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COVID-19: booster(s) *vs.* hospitalization and Intensive Care Unit admission

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Abstract. – OBJECTIVE: As the pandemic continues, different vaccine protocols have been implemented to maintain the protection of vaccines and to provide protection against new variants. The aim of this study was to assess hospitalized patients' vaccination status and document the efficacy of boosters.

PATIENTS AND METHODS: The patients that were hospitalized due to COVID-19 were enrolled from 28 hospitals in Turkey for five months from September 2021. 5,331 confirmed COVID-19 patients from collaborating centers were randomly enrolled to understand/estimate the distribution of vaccination status in hospitalized patients and to compare the efficacy of vaccination/booster protocols.

RESULTS: 2,779 men and 2,552 women of which 2,408 (45.2%) were admitted to Intensive Care Units participated in this study. It was found that the highest risk reduction for all age groups was found in groups that received 4 doses. Four doses of vaccination for every 3.7 people under 50 years of age, for every 5.7 people in the 50-64 age group, and for every 4.3 people over 65 years of age will prevent 1 patient from being admitted to intensive care.

Regardless of the type of vaccine, it was found that the risk of ICU hospitalization decreased in those who were vaccinated compared to those who were not vaccinated. Regardless of the type of vaccine, the ICU risk was found to decrease 1.25-fold in those who received 1 or 2 doses of vaccine, 1.18-fold in those who received 3 doses, and 3.26-fold in those who received 4 doses.

CONCLUSIONS: The results suggested that the addition of a fourth dose is more effective in preventing intensive unit care even in disadvantaged.

Key Words:
COVID-19, Booster, Vaccination, Hospitalization, Vaccine effectiveness.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), has quickly spread into a pandemic, with approximately 420 million cases of infection and more than 5.8 million deaths recorded worldwide as of February 18, 2022[1]. Vaccination is the most effective method of pandemic control; however, vaccination rates, particularly booster shot rates, remain below the target level in most countries[2], and cases/hospitalizations continue to rise despite the availability of effective vaccines. Vaccines of various types exist, including messenger ribonucleic acid (mRNA), vector, and inactivated vaccines, and population studies[3-7] have demonstrated their effectiveness. Except for one (Ad26.COV2.S, Johnson & Johnson-Janssen), all vaccination protocols required two injections at 1-2 month intervals. Immunity declines with time after vaccination, impaired response to vaccines in high-risk patients, and new virus variants necessitated modification of protocol changes and booster shots.

Turkey is one of the most affected countries, and it is currently experiencing the pandemic's fifth wave. Vaccination in Turkey began in January 2021, with only Sinovac[7] available at

Table I. Important dates of vaccination in Turkey.

Date	Action
January 2021	Sinovac*
April 2021	BioNTech**
July 2021	First booster dose (either Sinovac or BioNTech) for individuals who received two doses of Sinovac
August 2021	Second booster dose opportunity (only BioNTech) for individuals who received two doses of Sinovac for VISA and travel requirements
August 2021	Vaccination began for individuals aged <18 years
November 2021	Booster dose for individuals who received two doses of BioNTech after 6 months
December 2021	Booster dose for individuals who received two doses of BioNTech after 3 months and opportunity for four doses of Sinovac
December 26, 2021	***Turkovac
December 31, 2021	***Third booster (fifth) dose opportunity for individuals who received four doses

*Healthcare workers first, followed by older adults, starting from those aged >90 years and decreasing by 5 years. **Individuals aged 60-65 years and younger citizens had two choices (either Sinovac or BioNTech). ***Does not have any significant effect on our study design.

first (Table I). Despite anti-vaccine campaigns and vaccine hesitancy, vaccination programs are generally regarded as successful (>92% of the adult population received their first dose)[8]. Countries have different vaccines and protocols. A pandemic is a dynamic period in which our knowledge grows and new mutations emerge; thus, data sharing is critical. In August 2021, Turkey was the first country to offer a fourth (second booster) dose to residents. The goal of this multicenter study was to assess the hospitalized patients' vaccination status, to compare the efficacy of booster vaccine protocols and to define the risk factors of need of Intensive Care Unit in hospitalized COVID-19 patients.

Patients and Methods

Study Design

Prospective cross-sectional data were collected from 28 hospitals in 18 cities in Turkey for five months, beginning from September 2021 until January 2022.

Inclusion criteria

– Patients hospitalized aged over 18 years of age, during the first 10 days of each month from August 2021; hospitalized either in clinics or Intensive Care Unit.

Exclusion criteria

– Patients hospitalized due to social indications rather than the COVID-19 itself.

All patients participated in the study after the ethical approval from Cukurova University Non-Interventional Committee (114/2021) was obtained and they signed the informed consent consequently. The study is supported by Turkish Thoracic Society. Our cross-sectional August 2021 data were previously published[9].

Participants and Data Sources/ Measurement

Age, sex, vaccination status, and comorbidities (diabetes mellitus, hypertension, cardiovascular disease, chronic lung disease, cerebrovascular disease, cancer, chronic kidney disease, solid organ transplantation, and pregnancy) were investigated *via* a questionnaire applied by the corresponding doctor. Patients were categorized into two groups: intensive care group and clinic group. A government vaccine tracking system was used to determine patients' vaccination status and dates in available cases. Two types of vaccines are available in Turkey: Sinovac (inactivated) and BioNTech (mRNA).

The patients were categorized into four groups according to their vaccination status:

1. Unvaccinated;
2. Sinovac-based protocols (two doses of Sinovac, three doses of Sinovac, two doses of Sinovac plus one dose of BioNTech, or two doses of Sinovac plus two doses of BioNTech);
3. BioNTech-based protocols (two doses of BioNTech or three doses of BioNTech);
4. Others (one dose of Sinovac, one dose of BioNTech, four doses of Sinovac, three doses of Sinovac plus one dose of BioNTech, or last dose of any protocol performed less than 14 days after the last dose).

We also determined the last vaccination date for two doses of Sinovac plus one dose of BioNTech and two doses of Sinovac plus two doses of BioNTech groups (only for January 2022) and categorized them into two groups: <90 days and >90 days.

Variables

Primary outcome

– Determining the effectiveness of the COVID-19 vaccines (especially the boosters) by comparing the vaccination status of hospitalized patients.

Secondary outcomes

– To identify the vaccination schemes of the COVID-19 patients who were admitted to either clinics or Intensive Care Units.
– To criticize the effect of the fourth dose of COVID-19 vaccines.
– To define the risk factors for Intensive Care Unit in hospitalized COVID-19 patients.

Influencing factors: different vaccines, the need for hospitalization in clinics/Intensive Care Unit, comorbidities, gender, age.

Sample Size

We collected data from 5,331 hospitalized COVID-19 from collaborating centers. Each patient hospitalized for COVID-19 during study period has included. Patients hospitalized for social reasons or isolation were excluded.

We categorized patients into three groups according to age: <50 years, 50-64 years, and ≥65 years. Data were also obtained from the Ministry of Health website[10]. The study was approved by the Ministry of Health and Cukurova University non-interventional Ethical Committee and supported by Turkish Thoracic Society.

Statistical Analyis

The statistical analysis was performed by SPSS for Windows version 25 (IBM Corp., Armonk, NY, USA). The normality of the numerical variables was evaluated by the Shapiro-Wilk test. The Mann-Whitney U test was performed to compare patients with long term symptoms and those without for nonnormal numerical variables. In the multivariate analysis, variables were selected based on significance in the univariate analysis. Binary logistic regression analyses were performed to estimate ICU admission risk and calculate odds ratios (aORs) and 95% confidence intervals (CIs). p-value <0.05 was considered statistically significant.

Results

We enrolled 5,331 patients (2,779 men, 2,552 women; mean age 62.1 years) from hospitals, of which 2,408 (45.2%) were admitted to Intensive Care Units. Approximately one-third (37%) of patients were unvaccinated, and the next largest group comprised those administered two doses of Sinovac (23.6%). The vaccination status, mean age, and number of comorbidities of patients are shown in Table II. Table III provides more detailed information about comorbidities. The percentages of the patients who have two or more comorbidities were 25.4%, 43.6%, 53.4% and 64.1% in unvaccinated, vaccinated with one/two doses, vaccinated with three doses and vaccinated with four doses respectively (p<0.001). The percentages of the patients over 65 years were 29.7%, 53.2%, 71.1% and 65.4% in unvaccinated, vaccinated with one/two doses, vaccinated with three doses and vaccinated with four doses respectively (p<0.001). The comorbidities and age distribution of hospitalized COVID-19 patients can be seen in Figure 1 and Figure 2, respectively.

Table IV shows vaccination status of the hospitalized patients by month. Unvaccinated patients account for the largest group in all months varying between 32.9% and 47.5%.

The highest risk reduction for all age groups was found in groups that received 4 doses. Four doses of vaccination for every 3.7 people under 50 years of age, four doses of vaccination for every 5.7 people in the 50-64 age group, and four doses of vaccination for every 4.3 people over 65 years of age will prevent 1 patient from being admitted to intensive care. Relative risk reduction was also found to be higher for each age group in groups with four doses of vaccination in hospitalized COVID-19 patients. It was found that the risk of Intensive Care Unit hospitalisation would decrease by 76.6% in the group under 50 years of age, 39.5% in the 50-64 age group, and 42% in the group over 65 years of age (Table V).

The exact last vaccination date was available in 103 of 160 patients, 80 patients received two doses of Sinovac + one dose of BioNTech and 23 patients received two doses of Sinovac + two doses of BioNTech. The duration between the last vaccine dose and hospitalization dates was longer than 90 days in 75 of 80 (94%) and 11 of 23 (49%) patients who received two doses of Sinovac + one dose of BioNTech and two doses of Sinovac plus two doses of BioNTech, respectively. The logistic regression model created to predict the risk of In-

Table II. Vaccination status, sex, mean age, hospitalizations, and number of patients' comorbidities.

Vaccination status	Total number	Sex		Mean age (years)	Hospital		Mean number of comorbidities
		Male, n (%)	Female, n (%)		Clinics, n (%)	Intensive Care Unit, n (%)	
Unvaccinated	1,973 (37)	985	988	54.2±17.8	1,112	861	0.98±1.12
Sinovac-based protocols							
Two doses of Sinovac	1,256 (23.6)	600	656	68.5±13.1	631	625	1.66±1.21*
Three doses of Sinovac	781 (14.7)	461	320	72.1±11.8	396	385	1.74±1.26*
Two doses of Sinovac + one dose of BioNTech	452 (8.5)	270	182	70.6±13.7	217	235	1.81±1.32*
Two doses of Sinovac + two doses of BioNTech	61 (1.1)	38	23	66.9±15.8	45	16	1.93±1.2*
BioNTech-based protocols							
Two doses of BioNTech	382 (7.2)	207	175	54±14.9	267	115	1.15±1.18
Three doses of BioNTech	11 (0.2)	6	5	51.2±15.8	10	1	1.09±1.04
Others	415	212	203		245	170	
Total	5,331	2,779	2,552	62.1±17.2	2,923	2,408	1.37±1.24

*$p<0.001$, all Sinovac based groups had more comorbid diseases compared to unvaccinated patients.

tensive Care Unit hospitalisation was found to be significant (omnibus test $p<0.001$). The dependent variable of the model was Intensive Care Unit admission status, and the independent variables

Table III. Comorbidities of hospitalized patients by month.

	2021				2022
	September, n (%)	October, n (%)	November, n (%)	December, n (%)	January, n (%)
Diabetes mellitus	236 (24)	254 (25.7)	356 (30.2)	317 (28.5)	238 (22.1)
Hypertension	366 (37.4)	390 (39.5)	558 (47.3)	518 (46.6)	388 (36.1)
Cardiovascular disease	152 (15.5)	1 (0.1)	272 (23.1)	306 (27.5)	187 (17.4)
Chronic lung disease	110 (11.2)	118 (12)	147 (12.5)	158 (14.2)	143 (13.3)
Cerebrovascular disease	45 (4.6)	56 (5.7)	48 (4.1)	69 (6.2)	51 (4.7)
Cancer	47 (4.8)	76 (7.7)	120 (10.2)	101 (9.1)	79 (7.3)
Chronic kidney disease	65 (6.5)	67 (6.8)	104 (8.8)	65 (5.8)	72 (6.7)
Morbid obesity	3 (0.3)	2 (0.2)	9 (0.8)	10 (0.9)	15 (1.4)
Chronic degenerative neurologic disease	1 (0.1)	2 (0.2)	52 (4.4)	48 (4.3)	35 (3.3)
Solid organ transplantation	3 (0.3)	5 (0.5)	16 (1.4)	13 (1.2)	8 (0.7)
Rheumatologic disease	3 (0.3)	5 (0.5)	21 (1.8)	36 (3.29	24 (2.2)
Thyroid disease	10 (1)	3 (0.3)	6 (0.5)	18 (1.6)	17 (1.6)
Pregnancy*	12 (1.2)	2 (0.2)	4 (0.3)	14 (1.3)	2 (0.2)
Pulmonary emboli	2 (0.2)	0	0	3 (0.3)	0
Others	67 (6.9)	95 (9.6)	127 (10.8)	70 (6.3)	63 (5.9)

*26 of 34 pregnant patients (76%) were unvaccinated.

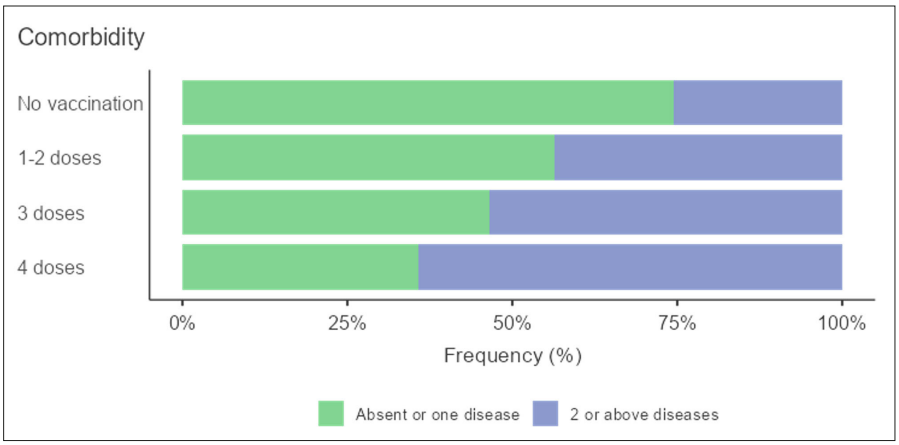

Figure 1. Comorbidities in hospitalized COVID-19 patients.

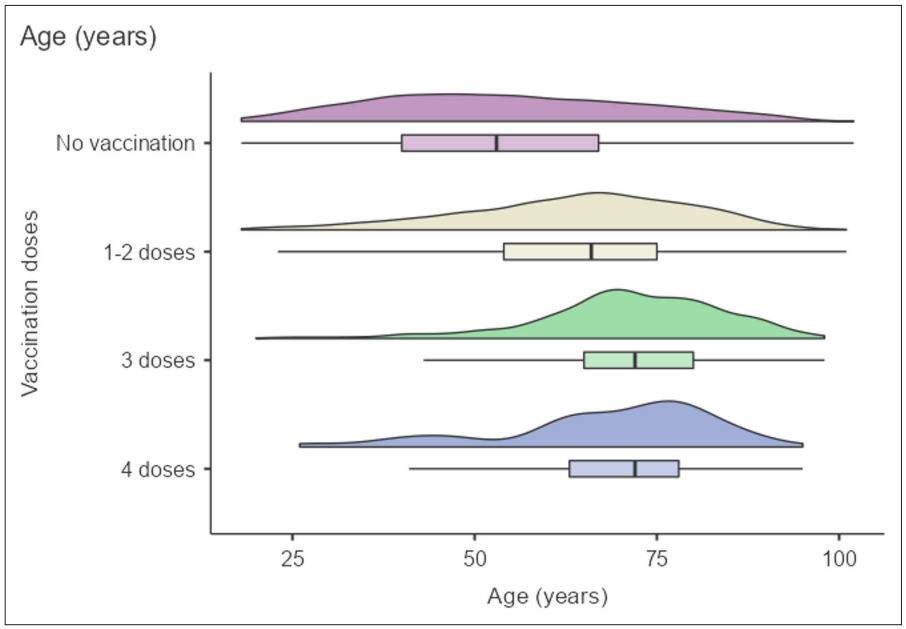

Figure 2. Age distribution of hospitalized COVID-19 patients.

were number of vaccine doses, comorbidity status, gender and age. Regardless of the type of vaccine, it was found that the risk of ICU hospitalisation decreased in those who were vaccinated compared to those who were not vaccinated. Regardless of the type of vaccine, the Intensive Care Unit (ICU) risk was found to decrease 1.25-fold (OR=0.797) in those who received 1 or 2 doses of vaccine, 1.18-fold (OR=0.841) in those who received 3 doses, and 3.26-fold (OR=0.306) in those who received 4 doses. The risk of ICU hospitalisation was found to be 1.5-fold increased in the group with 2 or more comorbidities and 1.22-fold increased in men (Table VI).

Discussion

The study presented clearly demonstrates the efficacy of booster vaccination in preventing the need for Intensive Care Unit. We used data from the first day of each month to determine the national unvaccination rate[10]. The results suggested that the addition of a fourth dose may be more

Table IV. Vaccination status of patients by month.

Vaccination status	2021				2022
	September, n (%)	October, n (%)	November, n (%)	December, n (%)	January, n (%)
Unvaccinated	465 (47.5)	389 (39.4)	402 (34.1)	363 (32.6)	354 (32.9)
Sinovac-based protocols					
Two doses of Sinovac	241 (24.6)	265 (26.8)	301 (25.5)	253 (22.8)	196 (18.2)
Three doses of Sinovac	58 (5.9)	97 (9.6)	177 (15)	236 (21.2)	215 (20)
Two doses of Sinovac + one dose of BioNTech	48 (4.9)	66 (6.7)	103 (8.7)	101 (9.1)	134 (12.5)
Two doses of Sinovac + two doses of BioNTech	10 (1)	5 (0.5)	11 (0.9)	9 (0.8)	26 (2.4)
BioNTech-based protocols					
Two doses of BioNTech	41 (4.2)	61 (6.2)	85 (7.2)	94 (8.5)	101 (9.4)
Three doses of BioNTech	0	0	0	1 (0.1)	10 (0.9)
Others	115 (11.8)	106 (10.7)	90 (7.6)	55 (4.9)	39 (3.6)
Total	978	987	1,179	1,112	1,075

Table V. Risk reduction by vaccination status for ICU admission.

Age group			ICU care admission		ARR	RRR	NNT
			Yes	No			
<50	Unvaccinated	n	553	305			
		%	64.5	35.5			
	Vaccinated with either 1 or 2 doses	n	274	96	9.6%	27%	10.4
		%	74.1	25.9			
	Vaccinated with 3 doses	n	43	30			
		%	58.9	41.1			
	Vaccinated with 4 doses	n	11	1	27.2%	76.6%	3.7
		%	91.7	8.3			
50-64	Unvaccinated	n	295	234			
		%	55.8	44.2			
	Vaccinated with either 1 or 2 doses	n	321	251	0.3%	0.006%	333.3
		%	56.1	43.9			
	Vaccinated with 3 doses	n	141	83	7%	15.8%	14.1
		%	62.9	37.1			
	Vaccinated with 4 doses	n	11	4	17.5%	39.5%	5.7
		%	73.3	26.7			
>65	Unvaccinated	n	264	322			
		%	45.1	54.9			
	Vaccinated with either 1 or 2 doses	n	528	542	4.2%	7.6%	23.8
		%	49.3	50.7			
	Vaccinated with 3 doses	n	439	508	1.2%	2.1%	76.9
		%	46.4	53.6			
	Vaccinated with 4 doses	n	35	16	23.5%	42%	4.3
		%	68.6	31.4			

ARR (absolute risk reduction) = CER (Control Event Rate) - EER (Experimental Event Rate). RRR (relative risk reduction) = CER (Control Event Rate) - EER (Experimental Event Rate)/CER (Control Event Rate). NNT (number need to treatment) = 1/ARR.

Table VI. Multivariate analysis of risk factors of İntensive care unit need in hospitalized COVID-19 patients.

Variables	B	p	OR	95% CI for OR	
				Lower	Upper
Vaccine dose group (ref: unvaccinated)					
Vaccine dose group (1 or 2 doses)	-0.227	<0.001	0.797	0.698	0.911
Vaccine dose group (3 doses)	-0.174	0.031	0.841	0.718	0.985
Vaccine dose group (4 doses)	-1.184	<0.001	0.306	0.182	0.515
Comorbidities (ref >2, risk≥2)	0.406	<0.001	1.500	1.329	1.694
Age group (<50 yeaers)					
Age group (50-64 years)	0.368	<0.001	1.445	1.226	1.704
Age group (≥65 years)	0.718	<0.001	2.051	1.751	2.402
Sex (ref: female, risk: male)	0.204	<0.001	1.227	1.097	1371
Constant	-0.511	<0.001	0.600		

effective in preventing Intensive Care Unit even in disadvangated groups. Males, older age groups and vaccination with less than four doses increases the need for Intensive Care Unit.

According to the Ministry of Health data, as of January 5, 2022[8], among the adult population, nearly 8% were unvaccinated, and approximately 33% received booster shots. In addition, there were regional differences. One of the limitations of our study is the absence of detailed national and regional data. It should be noted that, to compare different booster protocols, the distribution and tendency of fourth-fourth shots rather than the exact numbers is important.

During the only Sinovac era (January-April 2021), the efficacy and decreased number of deaths among healthcare workers in Turkey have been previously reported[11]. Our first study documented the decreased efficacy of two doses of Sinovac and lower hospitalization rates in individuals who received two doses of Sinovac plus one dose of BioNTech than in those who received three Sinovac doses[9]. The presented study revealed that the highest risk reduction for all age groups was found in patients that received four vaccine doses. Four doses of vaccination for every 3.7 people under 50 years of age, four doses of vaccination for every 5.7 people in the 50-64 age group, and four doses of vaccination for every 4.3 people over 65 years of age will prevent one patient from being admitted to intensive care. Aproximately 50% relative risk reduction was also found in groups with four doses of vaccination in all age groups. Since fourth dose of Sinovac was available in December 2021 and their number was limited, our data did not allow us to compare two doses of Sinovac plus two doses of BioNTech with four doses of Sinovac. We will not discuss the protective effect of the three doses of BioNTech because it has been documented many times[12-14].

The course of the pandemic in Turkey is similar to that in other countries in the Northern Hemisphere. The alpha, delta, and omicron variants dominated the third, fourth, and fifth wave, respectively. Since the third wave, effective vaccines have been developed. In Turkey, Sinovac (an inactivated vaccine) was primarily used in the third wave, whereas Western countries had used mRNA (BioNTech and Moderna) or vector vaccines (AstraZeneca and Johnson & Johnson-Janssen). More than 10 billion doses of COVID-19 vaccines were administered worldwide as of February 2022. Inactivated and mRNA vaccines are the two most commonly administered vaccine types. In literature, data regarding the efficacy and side effects of mRNA vaccines compared to those of inactivated vaccines are extensive. Sinovac and Sinopharm are inactivated vaccines that are mostly used in many countries such as China, Brazil, Chile, Indonesia, and Turkey. The efficacy of three doses of mRNA vaccines has been documented clearly[12-14]. Sablerolles et al[15] demonstrated the safety and efficacy of Ad26.COV2.S and mRNA boosters in healthcare workers who received a priming dose of Ad26.COV2.S vaccine. To the best of our knowledge, there are four reports[9,16-18] on booster shots following Sinovac in the delta variant era. Early estimates of booster shots of Sinovac, BioNTech, and AstraZeneca after Sinovac in Chile showed[16] similar decreased rates of hospitalizations: 84-88%, 84-87%, and 84-96%, respectively. Costa Clemens et al[17] measured antibody titers 28 days after a booster shot following two doses of Sinovac. They used four different vaccines (Ad26.COV2-S, Janssen or BNT162b2, Pfizer-BioNTech or AZD1222, Astra-

Zeneca or Sinovac) for booster shots. Heterologous boosting resulted in more robust immune responses than homologous boosting, and they concluded that heterologous boosting might enhance protection[17]. Cerqueira-Silva et al[18] reported increased vaccine efficacy against infection and severe outcomes 14-30 days after the booster. In our previous study[9], although the number of hospitalized patients after three doses was limited, the results suggested that the preference of BioNTech over Sinovac as the third dose in patients who had previously received two doses of Sinovac may be more effective in preventing hospitalization and severe disease. This study confirms our previous findings[9].

We had three booster groups following two doses of Sinovac: three doses of Sinovac, two doses of Sinovac plus one dose of BioNTech, or two doses of Sinovac plus two doses of BioNTech. The increased risk of hospitalization 90 days after administration of two doses of Sinovac plus one dose of BioNTech may support the necessity of a fourth dose. As previously mentioned, this is one of the limitations of our study, but our clinical and personal observations are compatible with our data, and we think there may be only minor changes that will not affect our conclusions.

In the omicron variant era, data regarding the effect of booster shots on severe disease in patients who previously received Sinovac were not available. Antibody studies in literature have evaluated the effects of Sinovac on omicron variants. Although the drug maker noted[19] that among 48 individuals who received three doses of Sinovac, 45 (94%) tested positive for neutralizing antibodies, another study[20] showed lower antibody response to Sinovac compared to BioNTech.

The emergence of the omicron variant called for a second booster shot (fourth dose). Only one study[21] from Israel showed that the fourth shot of an mRNA vaccine was less effective on the omicron variant. Chile, which mainly used Sinovac as initial vaccine nationwide, began second booster shot for high-risk populations in February, 2022[22]. Turkey was the first country to offer a fourth (second booster) dose to residents, beginning in August 2021. This study demonstrates that regardless of the vaccine type, it was discovered that people who received vaccinations had a lower probability of being admitted to an ICU than those who did not. Regardless of the vaccine type, it was discovered that receiving one or two doses of the vaccination reduced ICU risk by 1.25-fold, 3 doses reduced it by 1.18-fold and 4 doses reduced it by 3.26-fold. It was discovered that the likelihood of ICU hospitalization was 1.5 times higher in the group with 2 or more comorbidities and 1.2 times higher in men. These results suggest that the addition of a fourth dose may be more effective and these data gain value as there are very limited data in the literature.

Our results in January reflect the transition period from the delta to omicron era. The absence of variant analysis is another limitation of our study, but the high number of cases (record number of daily cases since the beginning of the pandemic in January 2022) and health officials' explanations support the effect of the omicron variant.

The research contains data from a variety of cities and hubs around the country, but it does not reflect the total population. The exact date of the last vaccine inoculation of all the participants in the trial has yet to be determined, limiting the evaluation of vaccine effects. Because mutations were not investigated in all samples obtained in accordance with the national policy, the individuals' SARS-CoV-2 mutation data are unknown.

Conclusions

The findings suggest that even in disadvantaged populations, the fourth dose of vaccine may be more beneficial in preventing the need for Intensive Care Unit follow-up, which increases mortality in COVID-19. The need for Intensive Unit Care increases in males, older age groups and those who receive less than four doses of vaccine.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Oya Baydar Toprak, Tekin Akpolat, Oguz Uzun,Nurdan Kokturk, Pelin Pınar Deniz, Efraim Guzel, Burak Mete. The first draft of the manuscript was written by Oya Baydar Toprak, Tekin Akpolat and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ministry of Health and supported by the Cukurova University Non-Interventional Ethical Committee (114/2021).

Informed Consent
Informed consent was obtained from all subjects involved in the study.

Availability of Data and Materials
The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Conflicts of Interests
The authors declare that they have no potential conflict of interest including any financial, personal or other relationships with the other people or organizations that could inappropriately influence, or be perceived to influence the presented work. The authors have no relevant financial or non-financial interests to disclose.

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References

1) World Health Organization. Coronavirus Disease (COVID-19) Dashboard. Available at: https://covid19.who.int/?mapFilter=cases (Accessed on February 1, 2022).
2) Our World in Data. Coronavirus (COVID-19) Vaccinations. Available at: https://ourworldindata.org/covid-vaccinations (accessed on February 1, 2022).
3) Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020; 383: 2603-2615.
4) Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, Kovyrshina AV, Lubenets NL, Grousova DM, Erokhova AS, Botikov AG, Izhaeva FM, Popova O, Ozharovskaya TA, Esmagambetov IB, Favorskaya IA, Zrelkin DI, Voronina DV, Shcherbinin DN, Semikhin AS, Simakova YV, Tokarskaya EA, Egorova DA, Shmarov MM, Nikitenko NA, Gushchin VA, Smolyarchuk EA, Zyryanov SK, Borisevich SV, Naroditsky BS, Gintsburg AL; Gam-COVID-Vac Vaccine Trial Group. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 2021; 397: 671-681.
5) Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, Brooks N, Smaja M, Mircus G, Pan K, Southern J, Swerdlow DL, Jodar L, Levy Y, Alroy-Preis S. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 2021; 397: 1819-1829.
6) Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, Pizarro A, Acevedo J, Leo K, Leon F, Sans C, Leighton P, Suárez P, García-Escorza H, Araos R. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med 2021; 385: 875-884.
7) Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, Köse Ş, Erdinç FŞ, Akalın EH, Tabak ÖF, Pullukçu H, Batum Ö, Şimşek Yavuz S, Turhan Ö, Yıldırmak MT, Köksal İ, Taşova Y, Korten V, Yılmaz G, Çelen MK, Altın S, Çelik İ, Bayındır Y, Karaoğlan İ, Yılmaz A, Özkul A, Gür H, Unal S; CoronaVac Study Group. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 2021; 398: 213-222.
8) Türkiye Cumhuriyeti Sağlık Bakanlığo. Available at: https://twitter.com/saglikbakanligi (accessed on February 1, 2022).
9) Uzun O, Akpolat T, Varol A, Turan S, Bektas SG, Cetinkaya PD, Dursun M, Bakan N, Ketencioglu BB, Bayrak M, Baris SA, Guner R, Gunal O, Nural S, Deniz PP, Toprak OB, Ozkan G, Gumus A, Kerget F, Ercelik M, Ataoglu O, Yuksel A, Ates G, Kutsoylu OE, Kose N, Kizilirmak D, Keskin S, Gultekin O, Coskun N, Yilmaz ES, Uslu S, Basyigit İ, Ergan B, Deveci F, Yakar MN, Zuhur C, Sagcan G, Yuce ZT, Kuluozturk M, Sezgin ME, Sezgin ENA, Havlucu Y, Cuhadaroglu C, Kilinc O, Boyaci H, Altunay H, Akti M, Dursun ZB, Kalem AK, Isik SA, Akyildiz L, Aykac N, Almaz MS, Kokturk N, Itil O. COVID-19: vaccination vs. hospitalization. Infection 2022; 50: 747-752.
10) T.C. Sağlık Bakanlığı Covid-19 Bilgilendirme Platformu. Available at: https://covid19.saglik.gov.tr/TR-66935/genel-koronavirus-tablosu.html#. (Accessed on February 1, 2022).
11) Akpolat T, Uzun O. Reduced mortality rate after coronavac vaccine among healthcare workers. J Infect 2021; 83: 20-21.
12) Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, Mizrahi B, Alroy-Preis S, Ash N, Milo R, Huppert A. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med 2021; 385: 1393-1400.
13) Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, Yaron S. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. N Engl J Med 2021; 385: 2413-2420.

14) Accorsi EK, Britton A, Fleming-Dutra KE, Smith ZR, Shang N, Derado G, Miller J, Schrag SJ, Verani JR. Association Between 3 Doses of mRNA COVID-19 Vaccine and Symptomatic Infection Caused by the SARS-CoV-2 Omicron and Delta Variants. JAMA 2022; 327: 639-651.
15) Sablerolles RSG, Rietdijk WJR, Goorhuis A, Postma DF, Visser LG, Geers D, Schmitz KS, Garcia Garrido HM, Koopmans MPG, Dalm VASH, Kootstra NA, Huckriede ALW, Lafeber M, van Baarle D, GeurtsvanKessel CH, de Vries RD, van der Kuy PHM; SWITCH Research Group. Immunogenicity and Reactogenicity of Vaccine Boosters after Ad26.COV2.S Priming. N Engl J Med 2022; 386: 951-963.
16) Early estimates of the effectiveness of booster shots in Chile. Available at: https://www.minsal.cl/wp-content/uploads/2021/10/2021-10-07-efectividad-dosis-de-refuerzo_eng.pdf (Accessed on February 1, 2022).
17) Costa Clemens SA, Weckx L, Clemens R, Almeida Mendes AV, Ramos Souza A, Silveira MBV, da Guarda SNF, de Nobrega MM, de Moraes Pinto MI, Gonzalez IGS, Salvador N, Franco MM, de Avila Mendonça RN, Queiroz Oliveira IS, de Freitas Souza BS, Fraga M, Aley P, Bibi S, Cantrell L, Dejnirattisai W, Liu X, Mongkolsapaya J, Supasa P, Screaton GR, Lambe T, Voysey M, Pollard AJ; RHH-001 study team. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. Lancet 2022; 399: 521-529.
18) Cerqueira-Silva T, Katikireddi SV, de Araujo Oliveira V, Flores-Ortiz R, Júnior JB, Paixão ES, Robertson C, Penna GO, Werneck GL, Barreto ML, Pearce N, Sheikh A, Barral-Netto M, Boaventura VS. Vaccine effectiveness of heterologous CoronaVac plus BNT162b2 in Brazil. Nat Med 2022; 28: 838-843.
19) China's Sinovac Claims Its Booster Shot Offers 94% Protection Against Omicron After Hong Kong Study Raises Alarm. Available at: https://www.forbes.com/sites/siladityaray/2021/12/16/chinas-sinovac-claims-its 3booster-shot-offers-94-protection-against-omicron-after-hong-kong-study-raises-alarm/?sh=27368c876f4d (Accessed on February 1, 2022).
20) Sinovac booster insufficient against omicron, study shows. Available at: https://asia.nikkei.com/Spotlight/Coronavirus/COVID-vaccines/Sinovac-booster-insufficient-against-omicron-study-shows (Accessed on February 1, 2022).
21) Israeli study shows 4th shot of COVID-19 vaccine less effective on Omicron. Available at: https://www.reuters.com/world/middle-east/israeli-study-shows-4th-shot-covid-19-vaccine-notable-block-omicron-2022-01-17/ (Accessed on February 1, 2022).
22) Chile will soon offer fourth COVID-19 shot. Available at: https://news.yahoo.com/chile-soon-offer-fourth-covid-214947214.html (Accessed on February 1, 2022).