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ORIGINAL RESEARCH

The Impact of Vaccination Against SARS-CoV-2 Virus on the Outcome of COVID-19 Disease

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Background: Coronavirus disease 2019 (COVID-19) is a rapidly spreading infection that is on the rise. New variants are continuously appearing with variable degrees of lethality and infectivity. The extensive work since the start of the pandemic has led to the evolution of COVID-19 vaccines with varying mechanisms. We aim to determine real-world data by looking at the different clinical outcomes associated with COVID-19 vaccination, focusing on the rate of hospitalization, severity, and mortality.

Methodology: A retrospective observational study included 624 patients with COVID-19 infection who were hospitalized at King Fahad Hospital of the University and King Fahad Military Medical City between April and July 2021. The cohort was divided into 3 groups: unvaccinated, partially vaccinated (PV), and fully vaccinated (FV). The severity and outcome of COVID-19 disease were compared among the three groups. Among the vaccinated group, we studied the effect of vaccine type on the severity and outcome of COVID-19 disease.

Results: We found that 70.4% of patients with COVID-19 disease who required hospitalization were unvaccinated. Un-vaccination was a significant predictor of critical COVID-19 disease (OR 2.31; P <0.001), whereas full vaccination was associated with significantly milder disease severity (OR 0.36; P 0.01). Moreover, un-vaccination status was an independent predictor of longer hospitalization (OR 3.0; P <0.001), a higher requirement for ICU admission (OR 4.7; P <0.001), mechanical ventilation (OR 3.6; P <0.001), and death (OR 4.8; P <0.001), whereas the FV group had a lower risk of ICU admission (OR 0.49; P 0.045). Unvaccinated patients with comorbidities had worse severity and outcome of COVID-19 infection (P<0.05). Both vaccine types (Pfizer and AstraZeneca) had similar protective effects against the worst outcomes of COVID-19 disease.

Conclusion: COVID-19 vaccination has been shown to be effective in reducing hospitalization, the severity of COVID-19 infection, and improving outcomes, especially in high-risk group patients. COVID-19 vaccination programs should continue to improve the outcome of such a disease.

Keywords: COVID-19 disease, COVID-19 vaccine, severity, outcome, mortality

Introduction

Coronavirus disease 2019 (COVID-19) which was first detected in December 2019 and declared a pandemic by the World Health Organization (WHO) in March 2020, is still an emerging and rapidly spreading disease.[1,2] The governments worldwide have done intense efforts to control the spread of the disease. However, there were new variants that have emerged over the last year with variable degrees of lethality and infectivity.[3] The countries including the Kingdom of Saudi Arabia (KSA) have faced multiple COVID-19 waves. The Saudi Ministry of Health (MOH) has reported the beginning of 3rd wave in December 2021 which was posing a public health compromise.[4] During the third wave, KSA has announced an average of 4000 cases per day and a peak number of 5928 cases per day on 19th January 2022.[5] The critical cases have increased as well to reach 1000 cases at the date of preparing this report.[4]

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Clinical features of COVID-19 disease are variable among the general population.[6] It predominantly affects the pulmonary system, resulting in mild to critical disease.[7] Critical cases could be complicated with acute respiratory distress syndrome (ARDS), respiratory failure, cytokine storm syndrome, and eventually death.[7] As of February 2022, there have been a total of 8900 death rates in KSA due to COVID-19 infection.[8]

Vaccines enhance people's immunity, improving and avoiding hazardous infections and death.[9] It is estimated that vaccines have the potential to prevent 6 million deaths from vaccine-preventable diseases annually.[9] As a result; there has been extensive work since the start of the COVID-19 pandemic to develop an effective vaccine. This resulted in the development of several vaccines like Pfizer BioNTech, AstraZeneca ChAdOx-S (Vaxzevria), Janssen Ad26.COV 2-S, Moderna mRNA-1273, Sinopharm BIBP, Sinovac biotech, Sputnik V, EpiVacCorona, CoviVac and Sputnik Light.[10–12] As of 12th January 2022, WHO has approved some vaccines to be used in the COVID-19 vaccination program: Pfizer BioNTech, AstraZeneca ChAdOx-S, Janseen Ad26.COV 2-S, Moderna, Sinopharm, Covovax, Sinovac, Covaxin, and Nuvaxovid.[13] Vaccine types, advantages, disadvantages, and doses are summarized in (Tables 1 and 2).

Saudi Arabia applied the COVID-19 vaccination program initially with Pfizer-BioNTech after receiving Saudi FDA approval in December 2020 and subsequently, AstraZeneca ChAdOx-S in February 2021.[14,15] Up to the date of writing this report, around 50 million vaccine doses have been given in KSA including the first and second doses.[4] Initial randomized controlled trials at the time of testing vaccine efficacy have shown a positive effect against COVID-19 symptoms, severity, hospitalization, and death.[10–12] Subsequently, there have been few population-based studies that showed similar results.[11,16,24]

However, real-world studies to evaluate the efficiency of the vaccine are scarce worldwide, specifically in Saudi Arabia. Therefore, such studies are warranted. As a result, this study will help to determine the different clinical outcomes associated with COVID-19 vaccination, focusing on the rate of hospitalization, COVID-19 severity, and

Table 1 COVID-19 Vaccine Types, Doses and Contraindications

	Vaccine	Type	Doses	Contraindications
1	**Pfizer BioNTech (BNT162b2)**	mRNA	2 (3 weeks apart) 2 booster dose	• History of severe allergic reaction to any component of the vaccine.
2	**Oxford/AstraZeneca (ChAdOx1-S)**	Viral vector (non-replicating)	2 (3 weeks apart)	• History of severe allergic reaction to any component of the vaccine • Age younger than 18 years.
3	**Janssen Ad26.COV2.S**	Viral vector (non-replicating)	2 (2–6 months apart)	• History of anaphylaxis to any component of the vaccine. • Body temperature over 38.5°C. • Age younger than 18 years.
4	**Moderna COVID-19 (mRNA-1273)**	mRNA	2 (4 weeks apart) 2 booster doses	• History of severe allergic reaction to any component of the vaccine. • Individuals who developed myocarditis or pericarditis following the first dose. • Age younger than 12 years.
5	**Sinopharm**	Inactivated virus	2 (3–4 weeks apart)	• History of anaphylaxis to any component of the vaccine. • Body temperature over 38.5°C
6	**Nuvaxovid & Covovax (NVX-CoV2373)**	Protein subunit	2 (3–4 weeks apart)	• History of anaphylaxis to any component of the vaccine. • Body temperature over 38.5°C. • Persons with acute PCR-confirmed COVID-19. • Age younger than 18 years.

Note: Data from World Health Organization.[34]

Table 2 Advantages and Disadvantages of Different Types of COVID-19 Vaccines

	Vaccine Type	Advantages	Disadvantages
1	**Inactivated virus**	• Good safety profile. • Better transportation and storage stability. • Long shelf life.	• Immunogenicity deficit. • Protection lasts less time. • Adjuvants are required. • A higher dose is required.
2	**Protein subunit**	• Fewer adverse effects.	• Immunogenicity is limited. • Adjuvants are required.
3	**mRNA**	• High adaptability to control immunogenicity. • Immunogenicity is high. • Long-term immunity.	• In-vivo stability.
4	**Recombinant viral vector**	• Unwanted antigens can be removed. • No adjuvants are required. • High efficiency in stimulating immune responses.	• The existence of pre-existing host immunity reduces efficacy. • Expensive.

Notes: Adapted from: Loo KY, Letchumanan V, Ser HL, et al. Covid-19: insights into potential vaccines. Microorganisms. 2021;9(3):605. doi:10.3390/microorganisms9030605.[35] Creative Commons Attribution License Attribution 4.0 International (CC BY 4.0); https://creativecommons.org/licenses/by/4.0/legalcode.

outcome in terms of intensive care unit (ICU) admissions, related complications, and deaths. The findings will aid in raising awareness about vaccination and its impact on hospitalization and the outcome of COVID-19 disease.

Methodology

To investigate the role of COVID-19 vaccination on hospitalization rate and outcomes in patients infected with COVID-19, a retrospective observational study of 1080 patients admitted with COVID-19 infection to King Fahad Hospital of the University (KFHU) and King Fahad Military Medical City (KFMMC) between April and July 2021 was conducted.

Patients who were hospitalized with the first documented COVID-19 pneumonia at KFHU and KFMMC irrespective of their vaccination condition were included in the study. Patients under the age of 18, pregnant women, patients who tested positive for COVID-19 infection before April 2021, and patients who were hospitalized for a reason other than COVID-19 pneumonia and had an incidental positive RT-PCR for SARS-CoV2 were excluded. The inclusion and exclusion criteria were then implemented for 1080 patients. As a result, 624 patients were qualified to participate in the study.

Data Collection Procedure

Data were collected from the electronic medical records at KFHU and KFMMC. To categorize data into different parts, a data collection form was used. The first part dealt with demographic information, such as the patient's age, gender, as well as nationality. The second part included the patient's laboratory peak tests while hospitalized, which included complete blood count (CBC), renal function test (RFT), lactate dehydrogenase (LDH), inflammatory markers, D-dimer, and ferritin. The following part included grading of the severity of COVID-19 disease by Saudi Ministry of Health 2020 protocols[7] into mild to moderate, severe, and critical disease. The criteria for grading different severity classes are presented in (Table 3). Next, we included the outcome of COVID-19 infection as measured by the length of hospitalization (LOH), the need for ICU admission, mechanical ventilation, and mortality. We used a cut-off of more than 7 days to define longer hospitalization which is correlated with the reported median duration of hospital stay in Saudi Arabia.[17] The last part was about vaccination data including the type of the vaccine, number of doses, and the date of the last dose.

The total population was then divided based on their vaccination status into three categories: unvaccinated, partially vaccinated (PV) (vaccinated with the first dose), and fully vaccinated (FV) (vaccinated with two doses). Next, the severity and outcome of COVID-19 infection in the three study categories were compared and analyzed. Finally, we examined the effect of the type of vaccine on the severity and outcome of COVID-19 infection.

Table 3 Association of Severity and Outcome of COVID-19 with the Vaccination Status

Variable	Vaccination Status			P-value
	Partially Vaccinated (PV)	Fully Vaccinated (FV)	Unvaccinated	
MOH Severity Criteria				
Mild-Moderate	36 (24.7%)	12 (30.8%)	78 (17.8%)	**<0.001**
Severe	59 (40.4%)	10 (25.6%)	96 (21.9%)	
Critical	51 (34.9%)	17 (43.6%)	265 (60.3%)	
Severe				
Pneumonia on chest x-ray	105 (71.9%)	25 (64.1%)	367 (84%)	**0.014**
Respiratory rate >30/minute	53 (36.3%)	9 (23.1%)	228 (52.2%)	**0.001**
SpO2 less than 93% on room air	99 (67.8%)	20 (51.3%)	328 (75.1%)	0.179
PaO2 and FiO2 ratio less than 300	10 (6.8%)	3 (7.7%)	26 (5.9%)	0.758
Lung infiltration >50% of lung fields within 24–48 hours	74 (50.7%)	19 (48.7%)	257 (58.8%)	0.29
Critical				
ARDS	33 (22.6%)	6 (15.4%)	169 (38.7%)	**<0.001**
Sepsis	11 (7.5%)	1 (2.6%)	82 (18.8%)	**<0.001**
Altered mental status	8 (5.5%)	1 (2.6%)	23 (5.3%)	0.57
Multiorgan failure	6 (4.1%)	2 (5.1%)	23 (5.3%)	0.448
Cytokine storm syndrome	67 (45.9%)	18 (46.2%)	265 (60.6%)	**<0.001**
Outcomes				
Length of hospitalization (> 7 days)	60 (40.3%)	14 (35.9%)	282 (64.8%)	**<0.001**
Need for ICU admission	28 (19.2%)	5 (12.8%)	217 (49.7%)	**<0.001**
Need for ventilation	10 (6.8%)	2 (5.1%)	87 (19.9%)	**<0.001**
Death	8 (5.5%)	2 (5.1%)	94 (21.5%)	**<0.001**

Note: significant p-values are shown in bold.
Abbreviations: SpO2, oxygen saturation; PaO2, partial pressure of oxygen; FiO2, fraction of inspired oxygen; ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Statistical Analysis

IBM SPSS was used to analyze the data. All categorical variables were shown as percentages and frequencies, while all continuous data was shown as the interquartile range (IQR) and median. The Fisher exact test or the Chi-square test were used to examine the relationship between variables, and the Kruskal Wallis test was used to compare the medians. A multivariate regression analysis was performed to eliminate the effect of other confounders and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A P-value less than 0.05 was used to determine statistical significance.

Ethics Approval and Consent to Participate

The study was approved by the Imam Abdurrahman Bin Faisal University (IRB-2021-01-261) and KFMMC (AFHER-IRB-2022-003) Institutional Review Board Committees. Confidentiality was maintained. Informed consent was not applicable or required from both centers' IRB since it is a retrospective observational study. The research protocol is carried out by the applicable guidelines. Our study complies with declaration of Helsiniki.

Results

Demographics

A total of 624 patients were involved in this research, 352 (56.4%) of them were males and 272 (43.6%) were females. The majority 433 (69.4%) were older than 40 years of age. The most prevalent comorbidities were diabetes mellitus (DM) in 315 (50.5%) followed by cardiac diseases in 153 (24.5%) and respiratory disease in 56 (9%). The majority of our patients (66.2%) had 1–3 comorbidities. As shown in (Table 4) there was no significant difference in terms of age, gender, and comorbidities among vaccinated and unvaccinated patients (P > 0.05).

Vaccination Status

We have found that 439 (70.4%) of patients were unvaccinated and 185 (29.6%) were vaccinated. Out of 185 vaccinated cases, 146 (78.9%) were PV while 39 (21.1%) were FV. The complete distribution of vaccination status is presented in (Table 5).

The Comparison of Laboratory Parameters Between the Three Study Groups

A comparison of laboratory parameters between the three study groups is presented in (Table 6). White blood cell (WBC) count was significantly more in unvaccinated patients compared to partially and fully vaccinated patients with a median of 12.2 (P 0.003) for the unvaccinated patients. In males, median hemoglobin was significantly lower in FV patients of 10.2 (P 0.027). Median lymphocyte count was significantly lower in the unvaccinated group of 1.5 (P 0.011), while neutrophils, CRP, and D-dimer were significantly higher in the unvaccinated group (P <0.05). LDH and ferritin were significantly higher in the PV group (P <0.05). All other parameters were statistically insignificant between the three study groups.

Association of COVID-19 Disease Severity and Vaccination Status

The association between COVID-19 severity and vaccination status is presented in (Table 3). The results of this study depicted that the majority of unvaccinated patients had a higher risk of developing severe to critical disease of COVID-19 in 82.2% (P <0.001). Pneumonia on chest x-ray was seen in 84% of unvaccinated patients compared to 71.9% and 64.1% of

Table 4 Demographics

Variable		Frequency	Vaccinated		Unvaccinated	P-values
			Partially	Fully		
Gender	Male	352 (56.4%)	86 (58.9%)	20 (51.3%)	246 (51.3%)	0.87
	Female	272 (43.6%)	60 (41.1%)	19 (48.7%)	193 (48.7%)	
Age	≤ 40	191 (30.6%)	41 (28.1%)	5 (12.8%)	145 (12.8%)	0.05
	> 40	433 (69.4%)	105 (71.9%)	34 (87.2%)	294 (87.2%)	
Comorbidities	Diabetes Mellitus	315 (50.5%)	68 (46.6%)	17 (43.6%)	230 (43.6%)	0.4
	Cardiac Disease	153 (24.5%)	31 (21.2%)	9 (23.1%)	113 (23.1%)	0.7
	Respiratory diseases	56 (9%)	17 (11.6%)	3 (7.7%)	36 (7.7%)	0.9
	Hematological Diseases	19 (3%)	2 (1.4%)	2 (5.1%)	15 (5.1%)	0.2
	Gastrointestinal diseases	26 (4.2%)	6 (4.1%)	1 (2.6%)	19 (2.6%)	0.3
	Rheumatological diseases	13 (2.1%)	3 (2.1%)	2 (5.1%)	8 (5.1%)	0.8
Number of Comorbidities	< 1 Comorbidity	197 (31.6%)	46 (31.5%)	13 (33.3%)	138 (28.7%)	0.65
	1–3 Comorbidities	413 (66.2%)	96 (65.8%)	25 (64.1%)	292 (60.8%)	0.8
	>3 Comorbidities	14 (2.2%)	4 (2.7%)	1 (2.6%)	9 (1.9%)	0.78

Table 5 The Results of Vaccine Information

Status of Vaccination		Frequency	Percent (%)
Vaccinated	Yes	185	29.6
	No	439	70.4
Status of Vaccination	Partially Vaccinated	146	78.9
	Fully Vaccinated	39	21.1
Type of vaccine (first dose)	Pfizer	102	69.9
	AstraZeneca	44	30.1
Type of vaccine (second dose)	Pfizer	38	97.4
	AstraZeneca	1	2.6
Date of the last dose	< 14 days	36	19.5
	≥ 14 days	149	80.5

Table 6 Comparison of Laboratory Parameters Between Vaccinated and Unvaccinated Groups

Variable		Vaccinated Median (IQR)		Unvaccinated Median (IQR)	P-values
		Partially Vaccinated	Fully Vaccinated		
WBC	(4.0–10.0 k/ul)	10.8 (6.8–14.8)	11.6 (8.1–15)	12.2 (8.4–18.5)	**0.003**
Hemoglobin	Males (13.0–18.0 g/dl)	13.6 (12.3–14.8)	10.2 (8.3–13.5)	13.6 (12.6–14.7)	**0.027**
	Females (12.0–16.0 g/dl)	11.9 (10.3–13.4)	12.6 (12.5–12.7)	12.3 (11.4–13)	0.614
Platelets	(140–450)	220.5 (163–318)	240 (200–353)	232.5 (174–345.5)	0.282
Lymphocytes	(1.0–5.0 k/ul)	1.735 (1.2–2.7)	1.8 (1.3–2.7)	1.5 (1–2.4)	**0.011**
Neutrophils	(2.0–7.5 k/uL)	7.2 (4.8–10.3)	7.4 (5.9–9.8)	8.8 (5.8–12)	**0.001**
BUN	(7–26 mg/dl)	11 (8–19.5)	13 (5.4–21.5)	10.35 (6–18)	0.346
Creatinine	(0.6–1.2 mg/dl)	0.84 (0.71–1.2)	0.88 (0.7–1.5)	0.83 (0.69–1.2)	0.553
NA	(136–146 mEq/L)	136 (132–139)	136 (131.25–139.75)	137 (134–139)	0.553
K	(3.5–5.1 mEq/L)	4.1 (3.8–4.6)	4.35 (4–4.95)	4.1 (3.8–4.58)	0.191
Cl	(98–107 mEq/L)	101 (98–105)	103.5 (100.25–106.75)	102 (99–105)	0.107
Co2	(20–31mEq/L)	21 (20–23)	22 (17.75–25.75)	22.5 (20–24)	0.227
LDH	(20–31mEq/L)	416 (278.5–627)	255 (216–414)	383 (292–578.5)	**0.003**
ESR	(0–20 mm/hour)	66 (37–88)	51 (31–92)	56 (33–83.5)	0.507
CRP	(0.1–0.5 mg/dl)	16.3 (6.34–50.3)	28 (11.22–64)	33 (11.3–108.4)	**<0.0001**
D-dimer	≤0.5 ug/mL	0.86 (0.48–2.14)	1.22 (0.55–2.96)	1.6 (0.745–5.26)	**<0.0001**
Ferritin	(21.81–274.66 ng/mL)	950.41 (201.9–1482)	343 (108–1025.56)	865(345.8–1781.7)	**0.031**

Note: significant p-values are shown in bold.

Abbreviations: IQR, interquartile range; WBCs, white blood cells; BUN, blood urea nitrogen; Na, sodium; K, potassium; Cl, chloride; CO2, carbon dioxide; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

patients who were partially and fully vaccinated, respectively (P 0.014). Respiratory rate greater than 30/minute was seen in 52.2% of unvaccinated patients versus 36.3% and 23.1% in partially and fully vaccinated patients, respectively (P 0.001). Among critical severity criteria, ARDS, sepsis, and cytokine storm syndrome were significantly higher in unvaccinated patients (P <0.001). The multivariate analysis illustrated that un-vaccination status was an independent predictor of critical COVID-19 disease (OR 2.31; P<0.001) while patients who were FV had a significantly milder COVID-19 disease (OR 0.36; P 0.01) (Table 7).

Association of COVID-19 Disease Outcome and Vaccination Status

The unvaccinated group had a worse outcome in terms of longer hospital stay, more requirements for ICU admission, and mechanical ventilation (P <0.001). Likewise, mortality was higher in the unvaccinated group 21.5% compared to 5.5% in the PV and 5.1% in the FV groups (P <0.001) (Table 3). Multivariate analysis showed that un-vaccination status was an independent predictor of longer hospitalization OR 3.0 (P <0.001), higher need for ICU admission OR 4.7 (P <0.001), mechanical ventilation OR 3.6 (P <0.001), and death OR 4.8 (P <0.001). On the other hand, patients who were FV had a significantly lower need for ICU admission (OR 0.49; P 0.045) (Table 8).

Association Between Severity of COVID-19 Infection with Age, Gender, and Co-Morbidities

Multivariate analysis demonstrated that older age was significantly linked to critical COVID-19 infection (OR 1.78; P 0.017). In addition, DM was significantly associated with both severe (OR 2.52; P 0.001) and critical (OR 3.18; P <0.001) COVID-19 disease (Table 7).

Table 7 Multivariate Analysis of the Association Between the Severity of COVID-19 with Age, Gender, Co-Morbidities, and Vaccination Status

Variable	Severity			
	Severe		Critical	
	OR (95% CI)	P-values	OR (95% CI)	P-values
Age	1.27 (0.76–2.12)	0.37	1.78 (1.11–2.85)	**0.017**
Gender (Male)	1.09 (0.67–1.77)	0.724	1 (0.64–1.56)	0.992
Diabetes mellitus	2.52 (1.49–4.27)	**0.001**	3.18 (1.96–5.16)	**<0.001**
Cardiac Disease	1.13 (0.67–1.91)	0.034	0.52 (0.28–0.95)	0.637
Respiratory diseases	1.13 (0.49–2.63)	0.771	1.31 (0.6–2.86)	0.507
Gastrointestinal diseases	0.63 (0.2–1.98)	0.427	0.25 (0.08–0.86)	**0.027**
Hematological diseases	1.48 (0.49–4.5)	0.487	0.76 (0.24–2.38)	0.637
Rheumatologic diseases	3.24 (0.54–19.47)	0.199	3.14 (0.53–18.42)	0.206
Unvaccinated	0.86 (0.53–1.4)	0.538	2.31 (1.44–3.7)	**<0.001**
Partially Vaccinated (PV)	1.97 (0.77–5.01)	0.157	1 (0.43–2.35)	1
Fully Vaccinated (FV)	0.36 (0.158–0.82)	**0.01**	1 (0.43–2.35)	1

Note: significant p-values are shown in bold.
Abbreviations: OR, odds ratio; CI, confidence Interval.

Table 8 Multivariate Analysis of the Association Between Outcome of COVID-19 with Age, Gender, Co-Morbidities, and Vaccination Status

Variable	Outcome							
	Hospital Stay		ICU Admission		Ventilation		Death	
	OR (95% CI)	P-values	OR (95% CI)	P-values	OR (95% CI)	P-values	OR (95% CI)	P-values
Age	3 (2–4.4)	**<0.001**	1.5 (1–2.3)	**0.04**	1.7 (1–2.9)	0.08	1.2 (0.7–2)	0.62
Gender (Male)	0.7 (0.5–1.1)	0.10	1.1 (0.8–1.6)	0.52	1.2 (0.7–1.9)	0.54	3 (1.7–5.1)	**<0.001**
Diabetes mellitus	1.9 (1.3–2.7)	**<0.001**	2.5 (1.7–3.6)	**<0.001**	2.3 (1.4–4)	**<0.001**	4.1 (2.4–7.2)	**<0.001**
Cardiac Disease	1.4 (0.9–2.2)	0.10	1.7 (1.1–2.6)	**0.01**	4.9 (3–8)	**<0.001**	3.9 (2.4–6.6)	**<0.001**
Respiratory diseases	1.2 (0.7–2.3)	0.49	0.8 (0.4–1.6)	0.61	1.8 (0.9–4)	0.12	1.7 (0.7–3.9)	0.21
Gastrointestinal diseases	0.6 (0.2–1.7)	0.38	0.6 (0.2–1.8)	0.34	0.3 (0–2.9)	0.32	0.4 (0–3.6)	0.39
Hematological diseases	1.6 (0.6–4)	0.32	1.8 (0.7–4.5)	0.20	1.5 (0.5–4.7)	0.50	0.8 (0.2–3.3)	0.78
Rheumatologic diseases	1.4 (0.4–4.9)	0.59	2.7 (0.7–10)	0.13	1.1 (0.2–6.3)	0.94	0.7 (0.1–6.2)	0.72
Unvaccinated	3 (2.1–4.4)	**<0.001**	4.7 (3–7.4)	**<0.001**	3.6 (1.9–7.1)	**<0.001**	4.8 (2.3–9.8)	**<0.001**
Partially Vaccinated (PV)	1.2 (0.6–2.6)	0.56	1.6 (0.6–4.4)	0.38	1.3 (0.3–6)	0.77	1.1 (0.2–5.3)	0.93
Fully Vaccinated (FV)	0.8 (0.4–1.7)	0.56	0.49 (0.245–0.99)	**0.045**	0.8 (0.2–3.8)	0.77	0.9 (0.2–4.6)	0.93

Note: significant p-values are shown in bold.
Abbreviations: OR, odds ratio; CI, confidence interval.

Association Between the Outcome of COVID-19 Infection with Age, Gender, and Co-Morbidities

The multivariate analysis illustrated that older age was significantly linked to a higher requirement of ICU admissions (OR 1.5; P 0.04) and longer hospital stay (OR 3.0; P <0.001). Additionally, the male gender was a predictor of mortality (OR 3.0; P < 0.001). In terms of comorbidities, patients with DM had a significantly higher risk of longer hospitalization (OR 1.9; P<0.001), ICU admission (OR 2.5; P<0.001), mechanical ventilation (OR 2.3; P<0.001), and death (OR 4.1; P<0.001). In addition, cardiac diseases were significantly associated with a higher rate of admission to ICU (OR 1.7; P 0.01), mechanical ventilation (OR 4.9 P<0.001), and death (OR 3.9; P<0.001) (Table 8).

The Effect of Vaccination Status on the Severity and Outcome of COVID-19 Disease in Relation to Age, Male Gender, Diabetes Mellitus, and Cardiac Diseases

Since our multivariate analysis showed worse severity and outcome in patients who are older in age, males, and have DM, and cardiac diseases (Tables 7 and 8), we studied the effect of vaccination status on the severity and outcome of COVID-19 disease in relation to the above comorbidities. We found that unvaccinated patients who were either older in age, males, or had DM or cardiac diseases had severe-critical COVID-19 disease, longer hospitalization, higher risk of ICU admission, mechanical ventilation, and death (P <0.0001) (Table 9).

Association Between Severity and Outcome of COVID-19 Disease and the Type of Vaccine

A comparison of the impact of vaccination types on the severity and outcome of COVID-19 disease did not show any statistically significant association (Table 10).

Discussion

This is an observational study of 624 patients from two tertiary care centers in Saudi Arabia's Eastern Province. It was aimed at assessing the impact of COVID-19 vaccination on the hospitalization rates and outcomes of hospitalized

Table 9 The Effect of Vaccination Status on the Severity and Outcome of COVID-19 Disease in Relation to Age, Male Gender, Diabetes Mellitus, and Cardiac Diseases

Variable	Severe/Critical n=331		P- value	Hospital Stay n = 356		P-value	ICU Admission n = 250		p-value	Ventilation n = 99		p-value	Death n = 104		p-value
	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated		Vaccinated	Unvaccinated		Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	
Age > 40 years	53 (16.1%)	186 (56.2%)	**<0.0001**	69 (19.4%)	208 (58.4%)	**<0.0001**	28 (11.2%)	155 (62%)	**<0.0001**	11 (11.1%)	66 (66.7%)	**<0.0001**	10 (9.6%)	65 (62.5%)	**<0.0001**
Male Gender	43 (13%)	151 (45.6%)	**<0.0001**	43 (12.1%)	153 (43%)	**<0.0001**	20 (8%)	131 (52.4%)	**<0.0001**	7 (7.1%)	56 (56.6%)	**<0.0001**	8 (7.7%)	73 (70.2%)	**<0.0001**
Diabetes Mellitus	25 (7.6%)	112 (33.8%)	**<0.0001**	42 (11.8%)	162 (45.5%)	**<0.0001**	18 (7.2%)	141 (56.4%)	**<0.0001**	7 (7.1%)	65 (65.7%)	**<0.0001**	4 (3.8%)	80 (76.9%)	**<0.0001**
GI diseases	2 (0.6%)	8 (2.4%)	0.06	4 (1.1%)	14 (3.9%)	**0.017**	2 (0.8%)	10 (4%)	**0.019**	1 (1.01%)	4 (4.04%)	0.17	1 (0.96%)	2 (1.92%)	0.56
Cardiac diseases	15 (4.5%)	80 (24.2%)	**<0.0001**	12 (3.4%)	88 (24.7%)	**<0.0001**	7 (2.8%)	71 (28.4%)	**<0.0001**	5 (5.1%)	48 (48.5%)	**<0.0001**	3 (2.9%)	48 (46.2%)	**<0.0001**

Note: Significant p-values are shown in bold.
Abbreviations: n, number; GI, gastrointestinal.

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Table 10 Association Between Severity and Outcome of COVID-19 Disease and Type of Vaccine

	Variable	The Study Groups Based on the Type of Vaccine		P-value
		Patients Who Received Pfizer-BioNTech Vaccine	Patients Who Received Oxford-AstraZeneca Vaccine	
Severity	**Mild-Moderate**	25 (17.9%)	10 (22.2%)	0.854
	Severe	38 (27.1%)	15 (33.3%)	
	Critical	39 (27.9%)	19 (42.2%)	
Outcome	**Hospital Stay Median (IQR) (days)**	8.5 (5–14.5)	7 (5–14.5)	0.582
	ICU Admission n (%)	32 (22.8%)	9 (20%)	0.36
	Mechanical ventilation n (%)	13 (9.2%)	3 (6.7%)	0.301
	Death n (%)	9 (6.4%)	4 (8.8%)	0.93

Abbreviations: IQR, interquartile range; N, number; %, percentage.

patients with COVID-19 infection. Our study showed the following significant key results: First, 70.4% of hospitalized patients were unvaccinated. Next, the unvaccinated group had higher WBCs, neutrophils, CRP, and D-dimer with a lower lymphocyte count, while the PV group had higher LDH and ferritin levels. In addition, un-vaccination status was a significant predictor of critical COVID-19 disease (OR 2.31; P <0.001), whereas full vaccination was associated with significantly milder COVID-19 disease severity (OR 0.36; P 0.01). Moreover, un-vaccination status was an independent predictor of longer hospitalization OR 3.0 (P <0.001), higher need for ICU admission OR 4.7 (P <0.001), mechanical ventilation OR 3.6 (P <0.001), and death OR 4.8 (P <0.001). Furthermore, full vaccination was linked to a significant reduction in the need for ICU admission. (OR 0.49; P 0.045). Finally, older age and DM were associated with worse severity, while older age, male gender, DM, and cardiac diseases were predictors of the worst outcome of COVID-19 infection.

Our findings are consistent with previous research which showed that unvaccinated patients have a higher risk of hospitalization.[16,18,19] We found that 70% of hospitalized patients in our cohort were unvaccinated. Similarly, Tenforde et al found that out of 4513 patients who were hospitalized with COVID-19 infection, 84.2% were unvaccinated.[16] In addition, Bahl et al reported that 91.9% of COVID-19 patients who required emergency care or hospitalization were unvaccinated, while only 1.1% were FV patients.[19] In addition, a large community-based study from the United Kingdom which looked at patients aged 80 years or older found that vaccination with either one dose of Pfizer or AstraZeneca vaccines provided a reduction in emergency care and hospital admission of 43% and 37%, respectively.[18]

A comparison of laboratory results data between the three study groups revealed that the unvaccinated group had higher COVID-19 severity markers including WBCs, neutrophils, CRP, and D-dimer with a lower lymphocyte count, while the PV group had higher LDH and ferritin levels. Several reports found that LDH, CRP, D-dimer, and ferritin were correlated with worse severity and outcome of COVID-19 disease.[20–22] Our results support the findings of worse severity and outcome in the unvaccinated group or the PV group, as we will discuss further in the paper. Most of the published data about the role of the COVID-19 vaccine on the severity of the disease did not investigate the differences in the laboratory parameters between vaccinated and unvaccinated patients.

We have shown that un-vaccination status increased the odds of critical COVID-19 disease by 2.31 times (P<0.001) while FV patients had a significantly milder COVID-19 severity (OR 0.36; P 0.01). Even though it did not show statistical significance in multivariate analysis, univariate analysis has shown that the majority of patients who received a single dose of the vaccine presented with either severe (40.4%) or critical (34.9%) COVID-19 disease. Our results are in line with the findings reported by Singh et al where individuals with FV had a lower likelihood of having severe disease on initial

presentation to the hospital (18.2%) compared to PV (31.8%) and unvaccinated (42.6%) cases (P 0.022).[23] Overall, FV patients were found to have a lower likelihood of experiencing severe disease (30.3%) during their illness compared to PV (51.3%) and unvaccinated (54.1%) cases in the same study (P 0.035).[23] Similarly, Mhawish et al reported more patients from the non-immunized group to have higher severity categories while fewer non-immunized individuals were in the lower severity categories compared to immunized people.[24] In addition, the same study found that at least one dose of immunization was related to a diminished odds of higher severity scale (OR 0.2; P < 0.001).[24]

The analysis of the outcome in our study has shown that un-vaccination status was an independent predictor of longer hospitalization OR 3.0 (P <0.001). We found that 64.8% of the unvaccinated group had a length of stay of more than 7 days. Singh et al investigated 577 COVID-19 cases that were matched with control cases and reported that the highest median length of stay was in the unvaccinated group of 12 days (P 0.028).[23] In addition, Olson et al found that the median length of hospital stay was longer in unvaccinated patients compared to vaccinated patients.[25] We also found a higher need for ICU admission OR 4.7 (P <0.001) and mechanical ventilation OR 3.6 (P <0.001) in the unvaccinated group. On the other hand, full vaccination reduced the odds of ICU admission (OR 0.49; P 0.045). Previous reports support our findings, as was reported by Mhwaish et al, where a minority of hospitalized patients in ICU (5 patients out of 611 patients) were FV.[24] In our cohort, only 5 FV patients out of 250 were admitted to ICU. On the same line, Olson et al reported that only 2 out of 180 patients who required ICU admission were fully vaccinated.[25] Moreover; Moghadas et al reported that COVID-19 vaccination led to a marked reduction of adverse outcomes, including non-ICU hospitalization by 63.5% and ICU hospitalization by 65.6%.[26]

Interestingly, our analysis showed that un-vaccination status increased the odds of death by 4.8 times (P <0.001). The same study by Mhwaish et al reported that the non-immunized group had a higher death rate (43.9% versus 29.4%; P 0.02).[24] Similarly, Tenforde et al found a higher risk of mechanical ventilation or death by day 28 in unvaccinated patients in a study of 1197 hospitalized COVID-19 patients.[16] Moreover, an observational study conducted by Haas et al reported a higher mortality rate among unvaccinated patients.[27] Additionally, Moghdas et al reported a reduced death rate in vaccinated patients by 69.3%.[26] Furthermore, another report found that at least a single dose of immunization lowered the adjusted odds of 30-day all-cause mortality (OR 0.45; P 0.02).[24] On the other hand, only one study reported similar outcomes of death and recovery across different groups of vaccinations.[23]

Our study showed no difference in the severity and outcome of COVID-19 disease between patients who received either Pfizer or AstraZeneca vaccines. Similarly, Bernal et al in a large community-based study reported that either Pfizer or AstraZeneca vaccines were associated with similar protection against symptomatic and severe COVID-19 disease in older adults.[18] In addition, Kaura et al found comparable effectiveness of both vaccines against hospitalization and mortality.[28]

According to our analysis, the presence of older age, male gender, diabetes mellitus, and cardiac diseases were associated with severe/critical COVID-19 infection and poor clinical outcomes as was previously published in the literature.[29–33] However, further analysis showed that the majority of patients with those comorbidities who had worse severity and outcome were unvaccinated (Table 9). This signifies the positive protective effect of the COVID-19 vaccine against severe disease and worse outcomes, especially in high-risk group patients.

Our study has shown that the majority of COVID-19 patients who required hospitalization were unvaccinated. In addition, un-vaccination status was an independent predictor of severe to critical COVID-19 disease, while full vaccination lowered the odds of critical COVID-19 infection. Moreover, un-vaccination status increased the odds of longer hospitalization, ICU admission, mechanical ventilation, and death. Therefore, our study confirms the positive impact of the COVID-19 vaccine in reducing the rate of hospital admission, severe to critical COVID-19 pneumonia, and worst outcomes and most importantly, mortality. Meanwhile, un-vaccination increased the risk of the worst outcome in patients with comorbidities. Finally, both types of COVID-19 vaccine that were included in the study had similar protective effects against the worst outcome of COVID-19 infection.

Strengths and Limitations

There are several strong points in our study. First, this is a double center study with an appropriate sample size and rigorous inclusion and exclusion criteria. Second, this is real-world data that was collected to assess and quantify the severity and outcome of COVID-19 infection in vaccinated versus unvaccinated patients admitted with COVID-19

infection. Third, the collected variables were extracted strictly using a particular protocol for minimizing extraction errors and missing values.

However, there are some limitations to this study that should be acknowledged. First, it is a retrospective research with limited generalizability. Second, the temporality from receiving the vaccine to the acquisition of infection was not addressed which would have resulted in a better understanding.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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