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Investigation of the Effect of Vaccination Status on the Prognosis of Covid-19 Patients Hospitalized in Pandemic Service

Pandemi Servisinde Yatan Kovid-19 Hastalarında Aşılanma Durumunun Prognoza Etkisinin Araştırılması

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ABSTRACT

Objective: We aimed to evaluate the effect of vaccination status on the prognosis of COVID-19 patients with varying vaccine combinations during hospitalization

Materials and Methods: The study was conducted with the data of 854 COVID-19 patients, of which 457 were female. The dependent variable in the comparisons was the need for intensive care, and the independent variables were gender, risk score, severity score, and vaccination status.

Results: The mean age of the patients was 57.7±15.71 with standard deviation (SD); 49.2% had never been vaccinated, and 18.3% needed intensive care. Three logistic regression models were developed using different vaccine combinations. Three doses of CoronaVac or two doses of CoronaVac and one dose of Comirnaty vaccine in the first model, three doses of CoronaVac vaccine in the second model, and receiving the vaccine solely (at least one dose in the 6 months before the disease) in the last model were found to reduce the risk of intensive care unit (ICU) admission by 82%, 77%, and 42%, respectively.

Conclusions: The effectiveness of vaccination in preventing the need for intensive care in inpatients was once again demonstrated, and it was observed that this effectiveness increased even more with booster vaccine doses.

Keywords: COVID-19, COVID-19 vaccines, inpatients, intensive care

ÖZ

Amaç: Hastanede yatış sırasında değişen aşı kombinasyonları ile aşı durumunun COVID-19 hastalarının prognozuna etkisini değerlendirmeyi amaçladık.

Materyal ve Metot: Araştırma 457'si kadın olmak üzere 854 COVİD-19 hastasının verileriyle gerçekleştirildi. Karşılaştırmalarda yer alan bağımlı değişken yoğun bakım ihtiyacı, bağımsız değişkenler; cinsiyet, risk skoru, şiddet skoru, aşılanma durumlarıdır.

Bulgular: Hastaların yaş ortalaması 57,7±15,71 standart sapma (SS) yıl olup, %49,2'si hiç aşı olmamış ve % 18,3'ününde yoğun bakım ihtiyacı olmuştur. Hastaların. Farklı aşı kombinasyonları kullanılarak üç lojistik regresyon modeli oluşturulmuştur. İlk modelde üç doz CoronaVac ya da iki doz CoronaVac bir doz Comirnaty aşısı, ikinci modelde üç doz CoronaVac aşısı, son modelde sadece aşı olmanın (hastalık öncesi 6 ayda en az bir doz) yoğun bakım ünitesi (YBÜ)'ne yatış riskini sırasıyla %82, %77 ve %42'lik azalma sağladığı saptanmıştır.

Sonuç: Aşılamanın yatan hastalarda yoğun bakım ihtiyacını önlemedeki etkinliği bir kez daha ortaya kondu ve rapel aşı dozlarıyla bu etkinliğin daha da arttığı gözlendi.

Anahtar Kelimeler: COVID-19, COVID-19 aşıları, yatan hastalar, yoğun bakım

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INTRODUCTION

COVID-19 disease has a wide spectrum ranging from asymptomatic course to multiorgan dysfunction and septic shock.[1] The clinical characteristics of COVID-19 are similar to other viral upper respiratory tract diseases, including nonspecific symptoms such as fatigue, cough, shortness of breath, and fever. The most common symptoms observed in patients are fever, fatigue, dry cough, and diarrhea.[2] Loss of taste and smell may be observed, and typical loss of smell is observed at the beginning of the disease.[3,4] Dyspnea tends to occur between days four and eight after the onset of symptoms in most patients but can also occur after ten days.[2]

The presence of co-morbidities such as coronary heart disease, pulmonary diseases including chronic obstructive pulmonary disease (COPD), liver diseases, obesity (body mass index >30), immune deficiencies, and malignancies increases the risk of death from COVID-19.[5]

In the guideline prepared by the Ministry of Health, poor prognosis markers (blood lymphocyte count <800/ µl or CRP>50mg/l upper limit value, ferritin>500ng/ml or D-DIMER>1000ng/ml) have been determined for admission blood in patients with COVID-19 pneumonia and should be evaluated for hospitalization in the presence of these criteria.[6]

Radiological imaging is an essential part of the management of COVID-19 patients. Chest radiography is usually the first choice in COVID-19 pneumonia. Although it is possible to observe some abnormalities on chest X-ray imaging, the presence of normality in X-ray results is not used to rule out disease. As the disease progresses, the likelihood of chest X-ray findings increases. COVID-19 involvement is bilateral, peripherally localized, with lower lobe involvement of the basal segments.[7]

There is no antiviral treatment with proven efficacy and safety for COVID-19. Thus, changes are experienced in treatment schemes as a result of studies and drug trials conducted by different countries and centers.[7]

The main goal of vaccines is to create immunity so that if the causative agent is reencountered, the infection can be managed asymptomatically or with mild symptoms. In various countries, mRNA, protein-based, and viral vector-based vaccine studies have been conducted. After demonstrating the effectiveness and safety of these vaccines, they have started to be administered worldwide against COVID-19. The primary goal of the COVID-19 pandemic is to reduce the severity of the disease and thus reduce mortality rates. Rapidly increasing vaccination rates are thought to be an essential part of ending the pandemic.

This study aimed to investigate how the vaccination status of patients with different vaccine combinations hospitalized in the COVID service affected the referral processes to the intensive care unit (ICU).

MATERIALS AND METHODS

Ethics Committee Approval: The study was initiated with the approval of Sakarya University Faculty of Medicine Non-Interventional Research Ethics Committee (date: 25.10.2021, decision no: E-71522473-050.01.04-74700-489), and the study group was expanded and determined as a thesis subject with the approval of the same ethics committee (date: 30.11.2021 decision no: E-71522473-050.01.04-835562-536).

The Type of Study: The present study was conducted with the data of inpatients 854 hospitalized in the COVID Service of a training and research hospital between 01.07.2021 and 31.10.2021 and is a cross-sectional descriptive study.

Data Collection Tools:

The data collection material consists of three parts: disease risk score and assessment form, disease severity score and assessment form, and vaccination process assessment form. The disease risk score and assessment form and the disease severity score and assessment form were developed based on the guidelines prepared by the Ministry of Health, General Directorate of Public Health.[8] The vaccination status of the patients was accessed through the "E-Nabız" or "Aşıla" application of the Ministry of Health.

Disease Risk Score and Assessment Form: The parameters used in disease risk assessment are as follows: age, smoking, body mass index (BMI), immunosuppression status (Bone marrow or organ transplantation, primary immunodeficiencies, use of corticosteroids equivalent to prednisolone >20 mg/ day for at least 14 days in the last 30 days, use of biologics such as infliximab in the previous 90 days, use of immunomodulators such as methotrexate, chemotherapy for cancer), comorbid conditions (Hypertension, Type 1 and Type 2 Diabetes, COPD, history of cardiovascular disease, asthma requiring daily medication, cancer). The parameters evaluated were scored as 1 point for age >60 years, smoking, BMI >30, immunosuppression status, and 1 point for each comorbidity. The risk assessment score for each patient was determined as a value between 0-9 points. Higher scores indicate an increased risk level for the patient.

Disease Severity Score and Assessment Form: The disease severity score form prepared by the researchers included parameters directly related to disease prognosis during COVID-19 disease follow-up. These parameters include lymphocyte count, CRP, ferritin, D-Dimer, respiratory count, Spo2 value, and

AC radiology imaging findings. Blood lymphocyte count <800/µl, CRP >50 mg/L, ferritin >500 ng/ml, D-Dimer >1000 ng/ml, respiratory rate 24 and above, and room air Sp02 93 and below were scored as 1 point, bilateral diffuse (>50%) involvement on AC radiology imaging was scored as 2 points, and non-diffuse involvement was scored as 1 point. The disease severity score is given a value in the range of 0-8.

Vaccination Process Assessment Form: This form records the vaccination status of the patients, if vaccinated, how many doses of which vaccine they received, the date of the last dose of vaccine, the date when the diagnosis of COVID-19 was confirmed by RT-PCR method, and their hospitalization in ICU during the disease process.

Statistical Analysis*:* The conformity of continuous variables to normal distribution was evaluated using the Kolmogorov-Smirnov Test and graphs. Descriptive statistics are given as mean ± standard deviation for normally distributed variables; median, 1st, and 3rd quartiles for non-normally distributed variables; and numbers and percentages for categorical variables. Categorical independent variables that might be associated with the dependent variable of ICU admission were analysed using Pearson's chi-square and Fisher's chi-square tests. Continuous variables that were not normally distributed were evaluated with the Mann-Whitney U Test. Predicting possible risks for ICU admission was evaluated with Binary Logistic Regression Analyses. In the regression model, p<0.25 was considered as the criterion for inclusion in the model related to intensive care hospitalization
with variables related to intensive care hospitalization in univariate analyses. Risk score and Severity score are also included in the model as variables. Hosmer Lemeshow goodness-of-fit statistics were used to assess model fit. P < 0.05 was considered statistically significant.

RESULTS

The study included 854 participants, 457 of whom were female, with a mean age of 57.7±15.71 Standard Deviation (SD). It was determined that 49.2% of the patients had never been vaccinated, 27.0% had two doses of Corona Vac, 6.4% had one dose of Comirnaty, 6% had three doses of Corona Vac, 4.8% had one dose of Corona Vac, 3.7% had two doses of Comirnaty, and 2.8% had two doses of Corona Vac and one dose of Comirnaty (Table 1).

Male gender and higher disease risk and severity scores were found to be statistically significant in the need for an ICU (p 0.01, 0.001, 0.001 and 0.001, respectively). Smoking status (p<0.001) and body mass index of 30 and above (p=0.006), which are disease risk score components, were found to increase the need for intensive care at a statistically significant level. The data that we found effective in the need for intensive care are given in Table 2.

Table 1. Distribution of disease risk score and components and vaccination status of the patients included in the study.

Specifications		n (%)
Age	≥60	370 (43.3)
	<60	484 (56.7)
Smoking status	Smoker	231 (27.0)
	Non-smoker	623 (73.0)
Body Mass Index	≥30	246 (28.8)
	<30	608 (71.2)
Immunosuppression	Yes	11 (1.3)
	No	843 (98.7)
Number of comorbid diseases	No	350 (41.0)
	1	149 (17.4)
	2	178 (20.8)
	3	145 (17.0)
	4 and >4	32 (3.7)
	unvaccinated	420 (49.2)
	1 dose of CoronaVac	41 (4.8)
	2 doses of CoronaVac	231 (27.0)
	3 doses of CoronaVac	51 (6.0)
	1 dose of Comirnaty	55 (6.4)
	2 doses of Comirnaty	32 (3.7)
	2 doses of CoronaVac and 1 dose of Comirnaty	24 (2.8)
The median risk score		2.00 (1.00-4.00)

Table 2. Comparison of disease risk score components and disease severity score components of patients included in the study based on intensive care needs.

Specifications			Intensive Care Need Yes n (/%)	Intensive Care Need No n (/%)	p
Risk Score (Median, 1-3rd quartile)			3.00 (1.0-4.0)	2.00 (1.0-3.0)	**0.001**[a]
Severity Score (Median, 1-3rd quartile)			6.00 (6.0-7.0)	4.00 (3.0-5.0)	**0.001**[a]
Gender		Male	87 (21.9)	310 (78.1)	**0.01***
		Female	69 (15.1)	388 (84.9)	
Disease Risk Score	**Age**	≥60	75 (20.3)	295 (79.7)	0.185*
		<60	81 (16.7)	403 (83.3)	
	Smoking status	Smoker	67 (29.0)	164 (71.0)	**0.001***
		Non-smoker	89 (14.3)	534 (85.7)	
	Body Mass Index	≥30	59 (24.0)	187 (76.0)	**0.006***
		<30	97 (16.0)	511 (84.0)	
	Immunosuppression	Yes	1 (9.1)	10 (90.9)	0.699**
		No	155 (18.4)	688 (81.6)	
	Number of comorbid diseases	No	52 (14.9)	298 (85.1)	0.187*
		1	28 (18.8)	121 (81.2)	
		2	37 (20.8)	141 (79.2)	
		3	30 (20.7)	115 (79.3)	
		4 and >4	9 (28.1)	23 (71.9)	
Disease Severity Score	**Lymphocyte**/µl	<800	102 (29.4)	245 (70.6)	**0.001***
		≥800	54 (10.7)	453 (89.3)	
	CRP ng/ml	>50	127 (21.4)	466 (78.6)	**0.001***
		≤50	29 (11.1)	232 (88.9)	
	Ferritin ng/ml	≥500	101 (30.1)	235 (69.9)	**0.001***
		<500	55 (10.6)	463 (89.4)	
	D dimer ng/ml	≥1000	61 (30.3)	140 (69.7)	**0.001***
		<1000	95 (14.5)	558 (85.5)	
	Respiratory Rate	≥24	143 (48.1)	154 (51.9)	**0.001***
		<24	13 (2.3)	544 (97.7)	
	SpO2	≤93	155 (26.4)	432 (73.6)	**0.001***
		>93	1 (0.4)	266 (99.6)	
	Pulmonary Infiltration	No	1 (2.9)	34 (97.1)	**0.01***
		Non-diffuse	1 (0.4)	237 (99.6)	
		Diffuse	154 (26.5)	427 (73.5)	
Need for intensive care		18.3%			

In COVID-19 patients, a one-unit increase in disease risk score increases the risk of ICU admission by 1.33-fold, and a one-unit increase in disease severity score increases the risk of ICU admission by 2.85-fold. Examination of vaccination status in the model in which all patients were included showed an 82% reduction in the risk of ICU admission with three vaccinations (three doses of CoronaVac or two doses of Corona Vac and one Comirnaty vaccine). A one-unit increase in the disease risk score resulted in a 1.26-fold increase in the risk of ICU admission, and a one-unit increase in the disease severity score resulted in a 2.79-fold increase in the risk of ICU admission. Detailed information is given in Table 3.

Table 3. Intensive care risk situations according to vaccination status.

		B	S.E.	Sig.	Exp(B)	95% C.I.for EXP (B) Lower	95% C.I.for EXP (B) Upper
Risk Score		0.287	0.073	0.000	1.332	1.154	1.538
Severity Score		1.049	0.091	0.000	2.854	2.386	3.415
Vaccination status*	**Vaccination (1)**	-0.271	0.406	0.504	0.763	0.344	1.689
	Vaccination (2)	-0.838	0.645	0.194	0.433	0.122	1.532
	Vaccination (3)	-1.712	0.494	0.001	0.180	0.068	0.476
	Vaccination (4)	-0.504	0.290	0.082	0.604	0.342	1.067
	Constant	-7.428	0.573	0.000	0.001	-	-
Increasing the risk score by one unit**	**Vaccination status**	-0.540	1	0.027	0.583	0.361	0.942
	Risk Score	0.236	1	0.001	1.266	1.106	1.450
	Severity Score	1.029	1	0.000	2.798	2.349	3.331
	Male gender	-0.082	1	0.713	0.921	0.596	1.425
	Constant	-7.280	1	0.000	0.001	-	-

*: Having one Sinovac or One Biontech vaccine (1); Having two Biontech vaccines (2); Three Sinovac or Two Sinovac One Biontech vaccines (3); Receiving two Sinovac vaccines (4); **: The omnibus test result in the model is X2 272,500 p 0.001, and the model is statistically significant. The Hosmer Lemeshow test, which evaluated the model fit, also shows that the model is compatible (p=0.305). The correct classification rate of the model is %85.9.

Patients vaccinated with at least one dose of the Comirnaty vaccine at least one week before and at least one dose of the Corona Vac vaccine at least two weeks before were considered effectively vaccinated. Those with more than 6 months between the date of last vaccination and the date of admission to hospital due to COVID-19 infection were considered unvaccinated. When considered in this way, 21.4% of the unvaccinated needed intensive care, while only 14.6% of the vaccinated needed intensive care, and it was found that vaccination statistically significantly reduced the need for intensive care (p=0.01) (Figure 1).

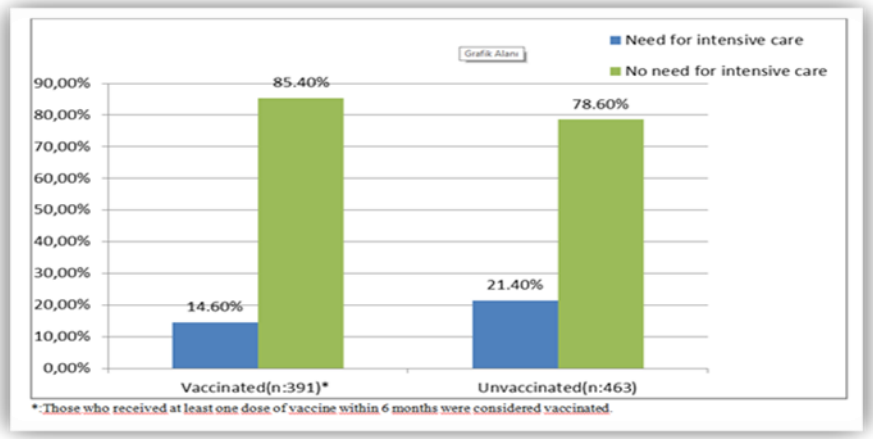

Figure 1. Comparison of intensive care needs and vaccination status of patients included in the study.

DISCUSSION AND CONCLUSION

We assessed the impact of COVID-19 vaccines on the need for an ICU in inpatients with COVID-19 and compared the prognosis of patients according to different vaccination statuses. Three doses of the vaccine resulted in an 82% reduction in the risk of ICU admission in the model in which all patients were analyzed. In an analysis excluding patients with more than one type of vaccine, a 77% reduction in the risk of ICU admission was found in patients who received 3 doses of the CoronaVac vaccine. Patients vaccinated with at least one dose of the Comirnaty vaccine at least one week before and at least one dose of the Corona Vac vaccine at least two weeks before were considered effectively vaccinated. Those with more than 6 months between the date of last vaccination and the date of admission to hospital due to COVID-19 infection were considered unvaccinated. When analyzed, it was discovered that 21.4% of unvaccinated individuals required intensive care, while only 14.6% of vaccinated individuals required the same, proving that vaccination significantly reduces the need for intensive care. Among the disease risk score components, smoking status and BMI of 30 and above were found to increase the need for intensive care at a statistically significant level. Disease severity score was found to statistically significantly increase the need for intensive care in the presence of components. Intensive care need was increased dramatically in patients with higher disease risk and severity scores. In COVID-19 patients, a one-unit increase in the disease risk score increases the risk of intensive care admission 1.33-fold, and a one-unit increase in the disease severity score increases the risk of intensive care admission 2.85-fold.

In our study, we found that 14.6% of patients who had received at least one dose of any COVID-19 vaccine needed intensive care, while 21.4% of unvaccinated patients required the same level of care. The risk of intensive care unit admission was reduced by 42% in patients vaccinated compared to those who had not. However, it's important to note that our study did not evaluate the number and type of vaccines administered, and it was conducted solely among hospitalized patients, so the relatively low rate of intensive care unit admissions may be subject to hospitalized patients. As a result of a study investigating the effectiveness of the Comirnaty vaccine against COVID-19, 92% protection was found for severe COVID-19.[9] In the study conducted with the Comirnaty and Oxford vaccines, the Comirnaty vaccine was found to be 93.7% and 88.0% protective against alpha and delta variants.[10] In the present study, the fact that vaccination showed significant protection against severe disease, while protection appeared to be relatively low, is an expected situation as the study was conducted only in COVID-19

patients receiving inpatient treatment. One factor that prevents the rate from being higher may be the high mortality rate of the disease in the early stages of the pandemic.

We found that the need for intensive care was significantly higher in male patients than in female patients. In studies, male gender was found to be associated with mortality as well as posing a high risk for COVID-19 disease.[11,12] Our study supports the literature data.

Considering the disease risk score parameters in our study individually, smoking and high BMI were found to be associated with the risk of having severe disease. Each point increase in disease risk scoring increased the risk of ICU admission by approximately 33% in inpatients with COVID-19. Xie et al. reported that patients with comorbidities and/or over 60 years of age are at high risk.[9] Docherty et al. evaluated 16749 COVID-19 patients receiving inpatient treatment in the UK and concluded that increasing age and comorbid conditions, including obesity, are associated with high mortality.[13] In our study, when risk parameters such as age, immunosuppression status, and comorbid diseases were compared individually, no statistically significant difference was found in the risk of severe disease. This could be attributed to the different vaccination status of patients in different age groups, the fact that our study was conducted on patients already receiving inpatient treatment and therefore had indications for hospitalization, the low number of immunosuppressive patients, the different age distribution of patients with comorbidities, and the different vaccination status.

Considering the changes in the parameters included in the disease severity score one by one, the changes were found to be statistically significant in increasing the risk of ICU admission in inpatients with COVID-19. Each one-point increase in the severity of the disease score was associated with a more than 2.8-fold increase in the need for ICU admission. Many studies reported that leukopenia, lymphopenia, prothrombin time, and D-dimer elevation are commonly observed in COVID-19 patients in need of intensive care. In another meta-analysis, it was reported that high CRP, PCT, D-dimer, and serum ferritin levels are associated with severe COVID-19 and increased need for intensive care.[13-16] Wu et al. evaluated the relationship between chest computed tomography imaging findings and the clinical course of the disease. In that study, lesions were scored based on whether they occupied more than 50% of the lung segment volume, and a significant correlation was found between the degree of pulmonary inflammation and clinical symptoms and laboratory results.[6]

It was conducted in a single center with data from inpatients over four months. Therefore, the number of patients included in the study was limited. As it was conducted only in inpatients, it does not provide insight into what extent patients protect vaccines against infections or hospitalization. As a cross-sectional descriptive study, the results cannot be generalized to the universe, and we do not claim to establish any cause-and-effect relationship.

In conclusion, it was recommended that it should not be disregarded that the increase in the disease severity score parameters used in the follow-up of COVID -19 patients receiving inpatient treatment increases the risk of severe disease and that the necessary interventions should be made and intensive care should be considered. Three doses of vaccination were found to be effective in preventing disease progression and reducing ICU admission in this study. The current situation serves as another reminder of the importance of vaccination and the significance of booster doses. Amid ongoing discussions about the effectiveness and potential side effects of COVID-19 vaccines, our study adds valuable insights to this discourse.

Ethics Committee Approval: The study was initiated with the approval of Sakarya University Faculty of Medicine Non-Interventional Research Ethics Committee (Date: 25.10.2021, decision no: E-71522473-050.01.04-74700-489), and the study group was expanded and determined as a thesis subject with the approval of the same ethics committee (Date: 30.11.2021, decision no: E-71522473-050.01.04-835562-536).

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – DÇ, HÇE, AA; Supervision – DÇ, MRA, AA; Materials – DÇ, MRA, HÇE, AA; Data Collection and/or Processing – DÇ, MRA, AA; Analysis and/or Interpretation – DÇ, HÇE, AA, MRA; Writing –DÇ, MRA, AA, HÇE.

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