



Impact of Vaccines on Mortality in Patients Treated in The Intensive Care Unit Due To COVID-19: A Multicenter Study

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Abstract

Introduction: The importance of vaccines is increasing day by day because the COVID-19 pandemic has been going on for about two years and there is no effective antiviral treatment. The purpose of this study was to compare the impact of vaccination status on the mortality of patients monitored in the intensive care unit with the diagnosis of COVID-19.

Methods: Three hundred and forty-four patients treated in intensive care due to COVID-19 in three hospitals in Gaziantep were included in the study. Demographic characteristics and pre-COVID-19 vaccination status of all patients were recorded, and the diagnosis of COVID-19 was made with nasopharyngeal polymerase chain reaction (PCR) test and Thorax Computed Tomography (CT).

Results: Of the patients, 172 (50%) were male, 172 (50%) were female, 152 (44%) were unvaccinated and 192 (55%) were vaccinated. The number of male patients (n=106) (55.2%) in the vaccinated group was significantly higher than female patients (n=86) (44.8%) (p<0.05). Although the vaccination rate was higher in patients over 65 years of age, intubation status, mortality rate, number of hospitalisation days, urea and creatinine values were significantly higher and haemoglobin and white blood cell values were lower in younger and middle age groups (p<0.05). The age and intubation rate of patients who died due to Covid 19 were significantly higher than those who were discharged (p<0.001). The vaccination rate of young patients (28.3%) was significantly lower than that of middle-aged (47.3%) and over-65 (65.9%) patients (p<0.05). Among all vaccinated individuals, death was encountered in 57 (76.0%) of CoronaVac vaccinated and 18 (24.0%) of BioNTech vaccinated patients; the difference was statistically higher (p<0.05). The mortality rate of vaccinated patients over 65 years old was 61 (60.4%), while the mortality rate of unvaccinated patients was 40 (39.6%) and the difference was not statistically significant (p>0.05).

Conclusion: The majority of the patients monitored in the intensive care unit with the diagnosis of COVID-19 were vaccinated, and over the age of 65, and the mortality was high. However, vaccination, hospitalization in the intensive care unit, and mortality rates were low in the younger age group. In patients over 65 years of age, the mortality-reducing effect of the vaccine is low. Advanced age and comorbidity reduce the efficacy of the vaccine. In all patients, the BioNTech vaccine reduces the death rate more than the CoronaVac vaccine.

Key words: Covid-19 vaccines, Intensive Care Unit, Efficacy, Mortality

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COVID-19 Nedeniyle Yoğun Bakım Ünitesinde Tedavi Eden Hastalarda Aşıların Mortaliteye Etkisi: Çok merkezli bir çalışma

Öz

Giriş: COVID-19 pandemisinin yaklaşık iki yıldır devam etmesi ve etkili bir antiviral tedavinin bulunmaması nedeniyle aşıların önemi her geçen gün artmaktadır. Bu çalışmanın amacı COVID-19 tanısı ile yoğun bakım ünitesinde izlenen hastaların aşılanma durumunun mortalite üzerine etkisini karşılaştırmaktır.

Yöntemler: Gaziantep'teki üç hastanede COVID-19 nedeniyle yoğun bakımda tedavi gören üç yüz kırk dört hasta çalışmaya dahil edildi. Tüm hastaların demografik özellikleri ve COVID-19 öncesi aşılanma durumları kaydedildi ve COVID-19 tanısı nazofarengeal polimeraz zincir reaksiyonu (PCR) testi ve Toraks Bilgisayarlı Tomografi (BT) ile konuldu.

Bulgular: Hastaların 172'si (%50) erkek, 172'si (%50) kadın, 152'si (%44) aşısız ve 192'si (%55) aşıydı. Aşılanan gruptaki erkek hasta sayısı (n=106) (%55,2) kadın hastalara (n=86) (%44,8) göre anlamlı derecede yüksekti (p<0.05). Aşılanma oranı 65 yaş üstü hastalarda daha yüksek olmasına rağmen, entübasyon durumu, mortalite oranı, hastanede yatış gün sayısı, üre ve kreatinin değerleri genç ve orta yaş gruplarında anlamlı olarak daha yüksek, hemoglobin ve beyaz kan hücreleri değerleri ise daha düşüktü (p<0,05). Covid 19 nedeniyle kaybedilen hastaların yaşı ve entübasyon oranı taburcu edilenlere göre anlamlı olarak daha yüksekti (p<0.001). Genç hastaların aşılanma oranı (%28,3) orta yaşlı (%47,3) ve 65 yaş üstü (%65,9) hastalarından anlamlı derecede düşüktü (p<0.05). Aşılanan tüm bireyler arasında CoronaVac ile aşılananların 57'sinde (%76,0) ve BioNTech ile aşılananların 18'inde (%24,0) ölümlerle karşılaşılmıştır; aradaki fark istatistiksel olarak daha yüksektir (p<0,05). Aşılanmış 65 yaş üstü hastaların ölüm oranı 61 (%60,4) iken aşılanmamış hastaların ölüm oranı 40 (%39,6) idi ve aradaki fark istatistiksel olarak anlamlı değildi (p>0.05).

Sonuç: COVID-19 tanısı ile yoğun bakım ünitesinde izlenen hastaların çoğunluğu aşısız ve 65 yaş üzerindeki ve mortalite yüksekti. Ancak genç yaş grubunda aşılanma, yoğun bakım ünitesinde yatış ve mortalite oranları düşüktü. 65 yaş üstü hastalarda aşının mortaliteyi azaltıcı etkisi düşüktür. İleri yaş ve komorbidite aşının etkinliğini azaltmaktadır. Tüm hastalarda BioNTech aşısı ölüm oranını CoronaVac aşısına göre daha fazla azaltmaktadır.

Anahtar kelimeler: Covid-19 aşıları, Yoğun Bakım Ünitesi, Etkinlik, Mortalite.

INTRODUCTION

The COVID-19 pandemic has been affecting the entire world for almost two years. Due to the lack of effective antiviral treatment, the importance of vaccines is increasing day by day. The aforementioned global epidemic continues to adversely affect public health and the overall health system. Vaccines are essential in the fight against the spread of infectious illnesses. In addition to preventing infection, COVID-19 vaccines have a positive impact on the rate of hospitalization and mortality¹.

Today, vaccination with COVID-19 vaccines continues rapidly all around the world; scientists do not have enough information about the efficacy and safety of COVID-19 vaccines. There are not enough systematic reviews and meta-analyses published. Therefore, the efficacy of vaccines is still among the issues that are point of interest and discussed.

In our country, the Sinovac/CoronoVac Vaccine started to be administered as of 13.01.2021, and the Pfizer/BioNTech vaccine as of April 2, 2021,

with the approval of the Turkish Medicines Medical Devices Agency (TITCK) scientific commission^{2,3}.

During the period we conducted this study, 108,998,490 doses of vaccine were administered as of September 28, 2021, within the scope of COVID-19 vaccination in Turkey, and 53,720,107 people received one dose of vaccine, 44,208,754 people received 2 doses, and 10,280,158 people received 3 doses⁴.

Vaccination studies are continuing rapidly all over the world as well as in our country, but hospitalizations in wards and intensive care units still continue due to COVID-19 infection. It is noted that the vast majority of patients lost due to COVID-19 are unvaccinated or incompletely vaccinated⁵. The vaccination process over the age of 13 is still ongoing in Turkey. Despite this, hospitalizations in the intensive care units and patient losses due to COVID-19 still continue.

The purpose of this study was to look into the association between the vaccination status of COVID-19 patients hospitalized in the intensive

care units of three hospitals in the province of Gaziantep and their clinical outcomes.

METHODS

Our research is a retrospective, descriptive observational study. The information utilized within the context of this study was collected anonymously by the hospital management, without comprising any personal data, through the electronic patient registration system.

Patients with a diagnosis of COVID-19 who were followed up in the adult tertiary care units of three hospitals between August 1, 2021 and December 31, 2021 were included in the study. While one of the hospitals where the study was conducted was a university hospital, the other two were secondary health care institutions. The diagnosis of COVID-19 was made by nasopharyngeal swab polymerase chain reaction (PCR) test and/or a chest computed tomography (CT) scan.

Demographic characteristics of all patients, age, gender, comorbidity, intubation status, mortality, laboratory values, and nasopharyngeal swab Polymerase chain reaction (PCR) results were evaluated. PCR and variant test results were analyzed. Thoracic CT scan results were evaluated according to the CORADS classification⁶.

At the time the SARS-CoV-2 test was positive, vaccination status was defined as follows:

1. Unvaccinated: Patients who have not received the COVID-19 vaccine.
2. Vaccinated: Patients who have received two doses of CoronaVac or two doses of BioNTech vaccine.

Those vaccinated with only one dose of vaccine was included in the unvaccinated group. Patients under the age of 18, those with a negative PCR, no available vaccination data, and inward patients were excluded from the study. Comparisons were made between vaccinated and unvaccinated patients, by age groups, surviving and deceased,

CoronaVac-BioNTech vaccinated patients. Patients were classified according to age groups: 18-45 young patients, 45-65 middle-aged, and 65-plus elderly patients.

Numerical data for descriptive statistics were presented as means and standard deviations, and categorical data were presented as percentages and numbers during the assessment of the research's statistics. Histogram visualizations were used to examine how numerical data was distributed. Student t test, Mann-Whitney U test and Kruskal-Wallis test were used for analysis.

The significance value was accepted as $p < 0.05$. The statistical analysis was conducted using the SPSS 23.0 package application.

This study was approved by the Republic of Turkey Ministry of Health COVID-19 Scientific Research Evaluation Commission on 03.10.2021 and the ethics committee approval was given by Gaziantep University Clinical Research Ethics Committee with protocol number 2022/50 dated 07.02.2022.

RESULTS

The study included 344 patients who were treated in intensive care due to COVID-19 in three hospitals in Gaziantep province. One hundred and seventy-two (50%) of the patients were male, 172 (50%) were female, 152 (44%) of the patients were unvaccinated and 192 (55%) were vaccinated. The number of male patients ($n=106$) (55.2%) in the vaccinated group was significantly higher than female patients ($n=86$) (44.8%) ($p < 0.05$) (Table-1).

There were 205 patients (59.6%) over the age of 65; 93 patients (27%) in the middle age group, and 46 patients (13.4%) in the younger age group. Vaccination rate, intubation status, mortality rate, number of hospitalization days, and urea and creatinine values were significantly higher in patients over 65 years of age compared to the young and middle age groups, while hemoglobin and white blood cell values were lower ($p < 0.05$) (Table-2).

Table I: Comparison of Vaccinated and Unvaccinated Patients in the Intensive Care Unit

Case	Vaccinated (n=192)	Unvaccinated (n=152)	P
Gender			
Male	106(55.2%)	66(43.4%)	0,03
Female	86 (44.8%)	86 (56.6%)	
Comorbidity	150(78%)	100(65%)	0,013
Intubation Status			
Yes	60(31.3%)	55(36.2%)	0,338
No	132 (68.8%)	97 (63.8%)	
Mortality			
Discharged	117(60.8%)	86(56.6%)	0,414
Deceased	75 (39.1%)	66 (43.4%)	
Age	69.31±14.17	61.29±18.06	<0.001
Number of Hospitalization Days	9.2±6.68	10.32±8.7	0,179
WBC (10 ³ /UI)	9.86±5.78	10.03±6.13	0,800
HGB (g/dL)	12.21±2.18	12.59±2.3	0,117
D-dimer (ng/ml)	4719.92±10094.84	4833.78±9608.21	0,916
Creatinine (mg/dl)	1.18±0.98	1.23±1.18	0,677
Lymphocyte count (10 ³ /UI)	0.94±0.78	0.91±0.59	0,743
Urea (mg/dl)	61.78±39.66	65.12±49.64	0,488
Platelets (10 ³ /uL)	218.33±124.29	238.28±114.55	0,127
CRP (C-Reactive Protein) mg/dl	120.26±89.28	127.41±91.14	0,465
ALT (alanine aminotransferase)U/L	53.41±110.73	48.13±83.37	0,626
AST (Aspartate aminotransferase)U/L	61.19±106.99	61.07±125.12	0,992
GGT (gamma-glutamyl transferase) U/L	64.86±86.22	67.54±68.05	0,754
Ferritin (ug/L)	502.75±520.38	719.7±1422.22	0,051

Table II: Comparison of Patients by Age Groups in the Intensive Care Unit

Patients by Age Groups	Age ≤ 44 (n = 46)	Age = 44 - 64 (n = 93)	Age ≥ 65 (n =205)	P
Gender				
Male	28(60.9%)	50(53.8%)	94(45.9%)	0,128
Female	18 (39.1%)	43 (46.2%)	111 (54.1%)	
Intubation Status				
Yes	12(26.1%)	22(23.7%)	81(39.5%)	0,014
No	34 (73.9%)	71 (%76.3)	124 (60.5%)	
Mortality				
Discharged	36(78.3%)	63(67.7%)	104(50.7%)	<0.001
Deceased	10 (21.7%)	30 (32.3%)	101 (49.3%)	
Vaccination Status				
Vaccinated	13(28.3%)	44(47.3%)	135(65.9%)	0,014
Unvaccinated	33 (71.7%)	49 (57.7%)	70 (34.1%)	
Age	36.15±6.01	55.39±5.03	77.12±7.77	<0.001
Number of Hospitalization Days	6.65±5.18	11.22±8.77	9.68±7.39	0,004
WBC (10 ³ /UI)	9.6±5.37	11.28±6.79	9.4±5.55	0,036
HGB (g /dL)	13.04±2	12.82±2.17	12.03±2.27	0,002
D-dimer (ng/ml)	5077.7±10830.48	3643.04±8011.33	5212.6±10398.74	0,435
Creatinine (mg/dl)	0.83±0.37	1.16±1.4	1.31±0.99	0,018
Lymphocyte count (10 ³ /UI)	0.94±0.53	1.04±0.59	0.87±0.77	0,149
Urea (mg/dl)	39.51±28.74	53.13±39.37	73.18±46.34	<0.001
Platelets (10 ³ /uL)	232.52±93.55	242.63±112.35	218.91±128.58	0,274
CRP (C-Reactive Protein) mg/dl	133.47±101.77	120.06±89.39	122.69±87.84	0,700
ALT (alanine aminotransferase)U/L	67.93±102.36	58.08±100.39	44.09±98.27	0,249
AST (Aspartate aminotransferase)U/L	60.89±79.74	65.01±114.15	59.43±122.54	0,928
GGT (gamma-glutamyl transferase) U/L	69.98±49.35	71.22±93.06	62.81±76.95	0,651
Ferritin (ug/L)	533.3±832.58	716.12±1713.51	559.95±533.4	0,429

The vaccination rate of young patients (28.3%) was significantly lower than that of middle-aged (47.3%) and over-65 (65.9%) patients ($p < 0.05$). Mortality rate was 49.3% in patients over 65 years of age, 32.3% in middle age, and 21.7% in young age, and it was inversely correlated with the vaccination rate. In a further evaluation of those over 65 years of age, it was found that 71.2% of the discharged patients were vaccinated, 28.8% were unvaccinated, 60.4% of the patients who died were vaccinated and 39.6% were unvaccinated (Table-3).

Table III: Vaccination Status Evaluation of Patients Over 65 Years of Age

Patient years of age	Vaccinated	Unvaccinated	P
Discharged	74 (71.2%)	30 (28.8%)	0.104
Deceased	61 (60.4%)	40 (39.6%)	

Patients who died as a result of Covid 19 related complications had significantly higher median age and greater intubation rates than those who were discharged ($p < 0.001$). In the comparison of the surviving and deceased patients, it was found that 93% of the patients who died were intubated. Age was shown to be the most significant factor affecting mortality (Table 4) and the rate of admission to the critical care unit was highest in the patient group over 65 years old ($n = 205$).

Table IV: Comparison of Surviving and Deceased Patients in the Intensive Care Unit

Case	Discharged (n = 203)	Deceased (n = 141)	P
Gender			0,584
Male	99(57.6%)	73(42.4%)	
Female	104 (60.5%)	68 (39.5%)	
Intubation Status			<0.001
Yes	8(7%)	107(93%)	
No	195 (85.2%)	34 (14.8%)	
Age	61.9±16.75	71.34±14.39	<0.001
Number of Hospitalization Days	8.72±6.33	11.09±9.07	0,179
WBC (10^3 /UI)	9.71±5.57	10.26±6.42	0,800
HGB (g/dL)	12.5±2.22	12.2±2.26	0,117
D-dimer (ng/ml)	4155.78±8959.43	5654.87±11020.52	0,916
Creatinine (mg/dl)	1.1±1.05	1.36±1.08	0,677
Lymphocyte count (10^3 /UI)	0.95±0.58	0.89±0.85	0,743
Urea (mg/dl)	55.06±37.06	75.06±50.91	0,488
Platelets (10^3 /uL)	239.19±106.25	209.8±136.63	0,127
CRP (C-Reactive Protein) mg/dl	106.65±85.59	147.56±91.1	0,465
ALT (alanine aminotransferase)U/L	47±87.53	57.01±114.76	0,626
AST (Aspartate aminotransferase)U/L	48.62±79.7	79.16±150.93	0,992
GGT (gamma-glutamyl transferase) U/L	63.62±81.94	69.53±73.7	0,754
Ferritin (ug/L)	446.73±407.35	817.27±1502.86	0,051

When the relationship between patient outcomes according to vaccine type and doses was analysed, the mortality rate was 43.4% in patients who were not vaccinated, 63.6% in those who received 1 dose of Sinovac vaccine, and 38.3 % in those who received 2 doses of Sinovac vaccine, 77.8% in those who received 3

dose of Sinovac vaccine, 26.7% of those who received 1 dose of Biontech vaccine, 27.3% of those who received 2 doses of Biontech vaccine, and 23.5% of those who received 2 doses of Sinovac + 1 dose of Biontech vaccine. The relationship between vaccine dose and results was found to be significant ($p < 0.05$) (Table 5).

These results show that Biontech vaccine is more effective than Sinovac.

Comparison of CoronaVac and BioNTech vaccinated patients revealed that 56.4% of the discharged patients had CoronaVac, 43.6% had BioNTech; 76.0% of the patients who died had CoronaVac and 24.0% had BioNTech ($p < 0.05$). The mortality rate of vaccinated patients over 65 years of age was 61 (60.4%), while the mortality rate of those who were not vaccinated was 40 (39.6%), and the difference was not statistically significant ($p > 0.05$) (Table 6). CORADS-5 was the most frequently involvement observed radiologically. The most common variant in these patients was delta variants, (n=331, 96.2%).

Table V: Patient Outcomes by Vaccine Type and Dose

		Result		Total
		Discharged	Ex	
No Vaccine	n	86	66	152
	%	56,6	43,4	100,0
1 sinovac	n	4	7	11
	%	36,4	63,6	100,0
2 sinovac	n	58	36	94
	%	61,7	38,3	100,0
3 sinovac	n	4	14	18
	%	22,2	77,8	100,0
1 Biontech	n	22	8	30
	%	73,3	26,7	100,0
2 Biontech	n	16	6	22
	%	72,7	27,3	100,0
2 Sinovac+1Biontech	n	13	4	17
	%	76,5	23,5	100,0
Total	n	203	141	344
	%	59,0	41,0	100,0

Table VI: Comparison of CoronaVac and BioNTech Vaccines

	CoronaVac	BioNTech	P
Discharged	66 (56.4%)	51 (43.6%)	<0.05
Deceased	57 (76.0%)	18 (24.0%)	

DISCUSSION

With the discovery of vaccines during the Covid-19 pandemic, vaccination rates increased rapidly all over the world, while vaccination

rates of young age groups remained low in many countries¹⁴.

The rate of immunization in our study was also low for the younger age group. However, young patients still did not experience high rates of intensive care unit hospitalization or lengthy stays in the ICU. Furthermore, mortality rates were low in this group. In a study investigating the efficacy of vaccines from Norway, similar to ours, it was found that the vaccination rate of the younger age group was low, as well as the hospitalization and mortality rates⁷.

In our study, we observed no significant difference between the vaccinated and unvaccinated groups regarding length of stay in critical care units or intubation rates. However, the vaccination rate in the male patients was significantly higher than that of the females. Similar to ours, Sevinç et al.'s study also showed no differences between the coronavac-vaccinated and non-vaccinated groups in terms of the length of critical care and hospital stays. ICU and hospital mortality rates were similar between the groups. The CoronaVac vaccine was found to have no effect on survival from COVID-19. Numerous studies conducted during the COVID-19 epidemic's delta phase reported a gradual decline in the vaccine's ability to protect against infection⁸.

In our study, the intensive care mortality rates were similar in the vaccinated and unvaccinated groups. It was concluded that both coronavac and BioNTech vaccines had no effect on survival. Similarly, in another study, no difference was observed in the length of stay in the intensive care unit or the risk of in-hospital death between vaccinated and unvaccinated patients⁹.

In this study, it was found that the vaccination rate for those over 65 years of age was high, and admission to the intensive care unit and the mortality rates were also high. A similar study found that the vaccine's efficacy in preventing

hospitalization was lower in the elderly group, indicating that factors other than vaccination, such as male gender, older age, and risk factors such as diabetes, obesity, immune suppression and kidney failure possibly affects patient outcomes. Evidence also points to an increase in mortality risk and ICU admission likelihood with extended hospitalization in the ICU¹⁰.

In our study, the vaccination rate, intubation status, mortality, and hospitalization days of patients over 65 years of age were found to be higher than those of the young and middle-aged groups. Therefore, in our study, it was concluded that advanced age and comorbidity were among the factors that reduced the efficacy of the vaccine, and the efficacy of the vaccines against the delta variant also decreased.

In a similar study by Lim et al, aging, geriatric syndromes, underlying chronic conditions, and multiple morbidities were recognized as the main predictors for adverse outcomes in older adults with a variety of clinical conditions, and COVID-19 was no exception¹¹. In another study by Niu et al., the adverse results of the geriatric syndromes on disease severity and mortality in elderly patients were among the factors that negatively affect the efficacy of vaccines and outcome of the COVID-19 infection¹².

In a research including 142 patients from 21 different regions of United States who received an mRNA vaccination, vaccinated patients had also lower disease severity, ICU length of stay, and mortality rates¹³.

In contrast, another study found no significant difference in ICU admission, mechanical ventilation, or mortality rates between the two groups when 129 patients were compared with those who were fully vaccinated with Comirnaty, Spikevax, or Janssen and those who were not. Similar results were found in our study. We believe further prospective trials are required to assess how factors such vaccine

type, amount of booster shots, and dose intervals influence disease outcomes¹⁴.

In their study, Sevinç et al. demonstrated that the SpO₂ and PaO₂/FiO₂ ratios were lower in the vaccinated group, indicating poor clinical respiration. This may be due to various reasons such as vaccine efficacy over 65 years of age, efficacy on different variants, and immunogenic response induced by a vaccine. The comparison between the CoronaVac and BioNTech vaccines revealed that the mortality rate in patients who were vaccinated with CoronaVac was significantly higher than the BioNTech vaccine. In a systematic review and network meta-analysis comparing the clinical efficacy by Victoria et al., the BioNTech vaccine was found to have the highest efficacy of all vaccines in preventing symptomatic disease, preventing severe disease, and preventing COVID-19 infection in patients over 60 years of age. It was reported that CoronaVac had no effect on the prevention of severe disease and the development of symptomatic disease in the elderly¹⁵. In our study, the mortality rate of the patients who had the BioNTech vaccine was found to be lower than the CoronaVac vaccine.

The COVID-19 vaccination effort raises a lot of challenges, both for this particular pandemic and for potential future pandemics. In the 16 months after the first vaccine trials, 2.8 billion doses of the COVID-19 vaccine have been administered, rendering it an outstanding medical achievement. Whether this feat can be repeated in upcoming pandemics is a crucial concern¹⁶.

Despite the extensive encouragement of vaccination by many nations, the inherent characteristics of the immune system remain to be fully understood, meaning that many populations may still be vulnerable to spread of similar infection^{17,18}.

As a result, the discovery and application of vaccines in the COVID-19 pandemic, which we

have been experiencing for 2 years, has revolutionized the protection against the disease all over the world, but the amount of efficacy of the vaccines continues to be much-debated.

Ethics Committee Approval: This study was approved by the Republic of Turkey Ministry of Health COVID-19 Scientific Research Evaluation Commission on 03.10.2021 and the ethics committee approval was given by Gaziantep University Clinical Research Ethics Committee with protocol number 2022/50 dated 07.02.2022.

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