The effect of variants and vaccines on prognosis in coronavirus disease 2019 patients: a retrospective observational study

Koronavirüs hastalığı 2019 hastalarında varyantların ve aşıların prognoza etkisi: retrospektif gözlemsel çalışma

Abstract

Aim: The effect of novel coronavirus disease 2019 (COVID-19) vaccines on variants of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is unclear. In this study, we aimed to investigate the prognostic effect of variants and vaccines in hospitalized COVID-19 patients.

Methods: This retrospective study was conducted on 588 hospitalized patients with COVID-19 between May 1st, 2021, and August 31st, 2021. The patients were divided into groups according to variant analysis and demographic characteristics, laboratory data, vaccination status, and in-hospital mortality rates were compared.

Results: Variants (Alpha [B.1.1.7], Beta [B.1.351], Delta [B.1.617.2]) were detected in 46.3% of the patients. The intensive care unit (ICU) admission rate was 46.8%, and the in-hospital mortality rate was 33.3%. There was no statistically significant difference between the patients with variant detection and those without variant detection in terms of ICU admission and in-hospital mortality. The rate of unvaccinated patients was 63.6%. The in-hospital mortality rate was similar in those vaccinated with two doses of CoronaVaC (37.1%) to that in the unvaccinated (32.9%) but higher than in those vaccinated with two doses of BNT162B2 (16.7%).

Conclusion: There was no increase in the mortality rates in hospitalized between patients with or without variants compared to those without. The mortality rate in those vaccinated with two doses of CoronaVaC was similar to that in those not vaccinated.

Keywords: BNT16B2; CoronaVaC, COVID-19 vaccine; SARS-CoV-2 variants

Öz

Amaç: Koronavirüs hastalığı 2019 (COVID-19) aşılarının şiddetli akut solunum yolu sendromu koronavirüsü 2 (SARS-CoV-2) varyantları üzerindeki etkisi belirsizdir. Bu çalışmadaki amacımız, hastanede yatan COVID-19 hastalarında varyantların ve aşıların prognostik etkisini araştırmaktır.

Yöntemler: Bu retrospektif çalışma, 01 Mayıs-31 Ağustos 2021 tarihleri arasında hastanede yatan 588 COVID-19 hastası üzerinde yapıldı. Varyant analizine göre gruplandırılan hastalar, demografik özellikleri, laboratuvar verileri, aşılanma durumları ve hastane içi ölüm oranları açısından karşılaştırıldı.

Bulgular: Hastaların %46,3'ünde varyant (Alfa [B.1.1.7], Beta [B.1.351], Delta [B.1.617.2]) saptandı. Yoğun bakım ünitesine (YBÜ) yatış oranı %46,8 ve hastane içi ölüm oranı %33,3 idi. Varyant saptanan hastalar ile varyant saptanmayanlar arasında YBÜ'ye yatış ve hastane içi mortalite açısından istatistiksel olarak anlamlı fark yoktu. Aşısız hasta oranı %63,6 idi. İki doz CoronaVaC ile aşılanan hastaların hastane içi mortalite oranları (%37,1) ile aşılanmayanların mortalite oranları (%32,9) benzerdi, ancak 2 doz BNT162B2 ile aşılananların hastane içi mortalite oranlarından (%16,7) daha yüksekti.

Sonuç: Hastanede yatan hastalarda varyant saptananlar ile varyantı olmayanlar arasında mortalite açısından anlamlı bir fark saptanmadı. İki doz CoronaVaC ile aşılananlarda ölüm oranı, aşılanmayanlarla benzerdi.

Anahtar Sözcükler: COVID-19 aşıları, ölüm oranı, SARS-CoV-2

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INTRODUCTION

The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) pandemic continues to be a global health concern. Although there are significant advances in the field of vaccines (1,2), new variants are still a cause of concern (3,4). With the global spread of SARS-CoV-2, the emergence of variants with mutations in the non-structural and structural proteins has increased dramatically (5). While most of these changes do not alter the basic properties of the virus, some changes termed "mutations" can significantly alter the basic properties of the virus and thus its effect (6-8). The World Health Organization (WHO) classifies variants of viruses as "Variants of Concern" (VOC) and "Variants of Interest" (VOI) (9); however, national classifications vary depending on the impact of variants according to geographic location (10). The organization warns that VOC mutations "may increase the infectiousness and risk of spread of the virus, alter its lethality or symptoms, and reduce the effectiveness of prevention and control measures." In addition, the WHO has assigned the names Alpha (20I/501Y.V1, lineage B.1.1.7), Beta (20H/501Y.V2, lineage B.1.351), Gamma (20J/501Y.V3, lineage P.1), and Delta (B.1.617.2) to 4 variants designated as VOCs (9).

Vaccines have been shown in clinical trials and in practice to be highly effective in preventing symptomatic diseases (1,11,12). However, the current vaccines were originally developed for earlier versions of the coronavirus, indicating that they may not be ideally suited for the new variants and, thus, may not work quite as well (3,4). Researchers have been still paying a great effort to clarify the transmissibility of the variants and the effects of the approved vaccines (13,14).

In the past, many studies were conducted to identify the factors affecting the prognosis of novel coronavirus disease 2019 (COVID-19) patients. However, due to the development of vaccines and the constant emergence of new variants, up-to-date studies are still needed. In the present study, we aimed to analyze the prognostic impact of available variants and vaccination status in hospitalized COVID-19 patients.

MATERIALS AND METHODS

This study was approved by Bakırköy Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (Date: 20/09.2021, No: 2021-18-06) and the Republic of Turkey, Ministry of Health (MoH) Coronavirus Research Advisory Board. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Setting and study population

This single-center, retrospective, observational study was conducted in the emergency department (ED) between May 1st, 2021, and August 31st, 2021. Our hospital with a total of 1,760 beds on two different campuses was designated by the MoH as a pandemic center in a region with a population of approximately 4 to 5 million (5 to 6% of the country's population) during the study.

Patients aged 18 years and older who were confirmed to be infected with SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (rt-PCR) testing on a nasopharyngeal swab and who were hospitalized were included in the study. Exclusion criteria were as follows: patients whose variant analysis was not performed with nasopharyngeal swabs, and patients whose data could not be accessed. Nasopharyngeal swabs collected from patients were analyzed for alpha, beta, and delta variants. In our routine practice, all patients admitted with suspected COVID-19 are screened in triage. Patients who arrive by ambulance, present severe symptoms, or have abnormal vital signs are admitted to the ED. The other patients are evaluated in the outpatient setting specifically for COVID-19.

Variant analysis

The Coronagen RT-qPCR SARS-CoV-2 variants detection kit V1.0 (Gensutek Health Technologies Inc., Turkey) was used for variant analysis. This kit is a multiplex-based qualitative PCR kit designed for the detection and differentiation of spike (S) protein variants with E484K and L452R mutations and D3L mutations. This kit detects the SARS-CoV-2 specific "*Orf1ab*" and "*N*" genes and the human "*RNaseP*" genes, as well as the genomic regions specific for the E484K, DL3, and L452R variants in the same tube.

Status of vaccination

The vaccines used in Turkey are CoronaVac (Sinovac Biotech, Beijing, China) and BNT162b2 (BioNTech-

Table 1: Distribution of patients infected with SARS-Cov-2 according to variant analysis.

	Variant analysis			Variant analysis positive		
	Variant not detected	**Variant detected**	**p**	**Alpha variant (B.1.1.7)**	**Delta variant (B.1.617.2)**	**p**
Male	175 (55.4)	145 (53.3)	0.615	115 (52.0)	26 (55.3)	0.682
Age, years	59 (45-73)	60 (49-76)	0.374	59 (49-76)	63 (45-76)	0.870
Diabetes	73 (23.1)	79 (29.0)	0.101	63 (28.5)	15 (31.9)	0.640
Hypertension	105 (33.2)	112 (41.2)	0.046	88 (39.8)	23 (48.9)	0.249
Coronary heart disease	50 (15.8)	44 (16.2)	0.907	36 (16.3)	7 (14.9)	0.813
Arrhythmia	14 (4.4)	13 (4.8)	0.840	10 (4.5)	2 (4.3)	0.647
Cerebrovascular diseases	15 (4.7)	15 (5.5)	0.673	13 (5.9)	2 (4.3)	0.659
COPD/asthma	31 (9.8)	44 (16.2)	0.021	38 (17.2)	6 (12.8)	0.457
Chronic kidney disease	24 (7.6)	12 (4.4)	0.108	12 (5.4)	0	NA
Chronic liver disease	2 (0.6)	3 (1.1)	0.667	3 (1.4)	0	NA
Malignancy	19 (6.0)	19 (7.0)	0.632	15 (6.8)	3 (6.4)	0.610
Rheumatic disease	6 (1.9)	7 (2.6)	0.579	4 (1.8)	3 (6.4)	0.106
Hyperlipidemia	10 (3.2)	9 (3.3)	0.921	7 (3.2)	1 (2.1)	0.576
Hypothyroidism	9 (2.8)	13 (4.8)	0.219	12 (5.4)	1 (2.1)	0.476
Neutrophil count, $\times 10^9$/L	5.16 (3.72-7.94)	6.18 (4.13-8.68)	0.374	6.18 (4.08-8.94)	5.73 (4.24-8.18)	0.524
Lymphocyte count, $\times 10^9$/L	0.87 (0.57-1.28)	0.98 (0.59-1.39)	0.014	0.96 (0.59-1.74)	1.03 (0.58-1.42)	0.592
Troponin I, ng/L	0.02 (0.01-6.25)	0.02 (0.01-7.32)	0.239	0.26 (0.01-7.68)	0.02 (0.01-3.61)	0.303
D-dimer, µg/mL	0.54 (0.35-1.10)	0.69 (0.43-1.13)	0.008	0.72 (0.47-1.18)	0.50 (0.31-1.01)	0.029
Fibrinogen, mg/dl	589 (494-687)	593 (507-695)	0.821	586 (498-684)	629 (523-720)	0.060
URE, mg/dL	36.5 (24.8-59.5)	38.7 (25.4-57.9)	0.795	38.8 (25.3-59.0)	35.8 (24.3-51.7)	0.273
Albumin, g/L	36.4 (32.6-39.9)	35.6 (31.3-39.3)	0.082	35.3 (31.4-39.1)	36.7 (30.7-41.0)	0.295
Ferritin, ug/L	498 (235-1050)	465 (227-930)	0.395	471 (225-945)	417 (226-796)	0.580
CRP, mg/L	81.0 (41.3-132.9)	89.4 (41.8-142.9)	0.394	88.1 (39.4-141.2)	97.2 (56.4-159.6)	0.180
Procalcitonin, ng/mL	0.15 (0.08-0.33)	0.14 (0.07-0.40)	0.731	0.14 (0.07-0.38)	0.12 (0.08-0.44)	0.746
Admission to ICU	141 (44.6)	134 (49.3)	0.260	115 (52.0)	17 (36.2)	0.048
Intubation	118 (37.3)	113 (41.5)	0.298	95 (43.0)	16 (34.0)	0.258
İn-hospital mortality	103 (32.6)	93 (34.2)	0.682	78 (35.3)	13 (27.7)	0.316
Hospital stays, days	12 (7-19)	13 (8-20)	0.235	13 (8-20)	11 (7-18)	0.208
Vaccination status of patients						
Unvaccinated[1]	189 (59.8)	185 (68.0)	0.039	162 (73.3)	21 (44.7)	<0.001
CoronaVac 1 dose[2]	5 (1.6)	15 (5.5)	0.026	13 (5.9)	2 (4.3)	0.688
CoronaVac 2 dose[2]	102 (32.0)	57 (21.0)	0.004	40 (18.1)	15 (31.9)	0.004
CoronaVac 3 dose[2]	3 (0.9)	1 (0.4)	0.623	0	1 (2.1)	NA
BNT162b2 1 dose[2]	11 (3.5)	11 (4.0)	0.795	5 (2.3)	6 (12.8)	0.001
BNT162b2 2 dose[2]	5 (1.6)	1 (0.4)	0.216	0	1 (2.1)	NA
C2B1[2]	2 (0.6)	2 (0.7)	0.983	1 (0.5)	1 (0.5)	NA

Variant detected: SARS-CoV-2 positive. Alpha variant, Beta variant, or Delta variant detected.

Variant not detected: SARS-CoV-2 positive, Alpha variant, Beta variant and Delta variant not detected.

Categorical data shown as number (percentage). Continuous variables displayed as median (interquartile range).

[1]Unvaccinated patients were statistically compared with those who received at least one dose of any vaccine.

[2] Each vaccine group was statistically compared with the unvaccinated patient group.

COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, CVD: Cerebrovascular diseases, ICU:Intensive care unit, C2B1: 2 doses of CoronaVaC followed by 1 dose of BNT162b2 vaccine, NA: not applicable.

Table 2: Demographic characteristics, laboratory data and vaccination status of subgroups according to prognosis.

	Alpha variant (B.1.1.7)			Delta variant (B.1.617.2)			Variant not detected		
	Survivor	**Non-surivor**	**p**	**Survivor**	**Non-surivor**		**Survivor**	**Non-surivor**	**P**
Male	70 (49.0)	45 (57.7)	0.214	18 (52.9)	8 (61.5)	0.596	98 (46.0)	43 (41.7)	0.075
Age, years	56 (47-65)	73 (58-82)	<0.001	60 (42-76)	67 (62-75)	0.140	55 (43-70)	70 (59-82)	<0.001
Diabetes	37 (25.9)	26 (33.3)	0.240	9 (26.5)	6 (46.2)	0.195	41 (19.2)	32 (31.1)	0.019
Hypertension	47 (32.9)	41 (52.6)	0.004	16 (47.1)	7 (53.8)	0.004	57 (26.8)	48 (46.6)	<0.001
CHD	19 (13.3)	17 (21.8)	0.102	3 (8.8)	4 (30.8)	0.080	25 (11.7)	25 (24.3)	0.004
Arrhythmia	7 (4.9)	3 (3.8)	0.720	1 (2.9)	1 (7.7)	0.481	8 (3.8)	11 (10.7)	0.015
CVD	8 (5.6)	5 (6.4)	0.805	1 (2.9)	1 (7.7)	0.481	11 (5.2)	4 (3.9)	0.781
COPD/asthma	22 (15.4)	16 (20.5)	0.334	3 (8.8)	3 (23.1)	0.326	17 (8.0)	14 (13.6)	0.116
CKD	6 (4.2)	6 (7.7)	0.353	0	0	NA	11 (5.2)	13 (12.6)	0.019
CLD	2 (1.4)	1 (1.3)	0.943	0	0	NA	1 (0.5)	1 (0.5)	0.546
Malignancy	6 (4.2)	9 (11.5)	0.038	1 (2.9)	2 (15.4)	0.181	82 (31.0)	11 (57.9)	0.015
Rheumatic disease	2 (1.4)	2 (2.6)	0.615	1 (2.9)	2 (15.4)	0.181	2 (0.9)	4 (3.9)	0.091
Hyperlipidemia	4 (2.8)	3 (3.8)	0.700	1 (2.9)	0	NA	9 (4.2)	1 (1.0)	0.175
Hypothyroidism	8 (5.6)	4 (5.1)	0.884	1 (2.9)	0	NA	5 (2.3)	4 (3.9)	0.480
Neu, $\times 10^9$/L	5.86 (3.61-8.06)	6.87 (4.64-11.56)	0.004	5.47 (3.97-7.90)	5.92 (4.55-8.30)	0.398	4.90 (3.68-7.09)	6.36 (3.79-9.66)	0.002
Lym × 10^9/L	1.96 (0.75-1.41)	0.62 (0.43-1.11)	<0.001	1.07 (0.69-1.44)	0.68 (0.30-1.42)	0.147	1.00 (0.67-1.46)	0.65 (0.42-0.93)	<0.001
Troponin I, ng/l	0.02(0.02-10.07)	0.04 (0.02-1.28)	0.029	0.02 (0.07-1.55)	0.02 (0.01-30.59)	0.360	0.02 (0.01-5.21)	0.05 (0.01-14.46)	<0.001
D-dimer, µg/mL	0.66 (0.38- 1.02)	0.85 (0.59-1.92)	0.001	0.47 (0.31-0.96)	0.57 (0.31-1.76)	0.510	0.49 (0.31-0.82)	0.89 (0.43-2.12)	<0.001
Fibrinogen, mg/dl	586 (501-701)	581 (472-680)	0.442	634 (523-717)	629 (500-726)	0.732	589 (505-686)	592 (483-690)	0.556
URE, mg/dL	32.0 (23.4-47.5)	53.8 (30.8- 74.3)	<0.001	32.3 (21.3-48.8)	41.0 (27.4-58.9)	0.116	31.5 (22.3- 46.6)	59.6 (32.9-109.0)	<0.001
Albumin, g/L	3.65 (3.38-4.00)	3.21 (3.02-3.61)	<0.001	3.71 (3.21-4.11)	3.36 (2.89-3.96)	0.216	3.80 (3.44-4.07)	3.35 (2.95-3.68)	<0.001
Ferritin, ug/L	419 (193-791)	646 (336-1263)	0.002	338 (214-628)	528 (297-1789)	0.085	408 (172-845)	766 (448-1567)	<0.001
CRP, mg/L	78.3 (39.6-132.5)	103.9 (37.8- 169.6)	0.089	86.3 (54.3- 161.9)	112.0 (77.5-174.5)	0.300	67.5 (35.9-115.5)	117.0 (58.3-191.0)	<0.001
Procalcitonin, ng/mL	0.11 (0.06-0.20)	0.35 (0.13-1.01)	<0.001	0.12 (0.08-0.37)	0.25 (0.09-0.59)	0.213	0.13 (0.63-0.24)	0.32 (0.14-1.04)	<0.001
Vaccination status of patients									
Unvaccinated[1]	108 (75.5)	54 (69.2)	0.312	13 (38.2)	8 (61.5)	0.151	129 (60.6)	60 (58.3)	0.695
CoronaVac 1 dose[2]	9 (6.3)	4 (5.1)	0.850	2 (5.9)	0	0.526	4 (1.9)	1 (1.0)	0.577
CoronaVac 2 dose[2]	21 (14.7)	19 (24.4)	0.095	11 (32.4)	4 (30.8)	0.721	67 (31.5)	35 (34.0)	0.656
CoronaVac 3 dose[2]	0	0	NA	1 (2.9)	0	NA	1 (0.5)	2 (1.9)	0.244
BNT162b2 1 dose[2]	4 (2.8)	1 (1.3)	NA	6 (17.6)	0	NA	8 (3.8)	2 (1.9)	0.727
BNT162b2 2 dose[2]	0	0	NA	1 (2.9)	0	NA	4 (1.9)	1 (1.0)	NA
C2B1[2]	1 (0.7)	0	NA	0	1 (2.1)	NA	0	2 (1.9)	NA

Variant detected: SARS-CoV-2 positive. Alpha variant, Beta variant, or Delta variant detected.

Variant not detected: SARS-CoV-2 positive, Alpha variant, Beta variant and Delta variant not detected.

Categorical data shown as number (percentage). Continuous variables displayed as median (interquartile range).

[1]Unvaccinated patients were statistically compared with those who received at least one dose of any vaccine.

[2] Each vaccine group was statistically compared with the unvaccinated patient group.

CHD: coronary heart disease, CKD: Chronic kidney disease, COPD: chronic obstructive pulmonary disease, CRP: C-reactive protein, CLD: Chronic liver disease, CVD: Cerebrovascular diseases, ICU:Intensive care unit, C2B1: 2 doses of CoronaVaC followed by 1 dose of BNT162b2 vaccine, Lym: Lymphocyte count, NA: not applicable, Neu: Neutrophil count.

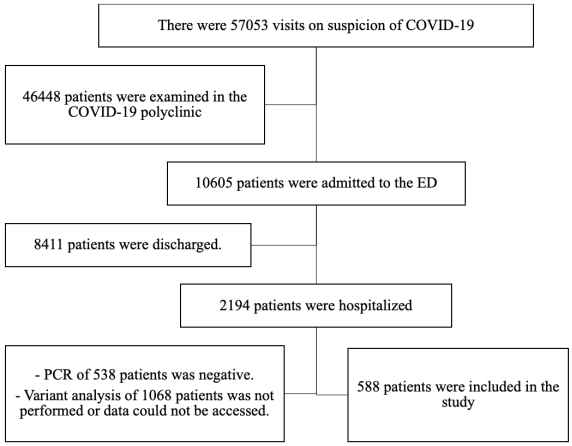

Figure 1: Study flow chart.

Pfizer, Mainz, Germany/New York, United States). At least a four-week interval is required between vaccinations. Mass vaccination campaigns in Turkey started with the CoronaVaC in January 2021, and BNT162b2 vaccine was widely used in April and May 2021. In our study, the vaccination status 14 days before the onset of symptoms was accepted as the current vaccination dose. The patient was considered fully vaccinated 14 days after the administration of two doses of any vaccine.

Data collection

Data including age, sex, concomitant diseases such as arterial hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, heart failure, active or previous cancer, chronic obstructive pulmonary disease, asthma, cerebrovascular disease, hyperlipidemia, rheumatic diseases, hypo/hyperthyroidism, chronic liver disease, and chronic kidney disease, laboratory data, pregnancy, vaccination status 14 days before symptom onset, rt-PCR result, variant analysis, intensive care unit (ICU) admission, length of hospital stay, and prognosis were recorded. All data were obtained from the hospital system and/or by interviewing patients or their relatives.

Hospital admission criteria

Patients were hospitalized and followed in accordance with the guidelines of the Turkish MoH and the Scientific Advisory Board as follows: a) patients with mild to moderate pneumonia with poor prognostic criteria in blood tests (lymphocyte count <800/μL or serum C-reactive protein [CRP] >10x upper limit of normal or ferritin > 500 ng/mL or D-dimer >1 ng/L) at the time of admission, b) Patients with severe pneumonia (with impaired consciousness, dyspnea, respiratory rate ≥30, SpO_2 on room air ≤90%, bilateral diffuse [>50%] lung involvement on imaging), c) Hypotension (mean blood pressure <65 mmHg), tachycardia (>100/min), d) Sepsis or septic shock, e) Myocarditis, acute coronary syndrome, cardiac arrhythmias, f) Acute renal injury.

Outcomes

The primary outcomes were to examine the effect of variant distribution and vaccination status on in-hospital mortality in hospitalized COVID-19 patients. Secondary outcomes were to examine the impact of demographic characteristics and laboratory data on in-hospital mortality in patients grouped by SARS-CoV-2 variants.

Statistical analysis

Based on the variant analysis, all patients were divided into two groups: variant (alpha, beta, and delta) detected, and no variant detected. In addition, patients with variants were further divided into subgroups (alpha, beta, and delta). A detailed analysis could not be performed, as the beta variant was detected in only four patients. The groups were compared in terms of demographic data (age, sex, concomitant diseases), laboratory data, vaccination status, hospitalization, ICU admission, and in-hospital mortality.

All statistical analyses were performed using the SPSS Statistics for Windows (Statistical Package for the Social Sciences package program version 25.0, IBM Corp., Armonk, N.Y., USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests and histograms were performed to check the normality of the sample data. Continuous data were expressed in median and interquartile range (IQR), while categorical data were expressed in number and frequency. The Mann-Whitney U test was used to compare the continuous groups and the chi-square ($\chi 2$) or Fisher's exact test was used to compare the categorical groups. A p value of < 0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

After the inclusion and exclusion criteria were met, a total of 588 consecutive patients were included in the study (Figure 1). The median age of the study population was 59.5 (range, 47 to 74) years, and 54.4% of the patients were males. At least one concomitant disease was present in 64.8% (n=381) of the patients. A variant was detected in 46.3% (n=272) of the patients. Of the patients with variants, 81.3% (n=221) were alpha, 1.5% (n=4) were beta, and 17.3% (n=47) were delta.

The median D-dimer value (0.69 [95% CI: 0.43 - 1.13] *vs.* 0.54 [95% CI: 0.35 - 1.11], p=0.008) and median lymphocyte count (0.98 [95% CI: 0.59 - 1.39] *vs.* 0.87 [95% CI: 0.57 - 1.28], p=0.014) were significantly higher in the group with detected variant than in the group without detected variant. The median D-dimer value was significantly higher in the group with alpha variant than in the group with delta variant (0.72 [95% CI: 0.47 - 1.18] *vs.* 0.50 [95% CI: 0.31 - 1.01], p=0.029). There was no significant difference in the other laboratory tests between the two variants (Table 1).

The overall ICU admission rate was 46.8% (n=313), the intubation rate was 39.3% (n=231), and the in-hospital mortality rate was 33.3% (n=196). There was no statistically significant difference between the patients with variant detection and those without variant detection in terms of ICU admission (49.3% *vs.* 44.6%, p=0.260), intubation (41.5% *vs.* 37.3%, p=0.298), and in-hospital mortality (34.2% *vs.* 32.6%, p=0.682). Similarly, there was no statistically significant difference between the patients with the alpha variant and patients with the delta variant in terms of intubation (43% *vs.* 34%; p=0.258) and in-hospital mortality (35.3% *vs.* 27.7%, p=0.316). However, the rate of ICU admissions was higher in patients with the alpha variant than in those with the delta variant (52% *vs.* 36.2%, p=0.048) (Table 1).

Among all hospitalized patients, the rate of patients who had never been vaccinated was 63.6% (n=374). The rate of unvaccinated patients was higher in patients with detected variant than in patients without variant (68% [n=185] and 59.8% [n=189], respectively, p=0.039). Similarly, the rate of unvaccinated patients was higher in patients with alpha variants than in those with delta variants (73.3% [n=162] and 44.7% [n=21], respectively, p<0.001). Demographic characteristics, laboratory data, vaccination status, and prognosis of patients after variant analysis are shown in Table 1.

In addition, there was no significant difference in the mortality rate between the vaccinated and unvaccinated patients with two doses of CoronaVaC (37.1% [n=59], 32.9% [n=123], p=0.347). The mortality rate was 16.7% in patients who received two doses of BNT162b2 (p<0.001).

In the subgroup analysis, high neutrophil counts, troponin, D-dimer, urea, ferritin, CRP, and procalcitonin levels, and low lymphocyte counts and albumin levels were associated with mortality in patients with the alpha variant and those without a variant. However, in patients with the delta variant, there was no significant difference in any of the laboratory tests included in the study between the patients who died and those who survived. Older age, hypertension, and malignancy were associated with mortality in patients with the alpha variant. In patients with the delta variant, there was no significant association between any comorbidity other than hypertension (p = 0.004), including age, and mortality. In all three patient groups (alpha, delta, and unproven variant), there was no statistically significant difference in the rate of unvaccinated patients between survivors and non-survivors (Table 2).

DISCUSSION AND CONCLUSION

In the current study, we investigated the factors affecting prognosis in hospitalized COVID-19 patients. For this purpose, we analyzed SARS-CoV-2 variant, demographic characteristics, vaccination status, and laboratory data of hospitalized patients. The results of our study showed that hospitalized patients with variants did not have an increased mortality rate compared to those without, and the mortality rate for those vaccinated with two doses of CoronaVaC was similar to those not vaccinated. Similar studies have been conducted in the literature (15); however, vaccine development and the emergence of new variants complicate decision-making based on new data from different regions of the world.

The COVID-19 pandemic has profoundly affected the entire healthcare system (16, 17). This includes ED visits and patients' behavior (17-19). New variants of

Sars-Cov-2 and waves in the pandemic remain a cause for concern. As of May 1st, 2021, when our study commenced, 1.39% of cases with the alpha variant and 0.69% of cases with the beta variant were reported in Turkey (16). Among the cases reported on August 23rd, the rate of alpha, delta, and gamma variants was 1.29%, 84.28%, and 0.01%, respectively (20). Eta, beta, and epsilon were not detected, and 5.10% were reported as the other variants (20). However, in our study, the rate of patients without alpha, beta, and delta variants was higher than the rate of patients with variants. These results suggest a new variant or variants that cannot be detected and are associated with more severe clinical manifestations, unlike the other variants. Another explanation is the possibility that the delta variant has a milder clinical course than expected since we included only hospitalized patients in our study. Furthermore, in the present study, there was no significant difference in the mortality rates between the patients in whom the alpha, delta, and variants were not detected. However, it is still unclear whether the cases in which the variants were not detected were wild types. Although there is no significant difference in mortality between the variants, if one variant is more contagious, it would lead to more deaths. The alpha variant is transmissible compared to the earlier wild-type variant and is the most common variant in Europe and North America until recently (7,21). According to previous studies, the delta variant is approximately two-fold more transmissible than the alpha variant (8). There are several reasons for the high transmission rate of the delta variant, including increased infectivity of the variant, waning vaccine-induced immunity, and enhanced immune defense by the variant (13,22,23). In addition, the *N501Y* mutation common to alpha, gamma, and beta variants may allow the virus to enter cells more easily and spread more rapidly from person to person (4). Unfortunately, the mutation cycle of the S protein is very rapid, and some mutations (such as E484K, N501Y, and K417N) affect both neutralization and transmission of the SARS-CoV-2 virus (4). It was previously shown that the neutralizing activity of CoronaVac was reduced 1.21-fold in the B.1.1.7 variant and 5.27-fold in the B.1.351 variant compared to the wild-type (14). The neutralizing effect of serum samples from patients vaccinated with Pfizer/BNT162b2 was reduced 7.85-, 5.12-, and 3-fold for the B.1.351, B.1.1.28, and B.1.617 variants, respectively, compared to the wild-type virus (24,25).

At the beginning of our study, 16.81% of the population in Turkey received at least one dose of the vaccine COVID-19 and 10.76% received two (15). At the end of the study on August 31st, 2021, 63.1% received at least one dose and 51.81% received two doses (16). In our study, a substantial proportion of hospitalized patients (63.6%) consisted of unvaccinated patients. Considering that the vaccination program targets the elderly and healthcare workers who are particularly exposed to the virus, the high rate of unvaccinated patients underscores the success of vaccines in controlling the disease. Vaccines provide a high level of protection against severe diseases with COVID-19, including infections caused by variants of concern (26). However, they are not fully effective and do not completely eliminate all risks (3). In our study, there was no statistically significant difference in mortality between unvaccinated patients and patients who received at least one dose of the vaccine. However, a significant proportion of vaccinated patients consisted of those who were vaccinated against COVID-19. Remarkably, the proportion of the patients who were vaccinated with two doses of BNT162b2 was very low among hospitalized patients. These results support the claim that BNT162b2 vaccine reduces hospitalizations (26). Since the CoronaVaC mass vaccination campaigns began in January 2021 and patients were vaccinated over a six-month period, most elderly persons and persons with comorbid conditions were vaccinated with the CoronaVaC before the BNT162b2 vaccine became widely available in April and May 2021. Those vaccinated with BNT162b2 tended to be slightly younger than those vaccinated with the CoronaVaC. However, 37.1% of patients who died were vaccinated with two doses of CoronaVaC. The Turkish MoH recommends that its citizens who receive two doses of CoronaVaC have a third dose of CoronaVaC or an additional dose of BNT162b2 vaccine, and our data support this recommendation.

In previous studies, high neutrophil counts, troponin, D-dimer, urea, ferritin, CRP and procalcitonin levels, and low lymphocyte counts and albumin levels were associated with poor outcomes in classic COVID19 patients (27, 28). In our study, we found

higher lymphocyte and d-dimer values in patients with variants compared to patients without variants. Dagcioglu et al. found that the lymphocyte count was higher in variant COVID-19 patients than in classic COVID-19 cases, whereas lower levels were observed in neutrophil count and ferritin values (29). Zhenkui Hu et al. found lower neutrophil counts, CRP, fibrinogen, procalcitonin, fibrinogen, and D-dimer levels in the patient group with the delta variant (unvaccinated) compared to the wild type (30). Although PCR contributes efficiently to the identification of SARS-CoV-2 infection, laboratory medicine has shown that it can significantly help differentiate severe and non-severe COVID-19 and predict prognosis (27, 28). However, in our study, no significant difference was found between survivors and non-survivors in patients with the delta variant in terms of the results of the tests performed. This further complicates clinicians' prediction of poor outcomes in patients with delta variants.

Nonetheless, there are several limitations of the current study. First, our study has a retrospective design. Second, as the variant analysis was unable to be performed in all hospitalized patients, we were only able to include approximately 30% of patients in the study. Variant analysis was not performed in many patients who were previously been confirmed to be infected with SARS-CoV-2 by PCR at various centers. The imperfect test sensitivity and specificity of the PCR assay may also have affected the detection of infection. In addition, the vaccinated individuals were vaccinated at different times, and the variants appeared at different times.

In conclusion, our results showed that a significant proportion of hospitalized patients consisted of patients without alpha, beta, and delta variants. There was no significant difference in in-hospital mortality between patients with and without variant detection. In addition, a significant proportion of hospitalized patients consisted of unvaccinated patients and patients with two doses of CoronaVaC doses. We recommend that these patients receive the third dose of vaccine.

Conflict-of-interest and financial disclosure

The author declares that she has no conflict of interest to disclose. The author also declares that she did not receive any financial support for the study.

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