



# Admission to Intensive Care Unit, Intubation and Pneumonia Development Status in Patients with COVID-19 Diagnosis According to Vaccination Status: The İstanbul Sample

## COVID-19 İnfeksiyonu Tanısı Alanların Aşılama Durumuna Göre Yoğun Bakıma Yatış, Entübasyon ve Pnömoni Gelişme Durumları: İstanbul Örneği

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### ABSTRACT

**Introduction:** The COVID-19 pandemic, which has been a global threat for more than two years, continues to impose a heavy burden on health services with its discovered and yet undiscovered various features, despite the measures to prevent, control, and avoid the spread of the disease. This study aimed to evaluate the clinical course, pneumonia development status, intubation status, and hospitalization based on the demographic characteristics and vaccination status of the COVID-19 cases who underwent SARS-CoV-2 variant analysis in İstanbul.

**Materials and Methods:** The study included 12.709 cases over the age of 18 in İstanbul, for whom variant analysis was performed between 1 and 15 September 2021.

**Results:** Of the cases, 4296 (33.8%) were fully vaccinated, 2082 (16.4%) were partially vaccinated, 1544 (12.1%) were unvaccinated (at least one dose of vaccination and less than 14 days past the last vaccination date), while 4787 (37.7%) did not get any vaccine for COVID-19. Of the 12.709 cases examined, 176 (2.4%) were admitted to the intensive care unit, 108 (1.5%) were intubated, 292 (3.9%) developed pneumonia, and 600 (4.7%) were followed up in the hospital. Delta variant was detected in 10.862 (85.5%) cases. In the logistic regression model created with variables that may affect intensive care unit admission, intubation, pneumonia development, and hospital follow-up, it was found that intensive care unit admission was 1.90 times higher for males than females, 1.09 times for all ages, and 1.85, 2.01, and 6.51 times higher for partially vaccinated, unvaccinated, and never vaccinated patients compared to fully vaccinated patients, respectively. Intubation was 1.66 times more common in males than in females, 1.09 times in all ages, and 1.99, 2.09, and 6.06 times higher in partially vaccinated, unvaccinated, and never vaccinated patients compared to fully vaccinated patients, respectively. The risk of pneumonia development was 1.07 times higher for all ages and 1.70, 2.15, and 4.80 times higher for partially vaccinated, unvaccinated, and never vaccinated compared to fully vaccinated, respectively. The risk of being followed in the hospital instead of the home was 1.37 times more common in men than in women, 1.09 times in all ages, and 2.14, 2.61, and 6.23 times higher in partially vaccinated, unvaccinated, and never vaccinated patients compared to fully vaccinated, respectively.

**Conclusion:** Fully vaccinated individuals have the least risk for admission to the intensive care unit, intubation, pneumonia, and hospitalization; however, the risk is increased in those who are partially vaccinated, unvaccinated, and never vaccinated. In conclusion, individuals protected by vaccines have a milder disease course for different variants, even if they have COVID-19 infection.

**Key Words:** SARS-CoV-2; Variant virus; Biontech vaccine; Coronavac vaccine

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## ÖZ

**COVID-19 İnfeksiyonu Tanısı Alanların Aşılama Durumuna Göre Yoğun Bakıma Yatış, Entübasyon ve Pnömoni Gelişme Durumları: İstanbul Örneği**Hatice İKİŞİK<sup>1</sup>, Mehmet Akif SEZEROL<sup>2</sup>, Yusuf TAŞÇI<sup>2</sup>, Çağrı Emin ŞAHİN<sup>3</sup>, Işıl MARAL<sup>1</sup><sup>1</sup> İstanbul Medeniyet Üniversitesi Tıp Fakültesi, Halk Sağlığı Anabilim Dalı, İstanbul, Türkiye<sup>2</sup> Üsküdar İl Sağlık Müdürlüğü, İstanbul, Türkiye<sup>3</sup> Türkiye Halk Sağlığı Genel Müdürlüğü, Aşı ile Önlenebilir Hastalıklar Bölümü, Ankara, Türkiye<sup>4</sup> İstanbul Medipol Üniversitesi Sağlık Bilimleri Enstitüsü, Epidemiyoloji Anabilim Dalı, İstanbul, Türkiye

**Giriş:** İki yılı aşkın bir süredir küresel bir tehdit olmaya devam eden COVID-19 salgını, hastalığın yayılımını önlemeye, kontrol altında tutmaya ve korunmaya yönelik önlemlere rağmen keşfedilen yönleri ve halen bilinmeyen pek çok yönüyle sağlık hizmetlerine ağır bir yük getirmeye devam etmektedir. İstanbul'da COVID-19 tanısı alıp SARS-CoV-2 varyant analizi yapılan vakalarının demografik özellikleri ve aşılama durumlarına göre klinik seyir, pnömoni gelişme durumu, entübasyon uygulanma durumları ve hastaneye yatışlarını değerlendirmek amaçlanmıştır.

**Materyal ve Metod:** 1-15 Eylül 2021 tarihleri arasında Halk Sağlığı Yönetim Sistemi'nden İstanbul'da varyant analizi yapılmış olan 18 yaş üstü 12.709 vaka çalışmaya dahil edilmiştir.

**Bulgular:** Vakaların 4296'sı (%33.8) tam aşı, 2082'si (%16.4) kısmi aşı, 1544'ü (%12.1) aşısız (en az bir doz aşı ve son aşı tarihinden 14 günden az süre geçmiş) ve 4787'si ise (%37.7) hiçbir COVID-19 aşısı olmayanlardır. İncelenen 12.709 vakanın 176'sı (%2.4) yoğun bakıma yatmış, 108'i (%1.5) entübe edilmiş, 292'sinde (%3.9) pnömoni gelişmiş ve 600'ü (%4.7) hastanede takip edilmiştir. Vakaların 10.862'sinde (%85.5) Delta varyantı saptanmıştır. Vakaların yoğun bakıma yatış, entübasyon, pnömoni gelişme ve hastanede takip durumlarını etkileyebilecek değişkenlerle oluşturulan lojistik regresyon modelinde yoğun bakıma yatış; erkeklerde kadınlara göre 1.90 kat, her yaş için 1.09 kat ve tam aşıllara göre kısmi aşı, aşısız ve hiç aşısızda sırasıyla 1.85, 2.01 ve 6.51 kat daha fazladır. Entübe olmak; erkeklerde kadınlara göre 1.66 kat, her yaş için 1.09 kat ve tam aşıllara göre kısmi aşı, aşısız ve hiç aşısızda sırasıyla 1.99, 2.09 ve 6.06 kat daha fazladır. Pnömoni gelişme riski; her yaş için 1.07 kat ve tam aşıllara göre kısmi aşı, aşısız ve hiç aşısızda sırasıyla 1.70, 2.15 ve 4.80 kat daha fazladır. Ev yerine hastanede takip edilme riski; erkeklerde kadınlara göre 1.37 kat, her yaş için 1.09 kat ve tam aşıllara göre kısmi aşı, aşısız ve hiç aşısızda sırasıyla 2.14, 2.61 ve 6.23 kat daha fazladır.

**Sonuç:** Yoğun bakıma yatış, entübasyon, pnömoni ve hastanede takip edilmede tam aşıllı olanlar en az riske sahipken kısmi aşı, aşısız ve hiç aşısız olanlarda risk artmaktadır. Sonuçta aşıyla korunan bireyler COVID-19 vakası olsalar bile farklı varyantlar için de hastalığı daha hafif geçirmektelerdir.

**Anahtar Kelimeler:** SARS-CoV-2; Varyant virüs; Biontech aşı; Coronavac aşı

**INTRODUCTION**

As of March 2022, the pandemic had caused close to 500 million cases and more than six million deaths worldwide<sup>[1]</sup>. From December 2019, since the first case was reported in the world, and March 2020, when the first case was reported in İstanbul, until today, various variants of the virus have emerged with mutations that change the receptor-binding site of the spike protein<sup>[2,3]</sup>. Mutations that are effective in the emergence of new SARS-CoV-2 variants can affect the structure of the protein. Thus, altering the spike protein's interaction with the human hACE2 receptor can alter the body's immune response and infection rates<sup>[4]</sup>. Viral transmission

potentials of new variants of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), that emerged rapidly among populations, are followed regarding the effects on the clinical disease severity, escape of the virus from natural immunity, and vaccine efficacy with a public health concern<sup>[5,6]</sup>. Despite the effectiveness of the unique infection prevention and control measures, as well as the public health and social measures taken around the world such as masks, social distance, hygiene, and quarantine; vaccination is still the best and safest way to control the growing epidemic with new mutant SARS-CoV-2 variants with high potential lethality and infectivity<sup>[7]</sup>. At the point reached today,

eleven vaccines are offered to the public with the emergency use approval by WHO for the rapidly increasing need for safe and effective COVID-19 vaccines with the growing pandemic<sup>[8]</sup>. Globally, more than 12 billion COVID-19 vaccine doses have been administered since July 2022<sup>[2]</sup>. Although the efficacy of COVID-19 vaccines in the immune response against symptomatic infection caused by non-variant strains, hospitalizations, and deaths due to COVID-19 is known, studies are continuing on the effectiveness of disease transmission, duration of protection, and mixed program applications with different vaccines<sup>[9]</sup>.

Even in the period when no cases were detected in Türkiye, there were concerns about how to protect healthcare workers and nurses from COVID-19<sup>[10]</sup>. Monitoring vaccines and mutations (variants) are an important strategy within the COVID-19 pandemic management strategy<sup>[11]</sup>. In October 2021, there were two different vaccines in use in Türkiye. On January 13, 2021, a nationwide vaccination campaign was launched after the CoronaVac, the coronavirus vaccine developed by Sinovac, was approved for emergency use<sup>[12]</sup>. In the campaign, vaccines were administered to the whole community in two doses, 28 days apart, with priority being given to those working in health institutions, the elderly, disabled people living in shelters, and people over the age of 65. In mid-April, the vaccination program was expanded to include the Pfizer-BioNTech vaccine, the first vaccine approved for emergency use by WHO. More than 54.57 million people have been vaccinated in the country since October 2021<sup>[13,14]</sup>.

In Türkiye and İstanbul, 85% of cases were Alpha variants in mid-April 2021, while more than 90% were Delta variants towards the end of August<sup>[15,16]</sup>. As of July 18, 2022 in the country, Omicron variant of 14.463, Delta variant of 60.200, Alpha variant of 2182, a Beta variant of 811, Gamma variant of 187, and Mu variant of two were reported<sup>[17]</sup>.

Also, despite the rapidly continuing vaccination efforts after the quarantine measures were lifted in many areas across the country in June 2021,

it was seen that the number of cases, which was at an average of five thousand per day in June, increased gradually. At the beginning of October, Türkiye became the third country with the highest number of cases in the world<sup>[18]</sup>. All of this has highlighted the proven transmission-reducing efficacy of public health and social measures, the importance of global strategies to reduce the occurrence of mutations with increasing adverse public health impacts, and the efficacy of COVID-19 vaccines against potentially SARS-CoV-2 variants<sup>[19]</sup>. Understanding the extent and duration of protection against infection or disease in all vaccinated age groups and populations has become increasingly important<sup>[20]</sup>. This study aimed to evaluate the clinical course, pneumonia development, intubation status, and hospitalization according to demographic characteristics and vaccination status of COVID-19 cases who had SARS-CoV-2 variant analysis between 1-15 September 2021 in İstanbul.

## MATERIALS and METHODS

### Study Design

Among the cases who underwent the variant analysis with Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2) infection confirmed by RT-PCR by the laboratory in İstanbul from the Public Health Management System (HSYS) between 1-15 September 2021 were included in the study. Public Health Management System (HSYS) is a surveillance system based on laboratory-confirmed COVID-19 cases by province across the country. PCR requests and analysis results made in public or private health institutions for Turkish citizens and other world citizens in the country must be entered into this system. Every confirmed SARS-CoV-2 infection in the HSYS surveillance system is reported by the district health directorate, where it is registered. In the epidemiological surveillance study, the test-positive cases were interviewed, and their contacts within the previous two days (48 hours) were determined and recorded in the HSYS system.

In the study, among the basic demographic data of the people in the HSYS, age, gender, nationality (TR/other), source (domestic/

abroad), case follow-up (home/hospital), infection status (re-infection/primary infection), and being a healthcare worker was included. Besides, the clinical spectrum of the infection (mild, moderate, severe, unspecified)<sup>[21]</sup>, admission to the intensive care unit, intubation status, and pneumonia development status are also data obtained from HSYS.

At the time of the study, the analysis was limited to adult cases >18 years of age, as under the age of 18 vaccination was very recent, and those vaccinated under the age of 18 were few.

The BioNTech vaccine is administered to people aged 18 years and older, with a total of two doses, at least four weeks apart. The CoronaVac vaccine is administered in two doses 14 days apart. The vaccine is not administered to an active COVID-19 patient, people who have had COVID-19 within 180 days (confirmed by PCR testing), and people who have been in contact with a confirmed COVID-19 case within ten days before administration of the vaccine<sup>[22]</sup>.

In the study, four groups were formed for vaccination situations (Figure 1)<sup>[23-25]</sup>. Variant types analyzed in the HSYS system were classified as Delta variant, Alpha variant, E484K (Delta plus), and others.

### Statistical Analysis

Chi-square or Fisher's exact tests were used for categorical variables for differences in infection percentages by vaccination status, and the medians were calculated using the Kruskal-Wallis tests. Logistic regression was used to estimate the probability of pneumonia development, intubation, and intensive care unit admission in cases

whose SARS-CoV-2 test was confirmed by PCR, according to vaccination status. Data were analyzed using SPSS v.22; the statistical significance level was  $p < 0.05$ .

### RESULTS

A total of 12.709 cases over the age of 18 whose variant analysis was performed in HSYS between 1-15 September 2021 in İstanbul were enrolled. Of the cases, 4296 (33.8%) were fully vaccinated, 2082 (16.4%) were partially vaccinated, 1544 (12.1%) were unvaccinated (at least one dose vaccinated and less than 14 days from the last vaccination date), and 4787 (37.7%) were never vaccinated. Among the fully vaccinated cases, the median time from fully vaccinated to diagnosis was 58 days (IQR 44-70). Among all adults over 18 years of age, fully vaccinated cases were older than partially vaccinated, unvaccinated, and never vaccinated cases [median age 42 years (IQR 34-53), 40 years (IQR 29-57), 34 years (IQR 25-44); 33 years (IQR 25-41)  $p < 0.001$ , respectively] 1994 (34.4%) men were fully vaccinated, and 2647 (38.3%) women were never vaccinated ( $p < 0.001$ ). Of the analyzed cases, 10.862 (85.5%) were Delta variants (Table 1).

Table 1 shows the basic demographic characteristics of the study group diagnosed with COVID-19 disease and analyzed for variants. Overall, those who were fully vaccinated were older, and the proportion of those who were never vaccinated was higher in both men and women in the 18-49 age group. Those with a mild clinical spectrum of infection were higher in those who were fully vaccinated, and those

Vaccination Status	
Fully Vaccinated	More than $\geq 14$ days after receiving the second dose from a two-dose series (BioNTech or CoronaVac).
Partially Vaccinated	More than $\geq 14$ days from the first dose and $< 14$ days after the second dose from a two-dose series (BioNTech or CoronaVac)
Unvaccinated	Less than 14 days from administration of a dose from a two-dose series (BioNTech or CoronaVac), or more than $\geq 180$ days from the second dose from a two-dose CoronaVac series <sup>[26]</sup> .
Never vaccinated	No COVID-19 vaccine.

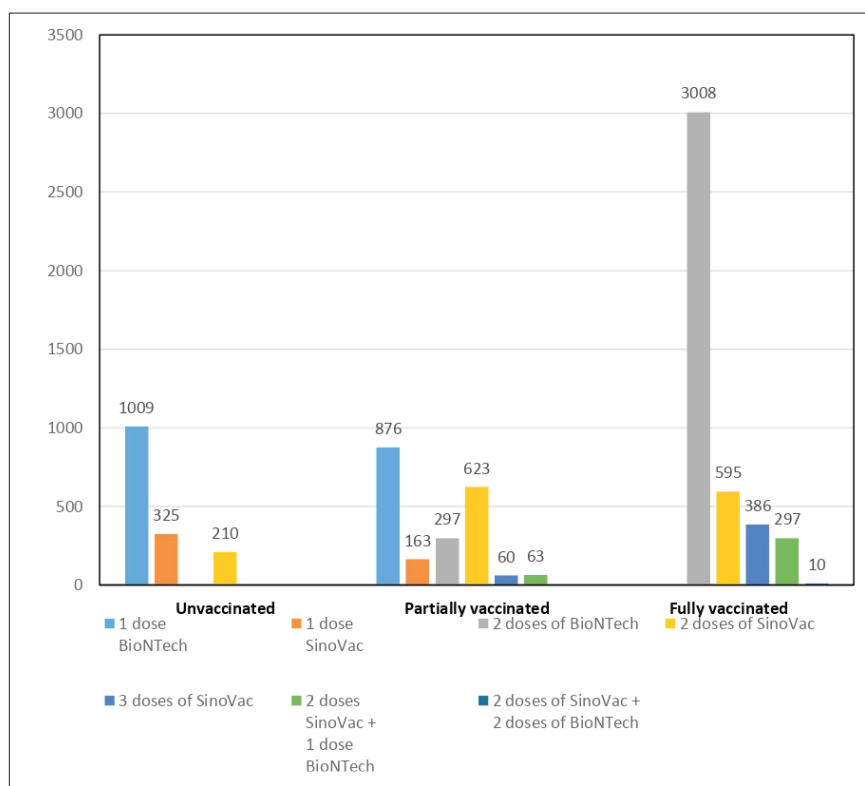


Figure 1. Distribution of vaccines according to vaccination status of patients.

with severe clinical manifestations were higher in those who did not have any vaccine. Besides, half of those hospitalized in the intensive care unit, intubated, and those who developed pneumonia were those who did not receive any vaccinations. Fully vaccinated status significantly impacted the development of intensive care unit admission, intubation, and pneumonia compared to partially vaccinated, unvaccinated, and never vaccinated patients (Table 1).

In the 18-39 age group, those who did not have any vaccine were the highest (47.4%), while those who had two doses of BioNTech (21.5%) were in second place. Those who received two doses of BioNTech in the 40-65 age group and two doses of Sinovac over the age of 65 had the highest rate.

Over 65 years of age, admission to the intensive care unit, intubation, pneumonia development, and hospital follow-up were higher than in other age groups. Although the rate of

admission to the intensive care unit, intubation, pneumonia development, and hospital follow-up was higher in men than in women, there was a statistically significant difference in admission to the intensive care unit for the male gender (Table 2). The rate of intubation and hospital follow-up was higher Delta variant ( $p < 0.05$ ) (Table 3).

Logistic regression models in which the variables of gender, age, and vaccination status, which may affect the patient's admission to the intensive care unit, intubation, pneumonia development, and hospital follow-up, were developed model (Table 4). Admission to the intensive care unit was 1.90 times (1.37-2.64) more in men compared to women, 1.09 times (1.08-1.11) for all ages, and 1.85 (1.10-3.11), 2.01 (1.13-3.59) and 6.51 (4.17-10.16) times higher in partially vaccinated, unvaccinated and never vaccinated compared to fully vaccinated patients, respectively.



**Table 1. Distribution of some characteristics of individuals according to their vaccination status**

Characteristic	Vaccination status, no. (%)					p
	Total	Fully vaccinated	Partially vaccinated	Unvaccinated	Never vaccinated	
<b>Total no. of cases</b>	<b>12.709</b>	<b>4296 (33.8)</b>	<b>2082 (16.4)</b>	<b>1544 (12.1)</b>	<b>4787 (37.7)</b>	-
<b>Median interval between final vaccine dose and infection, no. of days (IQR)</b>	-	58 (44-70)	26 (13.75-91)	13 (8-88)		-
<b>Median age, yrs (IQR)</b>	<b>37 (28-48)</b>	42 (34-53)	40 (29-57)	34 (25-44)	33 (25-41)	<0.001
<b>Age group, yrs</b>						
18-39	<b>7193 (56.6)</b>	1752 (24.4)	1039 (14.4)	996 (13.8)	3406 (47.4)	
40-64	<b>4483 (35.3)</b>	2120 (47.3)	745 (16.6)	397 (8.9)	1221 (27.2)	<0.001
65 years and over	<b>1033 (8.1)</b>	424 (41.0)	298 (28.8)	151 (14.6)	160 (15.5)	
<b>Sex</b>						
Female	<b>6910 (54.4)</b>	2302 (33.3)	1185 (17.1)	776 (11.2)	2647 (38.3)	<0.001
Male	<b>5799 (45.6)</b>	1994 (34.4)	897 (15.5)	768 (13.2)	2140 (36.9)	
<b>Race</b>						
TR	<b>12.076 (95.0)</b>	4228 (35.0)	2004 (16.6)	1496 (12.4)	4348 (36.0)	<0.001
Other	<b>633 (5.0)</b>	68 (10.7)	78 (12.3)	48 (7.6)	439 (69.4)	
<b>Clinical spectrum of infection</b>						
Mild	<b>6667 (90.8)</b>	2398 (36.0)	1083 (16.2)	822 (12.3)	2364 (35.5)	
Moderate	<b>542 (7.4)</b>	115 (21.2)	118 (21.8)	78 (14.4)	231 (42.6)	<0.001
Severe	<b>134 (1.8)</b>	21 (15.7)	25 (18.7)	24 (17.9)	64 (47.8)	
<b>Admission to Intensive Care</b>						
Yes	<b>176 (2.4)</b>	31 (17.6)	33 (18.8)	24 (13.6)	88 (50.0)	<0.001
No	<b>7260 (97.6)</b>	2519 (34.7)	1199 (16.5)	913 (12.6)	2629 (36.2)	
<b>Intubation</b>						
Yes	<b>108 (1.5)</b>	18 (16.7)	21 (19.4)	15 (13.9)	54 (50.0)	<0.001
No	<b>7328 (98.5)</b>	2532 (34.6)	1211 (16.5)	922 (12.6)	2663 (36.3)	
<b>Pneumonia Development</b>						
Yes	<b>292 (3.9)</b>	57 (19.5)	53 (18.2)	41 (14.0)	141 (48.3)	<0.001
No	<b>7146 (96.1)</b>	2494 (34.9)	1180 (16.5)	896 (12.5)	2576 (36.0)	
<b>Follow-up</b>						
At home	<b>12.109 (95.3)</b>	4181 (34.5)	1957 (16.2)	1460 (12.1)	4511 (37.3)	<0.001
At hospital	<b>600 (4.7)</b>	115 (19.2)	125 (20.8)	84 (14.0)	276 (46.0)	
<b>Infection</b>						
Re-infection	<b>292 (2.3)</b>	59 (20.2)	30 (10.3)	38 (13.0)	165 (56.5)	<0.001
Primary infection	<b>12.417 (97.7)</b>	4237 (34.1)	2052 (16.5)	1506 (12.1)	4622 (37.2)	
<b>HCP</b>						
Yes	<b>266 (2.1)</b>	98 (36.8)	27 (10.2)	81 (30.5)	60 (22.6)	<0.001
No	<b>12.435 (97.9)</b>	4198 (33.7)	2055 (16.5)	1463 (11.8)	4727 (38.0)	
<b>Variant type</b>						
Delta	<b>10.862 (85.5)</b>	3705 (34.1)	1748 (16.1)	1330 (12.2)	4079 (37.6)	
British	<b>228 (1.8)</b>	38 (16.7)	72 (31.6)	26 (11.4)	92 (40.4)	<0.001
E484K	<b>62 (0.5)</b>	15 (24.2)	9 (14.5)	8 (12.9)	30 (48.4)	
Other	<b>1557 (12.3)</b>	538 (34.6)	253 (16.2)	180 (11.6)	586 (34.6)	

**Table 2. Hospitalization, intubation, pneumonia development and patient follow-up status by age groups, gender and vaccine type**

	Admission to Intensive Care				Intubation status				Pneumonia development				Patient follow-up	
	No		Yes		No		Yes		No		Yes		Home	Hospital
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<b>18-39 years</b>	3942 (99.8)	9 (0.2)	3946 (99.9)	5 (0.1)	3909 (98.9)	42 (1.1)	3909 (98.9)	42 (1.1)	7101 (98.7)	92 (1.3)				
<b>40-64 years</b>	2661 (97.8)	61 (2.2)	2685 (98.6)	37 (1.4)	2609 (95.8)	115 (4.2)	2609 (95.8)	115 (4.2)	4262 (95.1)	221 (4.9)				
<b>Over 65 years</b>	657 (86.1)	106 (13.9)	697 (91.3)	66 (8.7)	628 (82.3)	135 (17.7)	628 (82.3)	135 (17.7)	746 (72.2)	287 (27.8)				
<b>p</b>	<b>p&lt; 0.001</b>		<b>p&lt; 0.001</b>		<b>p&lt; 0.001</b>		<b>p&lt; 0.001</b>		<b>p&lt; 0.001</b>		<b>p&lt; 0.001</b>			
<b>Female</b>	3974 (98.1)	79 (1.9)	4002 (98.7)	51 (1.3)	3896 (96.1)	157 (3.9)	3896 (96.1)	157 (3.9)	6602 (95.5)	308 (4.5)				
<b>Male</b>	3286 (97.1)	97 (2.9)	3326 (98.3)	57 (1.7)	3250 (96.0)	135 (4.0)	3250 (96.0)	135 (4.0)	5507 (95.0)	292 (5.0)				
<b>p</b>	<b>p= 0.01</b>		<b>p= 0.144</b>		<b>p= 0.811</b>		<b>p= 0.811</b>		<b>p= 0.131</b>					
<b>One dose BioNTech</b>	1057 (99.1)	10 (0.9)	1062 (99.5)	5 (0.5)	1048 (98.2)	19 (1.8)	1048 (98.2)	19 (1.8)	1848 (98.0)	37 (2.0)				
<b>One dose SinoVac</b>	291 (98.3)	5 (1.7)	291 (98.3)	5 (1.7)	285 (96.3)	11 (3.7)	285 (96.3)	11 (3.7)	461 (94.5)	27 (5.5)				
<b>Two doses BioNTech</b>	1872 (99.7)	5 (0.3)	1874 (99.8)	3 (0.2)	1856 (98.8)	22 (1.2)	1856 (98.8)	22 (1.2)	3274 (99.1)	31 (0.9)				
<b>Two doses SinoVac</b>	887 (95.3)	44 (4.7)	903 (97.0)	28 (3.0)	865 (92.8)	67 (7.2)	865 (92.8)	67 (7.2)	1273 (89.1)	155 (10.9)				
<b>Two doses SinoVac + One dose BioNTech</b>	219 (96.1)	9 (3.9)	226 (99.1)	2 (0.9)	215 (94.3)	13 (5.7)	215 (94.3)	13 (5.7)	337 (93.6)	23 (6.4)				
<b>Two doses SinoVac + Two doses BioNTech</b>	9 (100.0)	0	9 (100.0)	0	9 (100.0)	0	9 (100.0)	0	10 (100.0)	0				
<b>Three doses SinoVac</b>	296 (95.2)	15 (4.8)	300 (96.5)	11 (3.5)	292 (93.9)	19 (6.1)	292 (93.9)	19 (6.1)	395 (88.6)	51 (11.4)				
<b>p</b>	<b>p&lt; 0.001</b>		<b>p*</b>		<b>p&lt; 0.001</b>		<b>p&lt; 0.001</b>		<b>p&lt; 0.001</b>		<b>p&lt; 0.001</b>			

\*: The cases of admission to the intensive care unit, intubation application, pneumonia development and hospital follow-up in HSYS were not included in the analysis.

**Table 3. Hospitalization, intubation, pneumonia development and patient follow-up status by variant type**

	Admission to Intensive Care		Intubation status		Pneumonia development		Patient follow-up	
	No	Yes	No	Yes	No	Yes	Home	Hospital
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Delta</b>	6099 (97.8)	138 (2.2)	6157 (98.7)	80 (1.3)	6007 (96.3)	232 (3.7)	10386 (95.6)	476 (4.4)
<b>British</b>	149 (96.8)	5 (3.2)	150 (97.4)	4 (2.6)	145 (94.2)	9 (5.8)	215 (94.3)	13 (5.7)
<b>E484K</b>	27 (93.1)	2 (6.9)	28 (96.6)	1 (3.4)	26 (89.7)	3 (10.3)	59 (95.2)	3 (4.8)
<b>Other</b>	985 (96.9)	31 (3.1)	993 (97.7)	23 (2.3)	968 (95.3)	48 (4.7)	1449 (93.1)	108 (6.9)
<b>p</b>	p= 0.122		p= 0.04		p= 0.06		p< 0.001	

**Table 4. Logistic regression analysis to determine the risk factors of hospitalization in the intensive care unit, intubation, pneumonia development and hospital follow-up of the cases for which variant analysis was performed**

	Admission to Intensive Care		Intubation		Pneumonia		Being Followed in the Hospital	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Gender*	1.90		1.65		1.18		1.37	
Male	(1.37-2.64)	<0.001	(1.10-2.47)	0.018	(0.92-1.18)	0.192	(1.14-1.64)	0.001
Age	1.09		1.08		1.07		1.09	
	(1.08-1.11)	<0.001	(1.07-1.10)	<0.001	(1.07-1.08)	<0.001	(1.09-1.10)	<0.001
Vaccination*	1.85		1.99		1.70		2.14	
Partially vaccinated	(1.10-3.11)	0.020	(1.04-3.82)	0.046	(1.14-2.52)	0.009	(1.62-2.82)	<0.001
Unvaccinated	2.01		2.09		2.15		2.61	
	(1.13-3.59)	0.018	(1.01-4.29)	<0.001	(1.39-3.32)	0.001	(1.89-3.61)	<0.001
Never vaccinated	6.51		6.06		4.80		6.23	
	(4.17-10.16)	<0.001	(3.46-10.60)	<0.001	(3.43-6.70)	<0.001	(4.85-8.01)	<0.001

\*: Reference group (Female and fully vaccinated).

Being intubated is 1.66 times (1.11-2.48) more in men than in women, 1.09 times (1.07-1.10) for all ages, and is 1.99 (1.04-3.82), 2.09 (1.01-4.29) and 6.06 (3.46-10.60) times higher in partially vaccinated, unvaccinated and never vaccinated compared to fully vaccinated patients, respectively.

The risk of developing pneumonia is 1.07 times (1.07-1.08) higher for all ages and 1.70 (1.14-2.52), 2.15 (1.39-3.32), and 4.80 (3.43-6.70) times higher for partially vaccinated, unvaccinated, and never vaccinated, respectively, compared to fully vaccinated.

The risk of being followed in the hospital instead of the home is 1.37 times (1.14-1.64) more common in men than in women, 1.09 times (1.09-1.10) in all ages, and 2.14 (1.62-2.82), 2.61 (1.89-3.61) and 6.23 (4.85-8.01)

times more in partially vaccinated, unvaccinated and never vaccinated compared to fully vaccinated people, respectively.

## DISCUSSION

In the pandemic, it still seems to be the most effective method to prevent the emergence of variants by controlling the spread of the virus with a widespread and effective vaccination. Although it varies according to the type, it is known that the effectiveness of COVID-19 vaccines against the disease reaches 95%<sup>[27]</sup>. Although studies have reported a 10-20% decrease in the effectiveness of Delta variant vaccines, it was reported that all vaccines are highly effective in severe diseases and deaths<sup>[28,29]</sup>.

However, currently, only 67% of the world has been vaccinated with at least one dose of the COVID-19 vaccine<sup>[30]</sup>. Of these, according



to WHO data, only 57 countries, most of which are high-income countries, have vaccinated only 70% of their populations. Only 20% of low-income countries received at least one dose of the vaccine<sup>[31]</sup>.

Globally, more than 572 million confirmed cases of COVID-19 were reported in July 2022, with a total of more than 12 billion vaccine doses administered<sup>[30]</sup>. In the USA, the vaccine dose administered throughout the country from the age of five and onwards is close to 600 million, while 83.5% of those with at least one vaccine dose are vaccinated. While the rate of fully vaccinated people over the age of 18 in the country is 77.1%, this rate exceeds 91% for those over 65 years of age<sup>[32]</sup>.

Seventy-nine percent of the population in France, 76% in Germany, and 75% in the UK are fully vaccinated. In Iran, more than 170 million vaccine doses have been administered, and 66% of the population is fully vaccinated. In our country, in the same period, close to 178 million vaccine doses (68.2%) were administered against COVID-19. According to the data, 62.6% were vaccinated, and 5.6% were partially vaccinated<sup>[30]</sup>. At this point, vaccination remains the safest strategy to prevent SARS-CoV-2 infection and its complications.

According to our results, 85.5% of the cases in which variant analysis was performed were Delta variants. One-third of the cases were fully vaccinated, and nearly 40% were those who were not vaccinated at all. In the fourth wave of the COVID-19 pandemic, the Delta variant was dominant in Türkiye as well as in the world. While vaccine acceptance was seen in more than half of the population just before the start of the pandemic vaccination campaign in the country, the rate of full vaccination in the country was 48%, and the rate of partially vaccinated was 12.9% on September 15, 2021, when the study was conducted with the rapid spread of the disease, and there were 12.709 variant analysis cases<sup>[33,34]</sup>. In İstanbul, the first dose vaccination rates in all age groups were over 70%, while the second dose vaccination rates approached 60%<sup>[35]</sup>. In our results, 50% of those who were hospitalized in the intensive care unit, those who

were intubated, those who developed pneumonia, and those who had poor clinical status, were those who had never been vaccinated. At that time, the İstanbul Provincial Health Directorate reported that 56.8% of the patients hospitalized in İstanbul and 58.4% of the patients in the intensive care unit were unvaccinated<sup>[36]</sup>.

While there is an increasing trend of vaccination towards the end of 2021, the perception of the mild clinical course of the Omicron variant, the transition to summer months, and the complete removal of non-drug restrictions suggest the decrease in vaccination supply and increase in cases in the summer of 2022<sup>[37]</sup>.

Hesitation or rejection against the COVID-19 vaccine, our strongest weapon in the pandemic, continues to be a global problem, not just in Türkiye. According to January 2022 data, it is known that more than 19% of the population in Germany, more than 17% in France, and more than 9% in Spain are unvaccinated and do not want to be vaccinated<sup>[30]</sup>.

However, studies are showing that the estimated efficacy of the COVID-19 vaccine against re-infection leading to hospitalization, even during the Omicron-dominated era, is approximately 35% after the second dose and 68% after a booster dose<sup>[38]</sup>. In addition, vaccination with a single dose of BioNTech or ChAdOx1-S has been associated with a significant reduction in symptomatic COVID-19 and greater protection against the severity of the disease in older adults<sup>[39]</sup>.

There are studies reporting that the two-dose BioNTech vaccine is highly effective in all age groups (including adults aged  $\geq 16$  years, over 85 years) in preventing symptomatic and asymptomatic SARS-CoV-2 infections and COVID-19-related hospitalizations, severe illness, and death<sup>[40]</sup>. Our vaccination rates, which have not even reached 70% according to July 2022 data, are particularly worrying for risk groups, with the recent increase in cases showing that the epidemic is not over yet.

It is known that there is currently no effective and definitive treatment for COVID-19 disease. The “mask-distance-hygiene” triad that has been

applied since the beginning of the pandemic, along with vaccination, continues to be the most important manner to prevent the transmission of SARS-CoV-2. For COVID-19 to be brought under control in the community, vaccination studies should be continued in a way that will rapidly vaccinate 70-80% of the population<sup>[41]</sup>. In our study, it was observed that approximately 40% of the cases in which variant analysis was performed did not have any vaccine, and a quarter of them was vaccinated with two doses of BioNTech. The median age was the lowest, with 33 in those who did not have any vaccine, and the highest with 42 in those who were fully vaccinated. It was determined that more than 70% of those who had never been vaccinated were under the age of 40. It can be said that high vaccination rates are more successful for those over the age of 65 and those with chronic diseases in the population prioritized as a vaccination strategy in Türkiye. Also, the clinical spectrum of infection in those who were fully vaccinated was evaluated as “good” at a higher rate than in other vaccination situations and those who did not have any vaccination. Likewise, those who were intubated, those who were admitted to the intensive care unit, and those who developed pneumonia were found to be the lowest in those who were fully vaccinated. In a similar study conducted with hospital data in the country, it was revealed that 52% of hospitalized patients were infected despite being vaccinated<sup>[42]</sup>. In a study evaluating disease severity and hospitalizations according to variants, although Delta variant was found to be associated with higher negative outcomes in hospitalized adults in the United States, where the proportion of unvaccinated adults aged 18-49 who are hospitalized with delta variant dominance is increasing, studies are showing that there are no significantly higher rates of admission to the intensive care unit, intubation, or in-hospital death and hospitalization<sup>[43]</sup>. However, as the Delta variant has become more dominant, the proportion of unvaccinated adults aged 18-49 hospitalized with COVID-19 has steadily increased, which highlighted the critical importance of the COVID-19 vaccine, not only

in older adults but also in those under 50 who have relatively low immunization rates<sup>[42,44]</sup>. As a step towards this, a reminder dose application has been started in our country since the beginning of November 2021 for people over 60 years old, those aged 18-60 years with chronic diseases, and those working in high-risk professions, especially healthcare workers, after six months have passed since the second dose of mRNA vaccine. At the beginning of July 2022, a reminder dose was defined for people who had the BioNTech vaccine at least six months priorly.

SARS-CoV-2 variants stand before us as huge challenges for controlling the pandemic. It was shown in a modeling study for İstanbul that non-drug interventions will be effective in reducing the cases and deaths in controlling the COVID-19 pandemic<sup>[45]</sup>. However, increasing the immune response obtained with vaccination and existing vaccines will help to establish protective efficacy against variants and prevent further transmission of variants. Increasing the number of doses of vaccines and developing alternative vaccines will contribute to the immune response gained with the vaccine<sup>[46,47]</sup>.

Our study has some limitations. It is the PCR test used for diagnosis in cases, and there is a need to standardize test methods with emerging variants in pandemic follow-up studies. Besides, it should be kept in mind that clinical thresholds for hospitalization and admission to the intensive care unit may change due to the periodic increase in hospitalization and limited hospital capacity. Also, since our data does not include comorbidities and pregnancy status of the patients, sufficient, comprehensive interpretation cannot be made for hospitalization, intensive care unit admission, and intubation. Another limitation is the uncertainty in our country's variant sequence analysis work instructions and the lack of clear information on how many of the positive samples underwent variant analysis and/or genetic analysis or sequencing.

## CONCLUSION

In the results of this study, which was dominated by the delta variant, the possibility of

higher efficacy of full vaccination in preventing intensive care admission, intubation status, and the development of pneumonia was revealed. Other strategies such as increasing the number of vaccine doses, changing vaccines, developing new vaccines against variants, and improving the immunogenicity of existing vaccines are recommended in the fight of countries against the pandemic. In time, the questions will be answered about how long the vaccines will be protective, how often booster doses should be applied to maintain protection, whether it will be protective against the mild form of COVID-19 or whether it will be a vaccine that prevents serious complications and reduces the death rate. Our study showed that advanced age is a risk factor for the risk of intensive care admission, intubation risk, pneumonia risk, and hospitalization, and being male is also a risk factor for others, except for pneumonia. While age and gender are non-modifiable factors, vaccination is a modifiable and acceptable practice. While those who are fully vaccinated have the least risk, the risk of hospitalization in the intensive care unit, intubation, pneumonia, and hospitalization increases in those who are partially vaccinated, unvaccinated and unvaccinated. As a result, individuals protected by vaccines will have a milder illness, even if they have a case of COVID-19.

#### ETHICS COMMITTEE APPROVAL

This study was approved Zeynep Kamil Women and Children Diseases Training and Research Hospital Local Ethics Committee (Decision no: 165, Date: 06.10.2021).

#### CONFLICT of INTEREST

None of the authors had conflict of interest.

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Data Collection or Processing: ÇEŞ, MAS, YT

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Final Approval: All of authors

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