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CLINICAL STUDY

Risk factors and the impact of vaccination on mortality in COVID-19 patients

SEZEN Aysegul Inci, SENOGLU Sevtap, KARABELA Semsi Nur, YESILBAG Zuhal, BORCAK Deniz, CANBOLAT UNLU Esra, KORKUSUZ Ramazan, OZDEMIR Yusuf, KART YASAR Kadriye

Department of Infectious Diseases and Clinical Microbiology, Health Sciences University Faculty of Medicine, Bakırköy Dr. Sadi Konuk Application and Research Center, Istanbul, Turkey. **incinarin@hotmail.com**

ABSTRACT

INTRODUCTION: The novel coronavirus disease (COVID-19) pandemic has had a profound global impact economically, socially, and in many other areas. As vaccines are developed and introduced, their effect on the disease on both, the global and individual scale is a subject of intense curiosity. This study aimed to evaluate the relationship between risk factors for hospitalization, disease severity, and vaccination status in COVID-19 inpatients in a pandemic hospital.

METHODOLOGY: Patients hospitalized for COVID-19 between June and September 2021 were retrospectively analyzed in three groups: unvaccinated, incompletely vaccinated, and fully vaccinated. Disease severity was classified as moderate, severe, or critical according to World Health Organization criteria, and mortality risk factors and the prognostic effect of vaccination were analyzed.

RESULTS: The study included 486 patients, 228 women (46.9 %) and 258 men (53.1 %), with a mean age of 55.4 ± 16.5 years. Of these, 264 patients (54.3 %) were unvaccinated, 147 (30.2 %) were incompletely vaccinated, and 75 (15.4 %) were fully vaccinated. Older age, higher Charlson Comorbidity Index, greater disease severity, and being unvaccinated or incompletely vaccinated were associated with higher mortality.

CONCLUSIONS: The results of our study indicate that age, disease severity, comorbidities, and vaccination status were factors affecting COVID-19 mortality. Our findings support that full vaccination reduces COVID-19 -related mortality rates, disease severity, and length of hospital stay. However, large-scale studies with larger patient populations are needed *(Tab. 2, Ref. 22)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, mortality, vaccination.

Introduction

Infections caused by a novel coronavirus (SARS-CoV-2) were first recognized in December 2019, and on March 11, 2020 the disease (COVID-19) was declared a pandemic by the World Health Organization (WHO). Since its appearance, COVID-19 has had a profound impact on health services and cost the lives of over 5 million people worldwide (1). At present, there is no proven effective drug against COVID-19, just repurposed drugs that have been used without conclusive evidence to support their efficacy and safety. Controlling the spread of the pandemic and starting the normalization process can only be accomplished by increasing immunity rates in the population through vaccination (2). Vaccines appear to be the only short-term, cost-effective way to combat the pandemic (3). Since sequencing the SARS-CoV-2 genome, intense global research and development initiatives have led to the development of inactivated, live-attenuated, protein-based, vector, and mRNA vaccines (4).

As SARS-CoV-2 replicates, mutations in the RNA sequence result in variant viruses that may alter vaccine effectiveness by evading the immune response, exhibiting different proliferation and transmission rates, and causing different clinical findings. On June 15, 2021, the WHO began evaluating SARS-CoV-2 variants suspected of being more contagious, having worse prognosis, and reducing the effectiveness of vaccines under two main categories, "variants of concern" and "variants of interest" (5). The delta variant, which was first detected in India at the end of 2020 and was the most concerning of the variants of concern to date, spread rapidly in the UK especially and to all other countries of the world starting in April 2021.

Present in Turkey since June 2021, the delta variant is currently the most common variant in our country. As inactivated vaccines were reported to have limited efficacy against the delta variant, the relatively more effective mRNA vaccine has been recommended to health workers and people over 65 years of age who were previously immunized with an inactivated vaccine in our country (6).

Department of Infectious Diseases and Clinical Microbiology, Health Sciences University Faculty of Medicine, Bakırköy Dr. Sadi Konuk Application and Research Center, Istanbul, Turkey.

Address for correspondence: Aysegul Inci SEZEN, MD, Health Sciences University Faculty of Medicine, Bakırköy Doctor Sadi Konuk Application and Research Center, Infectious Diseases and Clinical Microbiology Department, Zuhuratbaba Mah, Dr. Tevfik Sağlam Cd No: 11, 34147 Bakirkoy, Istanbul, Turkey.
Phone: +0212.4147171

Tab. 1. Comparison of demographic characteristics according to vaccination status.

Variable		G1 + G2		G3		p
		n	%	n	%	
Sex	Female	190	46.2	38	50.7	0.479
	Male	221	53.8	37	49.3	
Age (years)	(Median)	53	(IQR=18–93)	62	(IQR=24–91)	**0.001**
CCI	0	200	48.7	8	10.7	
	1	63	15.3	12	16	
	2	77	18.7	32	42.7	
	3	46	11.2	13	17.3	
	4	16	4.9	7	9.3	
	5	7	1.7	1	1.3	
	≥6	2	0.5	2	2.7	
Disease severity	Moderate	203	49.4	43	57.3	**0.034**
	Severe	155	37.7	30	40	
	Critical	53	12.9	2	2.7	
Length of hospital stay (days)	(Median)	10	(IQR=1–64)	10	(IQR=3–30)	**<0.001**

Tab. 2. Prognostic factors associated with mortality.

Variable		Survivor		Nonsurvivor		p
		n	%	n	%	
Sex	Female	202	47.5	26	42.6	0.473
	Male	223	52.5	35	57.4	
Age (years)	(Median)	53	(IQR=18–93)	66	(IQR=30–85)	**<0.001**
CCI	0	196	46.1	12	19.7	**<0.001**
	≥1	229	53.9	49	80.3	
Disease severity	Moderate	245	57.6	1	1.6	**<0.001**
	Severe	159	37.4	26	42.6	
	Critical	21	4.9	34	55.7	
Fully vaccinated?	No	352	82.8	59	96.7	**0.005**
	Yes	73	17.2	2	3.3	
Vaccination status	Unvaccinated	228	53.6	36	59	**0.016**
	Incompletely vaccinated	124	29.2	23	37.7	
	Fully vaccinated	73	17.2	2	3.3	

All vaccines approved by the European Medicines Agency are reported to be safe and have an efficacy ranging from 72–95 %, and nearly all are administered in two doses except for the Janssen vaccine, for which a single dose is reported to be sufficient. For the mRNA-based vaccine BNT162b2 (BioNTech, Pfizer, Germany), efficacy rates after the first and second doses have been reported as 30.7 % and 88.0 % for the delta variant and 48.7 % and 93.7 % for the alpha variant, respectively (7). In light of these studies, administering two doses of vaccine has become standard practice.

In our center, outpatient and inpatient treatment of COVID-19 patients is provided in the 1006-bed annex that was added to our hospital during the COVID-19 pandemic to serve as a designated pandemic service. The aim of this study was to evaluate the relationship between risk factors for hospitalization, disease severity, and vaccination status in COVID-19 inpatients in our hospital.

Methodology

This retrospective study included patients admitted to our hospital due to COVID-19 between June 2021 and September 2021. The patients were divided into three groups, unvaccinated (G1), incompletely vaccinated (G2), and fully vaccinated (G3). Patients who received at least two doses of vaccine within the last 90 days were classified as fully vaccinated; patients who had received only the first dose of vaccine or who received both doses but had not received a booster after the total vaccination period exceeded 90 days were classified as incompletely vaccinated; and patients who had not received any vaccine were classified as unvaccinated.

The inactivated vaccine known as CoronaVac® (Sinovac, Beijing, China) was the first vaccine administered in Turkey. Starting on January 14, 2021, this vaccine was administered in two doses at a 4-week interval by the Ministry of Health to the priority groups of health workers and adults over 65 years of age, and subsequently to other adult age groups to facilitate vaccine delivery. As of April 2021, an mRNA vaccine (BioNTech Pfizer, Germany) became the second vaccine administered in our country, also in two doses at 3 to 8-week intervals. Due to the emergence of new variants and concern that the inactivated vaccine may not provide sufficient immunity, the mRNA vaccine was also recommended as a third dose for individuals who received two doses of inactivated vaccine.

This study included in-patients with SARS-CoV-2 PCR positivity or COVID-19 findings on lung tomography. Disease severity was classified as moderate, severe, or critical according to the WHO criteria (8). Moderate disease was defined as fever, respiratory symptoms, and pneumonia findings on computed tomography (CT). Severe disease was defined as a respiratory rate of ≥30 per minute, saturation (SpO_2) < 93 % in room air, $paO_2/FiO_2 \leq 300$ mmHg, and > 50 % progression on CT imaging within 24–48 hours. Critical disease was defined as respiratory failure, shock, extrapulmonary organ failure, and need for intensive care. The patients' comorbidities were evaluated using the Charlson Comorbidity Index (CCI).

Ethical approval for the study was obtained from the local ethics committee of our hospital.

Statistical analysis

Numerical variables were evaluated using mean and standard deviation (SD) or median and interquartile range (IQR); categorical variables were evaluated as number and percentage. Before between-group comparisons of numerical variables, parametric assumptions (normality and homogeneity of variances) were tested. Mann-Whitney U test was used to compare continuous variables. Statistical analyses were performed using IBM SPSS for Windows version 22.0 (IBM Corp, Armonk, NY). Level of significance was accepted as $p < 0.05$ for all analyses.

Results

The study included 486 patients, 228 women (46.9 %) and 258 men (53.1 %), with a mean age of 55.4 ± 16.5 years. Of these, 264 patients (54.3 %) were unvaccinated (G1), 147 (30.2 %) were incompletely vaccinated (G2), and 75 (15.4 %) were fully vaccinated (G3). The mean length of hospital stay was 12.1 ± 8.3 days. Disease severity was moderate in 246 patients (50.6 %), severe in 185 patients (38.1 %), and critical in 55 patients (11.3 %). A total of 102 patients (21 %) required intensive care. There was a statistically significant age difference in G3 compared to G1 and G2. The median age was 53 years (IQR: 18–93) in G1/G2 patients and 62 (IQR: 24–91) in G3 patients ($p=0.001$). The prevalence of critical disease was 12 % in G1/G2 and 2.7 % in G3 ($p=0.034$). Table 1 shows the comparison of demographic and clinical features between the groups.

Sixty-one patients in the study died (12.6 %). The median age of the nonsurviving patients was 66 years (IQR: 30–85), while the median age of the survivors was 53 years (IQR: 18–93) ($p< 0.001$). Forty-nine (80.3 %) of the nonsurviving patients and 229 (53.9 %) of the surviving patients had CCI ≥ 1 ($p<0.001$). Of the nonsurviving patients, 59 (96.7 %) were in G1 or G2, while only 2 (3.3 %) were in G3 ($p=0.005$). Prognostic factors associated with mortality are shown in Table 2.

According to our results, older age, higher disease severity, higher CCI, and not being fully vaccinated were significant factors associated with higher mortality.

Discussion

The COVID-19 pandemic has had a global impact in terms of both mortality and morbidity. With increasing vaccination efforts, numerous studies have been conducted on vaccines' efficacy, safety, and effects on hospitalization, mortality, and morbidity. There have also been studies examining the association of various factors, such as age, gender, and comorbidity, with vaccine efficacy, duration of protection, and effect on hospitalization and mortality. A study by Jablonska et al. showed that vaccination was slightly less effective against deaths associated with the delta variant lower than with other variants (9).

Studies conducted after vaccination started indicating that COVID-19 infection, hospitalization, and mortality rates were significantly higher in people who were not fully vaccinated compared to those who were fully vaccinated (10). In a vaccine efficacy study conducted in the UK, vaccination was associated with a significant reduction in the number of symptomatic COVID-19 infections in adults and greater protection against severe disease (11). Similarly, in our study the proportion of fully vaccinated patients who developed critical disease was significantly lower, and fully vaccinated patients also had significantly shorter mean length of hospital stay. These findings are related, as fully vaccinated patients were less likely to develop critical illness and require intensive care, and were therefore discharged earlier. In this study, we observed both a relatively milder disease course and lower mortality among fully vaccinated patients. The cumulative effect of inadequate immunity in undervaccinated patients and the increasing prevalence of the delta variant resulted in higher disease and mortality rates (12, 13). He et al reported that the mutations in the delta variant had increased its pathogenicity and infectivity (14).

There was no significant sex difference in mortality in this study, but older age was found to be associated with a higher mortality rate. It is known that mortality increases significantly as the severity of disease becomes critical. Some studies conducted in our country demonstrated higher mortality in patients who were hospitalized for COVID-19 and were evaluated as having poor prognosis (15, 16). Similarly, patients classified as having critical disease had a significantly higher mortality rate in our study. In addition, the fully vaccinated group (G3) had significantly lower mortality when compared with incompletely vaccinated and unvaccinated patients (G1+G2).

All COVID-19 studies have indicated that higher comorbidity risk affects both disease course and mortality (17). Christensen et al. showed that among patients classified as CCI 1–2, 3–4, and >4, all groups with comorbidities had significantly worse prognosis and higher mortality rates than patients with no comorbidities (18). A similar meta-analysis demonstrated more severe disease prognosis in patients with high comorbidity (19). Consistent with these studies, we observed a significant increase in mortality risk as patients' comorbidity index increased.

It has been reported in many studies that the course of COVID-19 is more severe in men. A systematic review and meta-analysis by Abate et al. showed that symptomatic COVID-19 was significantly more common among males (20). Similarly, Ortolon et al. found a correlation between male sex and COVID-19 severity and mortality risk (21).

In our study, we observed no significant difference between fully vaccinated and incompletely vaccinated/unvaccinated patients who required hospitalization for COVID-19 in terms of sex. Although male sex has been associated with poor prognosis in previous studies, the disappearance of the statistically significant prognostic effect of sex when comparing fully immunized patients with incompletely immunized patients suggests that the vaccine may improve the prognosis in men, but this speculation must be supported by additional analyses/studies (22). The fact that fully vaccinated patients had a significantly higher mean age than unvaccinated and undervaccinated patients in our study can be attributed to the priority given to older adults in the national vaccination program due to their high-risk status.

Limitations

This study was conducted in a single center and the patient sample was relatively small. Furthermore, the incompletely vaccinated group was heterogeneous. Another limitation is that we were not able to evaluate vaccination status in patients with different SARS-CoV-2 variants. Finally, the inability to perform regression analyses due to small patient numbers may have increased the bias.

Conclusion

To our knowledge, this is the first study from our country to compare the effectiveness of an inactivated COVID-19 vaccine in undervaccinated patients. We determined that age, disease severity, CCI, and vaccination status were significant factors associated with mortality. Our findings support that full vaccination reduces COVID-19-related mortality rates, disease severity, and length of hospital stay. However, large-scale studies with larger patient populations are needed.

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