate logistic regression analysis was performed to question the factors leading to death from COVID-19. All factors with $P < 0.05$ or considered significant in the literature were included in the multivariate logistic regression analysis, along with vaccination status. The Kaplan Meier analysis was applied to evaluate the prediction capacity of CCI for mortality in vaccinated patients with COVID-19.

The results were evaluated in a 95% Confidence Interval, and the statistical significance level was considered as

$P < 0.05$. The analyses were made by using the IBM SPSS-21 (Statistical Package for Social Sciences, Armonk, NY, USA) package program.

Ethical statement

This study was approved by local ethics committee (Decision No: 2022-14-10, Date: 18.07.2022). Written informed consent was waived, given the retrospective nature of this study.

RESULTS

A total of 854 patients were included in the study. Four-hundred and seventy-four patients (55.5%) were male, and the mean age was 47.9 ± 10.6 years. Of these, 230 patients (26.9%) were fully vaccinated, 97 (11.3%) were partially vaccinated, and 527 (61.7%) were unvaccinated. Of the fully vaccinated patients, 67% (n = 153) were vaccinated with CoronaVac and 33% (n = 77) were with Pfizer-BioNTech. All of the patients (n = 97) vaccinated with a single dose were vaccinated with Pfizer-BioNTech. The mean age of patients in the fully vaccinated (54.5 ± 8.2) group was statistically significantly higher than in the partially vaccinated (45.3 ± 10.7) and unvaccinated (45.5 ± 10.3) groups (P = 0.001). The mean length of hospital stay was 10.6 ± 8.4 days. Five (0.6%) patients had a history of COVID-19 before the vaccination. Mean leukocyte count was 6,650 ± 4,130 10^3 uL^{-1}, C-reactive protein (CRP) 88 ± 76 mg L^{-1}, ferritin 727 ± 1,006 µg L^{-1}, procalcitonin 0.49 ± 3.77 ng mL^{-1}, creatinine 1.03 ± 0.99 mg dL^{-1}, alanine aminotransferase (ALT) 38 ± 38 IU/L, aspartate aminotransferase (AST) 40 ± 33 IU/L, and d-dimer 0.70 ± 1.19 µgFEU mL^{-1} at the time of first admission. The comparison of demographic features, biochemical parameters, and clinical characteristics of the patients between the groups is shown in Table 1.

The CCI was "0" in 352 patients, "1–2" in 356 patients, and ">2" in 146 patients. CCI>0 was found in 87% of the fully vaccinated group, 54.6% of the partially vaccinated group, and 47.2% of the unvaccinated group (P = 0.001). Three-hundred and seventy-three (43.6%) patients had at

Table 1. Demographic characteristics and outcomes of patients hospitalized for COVID-19

	Total (n = 854)		Fully Vaccinated (n = 230)		Partially Vaccinated (n = 97)		Unvaccinated (n = 527)		P
	N	%	N	%	N	%	N	%	
Gender (Male)	474	55.5	136	59.1	54	55.7	284	53.9	0.193
Age (Mean ± SD)	47.9 ± 10.6		54.5 ± 8.2		45.3 ± 10.7		45.5 ± 10.3		**0.001**
Disease Severity									**0.014**
Non-Severe	395	46.3	121	52.6	48	49.5	226	42.9	
Severe	334	39.1	80	34.8	35	36.1	219	41.5	
Critically	125	14.6	29	12.6	14	14.4	82	15.6	
CCI									**0.001**
0	352	41.2	30	13.0	44	45.4	278	52.8	
1–3	429	51.3	158	68.7	46	47.4	225	42.7	
>3	73	8.5	42	18.3	7	7.2	24	4.5	
Hypertension	213	24.9	95	41.3	23	23.7	95	18.0	**<0.001**
Diabetes Mellitus	161	18.8	75	32.6	20	20.6	66	12.5	**<0.001**
CAD	81	9.5	43	18.7	12	12.3	26	4.9	**<0.001**
Asthma/COPD	70	8.2	24	10.4	11	11.3	35	6.6	0.105
CKD	36	4.2	19	8.2	2	2.1	15	2.8	**0.002**
Others	42	4.9	20	8.7	3	3.1	19	3.6	
Wbc (10^3 uL^{-1}) (Mean ± SD)	6.65 ± 4.53		7.18 ± 5.90		7.29 ± 4.40		6.30 ± 3.77		**0.014**
Ferritin (µg L^{-1}) (Mean ± SD)	727 ± 1,006		704 ± 1,312		572 ± 400		765 ± 926		**0.001**
CRP (mg L^{-1}) (Mean ± SD)	88 ± 76		108 ± 92		88 ± 71		79 ± 67		**0.001**
Procalcitonin (ng mL^{-1}) (Mean ± SD)	0.49 ± 3.77		0.90 ± 6.75		0.26 ± 0.59		0.35 ± 1.74		**0.001**
Creatinine (mg dL^{-1}) (Mean ± SD)	1.03 ± 0.99		1.22 ± 1.27		1.02 ± 1.10		0.95 ± 0.79		**0.001**
ALT (IU/L) (Mean ± SD)	38 ± 38		34 ± 42		38 ± 33		40 ± 37		**0.003**
AST (IU/L) (Mean ± SD)	40 ± 33		35 ± 32		37 ± 23		40 ± 37		**0.001**
D-dimer (µg FEU mL^{-1}) Mean ± SD)	0.70 ± 1.19		0.81 ± 1.61		0.48 ± 0.40		0.69 ± 1.06		0.365
Length of (Mean ± SD) hospital stay (days)	10.6 ± 8.4		10 ± 7.5		9.2 ± 4.9		11.1 ± 9.3		0.520
ICU admission	113	13.2	30	13.0	12	12.4	71	13.5	0.844
Intubation	100	11.7	23	10.0	12	12.4	65	12.3	0.382
Mortality	77	9.0	19	8.3	12	12.4	46	8.7	0.981

CCI: Charlson Comorbidity Index, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney cisease, ICU: Intensive care unit. Bold values represent statistical significance at the level of $P < 0.05$.

least one comorbidity. The most frequent comorbidities were hypertension (n = 213, 24.9%), diabetes mellitus (n = 161, 18.8%), coronary artery disease (n = 81, 9.5%), and asthma/chronic obstructive pulmonary disease (COPD) (n = 70, 8.2%). In the subgroup analysis, mortality was significantly lower in the fully vaccinated group compared to the unvaccinated and partially vaccinated groups in patients with hypertension (11.5 vs 25.9%, P = 0.02, OR = 2.38) and chronic kidney disease (5.2 vs 41.2%, P = 0.01, OR = 12.5). In patients with diabetes, coronary artery disease, and asthma/COPD, mortality was lower in the fully vaccinated group than in the other groups, but this difference was not significant (Table 2).

COVID-19 was non-severe in 395 patients (46.3%), severe in 334 patients (39.1%), and critical in 125 patients (14.6%). Non-severe disease was observed in 52.6% of the fully vaccinated group (n = 121/230), in 49.5% of the partially vaccinated group (n = 48/97), and in 42.9% of the unvaccinated group (n = 226/527) (P = 0.01). One hundred thirteen (13.2%) patients were followed up in the ICU admission. A hundred (11.7%) patients were intubated and 77 (%9.0) patients died. The need for ICU admission was 13% in the fully vaccinated group (n = 30/230), 12.4% in the partially vaccinated group (n = 12/97), 13.5% in the unvaccinated group (n = 71/527) (P = 0.84); intubation was 10% in the fully vaccinated group (n = 23/230), 12.4% in the partially vaccinated group (n = 12/97), 12.3% in the unvaccinated group (n = 65/527) (P = 0.38); mortality was 8.3% in the fully vaccinated group (n = 19/230), 12.4% in the partially vaccinated group (n = 12/97), and 8.7% in the unvaccinated group (n = 46/527) (P = 0.98).

In the multivariate analysis, advanced age (P = 0.003, 95% CI = 1.01–1.07, OR = 1.043) and high CCI (P = 0.004, 95% CI = 1.07–1.47, OR = 1.257) were predictors of the need for ICU admission. However, being fully vaccinated (P = 0.008, 95% CI = 0.30–0.83, OR = 0.503) was found as the only protective factor (Table 3). Similarly, advanced age (P = 0.028, 95% CI = 1.00–1.07, OR = 1.038) and higher CCI (P < 0.001, 95% CI = 1.20–1.69, OR = 1.425) were associated with increased mortality, while being fully vaccinated (P = 0.008, 95% CI = 0.23–0.80, OR = 0.435) was associated with survival in multivariate analysis (Table 4). Full dose vaccination reduced the need for intensive care admission by 49.7% (95% CI = 17–70) and mortality by 56.5% (95% CI = 20–77).

When the fully vaccinated group was evaluated, we found that death was observed more frequent in patients with CCI>3 (19.1 vs 5.8%, P < 0.01, OR = 3.7). Although death was more common in male gender (10.3 vs 5.3%, P = 0.18, OR = 2.04), patients with hypertension (11.6 vs 5.9%, P = 0.13, OR = 2.08), diabetes mellitus (12.0 vs 6.4%, P = 0.15, OR = 1.98), coronary artery disease (9.3 vs 8.0%, P = 0.78, OR = 1.18), asthma/COPD (12.5 vs 7.7%, P = 0.43, OR = 1.70), but this difference was not significant. There was no significant difference between COVID-19 vaccines (8.5 vs 7.8%, P = 0.85, OR = 0.95) (Table 5). In the regression

Table 2. Mortality rates of COVID-19 patients by comorbidity and vaccination status

		Total		Fully vaccinated		Unvaccinated + partially vaccinated			
	Exitus	*N*	%	*N*	%	*N*	%	*P*	OR
Hypertension	No	174	81.7	84	88.5	90	74.1	**0.02**	2.38
(*N* = 213)	Yes	39	18.3	11	11.5	28	25.9		
DM	No	134	83.2	66	88.0	68	79.1	0.13	1.92
(*N* = 161)	Yes	27	16.8	9	12.0	18	20.9		
cad	No	69	85.2	39	90.7	30	78.9	0.14	2.56
(*N* = 81)	Yes	12	14.8	4	9.3	8	21.1		
Asthma/COPD	No	59	84.3	21	87.5	38	82.6	0.59	1.47
(*N* = 70)	Yes	11	15.7	3	12.5	8	17.4		
CKD	No	28	77.8	18	94.8	10	58.8	**0.01**	12.50
(*N* = 36)	Yes	8	22.2	1	5.2	7	41.2		

DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease

Table 3. Univariate and multivariate analysis of the factors causing the need for intensive care admission

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Gender	1.118	0.75–1.66	0.581	–	–	–
Age	1.057	1.03–1.08	<0.001	1.043	1.01–1.07	**0.003**
Vaccination (Ref: Unvaccinated)						
Partially vaccinated	0.907	0.47–1.74	0.769	0.856	0.43–1.68	0.653
Fully vaccinated	0.963	0.61–1.52	0.873	0.503	0.30–0.83	**0.008**
Charlson Comorbidity Index	1.374	1.22–1.54	<0.001	1.257	1.07–1.47	**0.004**

Table 4. Univariate and multivariate analysis of factors causing mortality

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Gender	1.170	0.73–1.82	0.511	–	–	–
Age	1.065	1.03–1.09	<0.001	1.038	1.00–1.07	**0.028**
Vaccination (Ref: Unvaccinated)						
Partially vaccinated	1.47	0.75–2.90	0.259	1.399	0.68–2.84	0.353
Fully vaccinated	0.94	0.54–1.64	0.833	0.435	0.23–0.80	**0.008**
Charlson Comorbidity Index	1.49	1.31–1.69	<0.001	1.42	1.20–1.69	**<0.001**

Table 5. Comparison of characteristics of deceased and living persons in fully vaccinated patients

		Survival (n = 211)		Death (n = 19)			
	n	n	%	n	%	*P*	OR
Gender (Male)	136	122	89.7	14	10.3	0.18	2.04
Age (Median/IQR)	230	57 (11)		58 (14)		0.26	
COVID-19 vaccines						0.85	0.91
CoronaVac	153	140	91.5	13	8.5		
Pfizer-Biotech	77	71	92.2	6	7.8		
Post-vaccine duration						0.49	1.4
<90 days	69	62	89.8	7	10.2		
>90 days	161	149	92.5	12	7.5		
CCI						**<0.01**	3.7
0–3	188	177	94.1	11	5.8		
>3	42	34	80.9	8	19.1		
Hypertension	95	84	88.4	11	11.6	0.13	2.08
Diabetes mellitus	75	66	88.0	9	12.0	0.15	1.98
CAD	43	39	90.7	4	9.3	0.78	1.18
Asthma/COPD	24	21	87.5	3	12.5	0.43	1.70
CKD	19	18	94.7	1	5.3	0.62	0.60

CCI: Charlson Comorbidity Index, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic Kidney Disease, IQR: Interquartile range

analysis, we determined that CCI>3 was associated with 3.78-fold increased risk for mortality (P = 0.008). The survival rates of fully vaccinated patients according to vaccination time and CCI are shown in Fig. 1.

DISCUSSION

In this study, we present the demographic characteristics, clinical findings, biochemical parameters, and outcomes of vaccinated and unvaccinated adult patients hospitalized for COVID-19. We found that although unvaccinated patients were young and did not have comorbid diseases, hospitalization rate, and the disease severity were higher. We also showed that double-dose vaccination reduces the need for ICU admission and mortality in hospitalized patients by approximately 50 and 57%, respectively. However, we determined that CCI>3 in fully vaccinated patients was associated an about 4-fold increase in mortality.

In our hospital, SARS-CoV-2 genotype determination was not routinely performed in the COVID-19 patients. During the study interval, >90% of the patients with COVID-19 in our country were delta variants and the omicron variant had not yet been detected. At the same time, the rate of fully vaccinated patients in our city increased from 60 to 75% during this period [10]. Although vaccination rates in the community are at these levels, only 25% of hospitalized patients were fully vaccinated. Therefore, it can be concluded that double-dose vaccination of significantly reduces the need for hospitalization against the delta variant.

Studies conducted after community vaccinations have shown that people who are not fully vaccinated have significantly higher rates of COVID-19 development, hospitalization, and death than those with fully vaccinated [11–12]. However, it has been reported that the efficacy of the vaccine decreased from 91 to 66% during the delta variant dominant period. In addition, vaccine efficacy was found to be 85% in the first 120 days after vaccination, and 73% in the period of more than 150 days after vaccination [11] In another study, the efficacy of full vaccination against symptomatic COVID-19, COVID-19 pneumonia, and severe COVID-19 during the delta variant outbreak was 51, 62, 82%, respectively [12]. In our study, in which hospitalized COVID-19 patients were evaluated, a significantly higher rate of severe COVID-19 was detected in the unvaccinated and partially vaccinated group

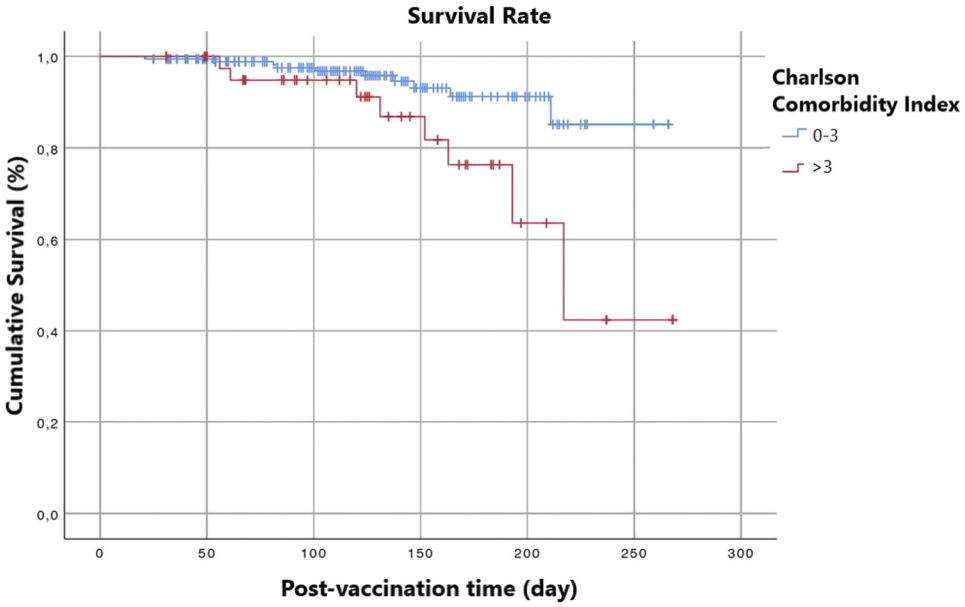

Fig. 1. Survival Analysis in vaccinated patients according to the Charlson Comorbidity Index

compared to the fully vaccinated group. In addition, the duration of hospitalization was longer in the unvaccinated group but there was no significant difference.

To date, many studies have revealed that comorbid conditions are associated with poor prognosis in COVID-19 [13–14]. In our study, hypertension, diabetes mellitus, coronary artery disease, and asthma/COPD were associated with by up to two-fold increased mortality regardless of vaccination status. Also, unvaccinated patients with chronic kidney disease had four-fold increased mortality, while patients with fully vaccinated chronic kidney disease had similar mortality rate with the general cohort. Moreover, while age, CCI, and vaccination status were the independent factors associated with mortality in general cohort, CCI was the only independent factor in vaccinated patients. Similarly, in the study of Sezen et al., mortality was found to be significantly higher in patients with CCI ≥1 [15].

Overall, the effectiveness of COVID-19 vaccines has been proven in different epidemiological studies [16–18]. However, studies comparing the mortality rates of vaccinated and unvaccinated patients, which take into account the demographic and clinical characteristics of patients in the delta variant dominant period, are limited. In the study of Sezen et al., mortality rates were higher in patients with advanced age, high CCI, and incomplete vaccination [15]. Alsaffar et al. reported that vaccination significantly reduced the need for ICU admission ($P = 0.063$, OR = 0.476) and death ($P = 0.034$, OR = 0.378). In addition, advanced age (≥65 years), asthma/COPD, and renal transplant were identified as independent risk factors for ICU admission and death, but male gender was a protective factor [19]. In our study, advanced age and increased CCI were independent risk factors for ICU admission and mortality, and full vaccination was a protective factor. No correlation was found between the time elapsed after vaccination and death. This may be related to the fact that the last vaccination date is usually within the last 6 months, and the elderly with waning immune response were not included in the study. Additionally, in Kaplan-Meier analysis, we found that the expected survival of vaccinated patients with CCI >3 decreased significantly during the time elapsed after the vaccination ($P = 0.009$). We concluded that booster dose vaccines should be administered earlier in patients with high CCI.

This study had several strengths. First, only younger patients (<65 years old) were included in the study. In this way, we provided patient homogenization by reducing the confounding factors due to advanced age. Second, to our knowledge, this is the first study to evaluate the factors affecting mortality in fully vaccinated younger patients with COVID-19 in our country. Third, the effect of vaccination was more clearly determined by adjusting the covariates factors in the multivariate analysis. However, our study had some limitations. First, this study was conducted retrospectively at a single center and the patient sample was relatively small. Second, only hospitalized patients were included in this study. Therefore, the impact of vaccination on the community could not be evaluated. Last, we included two different COVID-19 vaccines which could cause heterogeneity. However, the mortality rates between vaccines were similar.

In conclusion, full dose vaccination significantly improved survival in hospitalized adult COVID-19 patients. Nevertheless, the booster vaccine especially in individuals with comorbidities should not be delayed since the survival expectation is low in patients with a high comorbidity index.

Conflict of interest: This research did not receive any specific grant. No funding was used. The authors declare that they have no competing interests.

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

ACKNOWLEDGMENTS

The authors acknowledge all the healthcare professionals who contribute to the care of our patients.

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