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A retrospective evaluation of the effects of COVID-19 vaccines on the CRP, IL-6, ferritin, and D-dimer levels of patients admitted to the COVID intensive care unit

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Abstract

With its elevated mortality and morbidity rates and various complications, the highly contagious Corona Virus Disease - 2019 (COVID-19) infection that developed in association with the agent severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) led to the world's most deadly pandemic. However, COVID-19-related mortality declined with the development of vaccines. Elevated D-dimer, C-reactive protein (CRP), ferritin, interleukin-6 (IL-6) values in patients with COVID-19 pneumonia are markers that need to be monitored in terms of both severity of infection and prognosis. This article investigates the relationship between COVID-19 vaccination and these parameters. This retrospective, cross-sectional study involved patients aged over 18 diagnosed with COVID-19 pneumonia and admitted to a tertiary COVID intensive care unit. These were assigned to vaccinated or unvaccinated groups, as applicable. The vaccinated patient group was also divided into two subgroups, those who had been given the inactive COVID-19 vaccine and those administered the messenger RNA (mRNA) COVID-19 vaccine. Median age and the proportion of female patients (54.1%) were both higher in the vaccinated patient group. Higher rates of chronic obstructive pulmonary disease and hypertension were also observed in the vaccinated group. Median length of hospital stay and mortality rates (85.5%) were higher in the unvaccinated patient group. The median length of stay was lower in both the group given twin doses of mRNA COVID-19 vaccine and in the patients given the inactive COVID-19 vaccine. Significantly lower median D-dimer levels were determined in the vaccinated patient group (1.3 mg/L) and in the patients administered two doses of inactive COVID-19 vaccine (1.1 mg/L). D-dimer levels among patients admitted to the COVID intensive care unit were higher in the unvaccinated group and in those who had been given a single dose of inactive COVID-19 vaccine, and this represented a risk in terms of mortality.

Keywords: COVID-19 vaccine, C-reactive protein, interleukin-6, ferritin, D-dimer, intensive care unit

Introduction

Corona Virus Disease - 2019 (COVID-19), which is highly infectious and develops in association with the Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) agent, resulted in the world's greatest pandemic, with high morbidity, mortality, and various complication rates [1,2]. COVID-19 is a respiratory disease, the manifestations of which can be limited to asymptomatic disease or mild upper respiratory tract infection symptoms or else occur as pneumonias resulting in severe respiratory failure, multiorgan failure, and death, and can lead to widespread physical and psychological function impairment [3].

Interleukin-6 (IL-6), C-reactive protein (CRP), D-dimer, and ferritin values can accurately predict in-hospital mortality in patients with COVID-19 [4-6].

The emergence of COVID-19 toward the end of 2019, its rapid spread, and ability to cause severe and potentially-fatal disease made the search for a vaccine a worldwide priority [7].

Studies have estimated the general hospital mortality rate due to COVID-19 at approximately 15-20%, rising to 40% in patients requiring admission to the intensive care unit (ICU). However, different age groups exhibit differing mortality rates, from 5% in patients under 40 to over 60% in those aged 80-89 [8]. However, another study suggested that mortality rates were lower due to appropriate treatment and vaccination [9,10]. A single dose was 53% (15-91%) effective for COVID-19-related mortality, while two doses were 95% (92-98%) effective [11].

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Increases in D-dimer, CRP, ferritin, and IL-6 values in patients with COVID-19 pneumonia are important biomarkers that need to be monitored in terms of both the severity of infection and of prognosis. This research was intended to investigate how CRP, ferritin, IL-6, and D-dimer levels in cases diagnosed with COVID-19 pneumonia admitted to the COVID intensive care unit (ICU) varied between vaccinated and unvaccinated individuals, and their associations with mortality.

Material and Methods

Study Design and Population

This retrospective, cross-sectional research was conducted with patients aged 18 or over and diagnosed with COVID-19 pneumonia confirmed via nasopharyngeal swab reverse transcriptase polymerase chain reaction (RT-PCR) results and admitted to the Marmara University Pendik Teaching and Research Hospital tertiary COVID ICU, Türkiye, between 10.11.2021 and 10.05.2022. Patients with negative RT-PCR results, those whose vaccination status was unknown, those aged under 18, and pregnant women were excluded.

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines. Since the study was retrospective in nature, informed and written consent from patients or their relatives was not obtained. Following permission from the Turkish Ministry of Health, ethical approval was issued by the medical faculty clinical research ethical committee (ethics number: 09.2021.1209).

Data Collection

The study was performed by examining data in the hospital database of patients with positive RT-PCR tests diagnosed with COVID-19 pneumonia.

Patients' COVID-19 vaccination status on admission to the COVID ICU, the name of the vaccine, their demographic data, additional diseases, length of stay in intensive care, 28-day mortality, receipt of O2 therapy, and CRP, ferritin, IL-6, and D-dimer levels were recorded from the hospital database. The research investigated how these parameters changes between the vaccinated and unvaccinated patient groups, and their associations with mortality.

The patients were assigned to vaccinated or unvaccinated groups, as applicable. The vaccinated group was also divided into two subgroups, those receiving inactive COVID-19 vaccine and those given the messenger RNA (mRNA) COVID-19 vaccine.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) case-control checklist was employed during the preparation of the manuscript [12].

Three hundred ninety patients were admitted to intensive care during the study dates, of whom 24 were excluded due to negative RT-PCR results, three due to their RT-PCR results being unavailable, and eight due to their vaccination status being uncertain. Three hundred fifty-five patients were thus finally enrolled (Figure 1).

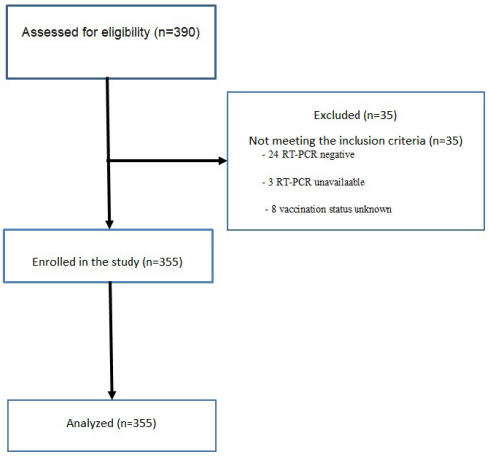

Figure 1. Flowchart of the study design

Statistical Analysis

Descriptive data were expressed as number and percentage and measurement data as mean±standard deviation or median (minimum-maximum), as appropriate. Categorical data were compared with the application of either the chi-square or Fisher tests, as appropriate. The Kolmogorov-Smirnov test and histogram charts were employed for the examination of normal distribution assumptions. Non-normally distributed data were compared using the Mann Whitney U test and Kruskal Wallis test, as appropriate. p values <0.05 were regarded as statistically significant. Bonferroni correction in p values was applied for post-hoc analyses. All data analyses were carried out on IBM SPSS version 23 statistical software (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA).

Results

Examination of the demographic and clinical characteristics showed that these differed significantly between the vaccinated and unvaccinated groups. Female patients represented a greater proportion of the vaccinated group than the non-vaccinated group ($p<0.001$). The median age of the vaccinated patients was also significantly higher than that of the unvaccinated patients ($p=0.001$). However, mortality rates were lower in the vaccinated patients ($p=0.003$). The mean length of hospitalization was significantly lower in the vaccinated patients than in the unvaccinated group ($p=0.020$). Higher hypertension and chronic obstructive pulmonary disease (COPD) rates were observed in the vaccinated group ($p=0.045$ and $p=0.002$, respectively). Significantly lower mean D-dimer levels were observed in the vaccinated patients ($p<0.001$). No significant associations were determined between vaccination status and the other parameters investigated (Table 1).

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Table 1. The patients' clinical and laboratory parameters

		Unvaccinated N (%)	Vaccinated N (%)	P
Sex	**Male**	136 (65.7)	68 (45.9)	**<0.001[c]**
	Female	71 (34.3)	80 (54.1)	
Patient age*		65.0 (29.0-94.0)	75.0 (23.0-94.0)	**0.001[m]**
Days of hospitalization*		19.0 (1.0-106.0)	17.0 (1.0-92.0)	**0.020[m]**
Departure	**Dead**	177 (85.5)	108 (73.0)	**0.003[c]**
	Alive	30 (14.5)	40 (27.0)	
Hypertension	**No**	109 (52.7)	62 (41.9)	**0.045[c]**
	Yes	98 (47.3)	86 (58.1)	
Diabetes mellitus	**No**	141 (68.1)	102 (68.9)	0.872[c]
	Yes	66 (31.9)	46 (31.1)	
Cardiovascular disease	**No**	170 (82.1)	112 (75.7)	0.138[c]
	Yes	37 (17.9)	36 (24.3)	
COPD	**No**	201 (97.1)	132 (89.2)	**0.002[c]**
	Yes	6 (2.9)	16 (10.8)	
Oxygenation	**Intubated**	165 (80.1)	109 (74.1)	0.345[f]
	Mask with reservoir	16 (7.8)	9 (6.1)	
	Simple face mask	3 (1.5)	4 (2.7)	
	HFNC	17 (8.3)	21 (14.3)	
	NIV	5 (2.4)	4 (2.7)	
IL-6*, pg/ml		67.0 (9.9-1717.0)	32.3 (9.4-345.0)	0.477[m]
Ferritin*, µg/L		1030.0 (53.7-15,000.0)	977.0 (151.7-15,000.0)	0.490[m]
D-dimer*, mg/L		2.3 (0.3-20.0)	1.3 (0.4-14.7)	**<0.001[m]**
CRP*, mg/L		100.6 (4.4-410.0)	99.0 (8.9-404.8)	0.152[m]

[c]chi-square test, [f]Fisher test, [m]Mann Whitney U test, *median (minimum-maximum)

Examination of the inactive COVID-19 dose administered and the patients' demographic and clinical characteristics revealed various significant differences according to the post hoc analysis results. The median length of hospitalization was lower in the patients receiving two doses of vaccine than in those receiving a single dose (p=0.001). Mortality rates were higher in those receiving three doses or more than in those receiving one or two doses (p=0.001). The presence of hypertension was significantly lower in patients vaccinated with three or more doses than in those with one or two doses (p=0.044). A higher incidence of diabetes was determined in patients receiving two doses than in those receiving one (p=0.014). Median IL-6 levels were lower among the single-dose patients than in those receiving three doses (p=0.003). Higher D-dimer levels were determined in the patients receiving a single dose of vaccine than in those receiving two doses (p=0.005). No statistically significant associations were determined between inactive COVID-19 vaccine dose numbers and the other parameters examined (Table 2).

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Table 2. The clinical and laboratory parameters of the inactive COVID-19 vaccine group

		Inactive COVID-19 vaccine			p
		Single dose	Two doses	Three or more doses	
		N (%)	N (%)	N (%)	
Sex	**Male**	14 (48.3)	40 (50.0)	13 (46.4)	0.946[c]
	Female	15 (51.7)	40 (50.0)	15 (53.6)	
Patient age*		73.0 (23.0-94.0)	76.0 (29.0-92.0)	77.0 (44.0-80.0)	0.668[k]
Days of hospitalization*		20.0 (5.0-39.0)	10.0 (3.0-92.0)	20.0 (1.0-51.0)	**0.001**[k]
Departure	**Dead**	20 (69.0)	50 (62.5)	28 (100.0)	**0.001**[c]
	Alive	9 (31.0)	30 (37.5)	0 (0.0)	
Hypertension	**No**	12 (41.4)	27 (33.8)	17 (60.7)	**0.044**[c]
	Yes	17 (58.6)	53 (66.3)	11 (39.3)	
Diabetes mellitus	**No**	25 (86.2)	49 (61.3)	23 (82.1)	**0.014**[c]
	Yes	4 (13.8)	31 (38.8)	5 (17.9)	
Cardiovascular disease	**No**	24 (82.8)	56 (70.0)	21 (75.0)	0.403[c]
	Yes	5 (17.2)	24 (30.0)	7 (25.0)	
COPD	**No**	26 (89.7)	71 (88.8)	24 (85.7)	0.872[f]
	Yes	3 (10.3)	9 (11.3)	4 (14.3)	
Oxygenation	**Intubated**	25 (86.2)	52 (65.0)	24 (88.9)	0.279[c]
	Mask with reservoir	0 (0.0)	8 (10.0)	1 (3.7)	
	Simple face mask	1 (3.4)	3 (3.8)	0 (0.0)	
	HFNC	3 (10.3)	14 (17.5)	2 (7.4)	
	NIV	0 (0.0)	3 (3.8)	0 (0.0)	
IL-6*, pg/ml		10.5 (9.4-11.0)	31.1 (22.6-164.2)	335.0 (334.0-339.0)	**0.004**[k]
Ferritin*, µg/L		806.6 (178.1-3245.0)	977.0 (151.7-10906.0)	990.0 (203.6-4560.0)	0.574[k]
D-dimer*, mg/L		3.0 (0.5-12.9)	1.1 (0.4-12.6)	2.2 (0.5-14.7)	**0.005**[k]
CRP*, mg/L		98.9 (52.6-309.0)	93.9 (8.9-395.0)	121.0 (13.4-313.0)	0.208[k]

[c]chi square test f Fisher test, [k]Kruskal Wallis test, *median (minimum-maximum) values

Examination of the mRNA COVID-19 vaccine doses and the patients' demographic and clinical characteristics revealed various significant findings at post hoc analysis. The proportion of male patients was higher in the two-dose group than in the single-dose group (p=0.004). The number of days of hospitalization was lower among the patients receiving two doses than those given a single dose (p=0.042). No statistically significant associations were determined between the number of mRNA COVID-19 vaccine doses and the other parameters investigated (Table 3).

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Table 3. The clinical and laboratory characteristics of the mRNA COVID-19 vaccine dose groups

		mRNA COVID-19 vaccine		p
		Single dose	Two doses	
		N (%)	N (%)	
Sex	**Male**	3 (15.8)	4 (100.0)	**0.004[f]**
	Female	16 (84.2)	0 (0.0)	
Patient age*		56.0 (41.0-81.0)	77.0 (75.0-90.0)	0.088[m]
Days of hospitalization*		11.0 (3.0-29.0)	3.0 (3.0-9.0)	**0.042[m]**
Departure	**Dead**	16 (84.2)	4 (100.0)	>0.999[f]
	Alive	3 (15.8)	0 (0.0)	
Hypertension	**No**	7 (36.8)	0 (0.0)	0.273[f]
	Yes	12 (63.2)	4 (100.0)	
Diabetes mellitus	**No**	10 (52.6)	3 (75.0)	0.604[f]
	Yes	9 (47.4)	1 (25.0)	
Cardiovascular disease	**No**	19 (100.0)	3 (75.0)	0.174[f]
	Yes	0 (0.0)	1 (25.0)	
COPD	**No**	17 (89.5)	4 (100.0)	>0.999[f]
	Yes	2 (10.5)	0 (0.0)	
Oxygenation	**Intubated**	12 (63.2)	1 (25.0)	0.082[f]
	Mask with reservoir	0 (0.0)	0 (0.0)	
	Simple face mask	0 (0.0)	0 (0.0)	
	HFNC	6 (31.6)	1 (25.0)	
	NIV	1 (5.3)	2 (50.0)	
IL-6*, pg/ml		189.5 (30.3-345.0)	(-)[±]	*
Ferritin*, µg/L		975.9 (151.7-15000.0)	720.5 (719.4-1415.0)	0.745[m]
D-dimer*, mg/L		1.0 (0.5-4.6)	1.7 (1.7-12.6)	0.104[m]
CRP*, mg/L		334.2 (26.7-404.8)	394.0 (32.0-395.0)	0.123[m]

[c]chi square test, [f]Fisher test, [m]Mann Whitney U test, *median (minimum-maximum) values; ±Evaluation could not be performed for IL-6 due to insufficient data

Discussion

Vaccination has reduced mortality and disease rates in numerous conditions. Mortality due to COVID-19 infection decreased significantly once vaccination commenced [10]. Several studies have confirmed that D-dimer, CRP, ferritin, and IL-6 are indicative of in-hospital mortality in cases of COVID-19 infection [4,5]. The present study is important in terms of showing the kind of association that exists between COVID-19 vaccination and these parameters. Elevated D-dimer levels in patient admitted to the COVID ICU appears to represent a risk in terms of mortality in the unvaccinated patient group and the group that received a single dose of inactive COVID-19 vaccine.

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Elevated CRP, ferritin, and IL-6 levels have been predicted to be among the markers of mortality among patients diagnosed with COVID-19, and mortality has been expected to be potentially associated with hyperinflammation [13,14]. Increased D-dimer (>1 μg/mL) levels have been found to be associated with disseminated intravascular coagulopathy and increased in-hospital mortality [15].

Due to the persistent development of SARS-CoV-2 variants, improving vaccination rates and coverage came to be recognized as the most effective means of halting the pandemic [11].

In the light of the worrying speed of transmission, safe and effective vaccines capable of covering susceptible populations and restoring life to normal were urgently needed [16].

Vaccine-based immunization significantly reduces mortality rates from COVID-19 and thus significantly prevents transmission and the disease progressing with a severe clinical course [17]. The effectiveness of the inactive COVID-19 vaccine was 66% [18], while that of the mRNA COVID-19 vaccine ranged between 90% and 95 [19,20], independently of the SARS-CoV-2 variants.

Rapid herd immunity acquisition by way of vaccination was of crucial importance if the development of mutations with the ability to completely evade immune surveillance was to be prevented [21]. Some patients were vaccinated with mRNA COVID-19 and others with inactive COVID-19 vaccine. In general terms, the most effective of the COVID-19 vaccines are RNA vaccines, followed by viral vector and inactive virus vaccines [22]. Another study described a single dose of COVID-19 vaccine as 53% effective in preventing COVID-19-related mortality (15-91%), while two doses were 95% (92-98%) effective [11].

The proportion of female patients in the vaccinated group was significantly higher compared to in the unvaccinated group ($p<0.001$). Severity and mortality rates in COVID-19 are known to be positively correlated with age [23]. Median ages were significantly higher in the vaccinated individuals than in the unvaccinated group ($p=0.001$). This may be due to vaccination priority being given to the elderly population. Lower mortality rates were determined in the vaccinated group ($p=0.003$). This finding was consistent with the previous literature [24].

Median D-dimer levels were significantly lower in the vaccinated patient group ($p<0.001$) and in the group receiving two doses of inactive COVID-19 vaccine ($p=0.005$). Mousavi et al. reported an association between D-dimer elevation and mortality [25]. Significantly elevated D-dimer levels in unvaccinated patients were thought to result in high mortality.

The median length of hospitalization was significantly lower in the vaccinated patients than in the unvaccinated group ($p=0.020$). Median lengths of hospitalization were also significantly lower among patients administered two doses of vaccine compared to those receiving only one, in terms of both mRNA COVID-19 ($p=0.042$) and inactive COVID-19 ($p=0.001$) vaccines ($p=0.042$). A number of previous studies support this finding [24].

The prevalences of hypertension and COPD were higher among the vaccinated group than in the unvaccinated patients ($p=0.045$ and $p=0.002$, respectively). This may be attributable to the vaccination priority attached to the at-risk group.

The mortality rate was significantly higher in patients receiving three or more doses of inactive COVID-19 vaccine compared to those receiving a single or two doses ($p=0.001$). Although immunity acquired through vaccination makes the disease milder and reduces hospitalization, risk factors including variant strains [26], the potential for immunity to decline over time [27], doubts concerning additional vaccines [28], age, and comorbidity [29] have been regarded as significant factors in addition to vaccination.

The incidence of hypertension was lower in patients receiving three of more doses of inactive COVID-19 vaccine ($p=0.044$), while the presence of diabetes was higher among patients receiving two doses of inactive COVID-19 vaccine compared to those with a single dose ($p=0.014$). These inconsistent findings in terms of comorbidities between the two groups may be associated with the low patient numbers. Mean IL-6 levels were lower in the patients receiving a single dose of inactive COVID-19 vaccine compared those receiving three doses ($p=0.003$).

A number of limitations should be considered when interpreting the study results. The first involves the single-center nature of the study, the relatively low sample size, the fact that second and third doses were not completed, and that variants were unknown. Its ability to detect differences between the vaccinated and unvaccinated groups is therefore limited. Evaluation was also limited by the small number of members of the group administered the mRNA COVID-19 vaccine, the most effective option. The second is that the patients' neutralizing antibody levels were not investigated. Another limitation is that since vaccination was encourage gradually, on the basis of age and risk, limited basic data could be obtained for specific populations. Finally, D-dimer, CRP, ferritin, and IL-6 values were not investigated in all patients.

Conclusion

D-dimer levels among patients admitted to the COVID ICU were high in the unvaccinated patient group and the group administered a single dose of inactive COVID-19 vaccine, and this represents a risk in terms of mortality. Further more extensive studies with larger patient numbers and in which vaccinations were fully completed are now needed.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethical approval was issued by the Marmara University Medical Faculty Clinical Research Ethical Committee (ethics number: 09.2021.1209).

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