Comparison of the Clinical and Laboratory Findings and Outcomes of Hospitalized COVID-19 Patients who Were Vaccinated with Coronavac or Unvaccinated: An Analytical, Cross Sectional Study

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Abstract

Purpose

COVID-19 vaccines have been shown to be highly effective; however, vaccine breakthrough infections resulting from hospitalization may still occur in a small percentage of vaccinated individuals. We investigated whether the clinical and microbiological features and outcomes were different between hospitalized COVID-19 vaccinated and unvaccinated COVID-19 patients.

Methods

This multicentre, prospective, cross-sectional study was performed between April and June 2021. All hospitalized COVID-19 patients who previously had at least one dose of Coronavac were included in the study, along with some unvaccinated patients. All epidemiologic, clinical and laboratory data of the patients were recorded and compared between the vaccinated and unvaccinated individuals.

Results

There were 69 fully Coronavac vaccinated and 175 unvaccinated patients. All breakthrough infections occurred in the first 3 months of vaccination. Fully vaccinated patients were older and had more comorbidities than unvaccinated patients ($p < 0.05$). There were minor differences between the groups in the symptoms, physical and laboratory findings, anti-spike IgG positivity rate, mean anti-SARS-CoV-2 S antibody level, and severity of COVID-19. The mortality rate of fully vaccinated patients was higher than the mortality rate in unvaccinated patients; however, vaccination was not an independent risk factor for mortality.

Conclusions

Hospitalized patients with breakthrough COVID-19 after Coronavac vaccination were usually older with comorbidities. The severity and clinical outcomes of these cases were similar to those of unvaccinated patients. Our findings suggest that the immune response elicited by Coronavac could be insufficient to prevent COVID-19-related severe disease and death within 3 months of vaccination among elderly people with comorbidities.

Introduction

After the administration of almost 8 billion doses of COVID-19 vaccines worldwide, it was understood that vaccines are highly effective in reducing COVID-19-related hospitalization, serious illnesses and death; however, the effectiveness of the vaccines varied by the vaccine type and sharply reduced over time; therefore, vaccine breakthrough infections resulting in hospitalization and death may occur in a small number of vaccinated, especially older and immunocompromised patients [1–4]. It was recently reported that 2.6% of fully vaccinated elderly individuals achieved a breakthrough SARS-CoV-2 infection, 20% and 2.2% of breakthrough infections needed hospitalization and resulted in death, respectively, and

34% of breakthrough hospitalizations needed ICU care [5]. Vaccinated people requiring hospital care due to severe COVID-19 breakthrough infection could have different clinical and laboratory features due to trained and previously acquired immunity. There are some reports of clinical and laboratory features of vaccine breakthrough infections after vaccinations with mRNA or adenoviral SARS-CoV-2 vaccines, but there is no article on the clinical characteristics of vaccine breakthrough infections after vaccination with Coronavac, which is an inactivated virus vaccine. In this study, we compared the clinical and microbiological features and outcomes of COVID-19 between Coronavac vaccinated and unvaccinated patients.

Material And Methods

This was a multicentre, prospective, analytical cross-sectional study. Patients who had at least one dose of Coronavac, had confirmed COVID-19 in the following days and were hospitalized in one of the five study hospitals between 01 April and 01 June 2021 were included in the study. Patients who had two doses of Coronavac separated at least 14 days and whose final dose was given at least 14 days earlier were accepted as fully vaccinated. For each vaccinated patient included in the study, 1 to 2 patients hospitalized in the same study hospital due to confirmed COVID-19, had no COVID-19 vaccination previously and preferably with similar comorbidities, and age was included as the control group. All epidemiologic, clinical and laboratory data of the patients were recorded in previously prepared forms. The clinical severity of COVID-19 on admission was determined with the National Early Warning Score (NEWS) [6], and the progression of all patients was evaluated and compared with the “Ordinal Scale for Clinical Improvement” of the World Health Organization (WHO) [7], which was defined on admission and on days 3, 5, 7, 10, 14 and 21 of hospitalization. One nasopharyngeal swab and 1 plain tube of blood were taken if possible on the day of admission for the determination of SARS-CoV-2 RNA, variants of concerns (VOCs) and SARS-CoV-2 spike IgG antibody. PCR for SARS-CoV-2 RNA was performed on a Rotor-Gene Q 5 Plex Real Time PCR device (Qiagen, Germany) using a Bio-Speedy® RT-qPCR detection kit (Bioeksan R&D Technologies Limited Company, Turkey). SARS-CoV-2 variant analysis was performed using a multiplex qRT-PCR assay (geneMAP™ variant detection kit kindly provided by the manufacturer Genmark Sağlık Ürünleri, Istanbul, Turkey), which is designed for the detection and identification of VOCs. SARS-CoV-2 IgG antibodies were detected by ELISA using an anti-SARS-CoV-2 IgG kit (Euroimmun, Germany). The epidemiologic, clinical and laboratory features of the vaccinated and unvaccinated patients were compared. Comparisons were performed using the chi-square, independent sample t test or Mann-Whitney U tests, where appropriate. Independent risk factors for mortality were defined by logistic regression analysis. IBM SPSS Statistics Version 21 was used for all of the statistical analysis.

The Ethical Committee of Istanbul University, Istanbul Faculty of Medicine approved the study on July 9, 2021, with a decision number of 14.

Results

A total of 292 patients who were hospitalized due to confirmed COVID-19 and either Coronavac vaccinated or not vaccinated previously were included in the study. Six patients were removed as they were vaccinated with the Biontec-mRNA COVID-19 vaccine. While 175 (60.8%) of the patients were unvaccinated, 111 received at least one dose of Coronavac. Twenty-five and 86 of the patients had one and two shots of vaccination, respectively. Sixty-nine patients were accepted as fully vaccinated as they were given two shots, with the second dose for at least 14 days earlier. The mean age of all cohorts was 66.44 ± 13.88 y, and 148 (51.4%) were female. All breakthrough infections occurred in the first 3 months of vaccination, and the mean time from the second dose to COVID-19 was 38.42 ± 16.82 , the median was 38 (range 14-84) days; the 25th, 50th, 75th and 100th percentiles were 25, 38, 50 and 84 days, respectively.

Fully vaccinated patients were older and more frequently had sore throat, hypertension, chronic kidney disease, higher fever, higher blood pressure, higher serum creatinine and troponin levels and a higher hospital mortality rate than unvaccinated patients ($p < 0.05$, Table 1).

Table 1

Comparison of the clinical and laboratory features and outcomes of patients who had either breakthrough COVID-19 after Coronavac vaccination or primary COVID-19.

Characteristics or results	Patients without any SARS-CoV-2 vaccination previously Total number: 217	Patients vaccinated with two doses of Coronavac at least 14 days earlier (n) Total number: 69	<i>p</i>
Age(y) mean $\pm$SD	65.57$\pm$13.95	75.63$\pm$9.06	<0.001
Gender, female, n (%)	111 (51.2)	37 (53.6)	0.720
Duration of symptoms, day, mean $\pm$ SD	7.88 $\pm$ 3.69	6.95 $\pm$ 3.40	0.064
Symptoms	76 (35.2)	17 (24.6)	0.104
Fever, n (%)	49 (22.6)	9 (13)	0.086
Shivering, n (%)	141 (65)	48 (69.6)	0.483
Cough, n (%)	44 (20.3)	11 (15.9)	0.426
Productive cough, n (%)	146 (67.3)	48 (69.6)	0.723
Fatigue, n (%)	173 (79.7)	47 (68.1)	0.046
Dyspnoea, n (%)	26 (12)	16 (23.2)	0.022
Sore throat, n (%)	18 (8.3)	3 (4.3)	0.274
Rhinorrhoea, n (%)	28 (12.9)	10 (14.5)	0.735
Anosmia, n (%)	29 (13.4)	14 (20.3)	0.161
Dysgeusia, n (%)	58 (26.7)	20 (29)	0.714
Headache, n (%)	105 (48.4)	31 (44.9)	0.616
Myalgia, arthralgia, n (%)	41 (19)	20 (29)	0.078
Nausea, vomiting, n (%)	21 (9.7)	6 (8.7)	0.808
Diarrhea, n (%)			

Characteristics or results	Patients without any SARS-CoV-2 vaccination previously Total number: 217	Patients vaccinated with two doses of Coronavac at least 14 days earlier (n) Total number: 69	<i>p</i>
Comorbidities	94 (43.3)	50 (72.5)	<0.001
Hypertension, n (%)	72 (33.2)	31 (44.9)	0.077
Diabetes Mellitus, n (%)	35 (16.1)	16 (23.2)	0.182
Chronic lung diseases, n (%)	15 (6.9)	12 (17.4)	0.010
Chronic kidney disease, n (%)	41 (18.9)	17 (24.6)	0.301
Coronary artery disease, n (%)	24 (11.1)	13 (18.8)	0.096
Other heart disease, n (%)	0 (0)	0 (0)	-
HIV infection, n (%)	3 (1.4)	2 (2.9)	0.403
SOT, n (%)	0 (0)	1 (1.5)	0.239
HCT, n (%)	17 (7.8)	9 (13)	0.190
Cancer, n (%)	15 (6.9)	5 (7.2)	0.925
Immunosuppressive treatment, n (%)			
NEWS score on admission, mean $\pm$ SD	5.93 $\pm$ 2.90	5.48 $\pm$ 2.77	0.255
Presence of fever, n (%)	76 (35.2)	17 (24.6)	0.104
Temperature on admission, $^{\circ}$C, mean $\pm$SD	36.53$\pm$0.56	36.74$\pm$0.69	0.013
The highest temperature during the course of the disease, $^{\circ}$ C, mean $\pm$ SD	37.04 $\pm$ 0.67	36.97 $\pm$ 0.61	0.485
Duration of fever, mean $\pm$ SD	2.51 $\pm$ 1.53	1.60 $\pm$ 0.69	0.074
Respiratory rate on admission, mean $\pm$ SD	23.00 $\pm$ 4.38	22.71 $\pm$ 3.95	0.642
The highest respiratory rate during the disease course, mean $\pm$ SD	27.31 $\pm$ 7.36	26.26 $\pm$ 5.69	0.368
Heart rate on admission, mean $\pm$ SD	86.54 $\pm$ 15.61	82.57 $\pm$ 16.22	0.080
The highest heart rate during the disease course, mean $\pm$ SD	103.04 $\pm$ 19.34	101.01 $\pm$ 19.38	0.300

Characteristics or results	Patients without any SARS-CoV-2 vaccination previously Total number: 217	Patients vaccinated with two doses of Coronavac at least 14 days earlier (n) Total number: 69	<i>p</i>
Blood pressure on admission, mean $\pm$ SD	121.18 $\pm$ 19.49	101.01 $\pm$ 19.38	0.370
The lowest blood pressure during disease course, mean $\pm$SD	101.25$\pm$17.00	106.54$\pm$17.41	0.009
O ₂ saturation on admission (SpO ₂), mean $\pm$ SD	86.68 $\pm$ 7.29	89.23 $\pm$ 5.68	0.908
The lowest SpO ₂ during the disease course, mean $\pm$ SD	82.91 $\pm$ 11.24	85.40 $\pm$ 6.88	0.528
PaO ₂ on admission, mean $\pm$ SD(n)	65.80 $\pm$ 28.11 (58)	68.11 $\pm$ 34.14 (18)	0.746
The lowest PaO ₂ during the disease course, mean $\pm$ SD(n)	55.58 $\pm$ 14.35 (60)	56.10 $\pm$ 17.86 (19)	0.899
Unilateral involvement on thorax CT, n (%)	17 (7.9)	5 (7.2)	0.851
Bilateral involvement on thorax CT, n (%)	194 (90.7)	61 (88.4)	0.586
50% involvement on thorax CT, n (%)	138 (64.5)	37 (53.6)	0.106
Blood WBC count on admission, mean $\pm$ SD	7 852.58 $\pm$ 3 657.02	9 998.26 $\pm$ 11 021.0	0.189
The highest blood WBC count during the disease course, mean $\pm$ SD	13 109.44 $\pm$ 6179.54	13 868.8 $\pm$ 6578.23	0.260
The lowest blood WBC count during the disease course, per microliter, mean $\pm$ SD	6 261.15 $\pm$ 2706.30	6 455.94 $\pm$ 3171.59	0.618
Blood haemoglobin level on admission, gr/dL, mean $\pm$ SD	12.45 $\pm$ 1.95	12.27 $\pm$ 1.90	0.500
The lowest blood haemoglobin level during the disease course, gr/dL, mean $\pm$ SD	10.99 $\pm$ 2.17	1.078 $\pm$ 1.92	0.455
Blood platelet count on admission, per microliter, mean $\pm$ SD	179 874 $\pm$ 123 599	163 791 $\pm$ 112 003	0.337
The lowest blood platelet count during the disease course, per microliter, mean $\pm$ SD	160 023 $\pm$ 115 627	138 031 $\pm$ 114 389	0.169

Characteristics or results	Patients without any SARS-CoV-2 vaccination previously Total number: 217	Patients vaccinated with two doses of Coronavac at least 14 days earlier (n) Total number: 69	<i>p</i>
Blood PNL count on admission, mean $\pm$ SD	6 185.49 $\pm$ 3 408.73	6 826.38 $\pm$ 4 365.70	0.521
The highest blood PNL count during the disease course, mean $\pm$ SD	10 897.58 $\pm$ 5 791.07	12 463.8 $\pm$ 8 927.46	0.246
Blood lymphocyte count on admission, mean $\pm$ SD	1 133.845 $\pm$ 821.75	1 088.99 $\pm$ 996.86	0.680
The lowest blood lymphocyte count during disease course, mean $\pm$SD	729.46$\pm$855.34	686.47$\pm$1 194.41	0.015
Serum CRP level on admission, mg/L, mean $\pm$ SD	92.77 $\pm$ 67.49	107.71 $\pm$ 69.85	0.076
The highest serum CRP level during the disease course, mg/L, mean $\pm$ SD	125.28 $\pm$ 87.96	143.23 $\pm$ 108.37	0.165
Serum procalcitonin level on admission, ng/ μ L, mean $\pm$ SD	0.43 $\pm$ 2.36 (190)	0.29 $\pm$ 0.46 (65)	0.295
The highest serum procalcitonin level during the disease course, ng/ μ L, mean $\pm$ SD	1.06 $\pm$ 5.23 (186)	1.27 $\pm$ 5.13 (64)	0.772
Serum ALT level on admission, U/L, mean $\pm$ SD	40.19 $\pm$ 92.50	27.02 $\pm$ 24.32	0.099
The highest serum ALT level during the disease course, U/L, mean $\pm$SD	197.98$\pm$1 024.87	62.39$\pm$62.89	0.019
Serum AST level on admission, U/L, mean $\pm$ SD	46.20 $\pm$ 92.22	39.52 $\pm$ 26.20	0.896
The highest serum AST level during the disease course, U/L, mean $\pm$ SD	302.99 $\pm$ 2 160	66.76 $\pm$ 76.42	0.827
Serum creatinine level on admission, mg/dL, mean $\pm$SD	1.04$\pm$0.86	1.17$\pm$0.61	0.021
The highest serum creatinine level during the disease course, mg/dL, mean $\pm$SD	1.25$\pm$1.12	1.33$\pm$0.72	0.027
Serum glucose level on admission, mg/dL, mean $\pm$ SD	173.84 $\pm$ 97.14	151.27 $\pm$ 52.46	0.642

Characteristics or results	Patients without any SARS-CoV-2 vaccination previously Total number: 217	Patients vaccinated with two doses of Coronavac at least 14 days earlier (n) Total number: 69	<i>p</i>
The highest serum glucose level during the disease course, mg/dL, mean $\pm$ SD	271.27 $\pm$ 128.43	259.10 $\pm$ 100.33	0.691
Serum ferritin level on admission, ng/mL, mean $\pm$SD	690.04$\pm$762.00	485.42$\pm$512.46	0.010
The highest serum ferritin level during the disease course, ng/mL, mean $\pm$ SD	1 206.61 $\pm$ 2 360.71	1 524.96 $\pm$ 4 265.98	0.069
Serum D-dimer level on admission, mg/L, mean $\pm$ SD	2.07 $\pm$ 6.47	2.34 $\pm$ 4.98	0.321
The highest serum D-dimer level during the disease course, mg/L, mean $\pm$ SD	3.92 $\pm$ 6.49	3.97 $\pm$ 6.49	0.358
Serum troponin level on admission, pg/mL, mean $\pm$SD(n)	21.18$\pm$ 45.92 (198)	28.61$\pm$ 42.60 (59)	<0.001
The highest serum troponin level during the disease course, pg/mL, mean $\pm$ SD(n)	37.72 $\pm$ 107.03 (201)	76.84 $\pm$ 254.90 (61)	0.083
Serum LDH level on admission, U/L, mean $\pm$ SD	396.55 $\pm$ 219.31	404.42 $\pm$ 515.57	0.077
The highest serum LDH level during the disease course, U/L, mean $\pm$ SD	722.34 $\pm$ 2620.94	467.36 $\pm$ 241.56	0.061
Serum IL-6 level on admission, mean $\pm$ SD(n)	72.72 $\pm$ 164.26 (20)	32.77 $\pm$ 50.08 (6)	0.242
The highest serum IL-6 level during the disease course, mean $\pm$ SD(n)	94.15 $\pm$ 96.51(11)	125.95 $\pm$ 11.24 (2)	0.662
Myocarditis, n (%)	0	0	-
Acute kidney injury, n (%)	12 (5.5)	4 (5.8)	1.000
DIC, n (%)	0	0	-
O ₂ supplement with nasal cannula, n (%)	171 (78.8)	49 (71)	0.181
O ₂ supplement with face mask with reservoir, n (%)	133 (61.3)	43 (62.3)	0.878

Characteristics or results	Patients without any SARS-CoV-2 vaccination previously Total number: 217	Patients vaccinated with two doses of Coronavac at least 14 days earlier (n) Total number: 69	<i>p</i>
O ₂ supplement with HFNC, n (%)	46 (21.2)	13 (18.8)	0.673
Non-invasive ventilation, n (%)	12 (5.5)	8 (11.6)	0.085
Mechanic ventilation, n (%)	16 (7.4)	9 (13)	0.146
Need for ICU support, n (%)	37 (17.1)	13 (18.8)	0.733
Need for vasopressors, n (%)	12 (5.5)	6 (8.7)	0.346
Need for ECMO support, n (%)	0	0	-
Need for CRRT, n (%)	4 (1.8)	2 (2.9)	0.594
Total duration of favipiravir treatment, day, mean ±SD	8.47±2.57	8.56±2.17	0.803
Glucocorticoid use for COVID-19, n (%)	198 (91.2)	63 (91.3)	0.988
Total administered dose of dexamethasone for COVID-19, mg, mean ±SD	37.79±33.26	42.54±37.76	0.448
Total administered dose of prednisolone for COVID-19, mg, mean ±SD	1 012.9±829.71	1 202.80±926.97	0.161
Anti-cytokine treatment for COVID-19, n (%)	36 (16.6)	8 (11.6)	0.316
Tocilizumab, n (%)	18 (8.3)	2 (2.9)	0.126
Anakinra, n (%)	21 (9.7)	6 (8.7)	0.808
Score of WHO ordinal scale on admission, mean ±SD(n)	3.42±0.98 (214)	3.435±0.9774 (69)	0.674
Score of WHO ordinal scale on day 3, mean ±SD(n)	3.93±0.64 (216)	3.95±0.49 (69)	0.674
Score of WHO ordinal scale on day 5, mean ±SD(n)	3.84±0.89 (216)	3.94±0.87 (68)	0.654
Score of WHO ordinal scale on day 7, mean ±SD(n)	3.64±1.17 (214)	3.71±1.29 (66)	0.654
Score of WHO ordinal scale on day 10, mean ±SD(n)	3.17±1.52 (209)	3.27±1.61 (65)	0.734

Characteristics or results	Patients without any SARS-CoV-2 vaccination previously Total number: 217	Patients vaccinated with two doses of Coronavac at least 14 days earlier (n) Total number: 69	<i>p</i>
Score of WHO ordinal scale on day 14, mean $\pm$ SD(n)	2.67 $\pm$ 1.64 (203)	2.93 $\pm$ 1.83 (62)	0.393
Score of WHO ordinal scale on day 21, mean $\pm$ SD(n)	2.15 $\pm$ 1.78(192)	2.32 $\pm$ 1.72 (56)	0.307
Nasopharyngeal swab SARS-CoV-2 PCR positivity on hospital admission, n(%)	42/58 (72.4)	33/36 (91.7)	0.033
Cycle threshold of SARS-CoV-2 PCR test, mean $\pm$ SD	32.07 $\pm$ 5.33	31.55 $\pm$ 5.58	0.340
Distribution of variants	15/17 (88.2)	12/16 (75)	0.521
Alpha, n(%)	1/17 (5.9)	3/16 (18.8)	
Alpha+E484K, n(%)Others, n (%)	1/17 (5.9)	1/16 (6.3)	
Presence of E484K mutation, n (%)	2/17 (11.8)	4/16 (25%)	0.398
Anti S antibody, S/CO, mean$\pm$SD (n)	5.14$\pm$2.57 (41)	6.11$\pm$3.19 (33)	0.025
Anti S antibody positivity, n (%)	36/41 (87.8%)	28/33 (84.8%)	0.712
Mortality, n (%)	17 (7.8%)	11 (15.9%)	0.048

Unvaccinated patients more frequently had dyspnea, higher serum ALT and ferritin levels, and higher blood lymphocyte counts on admission ($p < 0.05$, Table 1). NEWS scores were similar between the groups on admission and on days 3, 5, 7, 10, 14 and 21 of hospital stay. Additionally, laboratory findings on admission were similar between the vaccinated and unvaccinated patients, except vaccinated patients had higher blood WBC counts and serum troponin levels and unvaccinated patients had higher serum ALT and ferritin levels ($p < 0.05$). Results of on admission nasopharyngeal swab SARS-CoV-2 RNA PCR test and anti SARS-CoV-2 Spike IgG were available for 94 and 74 patients, respectively. The nasopharyngeal swab SARS-CoV-2 RNA PCR test positivity rate and mean anti-SARS-CoV-2 spike antibody S/CO ratio on hospital admission were higher in vaccinated patients than in unvaccinated patients ($p < 0.05$). The cycle threshold (Ct) of the SARS-CoV-2 PCR test on hospital admission was similar between the groups. However, the Ct values were significantly higher among 46 anti SARS-CoV-2 -S antibody-positive patients than among 9 anti SARS-CoV-2 -S antibody-negative patients (32.47 ± 4.180 vs 25.314 ± 6.885) ($p = 0.005$). SARS-CoV-2 variant analysis was performed for 33 patients, 16 of whom were fully vaccinated and 17 of whom were unvaccinated. The alpha variant was the most frequently isolated

variant whose presence rate was the same in the groups. Although the alpha+E484K variant was found to be more frequent (3/16 (18.8% vs 1/17 (5.9%)) among patients with vaccine breakthrough infections, the difference was statistically insignificant, probably due to the small number of patients. The presence of the E484K mutation was more frequent among fully vaccinated patients (4/16 (25%) vs 2/17 (11.8%)); however, the result showed no statistical significance.

In univariate analysis including all the patients, older age ($p=0.007$), number of comorbidities ($p=0.007$), chronic renal failure ($p=0.003$), chronic obstructive lung disease ($p=0.009$), heart disease other than coronary artery disease (congestive heart failure, heart valve diseases and hearth rhythm disorders) ($p=0.017$), cancer ($p=0.017$), full vaccination ($p=0.048$), body temperature on admission ($p=0.011$), hemoglobin ($p=0.021$), procalcitonin ($p=0.001$), creatinine ($p=0.009$) and troponin ($p=0.001$) levels, need for ICU ($p<0.001$), oxygen support with high flow nasal cannula (HFNC) or noninvasive ventilation or mechanical ventilation ($p<0.001$, for each), development of acute renal failure due to COVID-19 ($p<0.001$), ($p=0.009$) were found to be risk factors for mortality.

In multivariate logistic regression analysis including all the patients, the presence of chronic lung disease, cancer, chronic renal failure and other heart diseases, the need for oxygen with HFNC, and serum hemoglobin level on admission were found to be independent risk factors for mortality (Table 2).

Table 2
Results of multivariate analysis of mortality risk factors for COVID-19.

Variants	p	OR	95% Confidence Interval (CI)	
O ₂ supplement with HFNC, n (%)	<0.001	6.254	2.230	17.534
Blood haemoglobin level on admission	0.041	0.772	0.603	0.989
Presence of chronic lung diseases	0.031	2.999	1.108	8.111
Presence of cancer	0.022	4.345	1.234	15.296
Presence of chronic renal failure	0.014	4.049	1.335	12.283
Presence of cardiac diseases other than coronary heart disease	0.003	6.017	1.819	19.904

The mean age of fully vaccinated patients was 75 years (ranging 53-92 years). Age, presence of chronic kidney disease, development of acute kidney injury, need for ICU care, HFNC, vasopressors and mechanical ventilation were risk factors for mortality among fully vaccinated patients. Although the Ct of the SARS-CoV-2 PCR test was higher for surviving patients (32.01 ± 5.18 in 29 surviving vs 28.18 ± 8.01 in 4 deceased patients), the difference was statistically insignificant.

The NEWS scores on admission and on day 3 of hospital stay were not different between the deceased and surviving fully vaccinated patients, but the NEWS scores on days 5, 7, 10, 14 and 21 of hospital stay were higher in deceased patients ($p<0.05$) (Table 3).

Table 3
Comparison of the patients who recovered or died after vaccine breakthrough COVID-19.

Characteristics or results	Patients fully vaccinated with Coronavac n:69	Fully vaccinated patients who were recovered after COVID-19 n:58	Fully vaccinated patients who have died after COVID-19 n: 11	<i>p</i>
Age, mean $\pm$SD	75.63 $\pm$9.06	74.53$\pm$9.18	81.45$\pm$5.76	0.019
Gender, female, n (%)	37 (53.6)	34 (58.6)	3 (27.3)	0.097
Days after the second dose of the vaccine, mean $\pm$ SD	38.42 $\pm$ 16.82	33.18 $\pm$ 14.32	39.41 $\pm$ 17.18	0.263
Comorbidities	50 (72.4)	41 (70.7)	9 (81.8)	0.715
Hypertension, n (%)	31 (44.9)	29 (50)	2 (18.2)	0.095
Diabetes Mellitus, n (%)	16 (23.2)	11 (19)	5 (45.5)	0.056
Chronic lung diseases, n (%)	12 (17.4)	7 (12.1)	5 (45.5)	0.007
Chronic kidney disease, n (%)	17 (24.6)	16 (27.6)	1 (9.1)	0.270
Coronary artery disease, n (%)	0 (0)	0 (0)	0 (0)	-
HIV infection, n (%)	2 (2.9)	2 (3.4)	0 (0)	1.000
SOT, n (%)	1 (1.45)	1 (1.7)	0 (0)	1.000
HCT, n (%)	9 (13)	8 (13.8)	1 (9.1)	1.000
Cancer, n (%)	5 (7.3)	5 (8.6)	0 (0)	0.585
Immunosuppressive treatment, n (%)				
NEWS score on admission, mean $\pm$ SD	5.48 $\pm$ 2.77	5.53 $\pm$ 2.69	5.18 $\pm$ 3.28	0.702
O ₂ saturation on admission, mean $\pm$ SD	89.23 $\pm$ 5.68	89.12 $\pm$ 5.78	89.88 $\pm$ 5.30	0.732
Bilateral involvement on thorax CT, n (%)	61 (88.40)	52 (89.7)	9 (81.8)	0.604
>50% involvement on thorax CT, n (%)	37 (53.6)	31 (53.4)	6 (53.5)	0.947
Anti S S/Co ratio, mean $\pm$SD	6.11$\pm$3.19 (33)	6.53$\pm$2.99(28)	3.76$\pm$ 3.48 (5)	0.034

Characteristics or results	Patients fully vaccinated with Coronavac n:69	Fully vaccinated patients who were recovered after COVID-19 n:58	Fully vaccinated patients who have died after COVID-19 n: 11	<i>p</i>
Myocarditis, n (%)	0 (0)	0	0	-
Acute kidney injury, n (%)	4 (5.8)	1 (1.7)	3 (27.3)	0.011
DIC, n (%)	0 (0)	0	0	-
O ₂ supplement with nasal cannula, n (%)	49 (71.0)	42 (72.4)	7 (63.6)	0.556
O ₂ supplement with reservoir face mask, n (%)	43 (62.3)	35(60.3)	8(72.7)	0.437
O₂ supplement with HFNC, n (%)	13 (18.8)	6 (10.3)	7 (63.6)	<0.001
Mechanic ventilation, n (%)	9 (13.0)	2 (3.4)	7 (63.6)	<0.001
Need for ICU care, n (%)	13 (18.8)	4 (6.9)	9 (81.8)	<0.001
Vasopressors, n (%)	6 (8.7)	1 (1.7)	5 (45.5)	<0.001
Total duration of favipiravir treatment, day, mean ±SD	8.56± 2.17	8.36±2.26	9.63±1.20	0.074
Glucocorticoid use for COVID-19, n (%)	63 (91.3)	52 (89.7)	11 (100)	0.580
Total administered doses of dexamethasone for COVID-19, mg, mean ±SD	42.54±37.76	44.82±41.25	34.80±24.14	0.704
Total administered doses of prednisolone for COVID-19, mg, mean ±SD	1202.80±926.97	1138.64±921.67	1 502.22±945.75	0.290
Anti-cytokine treatment for COVID-19, n (%)	8 (11.6)	5 (8.6)	3 (27.3)	0.109
Tocilizumab, n (%)	2 (2.9)	2 (3.4)	0 (0)	1.000
Anakinra, n (%)	6 (8.7)	3 (5.2)	3 (27.3)	0.047
Score of WHO ordinal scale on admission, mean ±SD	3.46±0.90	3.46±0.88	3.45±1.03	0.831

Characteristics or results	Patients fully vaccinated with Coronavac n:69	Fully vaccinated patients who were recovered after COVID-19 n:58	Fully vaccinated patients who have died after COVID-19 n: 11	<i>p</i>
Score of WHO ordinal scale on day 3, mean $\pm$ SD	3.95 $\pm$ 0.49	3.98 $\pm$ 0.44	3.81 $\pm$ 0.75	0.598
Score of WHO ordinal scale on day 5, mean $\pm$ SD	3.94 $\pm$ 0.87	3.82 $\pm$ 0.79	4.60 $\pm$ 1.07	0.029
Score of WHO ordinal scale on day 7, mean $\pm$ SD	3.71 $\pm$ 1.29	3.44 $\pm$ 1.15	5.20 $\pm$ 1.03	<0.001
Score of WHO ordinal scale on day 10, mean $\pm$ SD	3.27 $\pm$ 1.61	2.90 $\pm$ 1.40	5.30 $\pm$ 1.15	<0.001
Score of WHO ordinal scale on day 14, mean $\pm$ SD	2.93 $\pm$ 1.83	2.38 $\pm$ 1.37	5.80 $\pm$ 1.13	<0.001
Score of WHO ordinal scale on day 21, mean $\pm$ SD	3.32 $\pm$ 1.72	1.83 $\pm$ 1.12	5.71 $\pm$ 1.38	<0.001

Discussion

In this study, we found that patients hospitalized due to breakthrough COVID-19 after Coronavac vaccination were older and had more comorbidities than unvaccinated hospitalized COVID-19 patients. The reported features of vaccine breakthrough COVID-19 cases after mRNA and/or adenovirus vector based vaccines were also quite similar the features found in our study; among cases hospitalized for COVID-19, fully vaccinated ones were older and more likely to have underlying medical conditions or to be immunosuppressed compared with unvaccinated cases [3, 8–11].

Our findings, along with others, show that older patients with comorbidities are among the most vulnerable population to severe vaccine breakthrough COVID-19. For this group of patients, close follow-up of vaccine response, administration of booster doses of vaccines if needed and continuation of non-pharmaceutical interventions, including social distancing and mask wearing after vaccination, are quite important.

There were minor differences in the symptoms and physical findings of COVID-19 patients who were either fully vaccinated or unvaccinated in our study. Additionally, the laboratory findings on admission of vaccinated patients were similar to the findings of unvaccinated COVID-19 patients in our cohort except

that the mean ferritin level of vaccinated patients was lower than the levels in unvaccinated patients (690.04 ng/mL vs 485.42 ng/mL). In another study from India, ferritin levels were also found to be lower in patients with vaccine breakthrough infections than in patients with primary infection (544.82 ng/mL vs 392.26 ng/mL) [12]; however, no significant differences were found in white blood count, absolute lymphocyte count nadir, C-reactive protein, interleukin-6, procalcitonin, oxygen saturation, lung involvement, and fever frequency between the recipients of the first and second vaccine doses in a study conducted in Poland [13]. It should be known that the clinical course or laboratory findings of patients hospitalized due to breakthrough COVID-19 after Coronavac vaccination may not reveal any distinctive features. Despite the lower ferritin level, the severity of the disease, incidence of complications including acute kidney injury, requirements for intensive care unit support and mortality rate were not different between the vaccinated and unvaccinated patients in our study; NEWS scores of vaccinated and unvaccinated patients on admission were found to be 5.53 and 5.18, respectively. The mortality rate of fully vaccinated patients was found to be higher than the mortality rate of unvaccinated patients in univariate analysis; however, vaccination was not found to be an independent risk factor for mortality in the multivariate analysis. In contrast to our study, the severity of the disease and a requirement for ventilator support were significantly lower in the vaccinated group than in the unvaccinated patients in the Indian study mentioned above; however, the mortality rate was not found to be significantly different between the groups in that study and similar to our study, no significant differences were seen in the incidence of acute kidney injury (AKI), requirement for renal replacement therapy (RRT) or thrombotic complications between the two groups [12]. In another study of 218 mRNA-vaccinated breakthrough delta variant COVID-19 cases hospitalized in a Singapore Hospital, despite significantly older age in the vaccine breakthrough group, the odds of severe COVID-19 requiring oxygen supplementation were significantly lower following vaccination, and vaccination was found to be associated with a faster decline in viral RNA load and a robust serological response [14]. In a USA study of 67,311 laboratory-confirmed COVID-19-associated hospitalized adult cases, there were no differences in the risk for ICU admission or in-hospital death between 30,967 unvaccinated and 1,255 fully vaccinated persons [3]. Finally, in a recent study from the USA, among patients hospitalized with COVID-19, mRNA vaccine breakthrough cases less commonly received ICU care and invasive mechanical ventilation than unvaccinated cases, and the likelihood of death was also lower in the vaccinated cases; but these findings did not differ by age group or immunocompromised status [11]. These differences in the clinical severity and outcomes of vaccinated and unvaccinated hospitalized COVID-19 patients between our study and other cohorts might be associated with two reasons: One is that compared with the Indian and Singapore cohorts [12, 14], our and USA's [3] vaccinated breakthrough cases were older (mean ages were 75 and 73 vs 58 and 56 years in our and USA and Indian and Singapore studies, respectively) and had more comorbidities (prevalence of HT+ DM were 72%+44% and 70%+39% vs 51% vs 7%+19% in our and USA [3] and Indian and Singapore cohort [12, 14], respectively). Both older age and comorbidities are well-defined risk factors leading to severe disease and lower antibody response and protection from vaccines or higher vaccine unresponsiveness. Coronavac was found to be 42% effective among elderly people (>70 years old) after ≥ 14 days of the 2nd dose; it declined with increasing age in a Brazilian study [15]. In another study from Poland, fully vaccinated breakthrough cases were more frequently confirmed to be

vaccine non-responders [13]. Confirming this hypothesis, in a recent study from the UK, among 10,024 vaccinated individuals with SARS-CoV-2 infection (9479 of them were matched to unvaccinated controls), COVID-19 vaccination was found to be associated with a lower risk of several, but not all, COVID-19 sequelae in those with breakthrough SARS-CoV-2 infection, but these benefits of vaccination were clear in younger people but not in people over 60 years of age [16].

Another reason could be the type of vaccine used for vaccination. We included patients only vaccinated with Coronavac. Although all WHO-approved SARS-CoV-2 vaccines were shown to be effective against COVID-19, none of the COVID-19 vaccines created an equal level of protection, and the reported effectiveness of those vaccines against symptomatic COVID-19 varied from 50–95% between the vaccine types. mRNA vaccines were reported to be the most effective vaccines, followed by adenoviral vaccines and then inactivated vaccines [17]. Additionally, all vaccine types, including inactivated and mRNA vaccines, were shown to have lower efficacy among elderly people in real life [15, 18].

It is widely accepted that protection from SARS-CoV-2 after vaccination is largely mediated by a neutralizing antibody (Nab) response, and there is a significant and positive correlation between serum anti-spike IgG levels and Nab titers [19, 20]. Vaccine-elicited neutralization levels measured early after vaccination were found to be correlated with the subsequent protective efficacy measured in phase 3 trials [21], and the duration of immunity mainly resulted from the starting Nab levels. Because of the major differences in vaccine-elicited Nab levels between different types of vaccines, it was foreseen that the duration of protection induced by vaccines would also differ between the different vaccine types. Coronavac-elicited Nab titers were found to be lower than convalescent patients in a phase 2 study, and it was predicted that booster doses will be needed within 3 months after the 2nd dose; this time span was supposed to be 9-12 months for mRNA vaccines [22]. Serum Nab titers were lower after the second dose of vaccines in both Coronavac- and Biontech mRNA-vaccinated older (>65 years old) people than in younger people [15, 22]. Additionally, the risk of symptomatic COVID-19 decreased with increasing levels of anti-spike IgG and anti-RBD IgG and Nab titer [23]. In real life, it was also seen that vaccine effectiveness decreases significantly over time. In an Israel study including almost 700.00 people, all of whom were vaccinated with the BioNTech/Pfizer mRNA BNT162b2 vaccine in a two-dose regimen, a significant correlation was found between time-from-vaccine and afforded protection against SARS-CoV-2 infection [24]. BNT162b2 mRNA vaccine-induced protection against SARS-COV-2 infection was shown to wane rapidly following its peak after the second dose, but protection against hospitalization and death persisted at a robust level for 6 months after the second dose[25]. The efficacy of the Coronavac vaccine against severe delta variant infection among elderly people was shown to be 79% 14-30 days after the second dose, and the efficacy decreased significantly 6-8 months later to 24% [26]. However, in our study, all breakthrough infections occurred during the first 3 months of vaccination, and the median time from the second dose to COVID-19 was 38.42 ± 16.82 days. As a result, it was concluded that not the decreasing level of Nabs but unresponsiveness or lower antibody response to the Coronavac vaccination is the main reason for the same rate of severe consequences of COVID-19 among fully vaccinated and unvaccinated cases in our cohort. As lower than 10% of our fully vaccinated cases had immunosuppressive treatment or conditions including SOT, BMT or active cancer chemotherapy in our

cohort, the main reason for vaccine ineffectiveness was immune senescence due to older age and other comorbidities. Our finding of the same rate of SARS-CoV-2 spike antibody positivity among fully vaccinated and unvaccinated patients also supports this idea. In a study of breakthrough COVID-19 after mRNA vaccinations, the frequency of detectable anti-Spike antibodies in vaccinated individuals was found to be higher (100%) than that in unvaccinated individuals (16%) [14].

Although the mean S/CO of anti-S IgG on the 7th day of complaints among Coronavac-vaccinated inpatients was higher than that among unvaccinated inpatients in our study, the numbers were found to be very close to one another, at 6.11 vs 5.14, respectively. However, it was shown that SARS-CoV-2 breakthrough infections are a strong booster of the humoral immune response among fully vaccinated patients, the anti-spike IgG antibody levels were increased significantly as low as 2 to 4 days after the onset of symptoms of breakthrough infections, and the levels were more than 10-fold higher in fully vaccinated infected individuals than in unvaccinated uninfected individuals [12, 27, 28]. These findings also support the lower response rate to the Coronavac vaccine among our cohort.

Corbett et al. recently described the immune correlates of protection by mRNA SARS-CoV-2 vaccine in a primate model. They found that S-specific IgG thresholds for protection from pneumonia and URT infections were >336 IU/mL and >645 IU/mL, respectively [29]. Those numbers translate into 7.5 S/CO and 14.5 S/CO levels, respectively, in the EuroImmune kit that was used in our study [30]. Our mean anti-S IgG levels of 5 S/CO and 6 S/CO among unvaccinated and vaccinated patients, respectively, were lower than the estimated level of protection for pneumonia despite the rapidly boosting effect of breakthrough infections among vaccinated people [28]. However, a protective threshold level of anti-SARS-CoV-2 spike IgG is not fully defined at the moment; as a result, it is impossible to draw a final conclusion with these results, and studies determining the protective level of antibodies against symptomatic COVID-19 and COVID-19 pneumonia are urgently needed. This type of level would be useful, especially among elderly and immunocompromised persons in whom unresponsiveness to the vaccine is expected.

We found a higher percentage of SARS-CoV-2 PCR positivity on admission among vaccinated patients, which could also be a reflection of the older age and comorbidities of those patients. We found no significant difference in Ct values between vaccinated and unvaccinated groups infected with SARS-CoV-2. There were numerous studies with similar results, especially during the delta surge [31–34]. Given the substantial proportion of asymptomatic vaccine breakthrough cases with high viral loads, interventions, including masking and distancing, should be considered for all vaccinated persons especially in the settings with elevated COVID-19 transmission [35].

This study was performed during the alpha peak of the COVID-19 pandemic in Turkey, and as a result, most of our included patients were infected with the alpha variant. The E484 mutation, either with alpha mutations or by itself, was more frequently determined in vaccinated people in our study; however, it showed no statistical significance. The E484K mutation is known to reduce susceptibility to antibody-mediated neutralization and is more prone to vaccine escape, which is also supported by our results [36].

Although Coronavac vaccination has been shown to reduce COVID-19-related hospitalization [37], our study is the first to evaluate the association between vaccination with Coronavac and progression to critical illness among hospitalized COVID-19 patients.

Our study has some limitations. As we included only hospitalized COVID-19 patients, we were unable to describe the effect of Coronavac on reducing hospitalization among COVID-19 patients. Additionally, while we included all the Coronavac vaccinated hospitalized COVID-19 cases, we were not able to include all the unvaccinated COVID-19 patients due to the high number of patients because of the COVID-19 alfa surge in Turkey during the study period. This could result in selection biases of unvaccinated patients and could affect the results of the comparisons, but the inclusion of nearly 3 times more unvaccinated patients than vaccinated patients could increase the power of our analysis.

Conclusions

Elderly people with comorbidities, who have been vaccinated with Coronavac should continue to practice non-pharmaceutical interventions, including social distancing and mask-wearing after vaccination, because of the ongoing risk of severe COVID-19, especially during uncontrolled infection transmission in the community. Our findings, including the occurrence of breakthrough COVID-19 in the first three months of vaccination, the same clinical and laboratory features and outcomes of COVID-19, the same rate of anti-spike IgG positivity, and minor differences in antibody levels among fully Coronavac vaccinated and unvaccinated patients, suggest that the immune response elicited by Coronavac could be insufficient to prevent COVID-19-related hospitalization and death within 3 months of vaccination among elderly individuals with comorbidities. It also suggests that the problem is not decreasing immunity by time but the insufficient immune response to the Coronavac among this group of patients from the beginning of the vaccination. Considering three or more doses for primary immunization with Coronavac, heterologous vaccinations with different vaccine types or using more immunogenic vaccines rather than Coronavac could be the solutions in which studies should be done.

Declarations

- a. Funding: GeneMAP™ variant detection kit kindly provided by the manufacturer Genmark Sağlık Ürünleri, Istanbul, Turkey. Other expenses were supported by authors.
- b. Conflict of interests: None
- c. Acknowledgement: None
- d. Availability of data: All the data and consent forms are available and could be obtained from the corresponding author.
- e. IBM SPSS Statistics Version 21 was obtained via Istanbul University Faculty of Medicine a registered user of the programme.
- f. The Ethical Committee of Istanbul University, Istanbul Faculty of Medicine approved the study on July 9, 2021, with a decision number of 14.

- g. Author's contributions: Serap Şimşek-Yavuz: Designed the study, analysed the data, wrote the paper, Gülşah Tuncer: Collected the data, Özlem Altunaş Aydın: Collected the data, Mehtap Aydın: Collected the data, Filiz Pehlivanoğlu: Collected the data, Yeşim Tok: Performed analysis, Sevim Meşe: Performed analysis, Alper Gündüz: Collected the data , Ceyda Geyiktepe Güçlü: Collected the data, İklîma Özdoğan: Collected the data, Börçe Hemiş: Collected the data, Pınar Soğuksu: Performed analysis, Aysun Benli: Collected the data, Seniha Başaran: Collected the data, Kenan Midilli: Performed analysis, Haluk Eraksoy: Collected the data.
- h. Freely-given, informed consent to participate in the study was taken from all of the participants of the study. The Informed Consent Form was prepared in accordance with WHO requirements.
- i. Consent for publication (include appropriate statements): We, all the authors, give our consent for all of our article details to be published in the European Journal of Clinical Microbiology and Infectious Disease . Kind regards.

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