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General Medicine

CHANGING COVID-19 CLINICAL PROFILE AFTER VACCINATION IN WESTERN INDIA

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ABSTRACT **Background:** Vaccines against SARS-CoV-2 have been used since January 2021 in India. Real-world data have shown the vaccines to be highly effective against COVID-19 and related severe diseases and death. Vaccine effectiveness may wane over time since the receipt of the second dose of the vaccines. Even after a hustling vaccination campaign against COVID-19, infection still persists in the community. **Methods:** This retrospective observational case-control study included a total of 464 admitted patients of COVID-19 with mild to severe disease. 247 patients were fully vaccinated for COVID-19 disease while 217 patients were unvaccinated. The patient's data concerning demography, clinical profile, comorbidities, the severity of disease, required oxygen support, Inflammatory markers, radiological imaging, and outcome were extracted from their medical records. All collected data were tabulated, compiled, and analyzed to establish the role of vaccination to prevent disease severity. **Results:** Patients in the vaccinated group were in the older age group with a high prevalence of comorbidity as compared to the unvaccinated group ($P<0.05$). Vaccinated patients as compared to unvaccinated counterparts had mild disease (77.73% vs 58.53%, $P<0.001$). In the unvaccinated patients, the prevalence of oxygen requirement was higher (41.47% vs 22.67%, $P<0.001$), had raised inflammatory markers (NLR 3.23 v/s 2.94; CRP 28.73 v/s 15.04 mg/L; D-dimer 1115.4 v/s 812.51 µg/mL, and IL-6 19.56 vs 12.48 pg/mL), more lung involvement (41.47% vs 23.88%), and longer hospital stay (7.87 v/s 5.54 days) as compared to the case of a vaccinated group. Conclusion: In the present scenario when most of people got vaccinated, COVID-19 disease may infect the fully vaccinated people but didn't produce so severe disease. Recently, the older age group with comorbid diseases are more infected with COVID-19 but these highly risky groups are fully vaccinated so didn't progress to severe disease, and patients were discharged early from the hospital without any significantly raised inflammatory markers.

KEYWORDS : COVID-19, Clinical profile, Inflammatory markers, Vaccination

INTRODUCTION

The wave of coronavirus disease 2019 (COVID-19) started at the end of 2019 in Wuhan, China [1,2]. The rapidity of disease spread was very high in the first and second waves which affected more than 200 countries around the world. The aerosol spread was the most common route for people-to-people transmission by this deadly end severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. The spread of COVID-19 was higher in Europe and the USA and it was lower in Africa [4,5]. The spread of COVID-19 disease and its severity are influenced by many factors including the immune status of the population [6]. The severity of infection was also varying from country to country ranging from about 4% mortality rate in China to about 15% in Italy [7]. Currently, the world is suffering from the third and fourth waves of COVID-19 and in some countries the fifth and sixth waves.

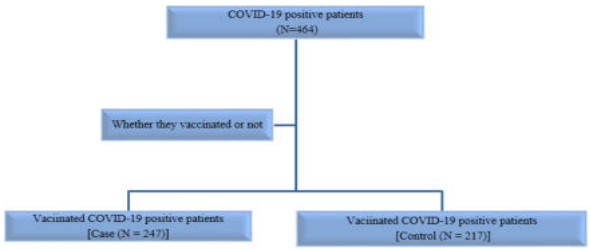
When Medical necessities are often in short supply, hospitals are overwhelmed, healthcare workers are exhausted after months of fighting an uphill battle, and the whole of the world fighting with this SARS-CoV-2 virus then the vaccination campaign against COVID-19 was proved to be the last nail in the coffin to prevent the spread of disease and minimize its severity. Like all CoV, SARS- CoV-2 encodes four structural proteins which are the S, N, M, and E proteins. The S protein mostly serves for Covs vaccine development due to its ability to induce neutralizing antibodies and T cell response. S protein also mediates viral entry into host cells. S has two domains S1 and S2. The S1 has the receptor-binding domain (RBD), and the S2 contains the fusion peptide, which is responsible for receptor binding and cell fusion, respectively [8,9].

Immunogenicity data indicate that antibody titers wane relatively rapidly after the receipt of two doses of vaccine, which suggests that waning may be an important factor in reported decreases in vaccine effectiveness over time, although decreases in antibody titers may be more rapid than decreases in protection [10].

In India the clinical presentation and severity of COVID-19 among the first, second, and third waves are different. Serological assessments provide an objective measure of vaccine responses which are important for comparing vaccines and schedules, but the interpretation of serological data is limited as the way in which it correlates with protection is unknown, and the recognition that neutralizing activity of antibodies and cellular immunity also plays an important role in protection [11, 12]. High concentrations of neutralizing antibodies targeting the SARS-CoV-2 spike protein offer considerable protection against SARS-CoV-2 reinfection, supported by data from common human coronaviruses and non-human primate models and vaccine studies [13, 14]. The present study aimed to compare the clinical profile and severity of the COVID-19 disease among vaccinated and unvaccinated patients using the available data of confirmed COVID-19 cases.

METHODS

Study Design: The present retrospective, observational study was conducted on 464 hospitalized *COVID-19*-positive patients, admitted to S.M.S. Medical College and Attached Hospitals, Jaipur, India from 1st May 2022 to 31st August 2022. This study was approved by the Institutional Ethics Committee of the Institution. In this study, we included 247 fully vaccinated COVID-19-positive patients as cases and 217 unvaccinated COVID-19-positive patients as control. These patients underwent serial observation to collect data till discharge from the hospital.



Data Collection: COVID-19 was diagnosed based upon World Health Organization interim guidance [15]. The patient information about demographic data, medical history, clinical presentation, oxygen support, duration of hospital stay, and the final outcome was extracted from the medical records for data analysis. In this study, the severity of COVID-19 patients was decided as per the Indian Council of Medical Research (ICMR) guidelines. Duration of illness and minimum oxygen saturation were extracted from the medical record. The outcome of patients was extracted by the duration of hospital stay and mortality among both groups.

Vaccination status for COVID-19 is still a question of debate but for our study purpose we defined the vaccinated group as:

A. Those people who got the two doses of vaccine with the second dose could not exceed more than 6 months according to the defined time interval because a study showed that, no evidence of protection against infection was seen at 20 weeks or more after mRNA vaccination [16]. or

B. Those people who got the booster dose of the COVID-19 vaccine under a defined time interval.
An unvaccinated group is defined as
A. Any patient who did not get any COVID-19 vaccine or
B. Any patient who got only a single vaccine
C. Any patient who could not be able to complete the given schedule of vaccines or
D. Any patient whose last dose of vaccine exceeds more than 6 months in double vaccinated people.

For patients of COVID-19 with or without vaccination, we extract data regarding age and gender distribution, disease severity, comorbidity and status of oxygen requirement, lung involvement by imaging, COVID-19-related inflammatory markers, and final outcome. All the relevant data was compiled, tabulated, interpreted, and compared among vaccinated cases and unvaccinated control groups to demonstrate the role of COVID-19 vaccination to slow down the progression of the disease and its severity. Standard of care treatment in both groups is similar and includes antiviral, antibiotics, anticoagulants, bronchodilators, mucolytic, systemic steroids, monoclonal antibodies, etc. as per indication.

Statistical analysis: Quantitative data were expressed as mean and standard deviation. Qualitative data were expressed as proportions. The parameters were compared among different groups using the chi-square test and z-score for significant differences. The level of significance was assigned at a p-value less than 0.05. Statistical Package for the Social Sciences (SPSS) and R program was used for statistical analysis.

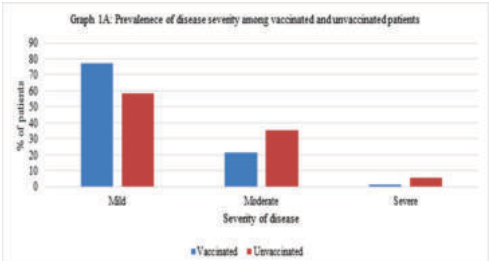
Results (Table 1, 2 & Graph 1):
A total of 464 hospitalized patients with positive RT-PCR were included in this study out of which 247 patients were vaccinated and 217 patients were unvaccinated. In this study, we try to evaluate the clinical scenario of COVID-19 infection after vaccination for COVID-19. Hence, we select matched control group to avoid the influence of variable demographic and vital parameters. In this study, we select hospitalized COVID-19 patients and retrospectively trace about vaccination status to categorize the sample group into the vaccinated and unvaccinated groups. COVID-19-infected patients were selected for the study group in the range of 30 to 70 years of age. The mean age of COVID-19 patients with full vaccination against the COVID-19 virus, was 57.25 years (57.25 ± 11.14) while in the unvaccinated control group it was 44.56 years (44.56 ± 12.19) with a statistically significant difference (p<0.01). The elderly group of patients was highly forward for COVID-19 vaccination as compared to the younger age group.

Male patients were affected more in both cases as well as the control group. In this study, 58.70% of vaccinated patients had underlying medical illnesses while among unvaccinated patients only 41.47% of patients had an underlying chronic medical illness with a statistically significant difference (P=0.0002). All selected patients were hospitalized with one or more COVID-19-related symptoms. All patients in the study group were divided into the mild, moderate, and severe categories on the basis of the severity of the disease. 77.73% of vaccinated patients had mild disease while only 58.53% of patients in the unvaccinated group had mild disease with a statistically significant difference (P < 0.001). Moderate and severe categories among COVID-19 patients were found to be higher in the unvaccinated group as compared to the vaccinated group (P < 0.05). The mean duration of illness at the time of hospitalization was found to be lower in the vaccinated group (3.5 days) as compared to the unvaccinated group (4.01 days) with a statistically significant difference (=0.0004). Oxygen dependency during the course of the disease was found to be higher (41.47%) in the unvaccinated group while it was lower (22.67%) in the vaccinated group (P < 0.001).

Table 1: Changing COVID-19 Clinical Profile after Vaccination

Characteristics	Case (N=247) (Vaccinated)	Control (N=217) (Unvaccinated)	Level of Significance
	Mean ± SD	Mean ± SD	
Age	57.25 ± 11.14	44.56 ± 12.19	P<0.01
Gender			
Male	161 (65%)	140 (64.51%)	Z=0.15, P=0.880
Female	86 (35%)	77 (35.49%)	
Comorbidities			
Yes	145 (58.70%)	90 (41.47%)	Z = 3.704, P = 0.0002
No	102 (41.30%)	127 (58.53%)	
Disease Severity			
Mild	192 (77.73%)	127 (58.53%)	Z=4.453, P < 0.001
Moderate	52 (21.05%)	77 (35.49%)	Z=3.462, P=0.0005
Severe	3 (1.22%)	13 (5.99%)	Z= 2.813, P=0.0049
Duration of illness (Days)	3.5 ± 1.6	4.01 ± 1.44	P = 0.0004
Oxygen dependency	56 (22.67%)	90 (41.47%)	Z = 4.351, P < 0.001
Mean Oxygen saturation at room air	95.2 ± 2.13	94.18 ± 4.61	P = 0.0019
Laboratory markers			
NLR	2.94 ± 1.05	3.23 ± 1.66	P = 0.0233
CRP (mg/L)	15.04 ± 9.19	28.73 ± 10.97	P < 0.001
D-DIMER (µg/mL)	812.51 ± 203.21	1115.4 ± 345.54	P < 0.001
IL-6 (pg/mL)	12.48 ± 8.19	19.56 ± 9.50	P < 0.001
Lung Involvement in HRCT chest	59 (23.88%)	90 (41.47%)	Z = 4.048, P < 0.001
CTSS in HRCT chest			
CTSS<10	43 (72.88%)	38 (42.22%)	Z = 3.674, P
CTSS>10	16 (27.12%)	52 (57.78%)	
Outcome			
Duration of Hospital Stay (days)	5.54 ± 2.87	7.87 ± 6.12	P < 0.001
COVID-19 related mortality	0 (0.00%)	2 (0.92%)	Z= 1.512, P=0.1310

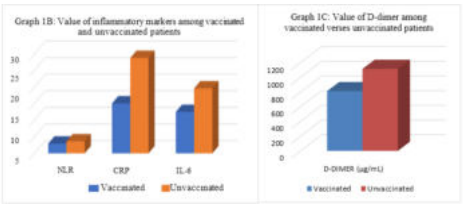
Table 2: Multivariate logistic regression analysis to show odds ratio and 95% Confidential Interval among the vaccinated and unvaccinated groups of the study population



Covariate	Odds ratio	95% CI	Z statistics
Comorbidities	2.0060	1.3853 to 2.9049	3.685
Mild Disease	2.4739	1.6525 to 3.7034	4.400

Moderate Disease	0.4848	0.3207 to 0.7331	3.432
Severe Disease	0.1929	0.0542 to 0.6864	2.541
Oxygen dependency	0.4137	0.2768 to 0.6185	4.302
Lung Involvement	0.4428	0.2974 to 0.6594	4.010
COVID-19 related mortality	0.1741	0.0083 to 3.6474	0.2601

COVID-related inflammatory markers including NLR, D-dimer, CRP, and IL-6 were found to be higher in the unvaccinated group as compared to the vaccinated group (P<0.05). Lung involvement in chest imaging showed typical bilateral COVID-like pneumonia in 41.47% of patients in the unvaccinated group and 23.88% among the vaccinated group with a statistically significant difference (P < 0.001). The duration of hospital stay among the vaccinated group was lower (5.54 days) while it was higher (7.87 days) in the unvaccinated group (P < 0.001). COVID-19-related mortality was also observed in the unvaccinated group while it was nil in the vaccinated group but the difference was not found statistically significant.



Discussion:

In this study, we evaluate the effectiveness of COVID-19 vaccination to prevent the progression of the disease and halting its severity. This study was carried out to know the actual real-life clinical scenario of COVID-19 disease in the present time period. This is a retrospective case-control observational study that includes hospitalized mild, moderate, and severe categories as per ICMR guidelines while critically ill patients were excluded from this study. It is already explained that vaccination protects from COVID-19 but even after vaccination, many patients are re-infected with COVID-19 thus creating a seen of suspension regarding the quality and effectiveness of the vaccine. Although rare, emerging reports describe breakthrough SARS-CoV-2 infections in fully vaccinated individuals (17). In this study, we try to search for clinical, laboratory, and radiological profiles of COVID-19 patients who got reinfection even after a full dose of vaccination.

In this study, we found that out of a total of 464 infected COVID-19 patients, 247 patients (53.2%) were vaccinated while 217 patients (46.8%) were unvaccinated. As per the ministry of health and family welfare, nearly 68.4% population are fully vaccinated as of 1st September 2022 while only 31.6% population are partially vaccinated or unvaccinated. But in this study, we found that percentage of unvaccinated people who falls ill is much higher than the general population (46.8% vs 31.6%). Hence, in the present scenario, people who did not get vaccinated were found to be more prone to capture COVID-19 infection. The myth concept behind COVID-19 was that vaccinated people didn't get infection was found to be totally false. In this study we found that more than half of COVID-19 infected patients were fully vaccinated besides this they got this infection. Hence in the present scenario, nearly half of COVID-19 infected patients are vaccinated and another half are unvaccinated. In our study, we found that vaccinated patients were in the elderly age group while unvaccinated people were in the younger age group. As per the literature, we know that older age itself is a risk factor for multiple communicable and non-communicable diseases. COVID-19 disease is also highly prevalent in this riskiest older age group. It is also reassuring that older patients appeared to benefit as much as their younger peers. Studies assessing protection from symptomatic infection in healthy individuals have reported either lower efficacy in older people (for example, from BNT162b2 in those over 70) (18) or similar efficacy (for example, from AZD1222; efficacy: 84% [54%–91%] in those over 65 versus 73% [63%–80%] in those under 65) (19). No gender discrepancy was observed to attract COVID-19 infection among both groups. Protection from more severe COVID-19 outcomes, such as admission, appears similar; for example, first-dose vaccination was 83% effective in preventing admission in those over 80 (20).

Underlying chronic medical illness was also found to be higher in the vaccinated group as compared to the unvaccinated group, mostly related to the older age group. The government of India also started the COVID-19 vaccination campaign in the older age group and high risky group in the first phase so they completed their vaccination. Besides these risk factors, the severity of COVID-19 was found to be lower in the vaccinated group as compared to the unvaccinated group. More than three fourth of patients in the vaccinated group had only milder severity of COVID-19 infection while less than one-fourth of these patients had moderate to the severe category of disease severity. On the opposite hand, patients categorized under moderate and severe diseases were mostly unvaccinated. In our study, we observed that vaccinated patients are more sensitive to their medical health problems and they seek medical attention in the early stage of disease as compared to their unvaccinated counterparts. As unvaccinated patients are more prone to severe infection of COVID-19, hence oxygen dependency was also found to be more in the unvaccinated group. After the vaccination campaign against COVID-19, lesser patients need oxygen as they may be mild or asymptomatic and didn't require oxygen support while on the other hand, unvaccinated patients required oxygen support in greater proportion. Similarly, mean oxygen saturation at room air in the vaccinated group is nearly normal while it was lower in the unvaccinated group.

COVID-19-related inflammatory markers like Neutrophil-Lymphocyte ratio (NLR), C-reactive protein, D-dimer, and Interleukin-6 were raised significantly in the unvaccinated group as compared to the vaccinated group. Inflammatory markers represent the severity of the disease, which was not raised significantly after vaccination thus it prevents life-threatening complications. However, in this study, we found that even after a full dose of COVID-19 vaccination markers of inflammation like CRP, markers of hypercoagulation like D-dimer and a marker of cytokine storm like IL-6 also raised but didn't progress to life-threatening complications. For effective management of COVID-19 lung imaging with high-resolution computed tomography images are essential, in this study, we found that lung involvement in the form of bilateral peripheral ground glass opacities was more prevalent in the unvaccinated group. After full vaccination against COVID-19, pulmonary invasion by the virus reduced and hence decrease progression towards the severity of the disease.

The final outcome in COVID-19 patients was represented by the mean duration of hospital stay, which was much higher in the unvaccinated group. Lesser severity of COVID-19 infection after a full dose of vaccination allows patients for early discharge from the hospital as they recovered from COVID-19 illness in early time periods. In this study, none of the mortality was observed in patients of the vaccinated group while one patient died in the unvaccinated group.

Conclusion:

Our study highlights the use of vaccination against COVID-19 to prevent from progression and severity of the disease. Although full vaccination against COVID-19 never guaranteed protection from infection but it halts the severity of the disease. This study concluded that in the present scenario when most of the people got vaccinated, COVID-19 disease may infect the fully vaccinated people but didn't produce so severe disease. Recently, the older age group with comorbid diseases are more infected with COVID-19 but these highly risky groups are fully vaccinated so didn't progress to severe disease, and patients were discharged early from the hospital without any significantly raised inflammatory markers.

Limitation: There are several limitations to this study. The number of patients was rather limited and needs to be studied on a larger patient cohort. It was a single-center retrospective observation study and a possibility of recall bias couldn't be ruled out.

Ethical approval: This study was approved by the ethical and research committee of SMS medical college and Hospital, Jaipur, India.

Author contributions: S. Bhandari and G. Rankawat formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript. G. Rankawat, A. Lohmror and A. Singh collected and analyzed data for study. G. Rankawat and Shiven Bhandari writes the manuscript. S. Bhandari and A. Singh conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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