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The Impact of Early Phase COVID-19 Vaccination on Hospitalized COVID-19 Patients

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The number of cases of coronavirus disease-2019 (COVID-19) globally is over 225 million, and disease-related deaths are over 4 million. The type, prevalence, and antibody susceptibility of the virus variants of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the vaccination rate and coverage are considered critical factors in the progress of COVID-19. We aimed to compare the clinical and laboratory parameters of the patients hospitalized due to COVID-19 in pre-vaccination and post-vaccination periods. We conducted this retrospective cross-sectional study in a tertiary clinic in Turkey. The files of the patients over the age of 18, whose real-time polymerase chain reaction (RT-PCR) tests were positive and who were hospitalized before (November-December 2020, Group 1) and after (March-April 2021, Group 2) COVID-19 vaccination were scanned. Patients' demographical data, clinical severity, laboratory parameters, thorax computed tomography involvement, and mortalities were recorded. The obtained data were compared among the groups. 601 patients (344 male, 57% and 257 female, 43%) were included in the study. It was observed that the patients in the Group 2 were younger (60.71 ± 14.06 vs. 66.95 ± 14.57, $p < 0.001$), and a significant decrease in mortality [83 (28.6%) vs.139 (44.6%), $p = 0.001$] were observed in Group 2. The number of patients who needed ventilatory support and the rate of pulmonary involvement was lesser in Group 2, but the difference was non-significant. C-reactive protein, D-dimer, procalcitonin levels were significantly lower in Group 2 patients. Our study shows that the age and mortality of hospitalized COVID-19 patients decreased significantly after vaccination. An increase in the number of booster doses in individuals with advanced age (age > 75) and comorbidity (especially malignancy) may contribute to the control of the disease and immunity in this population.

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Introduction

Coronavirus disease-2019 (COVID-19), an infectious disease caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus, originated in Wuhan city of People's Republic of China at the end of 2019 and has been rapidly widespread worldwide. SARS-CoV-2 belongs to the *Coronaviridae* family, *Betacoronavirus* subgroup (Shereen et al. 2020). As of September 14, 2021, the number of cases globally is over 225 million, and disease-related deaths are over 4 million. Considering the statistics in our country, the number of cases is around 6.5 million, and the number of deaths is over 60 thousand in Turkey. However, it has been reported that more than 5.7 billion doses of vaccination have been administered globally as of September 14, 2021 (CSSE 2021). Vaccination coverages vary depending on the economic conditions of the countries (Our World in Data 2021). The type, prevalence, and antibody susceptibility of SARS-CoV-2 virus variants and the vaccination rate and coverage are considered two critical factors in the progress of COVID-19 pandemics. It is vital to develop and administer the vaccines rapidly to reach herd immunity and limit the spread of infection. Besides currently-administered vaccines, pre-clinic and clinic

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researches of many vaccines are ongoing (WHO, World Health Organization 2021a).

In Turkey, the COVID-19 vaccination was started on January 14, 2021 with healthcare providers for the first time. Then it was continued with the first dose administration of the individuals over 65 years old on February 11, 2021. At first, an intense vaccination was applied in March-April 2021 with CoronaVac, which started to be used and received emergency use authorization. The mRNA vaccine produced by Pfizer-BioNTech received emergency use authorization on April 12, 2021. The vaccination was continued with two types of vaccines since that date. In September 2021, the number of people who received 1st dose of the vaccine was over 50 million, while the number of people who received 2nd dose was 40.6 million (65.47%) (Republic of Turkey Ministry of Health 2021).

The study aimed to compare the demographic characteristics and disease profiles of the patients hospitalized in COVID clinics of a tertiary hospital in November-December 2020 (when the number of COVID-19 cases peaked for the second time in our country) and in March-April 2021 (when the number of COVID-19 cases peaked for the third time and; also the individuals over the age of 65 years were vaccinated).

Materials and Methods

Study protocol

The approval was obtained from the local ethical committee (dated June 25, 2021 and numbered B.30.2.ODM.0.20.08/433). The files of the patients over the age of 18 years who were hospitalized with positive real-time polymerase chain reaction (RT-PCR) test before (November-December 2020, Group 1) and after (March-April 2021, Group 2) COVID-19 vaccination performed in our tertiary healthcare center, were scanned retrospectively. On February 11, 2021, the vaccination of people over 65 years old started with the CoronaVac vaccine in our country. All of the vaccinated patients in our study were vaccinated with CoronaVac. Treatment was similar in both groups. Patients with pulmonary involvement in both groups received steroid and anticoagulant therapy; on the other hand, patients without pulmonary involvement received supportive treatment.

Patients' demographical data, clinical severity of the disease [non-severe (absence of signs of severe or critical disease), severe (sPO_2 < 90%, respiratory rate > 30 in adults, signs of severe distress) and critical (requirement of life-sustaining treatment, acute respiratory distress syndrome, sepsis, septic shock)] (WHO 2021b), applied ventilatory support [those who do not need ventilation, those who used high flow nasal oxygen (HFNO), non-invasive mechanical ventilation (NIMV) and invasive mechanical ventilation (IMV)], laboratory parameters [the number of leukocytes, neutrophils, monocytes, platelets, hemoglobin value, C-reactive protein (CRP), D-dimer, ferritin, aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), procalcitonin values], thorax computed tomography (CT) involvement and mortalities were recorded. The obtained values were compared between the two groups.

Statistical analysis

The collected data were analyzed using the SPSS version 26 package program. Pearson Chi-Square analysis was used in the hypothesis testing of the categorical data. Parametric or non-parametric independent unpaired test methods were used in hypothesis testing of the metric data. All hypotheses were tested at a 0.05 significance level.

Results

In total, 601 patients, as 344 male (57%) and 257 female (43%) were included in the study. The mean age of the participants was 63.95 ± 14.65 years. The patients were separated into Group 1 (n = 311, 51.8%) and Group 2 (n = 290, 48.2%) based on the admitting time. While the sexes in the groups were similar (Male/Female: 179/132 vs. 165/125, p = 0.870), it was observed that the patients in the Group 2 were younger (60.71 ± 14.06 vs. 66.95 ± 14.57, p < 0.001) (Table 1).

When we evaluated the clinical severity, there was a decrease in the number of critical patients in Group 2; however, their difference could not reach statistical significance (p = 0.077, Table 1). Even though the number of patients who needed ventilatory support (HFNO, NIMV, and IMV) was less in Group 2, the difference between them was statistically non-significant (p = 0.281, Table 1). Less pulmonary involvement in the patients in Group 2 was found as statistically non-significant [n = 272 (93.7%) vs. n = 296 (95.1%), p = 0.457, Table 1]. There was a significant decrease in mortality [83 (28.6%) vs. 139 (44.6%), p = 0.001] of the patients in Group 2 (Table 1).

In the comparison of the laboratory data, while hemoglobin levels (12.8 vs. 12.2 g/dL, p < 0.001) were observed to be significantly higher in Group 2, CRP (95.1 vs. 111.1 mg/L, p = 0.016), D-dimer (1,719 vs. 2,606 ng/mL, p < 0.001), procalcitonin (1.3 vs. 2.2 ng/mL, p < 0.001) levels were found to be significantly lower. Other laboratory parameters were similar in the groups (Table 2).

When vaccination status and clinical conditions of the patients in Group 2 were evaluated, it was observed that 27 patients had received two doses and passed at least two weeks after the second dose. 9 patients had received two doses of vaccine but did not pass 15 days after the second dose. 49 patients had received only the first dose of vaccine. It was determined that out of 27 fully vaccinated patients, 11 patients were severe, and 16 patients were mild. Seven of those who were severe died. It was determined that the mean age of the seven dead patients was 79.42 years, and 5 of them had concomitant malignancy (chronic lymphocytic leukemia, lymphoma, acute myeloid leukemia, gastric and laryngeal malignancy) (Table 3).

Table 1. Comparison of the demographics, clinical, and imaging data between Group 1 and 2.

Variables	Group 1 (n = 311)	Group 2 (n = 290)	p
Age (mean ± SD)	66.95 ± 14.57	60.71 ± 14.06	< 0.001
Sex (Male/Female)	179/132	165/125	0.870
Clinical severity			0.077
Non-severe, n	135	121	
Severe, n	137	147	
Critical, n	39	22	
Respiratory support			0.281
No MV, n	171	181	
HFNO, n	99	81	
NIMV, n	14	10	
IMV, n	27	18	
Thorax CT			0.457
Positive, n	296	272	
Negative, n	15	18	
Mortality, n	139	83	0.001

MV, mechanical ventilation; HFNO, high flow nasal oxygen; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation; CT, computed tomography.
Thorax CT positive: the findings of COVID-19 on chest CT such as ground-glass opacities, linear densities, crazy paving, consolidation, randomly distributed nodules, bronchiectasis.
Thorax CT negative: no findings of COVID-19 on chest CT; normal chest CT.

Table 2. Comparison of the laboratory values between Group 1 and 2.

	Group 1 (n = 311)		Group 2 (n = 290)		
	Minimum-max	Mean ± SD	Minimum-max	Mean ± SD	p
WBC, /μL	510-27,160	8,476 ± 4,863.8	460-38,940	7,739.4 ± 4,763.5	0.101
Neutrophils, /μL	0-25500	6,744.4 ± 4,538.8	20-35,130	6,107.5 ± 4,562	0.062
Lymphocytes, /μL	80-10,060	1,079.8 ± 909.8	130-5,080	1,105.8 ± 677.8	0.177
Hemoglobin, g/dL	5.7-18.9	12.2 ± 2.1	5.9-17.4	12.8 ± 2.2	< 0.001
Monocytes, /μL	1-16,200	567.4 ± 1,178.6	0-2,560	465.1 ± 335	0.286
Platelets, $10^3/\mu$L	10-552	201.7 ± 88.9	5-891	214.6 ± 102.2	0.094
CRP, mg/L	1-816	111.1 ± 96.8	0.7-539	95.1 ± 90.6	0.016
D-dimer, ng/mL	107-10,000	2,606.7 ± 3,110.2	106-10,000	1,719.4 ± 2,332.3	< 0.001
Ferritin, ng/mL	11.6-14,097	926.2 ± 1,585.2	15-5,211	768.5 ± 865.5	0.751
AST, U/L	10-533	45.4 ± 47.2	6-564	45.7 ± 49	0.509
ALT, U/L	3-473	35.3 ± 44.7	3-306	33.4 ± 33.4	0.279
GGT, U/L	3 -629	56.2 ± 71.1	3-1,482	60.6 ± 112.2	0.757
LDH, U/L	123-2,923	450 ± 301.5	123-3,246	455.7 ± 290.8	0.302
Procalcitonin, ng/mL	0-100	2.2 ± 9.1	0-100	1.3 ± 8.4	< 0.001

WBC, white blood cell; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase.

Discussion

Our study shows that the age and mortality of hospitalized COVID19 patients decreased significantly after vaccination. The level of acute-phase reactants (CRP, procalcitonin, and D-dimer) also decreased, and hemoglobin levels increased significantly in hospitalized COVID19 patient population after vaccination.

In Turkey, the COVID-19 vaccination was started on January 14, 2021 with healthcare providers for the first time; then, it was continued with the vaccination of individuals over the age of 65 years starting from February 11, 2021. In our study, as the patients included in the post-vaccination group (Group 2) were the ones who were hospitalized in March and April 2021, in this period, only healthcare providers and individuals over the age of 65 years were vaccinated the CoronaVac vaccine (Republic of Turkey Ministry of Health 2021). In our study, while the

Table 3. Evaluation of vaccination status of Group 2 patients.

Vaccination Status	Non-severe	Severe + Critical	Exitus	Total
Fully vaccinated	16 (60%)	11 (40%)	7 (26%)	27 (100%)
Incompletely vaccinated				
2 doses were administered but < 2 weeks passed from the last dose	3 (33%)	6 (67%)	2 (22%)	9 (100%)
Single-dose	19 (39%)	30 (61%)	12 (24%)	49 (100%)
No vaccination	83 (40%)	122 (60%)	62 (30%)	205 (100%)

Fully vaccinated: 2 doses + > 2 weeks passed after the last dose.

mean age of the patients hospitalized in our clinic before the vaccination was 66.9 years, the mean age reduced to 60.7 years in the March-April 2021 period when the individuals over the age of 65 years were vaccinated. Vaccination has decreased the hospitalization of patients over the age of 65 years. Similarly, it was shown in the Centers for Disease Control (CDC) Morbidity and Mortality Weekly Report dated June 8, 2021 that hospitalization of the patients over the age of 70 years significantly decreased in the post-vaccination period (Christie et al. 2021). Haas et al. (2021) found in the study they conducted in the post-vaccination period that COVID-19-associated hospitalization, severe disease, and death decreased in those who had received two doses of BNT 162b2 vaccine. It has also been found out in the Phase 3 study of the CoronaVac vaccine that COVID-19-associated hospitalization decreased in individuals who had received two doses of vaccine and who received their second dose at least 14 days ago (Tanriover et al. 2021). In our study, the decrease in the mean age of the patients requiring hospitalization after the starting of vaccination shows the vaccine's efficacy. When the hospitalization status of the fully vaccinated 27 patients was evaluated, it was observed that the statuses of the patients of advanced age with comorbidity were mortal. In contrast, those who had less comorbidity were mildly surviving the disease. In a study conducted in Israel, it was determined that there is a decrease in the need for mechanical ventilation of the patients over the age of 70 years in the post-vaccination period, and this shows that vaccination has helped the patients of advanced age to have a milder disease period. In addition, the number of severe cases decreased after the vaccination (Rinott et al. 2021). Even though the current study found that the need for mechanical ventilation decreased due to the reduction in the severity of the disease in the post-vaccination period, this was not statistically significant. We observed that the need for hospitalization of the patients over the age of 65 years has decreased in the post-vaccination period; however, most of the hospitalized patients over the age of 65 years were not vaccinated. This can be the reason why there was no statistically significant reduction in the need for mechanical ventilation in our study. It was observed that the patients who were fully vaccinated but died were of advanced age (mean = 79.42 years), and most of them had hematological and non-hematological malignancies likely to affect the immune system (Table 3).

The literature found that hemoglobin levels were significantly lower in patients with severe disease than those with mild diseases (Guan et al. 2020; Lippi and Mattiuzzi 2020; Yang et al. 2020; Az et al. 2021). In the study conducted by Az et al. (2021) on disease severity and mortality in COVID-19 patients, it was found that CRP, procalcitonin, D-dimer, ferritin, LDH and troponin levels were significantly lower in patients with mild disease and the survivors. However, hemoglobin levels and lymphocyte count were significantly low in the non-surviving patient group (Az et al. 2021). Previous studies also showed that advanced age, increased D-dimer, CRP, ferritin, and troponin levels, and decreased lymphocyte count were associated with COVID-19 related mortality (Du et al. 2020; Liu et al. 2020). Similarly, in the current study, while CRP, D-dimer, and procalcitonin values were determined to be significantly lower in Group 2, hemoglobin value was determined to be statistically significantly higher.

In our study, it has been observed that mortality statistically significantly decreased in the post-vaccination period, and the mean age of the patients requiring hospitalization in Group 2 was lower when compared to Group 1. This can be explained by the fact that only the patients over the age of 65 years and healthcare workers were vaccinated during the period in which this study was conducted. In a survey conducted in the presence of Gamma variant associated epidemic of COVID-19 in Brazil, it was found that hospital visits and deaths decreased in the individuals who were at least 70-year-old, who had received two doses of CoronaVac vaccine, and whose second dose was applied at least 14 days ago (Ranzani et al. 2021). Our current study also affirms this observation in the literature. In the CDC Morbidity and Mortality Weekly Report, it has been found that hospitalizations closely related to mortality significantly decreased in fully-vaccinated individuals between May 3-July 25 in New York (Rosenberg et al. 2021). The study conducted by Chen et al. (2021) found that primary vaccination of the group with the high risk of COVID-19 (especially patients at an advanced age) decreased the mortality rates.

Our study has some limitations, such as being retrospective and single-center hospitalized patient design. Since only people over the age of 65 years were vaccinated in our country at the time of the study, the demographical

properties and clinical severity of hospitalized COVID-19 patients were affected.

In conclusion, our study shows that the age and mortality of hospitalized COVID-19 patients decreased significantly after vaccination. Therefore, COVID-19 vaccination is the key point to control the pandemic and reduce deaths. An increase in the number of booster doses in individuals with advanced age (age of > 75 years) and comorbidity (especially malignancy) may contribute to the control of the disease and immunity in this population. On the other hand, viral mutation seems to be an important risk factor, particularly for the fragile patient group. Regular booster vaccination continues to be important in reducing hospitalization and mortality in fragile patients and patients with comorbidities. In addition, COVID-19-related hospitalization and deaths may be decreased by providing social distance and the use of a mask.

Author Contributions

Y. T. G. designed the study, performed data acquisition, analyzed and interpreted the data, drafted the manuscript, and critically reviewed the manuscript. E. K. performed data acquisition. N. T. T. and N. Kö, N. Ko. analyzed and interpreted the data, and critically reviewed the manuscript. All authors agreed with the integrity of the study and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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