RESEARCH

PROGNOSIS OF GERIATRIC COVID-19 PATIENTS ADMITTED TO INTENSIVE CARE UNIT ACCORDING TO VACCINATION STATUS

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Abstract

Introduction: As of June 27, 2022, the COVID-19 pandemic has caused over 540 million infections and 6.3 million deaths. We aimed to investigate the effect of the vaccine on the clinical course of elderly patients hospitalized in the intensive care unit and to determine the prognosis of the patients according to their vaccination status.

Materials and Methods: The study included 157 patients over the age of 65. Patients were divided into two groups. The first group consisted of patients who were vaccinated with two doses of CoronaVac, and the second group consisted of patients who were not vaccinated. Demographic data of the patients, prehospital clinical frailty scales, Charlson Comorbidity Indexes, APACHE II scores, laboratory values, and patient prognoses were recorded.

Results: Of the 157 patients, 93 (59.2%) were female, and the median age was 76 years (65–99). 96 (61.1%) patients were vaccinated and 61 (38.9%) patients were unvaccinated. Patients were grouped as survivors (n=26) and deceased. We found that APACHE II, prehospital clinical frailty scales, and Charlson Comorbidity Indexes scores were higher in patients who died. There was a significant difference between blood lymphocyte and ferritin levels and survival. The 28-day survival rate was higher and intensive care unit overall survival time were longer in the vaccinated group.

Conclusions: We observed that the vaccinated patients had higher survival times and lower mortality rates than those who were not vaccinated. We think that it is important to vaccinate elderly patients and that additional doses may be needed.

Keywords: COVID-19; Aged; Critical Care; Vaccines.

INTRODUCTION

As of June 27, 2022, the COVID-19 pandemic had caused over 540 million infections and 6.3 million deaths (1). The severity of COVID-19 infection may be limited to mild symptoms but can also result in symptoms that require intensive care unit (ICU) admission. The progression of these symptoms can include hospitalization, respiratory failure, and organ failure, which may lead to serious clinical consequences or death (2). Prehospital data may be important markers of mortality and morbidity in elderly patients admitted to the ICU, and frail elderly may have greater difficulty adapting to various stressful situations such as acute illness and trauma (3,4). COVID-19 is more serious in elderly individuals than in younger individuals, especially those over 60 years of age with increased frailty and underlying chronic diseases. Studies have shown that elderly individuals have a higher risk of death, which increases with age (3,5). Weakening of the immune system caused by aging occurs with increased susceptibility to infectious diseases and cancer, and can also cause autoimmune disorders. These changes in the immune system result in immunosenescence. This effect on immunity generally causes a decrease in vaccine effectiveness in elderly individuals. However, COVID-19 vaccines are necessary to control the pandemic and reduce its life-threatening effects, especially in at-risk individuals (3,6,7).

In the literature, there are limited number of studies examining the clinical course of ICU patients over 65 years of age who were vaccinated with two doses of CoronaVac/Sinovac and those who were not vaccinated. In our study, we examined vaccinated and unvaccinated COVID-19 polymerase chain reaction (PCR)-positive patients, especially elderly individuals admitted to the ICU and at high risk of death. We aimed to investigate the effect of the vaccine on the clinical course of these patients and to determine patient prognosis between the two groups.

MATERIALS AND METHODS

Vaccination of the elderly

With the introduction of CoronaVac/Sinovac vaccines, vaccinations for priority groups in Turkey began on January 13, 2021 for healthcare workers and at-risk age groups. Vaccinations for individuals over the age of 65 started on February 12, 2021 (8).

Study design and data collection

Permission for the study was acquired from the ethics committee of Turgut Ozal University non-interventional clinical research (Decision number: 2021/101). This single-center retrospective study was carried out between January 7, 2021, and November 30, 2021, in the Level 3 COVID-19 ICUs of our hospital. The study included a total of 157 patients over the age of 65, who were classified as elderly according to the World Health Organization (WHO). Patients admitted to the ICU were separated into two groups. The first group consisted of patients who received a double dose of CoronaVac/Sinovac vaccine and had a minimum of 14 days since vaccination, and the second group consisted of patients who were not vaccinated. Patients under 65 years of age, those who received a non- CoronaVac/Sinovac vaccine, those who received a single dose of the CoronaVac/Sinovac vaccine, and those who used immunosuppressive drugs were excluded from the study.

Demographic data of the patients, prehospital clinical frailty scales (CFS), Charlson Comorbidity Indexes (CCI), lengths of stay in the intensive care unit (LOS), times from PCR positivity to ICU admission, comorbidities, APACHE II scores, ICU timing of intubation, laboratory values, and patient prognoses were recorded. The prehospital frailty statuses of the patients were evaluated according to CFS (4). Patients with a CFS score ≥ 5 were defined as frail. CFS scores were calculated based on the patients' medical records and interviews with the

patient and/or relatives. Patients were followed during their stay in the intensive care unit or until their death. Twenty-eight-day mortality was defined as death within 28 days of admission to the intensive care unit. Mortality data of the patients were gathered from the hospital's medical record system.

Statistical analysis

The data obtained from the hospital database were organized and entered into the SPSS 21.0 (Statistical Package for Social Sciences, IBM Corp) program for statistical analysis. The results were evaluated at the 95% confidence interval, with a significance level of $p < 0.05$. The homogeneity and distribution of the variables were evaluated using the Kolmogorov–Smirnov test. Percentage and frequency were used for categorical data. Continuous variables were presented as mean ± standard deviation or median (min–max). We compared the variables between vaccinated and non-vaccinated patients, survivors, and non-survivors. The independent samples t-test was used to analyze the parametric data of two independent groups, and the Mann–Whitney U test was used for non-parametric data. Categorical variables were compared using the chi-square test. Kaplan–Meier analysis was used to determine the patients' overall hospital stay and 28-day survival rates, and the longrank test was used to compare the survival differences between the groups. Cox regression analysis was used to evaluate univariate survival analysis and multivariate survival analysis.

RESULTS

A total of 157 patients were included in the study; of these, 93 (59.2%) were female. The median age of the patients was 76 years (range,65–99 years). Of these patients, 96 (61.1%) were vaccinated and 61 (38.9%) were unvaccinated. The time that had elapsed since the previous dose of CoronaVac ranged from four to eight months. Hypertension (58%), coronary artery disease (52.2%), chronic obstructive pulmonary disease (24.2%), diabetes mellitus (31.2%), and chronic kidney failure (8.3%) were the most common comorbidities. The mean (SD) duration of stay in the ICU was 13.21±9.22 days. Patients were categorized as survivors (n = 26) or deceased (n = 131). We found that age, sex, and LOS had no significant effects on mortality. Only three of the surviving patients were intubated. The ICU intubation timing was not significant in the groups according to vaccination status (p = 0.086).

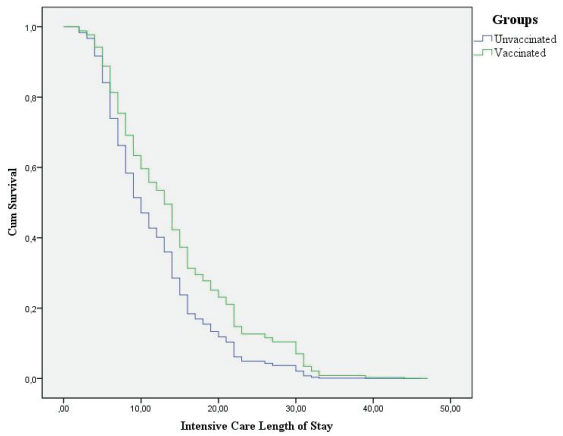
In addition, we found that APACHE II, CFS, and CCI scores were higher in patients who died (p <0.05). Blood lymphocyte levels were lower and ferritin levels were higher in patients who died (p= 0.005 and p = 0.036, respectively). A comparison of the main clinical features and laboratory findings of the two groups is presented in Tables 1 and 2, respectively.

In the analysis based on vaccination status, both groups showed similar characteristics (Tables 1 and 2). We found higher blood lymphocyte and lower ferritin levels in vaccinated patients (95% CI, p = 0.047, p = 0.014, respectively) (Table 2).

In this study, the 28-day mortality and overall mortality in the ICU were 75.2% and 83.4%, respectively (regardless of vaccination status). Multivariate Cox regression analysis was used to identify independent risk factors for mortality. The results of the Cox regression analysis for the effects of vaccination status, CFS score, CCI score, Apache II score, and ICU intubation timing on the survival times of patients are shown in Table 3. Vaccination status (95% CI:0.423–0.874, p = 0.007) and CCI score (95% CI:1.031–1.479, p = 0.022) were significant prognostic factors (Table 3). In addition, the vaccination status and intubation timing of patients in the ICU were significant prognostic factors (p = 0.040 and p <0.001, respectively) (Table 3 and Figure 1).

The overall mortality rate was 86.8% in the unvaccinated group and 81.2% in the vaccinated group.

Figure 1. Vaccination status and intubation timing



No statistical correlation was found between vaccination and mortality (p= 0.355) (Table 1). When the vaccination status of the patients in the ICU was evaluated in terms of 28-day mortality, 83% of the unvaccinated individuals died, while 69.8% of the vaccinated individuals died (95% CI, p =0.05) (Table 3). We used the Kaplan–Meier estimator to analyze the distribution of survival time based on vaccination status: the 28-day and ICU total survival times were statistically significant (according to the log-rank test, p = 0.010 and p = 0.08, respectively) (Figure 2A and 2B).

Table 1. Baseline characteristics of the patients.

		All patients (n = 157)	Survivors (n = 26)	Nonsurvivors (n = 131)	***P* value**	Vaccinated (n = 96)	Unvaccinated (n = 61)	***P* value**
Median age, years (min-max)		76 (65-99)	76(65-86)	76 (65-99)	0.613	76 (65-99)	77 (65-93)	0.494
Sex, n (%)	**Male**	64 (40.8)	10 (38.5)	54 (41.2)	0.794*	41 (42.7%)	23 (37.7%)	0.534*
	Female	93 (59.2)	16 (61.5)	77 (58.8)		55 (57.3%)	38 (62.3%)	
Comorbid disease, n (%)	**Hypertension**	91 (58)	17 (65.4)	74(56.5)	0.401*	56 (58.3%)	35 (57.4%)	0.906*
	COPD	38 (24.2)	4 (15.4)	34 (26)	0.250*	24 (25%)	14 (23%)	0.770*
	DM	49 (31.2)	7 (26.9)	42 (32.1)	0.606*	34 (35.4%)	15 (24.6%)	0.154*
	CRF	13 (8.3)	1 (3.8)	12 (9.2)	0.369*	10 (10.4%)	3 (4.9%)	0.223*
	CAD	82 (52.2)	11 (42.3)	71 (54.2)	0.268*	58 (60.4%)	24 (39.3%)	**0.010***
APACHE-II scores, (Me ± SD)		19.08±5.65	16.38±4.9	19.61±5.65	**0.010**	19.21±5.74	18,8±5.54	0.751
CFS score, (Me ± SD)		4.52 ±1.26	4 ±0.89	4,62 ±1.30	**0.028**	4.48±1.30	4.57±1.21	0.504
CCI, (Me ± SD)		4.83 ±1.43	4.23 ±1.21	4.95 ±1.45	**0.021**	4.95±1.42	4.63±1.44	0.206
CFS Groups, n (%)	**<5**	88 (56.1)	20 (76.9)	68 (51.9)	**0.019**			
	≥5	69 (43.9)	6 (23.1)	63 (48.1)				
ICU Intubation Time. (day), (Me ± SD)		6.53 ±7.51	1.33±0.57	6.65 ±7.55	**0.021**	7.63±8.85	4.90±4.48	0.086
Day of admission to intensive care. (day), (Me ± SD)		5.9 ±4.15	6.30±4.69	5.90 ±4.06	0.820			
Length of stay in the Intensive care unit. (day), (Me ± SD)		13.21 ±9.22	10.46±6.74	13.75±9.56	0.094	14.58±10.1	11.04±7.06	**0.036**
Groups (Vaccinated/ Unvaccinated), n (%/%)		96/61 (61.1/38.9)	18/8 (69.2/30.8)	78/53 (59.5/40.5)	0.355*			

Mann-Whitney U test, *Chi square test, ICU: intensive care unit; CRF: Chronic renal failure; CAD: coronary artery disease; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease;CCI: Charlson Comorbidity Index; APACHE-II: Acute physiology and chronic health evaluation II; CFS: Clinical frailty scale; Me: mean; SD: standard derivation

Table 2. Baseline laboratory findings of the patients.

	All patients (n = 157)	Survivors (n = 26)	Nonsurvivors (n = 131)	**P value**	Vaccinated (n = 96)	Unvaccinated (n = 61)	**P value**
Wbc (10^3/μL)	11.93 ±5.14	11.72 ±5.75	11.97 ±5.04	0.536	11.53±4.84	12.56±5.57	0.216
Lymph (10^3/μL)	0.74 ±0.46	1 ±0.56	0.68 ±0.42	**0.005**	0.81±0.51	0.63±0.36	**0.047**
Urea (mg/dL)	81.7 ±46.9	70 ±40.61	83.97 ±47.97	0.206	83.1±45.8	79.6±49.06	0.340
Crea (mg/dL)	1.36 ±1.12	1.17 ±0.74	1.40 ±1.18	0.374	1.47±1.28	1.19±0.79	**0.041**
AST (U/L)	52.37 ± 85.3	49.03±60.18	53.03±89.62	0.385	59.42±106	41.27±28.2	0.656
ALT (U/L)	43.01±84.9	43.07±51.15	43±90.31	0.944	49.31±106.9	33.09±22.4	0.480
LDH (U/L)	582.81±6.7	501.96±214.21	598.86±341.6	0.153	555.4±337.6	625.8±303.0	0.054
Ferritin	846±605.7	607.72±475.79	893.40±619.03	**0.036**	767.56±602.44	969.6±595.02	**0.014**
Procalcitonin	1.62 ±4.02	2.15±6.48	1.52 ±3.36	0.676	2.07±4.78	0.91±2.23	0.268
D-dimer	3.78±4.63	4.43 ±5.42	3.65 ±4.47	0.630	3.06±3.66	4.91±5.7	0.112
CRP (mg/dL)	9.93±6.7	8.93±6.80	10.13±6.69	0.290	10.87±7.4	8.45±5.06	0.057
Lactate (mmol/L)	2.92±1.91	2.37 ±0.87	3.03±2.04	0.135	2.89±1.75	2.97±2.16	0.860

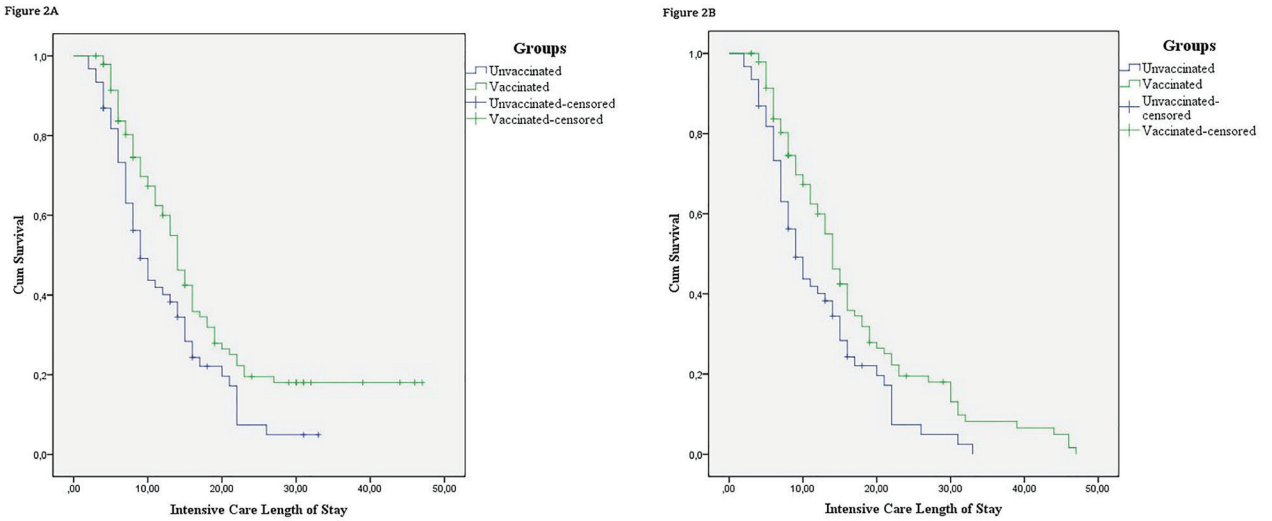
mean (standard deviation); Mann-Whitney U test; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Wbc: white blood cell; Lymph: lymphocytes; Crea: creatinine

Table 3. Multivariate Cox regression analysis of mortality and 28-day mortality analysis

Variables in the Equation	**B**	***P* Values**	**Exp(B)**	**95,0% CI for Exp(B)**	
				Lower Bound	**Upper Bound**
Vaccination status	-0.498	**0.007**	0.608	0.423	0.874
CFS score	-0.144	0.195	0.866	0.696	1.076
Charlson Comorbidity Index	0.211	**0.022**	1.235	1.031	1.479
Apache-II	-0.013	0.431	.987	0.955	1.020
Variables in the Equation					
Vaccination status	-0.376	**0.040**	0.686	0.479	0.983
Intubation Timing	-0.076	**0.000**	0.927	0.900	0.955
28-Day Mortality					
Mortality	**Groups**				**Total**
	Unvaccinated		**Vaccinated**		
Survivors (%)	10 (16.4)		29 (30.2)		39
Nonsurvivors (%)	51 (83.6)		67 (69.8)		118

CCI:Charlson Comorbidity Index; CFS: Clinical Frailty Scale; Apache-II: Acute physiology and chronic health evaluation II; 95% Confidence Interval; *P*=0.05

Figures 2A and 2B. 28-day survival analysis and analysis of overall survival



DISCUSSION

COVID-19 can cause serious disease, especially in frail elderly patients. The ongoing COVID-19 pandemic continues to place a serious burden on the healthcare system, particularly with the increased need for intensive care beds. Therefore, vaccination is particularly important for frail older adults. In our study, the effect of vaccination on individuals aged ≥ 65 years who were hospitalized in the ICU due to COVID-19 was evaluated. The results showed that being fully vaccinated (i.e., having received two doses of CoronaVac >14 days after the previous dose) did not have a significant effect on mortality in this age group based on the total length of ICU stay; however, it was significant on the 28-day mortality. Factors such as fragility, immunosenescence, comorbidities, and time elapsed since the previous vaccine dose are significant in this age group; thus, prolonged life expectancy due to vaccination is important (3,4,9,10). Our study showed a statistically significant difference between vaccinated and unvaccinated individuals in the 28-day survival analysis (p=0.010). In addition, lymphopenia and high CCI scores were associated with increased mortality (P =0.005 and P =0.021, respectively).

Previous studies on CoronaVac have found different efficacy rates in different age groups. In a study on CoronaVac conducted in Turkey that included participants between the ages of 18 and 59 years, vaccination provided 83.5% protection against symptomatic infection compared with placebo (11). A Chilean study reported 65.9% effectiveness for the prevention of COVID-19, 90.3% for the prevention of ICU admission, and 86.3% for the prevention of death (12).

In a study conducted on individuals aged over 75 years in Brazil, 83% of vaccinated individuals received the CoronaVac or Sinovac/Butantan vaccine, whereas 17% received the Oxford-AstraZeneca/Fiocruz vaccine. When unvaccinated elderly individuals were compared with elderly individuals who received two doses, mortality was more than 132 times greater in the unvaccinated group, and the rate of protection against death achieved in vaccinated individuals was 99.2% (13).

In another study, the efficacy of the vaccine against symptomatic COVID-19 at ≥ 14 days after the second dose was 59.0% in those aged 70–74 years (range:43.7%–70.2%), 56.2% in those aged 75–79

years (range:43.0%–66.3%), and 32.7% in those ≥80 years (range:17.0%– 45.5%). The effectiveness of the vaccine to prevent death was 83.9% in those aged 70–74 years (range:59.2%–93.7%), 78.0% in those aged 75–79 years (range:58.8%–88.3%), and 44.0% in individuals aged ≥ 80 years (range:20.3%–60.6%) (14).

In other vaccine types, one study provided early real-world evidence of the efficacy of the Pfizer/BioNTech mRNA and Oxford/AstraZeneca ChAdOx1-S vaccines to prevent hospitalization and death in elderly people in England. The results showed that a single dose of Pfizer/BioNTech vaccine prevented symptomatic disease in adults aged ≥ 70 years and that the vaccines were 60–70% effective, while two doses of the vaccine were approximately 85–90% effective. Those who were vaccinated and had symptoms had a 44% lower risk of hospital admission than unvaccinated individuals (15).

While vaccination efforts are ongoing worldwide, it is important to note that over time. there is a decline in the immunity conferred by two doses of the vaccine, and a third dose is likely necessary (16). A greater number of neutralizing antibodies are obtained with a third vaccination (17). In addition, a study reported that neutralizing antibody titers declined to near or below the lower limit of seropositivity 6 months after the second dose, and the efficacy of vaccination is uncertain, as the threshold of protection of antibody titers against COVID-19 is unknown (10,18).

The antibody titers of the vaccinated patients in our study were unknown. However, the time since the previous dose ranged from four to eight months. When we compared vaccinated patients with unvaccinated patients, we found that the mortality rate was higher in the unvaccinated group (83.6%). The 28-day mortality rate of all patients was 75.2%. In a previous study conducted on COVID-19 patients in the ICU, the death rate was 40.8%; however, the median age in this study was 55 years (19); in our study, the median age was 76 years. In addition, in two previous studies on critically ill COVID-19 patients, the mean age was 59.7 years, and the 28-day mortality rate was 61.5% in one study, whereas in the other, the average age was 55 years, 15 of 29 patients died, and the 28-day mortality rate was 51.7% (20,21). We believe that lower vaccine effectiveness with advanced age and comorbidities increases the risk of death.

Previous studies have reported that lymphopenia observed in patients may be associated with disease severity and mortality in critically ill COVID-19 patients (21). Similarly, we found lower lymphocyte levels in patients who did not survive. In addition, when we analyzed the patients according to their vaccination status, unvaccinated patients had lower lymphocyte counts ($p = 0.04$).

Comorbidity and frailty, which are among the factors that play important roles in mortality, may result in an increased mortality rate in elderly patients. The fragility of elderly patients with difficulties adapting to stressful situations, such as acute illness and trauma, can be determined by performing a CFS assessment. A high CFS score (>5) in ICU patients is an important predictor of mortality (4,22). In addition, the Charlson comorbidity index (CCI), which was developed in 1987 and is used to determine the risk of death due to comorbid diseases, has been used as an indicator of long-term survival and prognosis in many studies (23,24). The CCI score may be useful in determining the prognosis of patients hospitalized for COVID-19: a systematic review and meta-analysis found that each one-point increase in the CCI score of patients with COVID-19 increased mortality by 16% (25). In our study, we found that mortality increased with high CFS and CCI scores in all the patients. Multivariate Cox regression analysis performed according to vaccination status revealed a significant relationship between CCI scores and mortality ($p = 0.022$).

LIMITATIONS

This study is limited by some factors. First, it was conducted in a single center and included only patients hospitalized in the ICU. Additionally, only patients vaccinated with a double dose of CoronaVac/Sinovac were included. Next, the antibody titers of the patients at admission were unknown. Finally, patients in critical condition followed up in ICU s have a high mortality rate regardless of their vaccination status.

CONCLUSION

In our study, although the antibody titers in individuals vaccinated with two doses of CoronaVac/Sinovac were not known, vaccination showed prolonged survival in patients and the 28-day mortality rate was lower in vaccinated patients than in those who were not vaccinated. We believe that it is important to vaccinate elderly patients; further, since immunity conferred by vaccination may decline over time, mortality rates decrease with the administration of additional doses.

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Conflict of interest

The authors have no conflicts of interest to declare connection with this article.

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