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Clinical and Laboratory Characteristics of Hospitalized Patients With COVID-19 After Vaccination in Quchan-Iran

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ABSTRACT

Background: COVID-19 is the latest and most important global health crisis, which challenged even the most advanced healthcare systems in the world. Effective vaccination is the only solution to prevent infection and reduce the disease severity and mortality rate. The present study aimed to determine the clinical and laboratory characteristics of hospitalized patients with COVID-19 after vaccination in Quchan County, Iran.

Materials and Methods: This is an observational analytical study with a cross-sectional scheme. The study population includes the one-year data of COVID-19 patients admitted to Musa Ibn Jafar Hospital in Quchan, Iran from March 2021 until March 2022. The data were divided into two groups vaccinated (n=123) and un-vaccinated (n=123). Three post-vaccination time windows of "no immunity", "partial immunity", and "full immunity" were defined to determine the length of hospitalization and death rate due to COVID-19 based on the type of vaccine. The data were collected from patient's medical files recorded in the archive system of the hospital, the SIB system, or by calling patients or their families.

Results: The mean age of vaccinated patients was higher than that of un-vaccinated patients (P<0.001). Chest pain, muscle pain, and vomiting were significantly less common in vaccinated patients (P<0.05, P<0.01, P<0.05, corresponigly), while shivering was more common (P<0.001). The serum levels of C-reactive protein (CRP) were significantly higher in vaccinated patients (P<0.01), while the white blood cell (WBC) count was lower (P<0.05). Mortality rate (P<0.01) and the length of hospitalization (P<0.001) were significantly higher in un-vaccinated patients. Sinopharm (73.98%) and AstraZeneca (17.7%) were the most administered vaccines. All death cases occurred in the full immunity time window (two weeks after receiving the second dose of vaccine).

Conclusion: Vaccination can reduce the length of hospitalization and mortality rate in COVID-19 patients. Therefore, further vaccination coverage is necessary to reduce the severity of disease, length of hospitalization, and mortality rate in these patients.-

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Introduction

The spread of newly emerging and re-emerging infectious diseases has always been considered a threat to human societies, such that the epidemics and pandemics of these diseases have sometimes caused a global health crisis. The coronavirus disease 2019 (COVID-19) is the latest and most important global health crisis, which challenged even the most advanced healthcare systems in the world [1]. The COVID-19 virus belongs to the family of coronaviruses (CoVs). This family includes a group of single-stranded RNA viruses that can cause respiratory, intestinal, hepatic, and neurological diseases [2]. Human angiotensin-converting enzyme 2 (ACE2) is the functional receptor for the SARS-CoV-2. It is a membrane protein expressed in the lungs, heart, kidneys, intestines, and other tissues [3].

The mortality rate due to COVID-19 in the first year of its outbreak was equal to the mortality rate due to the AIDS epidemic and drug overdose in recent decades [4]. This disease, with an incubation period of 0-24 days, has varying degrees of symptoms ranging from asymptomatic or mild flu-like symptoms to severe symptoms and death [3]. Different body organs are affected by this disease. Some of the most common symptoms are headache, fever, fatigue, cough, shortness of breath, sore throat, muscle pain, changes in the sense of smell and taste, phlegm, pneumonia, and hypoxemia, and patients are usually recovered with proper nutritional, hygiene, and medical interventions without the need for hospitalization [5]. According to the studies, severe COVID-19 occurs in 14-30% of cases, which leads to hospitalizations of patients in special care units [6]. Death occurs in 2-6% of cases [7]. Cardiovascular, digestive, pulmonary, neurological, and immune system complications are important complications of COVID-19; therefore, underlying diseases can aggravate the condition and increase the mortality rate of patients [8, 9]. Infected patients are the main source of COVID-19, but asymptomatic infected individuals may also be potential sources of this virus [10]. The patients recovered from COVID-19 also had positive PCR, which is unprecedented. In other words, either infected individuals without symptoms or recovered cases may pose severe challenges to disease prevention and control [11].

Some demographic factors, such as age, gender, occupation, and race, are effective in the prevalence, severity, and mortality rate of COVID-19. Other effective factors are genetic or physiological differences, lifestyle, health-related behaviors, accessibility to healthcare facilities, the frequency of contact with patients, and the degree of protection against pathogenic agents [12]. Effective vaccination is the most efficient strategy for inducing a protective immune response and, thus, preventing the spread of infection and reducing death rate. At the time of this study, there were 137 COVID-19 vaccines in clinical and 194 vaccines in preclinical development, which had been designed based on a wide range of vaccine platforms, including live attenuated vaccines, inactivated vaccines, vector-based vaccines, DNA vaccines, RNA, etc. [13]. Clinical data on mRNA vaccines showed no detectable viral RNA in monkeys' bronchoalveolar lavage fluid or nasal swabs after exposure to the COVID-19 virus. This indicated the protection of animals against SARS-CoV-2 infection [14]. Theoretically, the formation of immunological memory by the COVID-19 vaccine may play an essential role in preventing reinfection. A recent study showed a significantly higher production of SAR-CoV-2 protein-specific antibodies after a single dose of BNT162b2 in subjects infected in the past 9-12 months, compared to subjects without a history of infection. This suggests that vaccination can enhance immune memory and prevent reinfection [15].

The beneficial effects of different vaccines on the severity of COVID-19 and their clinical outcomes require further investigation during the development of immunological memory. In Iran, at the time of this study, there was no enough information about the nature and clinical and paraclinical characteristics of people hospitalized with COVID-19 after vaccination. In this regard and considering the importance of knowing the prevalence and nature of COVID-19 after vaccination, the present study examined the clinical and laboratory characteristics of hospitalized patients with COVID-19 after vaccination in Quchan County, Iran.

Materials and Methods

This is an analytical-observational survay with a cross-sectional design. The study population included the data of all hospitalized patients diagnosed with COVID-19 admitted to Musa Ibn Jafar Hospital in Quchan, Iran for one year from March 2021 until March 2022. The entry criteria were the positive RT-PCR test. Due to the significant difference in the number of vaccinated and unvaccinated patients in this period, the data were divided into two groups of 123, including vaccinated and unvaccinated cases. In addition, to determine the length of hospitalization and mortality rate caused by COVID-19 based on the type of vaccine, three-time windows: From day 0 to day 14 after the first dose (no immunity), from day 14 after the first dose to day 14 after the second dose

(partial immunity), and from day 14 after the second dose onwards (full immunity).

The sampling was done by a census method. After approving the project and receiving the code of ethics, the required data were collected from the medical files of patients, the SIB system, or by calling the patients or their families using a researcher-made checklist that surveys demographic information, underlying diseases, initial symptoms, date of vaccination, duration of infection after vaccination, etc. Exclusion criteria were the incomplete clinical and paraclinical information of patients, insufficient information about vaccination in the SIB system, or unwillingness of patients to cooperate after calling them.

Data analysis was done in SPSS software, version 16. The Kolmogorov-Smirnov test was used to test the normality of data distribution. Mean and standard deviation and independent t-test were used for quantitative variables, and the chi-square test or Fisher's test was applied for qualitative variables in two groups. In some cases, the regression technique for performing survival analysis was used. The significance level was set at 0.05.

Results

Demographic characteristics

The mean age of vaccinated patients was significantly higher than that of un-vaccinated patients (66.67 years vs 60.6 years, P<0.001) (Table 1). The most of vaccinated patients were male (n=72), while the number of males and females was almost equal in un-vaccinated patients. However, there was no significant gender difference between the vaccinated and un-vaccinated patients. No significant difference was detected between the two groups in terms of occupation, place of residence, and marital status, either (Table 1).

Table 1. Demographic characteristics of vaccinated and un-vaccinated patients

Variables		Mean±SD/No. (%)		Sig.
		Groups		
		Vaccinated (n=123)	Un-vaccinated (n=123)	
Age (y)		66.67±1.2	60.6±1.49	0.001
Sex	Female	51(41.46)	63(51.22)	0.159
	Male	72(58.54)	60(48.78)	
Marital status	Single	1(0.8)	1(0.8)	0.275#
	Married	104(84.6)	112(91.1)	
	Widow/Widower	18(14.6)	10(8.1)	
Occupation	Unemployed	13(10.57)	7(5.69)	0.349*
	Housekeeper	49(39.84)	58(17.15)	
	Self-employed	34(27.64)	35(28.46)	
	Employed	6(4.88)	6(4.88)	
	Retired	2(1.63)	6(4.88)	
	Worker	5(4.07)	3(2.44)	
	Other	14(11.38)	8(6.5)	
Place of residence	City	85(69.1)	70(56.9)	0.64&
	Village	38(30.9)	53(43.1)	

&Fisher's test, *Independent t-test, #Chi-Square test.

Clinical symptoms

Table 2 presents the frequency of clinical symptoms in two groups of vaccinated and un-vaccinated patients. Chest pain (P=0.05), muscle pain (P=0.002), and vomiting (P=0.013) were significantly lower in the vaccinated group than in the un-vaccinated group. Also, shivering was significantly higher in the vaccinated group than in the un-vaccinated group (P=0.000). No significant difference was found between the two groups in other clinical symptoms (Table 2).

Laboratory findings

The results of laboratory tests are presented in Table 3. As can be seen, the C reactive protein (CRP) level was significantly higher in the vaccinated group than in the un-vaccinated group (P<0.01). The erythrocyte sedimentation rate (ESR) showed no significant difference between the two groups. In addition, the white blood cell (WBC) count was significantly lower in the vaccinated group (P<0.01).

Mortality rate

The results of measuring the mortality rates in two study groups are presented in Table 4. In the vaccinated group, the number of patients who survived after contracting COVID-19 was 116(94.3%), while the number of survived patients in the un-vaccinated group was 96(77.04%). Also, the number of deceased people in the vaccinated group was 7(4.7%), while the number of deceased people in the un-vaccinated group was 27(21.95%). The statistical analysis showed a significant difference between the two groups (P<0.01).

Table 2. Frequency of clinical symptoms in vaccinated and un-vaccinated patients

Variables	No. (%)		P
	Vaccinated (n=123)	Un-vaccinated (n=123)	
Dyspnea	87(70.7)	92(74.8)	0.283
Weakness	74(60.2)	79(64.2)	0.300
Chest pain	2(1.6)	8(6.5)	0.05
Sore throat	0(0.0)	0(0.0)	-
Shivering	39(31.7)	15(12.2)	0.00**
Anorexia	14(11.4)	16(13.0)	0.423
Fatigue	4(3.3)	9(7.3)	0.123
Muscle pain	3(2.4)	17(13.8)	0.002**
Diarrhea	4(3.3)	9(7.3)	0.127
Vomiting	6(4.9)	17(13.8)	0.013**
Cough	32(26.0)	31(25.2)	0.500
Sneezing	0(0.00)	0(0.00)	-
Abdominal pain	3(2.4)	5(4.1)	-
Runny nose	6(4.9)	0(0.00)	-
Headache	38(30.9)	53(43.1)	0.500
Vertigo	1(0.8)	5(4.1)	0.106
Anosmia	6(4.9)	5(4.1)	0.500
Loss of consciousness	12(9.8)	15(12.2)	0.342

*Chi-square test, **Significant (P<0.05).

Table 3. Laboratory findings in vaccinated and un-vaccinated patients

Variables	Mean±SD		Test Results*
	Vaccinated (n=123)	Un-vaccinated (n=123)	
CRP	86.08±7.05	62.97±5.26	0.009**
ESR (mm/h)	42.97±5.41	36.58±2.43	0.904
WBC (*1000/µl)	7.08±0.31	8.92±0.82	0.039**

SD: Standard deviation.

*Independent t-test; **Significant (P<0.05).

Table 4. Mortality rate in vaccinated and un-vaccinated patients

Variables		No. (%)		Test Results		
		Vaccinated (n=123)	Un-vaccinated (n=123)	X^2	df	Sig.
Mortality rate	Survived	116(94.3)	96(77.04)	13.651	1	0.01
	Deceased	7(4.7)	27(21.95)			

Length of hospitalization

Table 5 shows the length of hospitalization in two study groups. The mean length was 4.13 days in the vaccinated group and was 5.47 days in the un-vaccinated group, and the difference was statistically significant (P<0.001).

Relationship of mortality rate with age and sex

Statistical analysis using Spearman's correlation test showed no significant relationship between mortality rate and age or between mortality rate and sex in any groups (Tables 6 and 7).

Table 5. Length of hospitalization in vaccinated and un-vaccinated patients

Variables	Mean±SD		Statistical Results*		
	Vaccinated (n=123)	Un-vaccinated (n=123)	t	df	Sig.
Length of hospitalization (day)	4.13±0.22	5.47±0.31	3.229	244	0.001

*Independent t-test.

SD: Standard deviation.

Table 6. Relationship between mortality rate and age

Variables		No. (%)/Mean±SD	
		Vaccinated (n=123)	Un-vaccinated (n=123)
Mortality rate	Survived	116(94.3)	96(77.04)
	Deceased	7(4.7)	27(21.95)
Age (y)		66.67±1.2	60.6±1.49
Sig.*		0.597	0.765

*Spearman's correlation test.

SD: Standard deviation.

Table 7. Relationship between mortality rate and sex

Variables		No. (%)	
		Vaccinated (n=123)	Un-vaccinated (n=123)
Mortality rate	Survived	116(94.3)	96(77.04)
	Deceased	7(4.7)	27(21.95)
Sex	Female	51(41.46)	63(51.22)
	Male	72(58.54)	60(48.78)
Sig.*		0.291	0.975

SD: Standard deviation.

*Spearman's correlation test.

Table 8. Frequency and percentage of hospitalization in patients with COVID-19 in different time windows after vaccination

Vaccine	No. (%)	No. (%)		
		Immunity		
		No	Partial	Full
Sputnik	3(4.2)	0	1(33)	2(67)
Baharat	3(4.2)	1(33)	2(67)	0
AstraZeneca	21(17.7)	4(19.4)	5(23.8)	12(57.14)
Sinopharm	91(73.98)	7(7.4)	26(28.7)	58(63.9)
Barakat	5(4.06)	0	2(40)	3(60)

Number of hospitalized patients in different time windows after vaccination

Table 8 shows the number of hospitalized patients with COVID-19 in different time windows after vaccination based on the type of vaccine. Sinopharm was the most common vaccine (n=91, 73.98%). Among those who received this vaccine, 7(7.4%) were infected with COVID-19 within 14 days after receiving the first dose (no immunity), 26(7% 28) were infected from day 14 after the first dose to day 14 after the second dose (partial immunity), and 58(63.9%) were infected after more than 14 days passed since receiving the second dose (full immunity). After the Sinopharm, the most common vaccine was AstraZeneca (n=21, 17.07%). Most hospitalizations occurred after vaccination by Sputnik, AstraZeneca, Sinopharm, and Barakat in the full immunity induction period (two weeks after the second dose).

Death cases in different time windows after vaccination

Table 9 shows the frequency of death cases in different time windows after vaccination based on the type of vaccine. As can be seen, all death cases caused by COVID-19 in vaccinated patients were related to those who received Sinopharm (n=7, 5.4%). The majority of deaths (n=4, 57.14%) occurred two weeks after the second dose (full immunity induction period).

Discussion

Although most COVID-19 vaccines are well tolerated, some rare side effects, such as myocarditis, thrombocytopenia, and cerebral thrombotic events have been reported following their administration [16]. Considering the lack of sufficient information about the nature of clinical and paraclinical characteristics of the COVID-19 disease after immunization with existing vaccines and the importance of knowing the severity of infections after vaccination, the present study examined the clini-

Table 9. Frequency and percentage of death cases caused by COVID-19 in different time windows after vaccination

Vaccine	No. (%)	No. (%)		
		Immunity		
		No	Partial	Full
Baharat	0(0)	0(0)	0(0)	0(0)
AstraZeneca	0(0)	0(0)	0(0)	0(0)
Sinopharm	7(5.4)	1(14.28)	2(28.57)	4(57.14)
Barakat	0(0)	0(0)	0(0)	0(0)

cal and laboratory characteristics of hospitalized patients with COVID-19 patients in Quchan, Iran, after vaccination.

The mean age of vaccinated patients was higher than that of un-vaccinated patients, indicating that older people are more likely to get vaccinated. Similar studies have also reported a higher age of vaccinated people [17]. Chronic inflammatory conditions weaken immunity against infectious diseases, and age-related immune decline can increase tissue damage resulting from infections in older individuals [18]. Also, the increased level of pro-inflammatory cytokines at higher ages may contribute to the worsening of infections [19]. Therefore, awareness of these conditions might cause older people to get vaccinated more than younger people.

Among the clinical symptoms, chest pain, nausea, and muscle pain were more common in un-vaccinated patients than in vaccinated patients. In other studies, cardio-respiratory symptoms were reported higher in vaccinated patients [20], possibly due to the higher age range of patients and, as a result, more associated diseases.

C-reactive protein (CRP) is one of the inflammatory markers synthesized by the hepatocytes in the acute phase. The elevated serum CRP levels in COVID patients could be an indicator of exaggerated inflammatory responses and may contribute to the disease severity [21]. In the present study, serum CRP levels were higher in vaccinated patients which is compatible with other studies [22, 23]. The increase in CRP levels is a natural inflammatory immune response to vaccination and indicates the body's appropriate response. Disease recovery due to vaccination has been attributed to the suboptimal humoral responses associated with augmented binding to neutralizing antibodies that lead to increased deposition of immune complexes and exacerbated inflammatory response. This could account well for the higher levels of CRP in the vaccinated group in our findings [24]. In a study, an initial increase in the level of acute phase reactants such as CRP and procalcitonin was associated with the severity of hypoxia, multi-organ failure, and the need for admission to the intensive care unit [23]. However, in Behera et al.'s study, the level of these markers was not significantly different between the vaccinated and un-vaccinated groups [23]. This discrepancy can be due to differences in the type and dose of vaccines as well as the presence of underlying diseases.

The WBC count in the vaccinated patients was significantly lower. Considering that vaccination is used for the induction of immune reactions in response to the same pathogen, vaccination can sometimes lead to dangerous and complicated changes in the WBC count and, as a result, the negative consequences outweigh the benefits. In a study on 139 patients who received the Pfizer vaccine, about 5% had moderate to mild granulocytopenia or leukocytopenia [25]. In addition, leukopenia was reported in about 0.01% of patients receiving the Pfizer vaccine in phase four of the clinical trial, and a 6.25% death rate was reported for them. In some studies, neutrophil to lymphocyte ratio (NLR) has been measured and reported to be elevated in COVID patients and considered as a risk factor for in-hospital patients. Despite the increase in serum neutrophil levels after vaccination, the levels of lymphocytes are reduced which results in the NLR elevation of COVID patients [22, 23]. Some publications associated the severity of the disease with the increased NLR [26]. This evidence altogether suggests that COVID-19 vaccination may have deep influences on inflammatory responses.

Vaccination can affect the number of admissions, length of hospitalization, severity of disease, complications, mortality rate, and consequently healthcare costs. Reducing the length of hospitalization not only can reduce the complications of the disease, but also can improve the care of critically ill patients by lowering the socioeconomic burden of disease, and thus reducing the mortality rate [27]. In the present study, the comparison of the mortality rate and length of hospitalization between two vaccinated and un-vaccinated groups indicated a higher mortality rate and length of hospitalization in un-vaccinated patients. This is consistent with the results of other studies. In a study on 915 hospitalized patients during the COVID-19 pandemic, it was found that previous vaccination, regardless of the doses or duration after vaccination, significantly reduced the number of deaths compared to un-vaccinated patients. A few people were hospitalized after immunization against COVID-19 [28]. A retrospective cross-sectional study in India on January 10 and February 9, 2022, examined the effect of vaccination on COVID-19 outcomes in 246 fully vaccinated, semi-vaccinated, and un-vaccinated patients. The percentage of underlying diseases was the same in all three groups. Fully vaccinated patients had a higher level of oxygen saturation (30.9% vs 26.1% and 3.9%), less need for mechanical ventilation (6.2% vs 15.2% and 21.4%), shorter length of hospitalization (4.2 days vs 5.3 and 7.2 days), and showed mortality (9.3% vs 21.7% and 33%) [29]. A study in Norway also showed that complete vaccination in hospitalized patients with COVID-19 reduced hospitalization length and the rate of admission to special care units [30].

In the present study, there was no significant relationship between the factors of age and sex and the death rate in vaccinated or un-vaccinated groups, which indicates that the death rate in the two groups was not influenced by age and gender. Studies show that the severity of the disease, the length of hospitalization in special care units, and mortality caused by COVID-19 were higher in male patients [31]. Male gender in the prognosis of COVID-19 is considered a vital risk factor for higher mortality rates caused by immune system dysfunction, aging, co-morbidities such as cardiovascular diseases, and lifestyle [32, 33]. Due to more underlying diseases in old age, age has been proposed as one of the most critical factors in determining the severity, hospitalization length, and mortality of COVID-19 patients, but it was not reported in the present study. This may be due to the small size of samples, cross-sectional design, and lack of a follow-up phase in our study.

This study showed that most infections and deaths occurred two weeks after receiving the second dose of vaccines (full immunity induction period). The Centers for Disease Control has reported that it takes two weeks after vaccination for the body to produce optimal antibodies and reach standard immunity. Therefore, although vaccination was associated with a significant decrease in the death rate, a low death rate was reported in the full immunity induction period. This can be due to some factors such as psychological effects and inductions in vaccinated people, which reduced the mortality rate by increasing life expectancy.

In conclusion, the age of vaccinated patients with COVID-19 is higher than that of un-vaccinated patients, and vaccination reduces some clinical symptoms and causes changes in some laboratory test results in these patients. Moreover, vaccinated patients have shorter lengths of hospitalization and lower mortality rate, compared to un-vaccinated patients. Therefore, vaccination coverage is necessary to reduce the severity of infection, length of hospitalization, and mortality rate caused by COVID-19.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Code: IR.MUMS.REC.1400.268).

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Authors contribution's

Conceptualization, supervision, funding acquisition and writing: Vahid Hajali; Methodology: Bahareh Payvar; Software: Bahareh Payvar and Hanieh Esfahani; Formal analysis: Hanieh Esfahani; Validation and data curation: Ehsan Saburi; Investigation: Alireza Fattahi, Kosar al-Zahra Izadpanah and Zahra Fard Tadaion.

Conflict of interest

The authors declared no conflict of interest.

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