

Comparative Study of Outcomes of COVID-19 Infection in Vaccinated and Unvaccinated Patients- A Retrospective Analysis

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ABSTRACT

Introduction: Vaccine development was the highest priority during the Coronavirus disease 2019 (COVID-19) pandemic. An ideal vaccine should decrease the risk of infection and reduce the incidence and severity of the disease. Risk of disease or infection following COVID-19 vaccination needs to be evaluated for its efficacy and effectiveness.

Aim: To compare the severity of the disease, oxygen requirement, and mortality between vaccinated and unvaccinated COVID-19 patients.

Materials and Methods: This retrospective study was done on the data of the patients who were admitted to Nizams Institute of Medical Sciences, Hyderabad, Telangana, India. All the admitted patients with COVID-19 disease, diagnosed by either Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) or rapid antigen detection method from April 2021 to October 2021, were included. Parameters recorded were: age, gender, co-morbidities, clinical staging as per institute protocol, vaccination status, oxygen requirement, the requirement of non invasive or invasive ventilation, inflammatory markers like C-Reactive Protein (CRP), ferritin, D dimer, Computed Tomography (CT) severity index, and outcomes.

Results: The mean age of patients was 49.7 ± 14.8 yrs in the unvaccinated group, and 52.75 ± 16.2 yrs in the vaccinated group. Out of 175 patients, 102 (58.28%) were unvaccinated. There were 25 (14.28%) deaths, of which 20 (80%) were unvaccinated and 5 (20%) were vaccinated. Oxygen requirement was more among the unvaccinated 73/96 (76.04%). High flow oxygen/mechanical ventilation requirement was higher in unvaccinated compared to vaccinated, 38 (76%) vs 12 (24%), respectively (p -value < 0.005). The mortality rate was higher in unvaccinated patients with co-morbidity, with an odds ratio of 3.32 (1.2-9.3), p -value=0.02. Serum ferritin levels were significantly higher in the unvaccinated group, 858.15 ± 935.5 vs 473.4 ± 663.2 ng/mL, p -value 0.007. CT severity index in the unvaccinated group was 13.82 ± 5.4 , and for the vaccinated group, it was 11.58 ± 5.49 .

Conclusion: Severe disease, oxygen requirement, and mortality were low in vaccinated patients. Vaccination has also resulted in a statistically significant decrease in mortality in patients with co-morbidities. Serum ferritin levels were also found to be lower in vaccinated patients.

Keywords: Co-morbidities, Coronavirus disease 2019 vaccination, Mortality, Oxygen requirement, Serum ferritin

INTRODUCTION

COVID-19 caused a total of 278 million infections and 5.4 million deaths as of December 26th, 2021 [1]. The rapid development of a vaccine became the highest priority because of the faster spread of infection throughout the globe and lead to the development of several types of vaccines using different platforms introduced into the market. Although the ideal vaccine should decrease the infection and disease, as of now vaccine efficacy is measured by its efficacy in decreasing the risk of disease i.e. a successful vaccine should decrease the disease risk by 50% according to the World Health Organisation (WHO)[2]. Evidence of decreasing the viral load in the lower respiratory but not upper respiratory tract suggests a possibility of spread of infection despite vaccination and highlights the importance of non pharmacological interventions like using a face mask, social distancing, and hand washing. Antigenic drift, waning antibodies and heterogeneous response to the initial infection decide the durability along with seasonal variations in humidity affecting the spread of the infection necessitating the administration of the vaccine at right time to decide overall vaccine efficacy [3].

Vaccination trials for the prevention of disease started in early 2020. Various platforms have been used for the preparation of vaccines like mRNA, protein subunit-based, vector-based, and inactivated forms have led to the release of good numbers of vaccines into the market. Phase 3 results of mRNA vaccines, both manufactured by Pfizer and Moderna showed good efficacy of

94.1% and 95%, respectively [4]. In the real-world experience of healthcare workers, the efficacy of mRNA vaccines was shown to be 90% and 80% after full and partial vaccination [5]. India started a vaccination program with Adenovirus vector-based vaccine (ChAd Ox1nCoV-19-Covishield®) for healthcare workers initially in January 2021 followed by an inactivated whole virion vaccine (Covaxin®) subsequently. The incidence of COVID-19 disease or infection following vaccination needs to be tested for its efficacy in the field and also its effectiveness against possible mutant viruses since it can lead to breakthrough infections. In a study done by Keehner J et al., on healthcare workers at the University of California, the positivity rate for breakthrough infections following mRNA vaccines was 0.05% [4]. Breakthrough infection after 14 days of the second dose of covishield developed in 13.3% of patients and 16.9% of persons who received any dose of vaccine [6].

In a study by Alexander Underwood, it was found that sustained neutralising IgG response up to 6 months following mild COVID-19 infection and IgA levels dropped [7].

The safety and side-effects of vaccines have been a major concern among the normal population because of various conspiracy theories and misinformation. It was found that the most reliable information was available from health workers and the ministry of health and COVID-19 vaccine acceptance rate was in parallel with a flu vaccination [8]. The second dose gives a robust response to the vaccine and the effect declined with time reaching to first dose-response or postconvalescent phase of infection at six months.

Antibody response was found to be negatively associated with age and positively associated with the total score of vaccination side-effects. Memory T cell response to spike protein was seen in 87% of individuals who received the vaccine [9]. BNT162b is associated with an increased risk of myocarditis, lymphadenopathy, appendicitis, and zoster infection in a study on the Israeli population [10]. This study was aimed to compare the severity of disease, need for oxygen requirement, and mortality in vaccinated and unvaccinated patients.

MATERIALS AND METHODS

This retrospective study was done on the data of the COVID-19 patients who were admitted to Nizams Institute of Medical Sciences, in Hyderabad, Telangana, India from April 2021 to October 2021. Institutional Ethical Committee approval was taken for this study (EC/NIMS/2968/2022).

Inclusion criteria: All the admitted patients with COVID-19 disease, diagnosed by either RTPCR or rapid antigen detection method were included in the study.

Exclusion criteria: Patients who left against medical advice were excluded from the study.

Sample size calculation: The sample size was estimated to be 189 considering the odds ratio to be 0.51, based on a similar study done in the UK. The expected prevalence of severe COVID-19 infection in unvaccinated is 10.7%, and the ratio of vaccinated to unvaccinated as 0.5, with an anticipated relative precision as 70% and confidence interval of 95% [11].

Study Procedure

The data was collected from case records. Clinical staging was based on institutional protocols:

- Mild disease-fever, upper respiratory symptoms, myalgias, headache, anosmia, ageusia, vomiting, diarrhoea,
- Moderate disease -pneumonia with no signs of severe disease, chest X-ray infiltrates involving less than 50% of lung fields, respiratory rate: 24-29/min, SpO₂ 90-94% on room air, and
- Severe disease-pneumonia with signs of severe disease, chest X-ray infiltrates involving more than 50% of lung fields, RR ≥30/min, SpO₂ <90%, multiorgan dysfunction, cytokine storm, and shock [12].

Age, gender, co-morbidities, clinical staging as per institute protocol, oxygen requirement, the requirement of non invasive or invasive ventilation, inflammatory markers like CRP, ferritin, D-dimer, CT severity index, and outcomes: alive or dead. A total of 175 subjects were enrolled in the study.

STATISTICAL ANALYSIS

Statistical analysis was done using Statistical Package for the Social Science (SPSS) software version 17.0 software. Continuous variables were presented as mean and Standard Deviation (SD). The odds ratio was used to calculate the risk of mortality between unvaccinated and vaccinated. Categorical variables were expressed as frequencies and percentages. Nominal categorical data between the groups were compared using the Chi-squared test after the construction of the 2x2 table. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference.

RESULTS

In this study, data of 175 patients with COVID-19 infections were included. The data was divided into two groups based on the history of COVID-19 vaccination-unvaccinated and vaccinated; 102 patients were unvaccinated and 73 patients were vaccinated. Among the 73 vaccinated patients, 33 (45.2%) received only one dose of vaccination while the rest 40 (54.8%) completed two doses. The clinical and biochemical characteristics of these patients in each of these groups are shown [Table/Fig-1].

Variables	Unvaccinated (n=102)	Vaccinated (n=73)	p-value
Age (in years) (Mean±SD)	49.7±14.8	52.75±16.2	0.15
Gender			
Male, n (%)	68 (66.6%)	51 (69.86%)	0.74
Female, n (%)	34 (33.3%)	22 (30.14%)	
Co-morbidities, n (%)	69 (67.64%)	51 (69.86%)	0.86
CT severity (Mean±SD) (n=97)	13.82±5.4	11.58±5.49	0.08
Clinical stage, n (%)			
Mild	19 (18.62%)	40 (54.79%)	<0.0001
Moderate	29 (28.43%)	17 (23.28%)	
Severe	54 (52.94%)	16 (15.68%)	
Oxygen requirement, n (%)			
Oxygen not required	29 (28.43%)	50 (49.01%)	<0.0001
Low flow required	35 (34.31%)	11 (10.78%)	
High flow required	23 (22.54%)	7 (6.86%)	
Intubation	15 (14.70%)	5 (4.9%)	
Serum ferritin (ng/mL)	858.15±935.5 (n=90)	473.4±663.2 (n=59)	0.007
Serum CRP >24 mg/dL, n (%)	60 (67%) (n=90)	26(43%) (n=60)	0.001
D-Dimer (ng/mL)	2036.7±4067.8 (n=90)	1334±4924.1 (n=61)	0.34

[Table/Fig-1]: Clinical and biochemical features.

CT: Computed tomography; CRP: C-reactive protein; A p-value <0.05 was considered to be significant

The mean age of the unvaccinated group was 49.7±14.8 yrs, whereas, it was 52.75±16.2 yrs in the vaccinated group. Males constituted 67.42% of the total study group whereas females were 32% of the total; 30.14% of the vaccinated and 33.3% of unvaccinated were females. CT chest was done in 97 patients. CT severity index in the unvaccinated group was 13.82±5.4, whereas for the vaccinated group 11.58±5.49 (p-value of 0.08).

A significantly higher number of unvaccinated patients (52.9%) had a severe disease while 15.68% of the vaccinated had a severe disease. The presence of co-morbidity has led to a statistically significant increase in the mortality of unvaccinated patients [Table/Fig-2]. Oxygen requirement (both low flow and high flow/mechanical ventilation) was higher in the unvaccinated group. Overall 80% of the deaths occurred in unvaccinated patients [Table/Fig-3]. Unvaccinated patients constituted 3/4th of severe COVID-19 disease. Clinical outcomes between the unvaccinated and vaccinated groups were analysed using the odds ratio. The odds of death, need for oxygen therapy and odds of developing severe COVID-19 infection were found to be significantly higher in the unvaccinated group when compared to the vaccinated group.

Parameters	Unvaccinated (N=102)	Vaccinated (N=73)	Odd's ratio (95% CI)	p-value
Overall mortality	20 (19.6%)	5 (6.84%)	3.32 (1.2-9.3)	0.02
Oxygen requirement	73 (71.56%)	23 (31.5%)	5.72 (2.9-11.1)	<0.0001
High flow oxygen/intubation requirement	38 (37.25%)	12 (16.43%)	2.97 (1.4-6.2)	0.004
Severe COVID-19	54 (52.94%)	16 (21.91%)	4.1 (2-7.9)	<0.0001

[Table/Fig-2]: Showing data for severe disease, oxygen requirement, and mortality. A p-value<0.05 was considered to be significant

The serum CRP was done semi-quantitatively. In the unvaccinated group, of the 90 patients in whom CRP was done, 67% of patients had CRP >24 mg/mL while in the vaccinated group, of the 60 patients in whom CRP was done, 43% of patients had CRP >24 mg/mL.

The serum levels of ferritin and D-Dimer were done in symptomatic cases and were compared between vaccinated and unvaccinated

Co-morbidity	Unvaccinated (N=102)	Vaccinated (N=73)
Diabetes mellitus	32 (31.37%)	31 (42.46%)
Hypertension	32 (31.37%)	24 (32.87%)
Cardiac disease	5 (4.9%)	5 (6.84%)
Pulmonary disease (other than COVID-19)	5 (4.9%)	3 (4.1%)
Chronic kidney disease	5 (4.9%)	2 (2.73%)
Immunocompromised	4 (3.92%)	1 (1.36%)
Cerebrovascular disease	1 (0.98%)	2 (2.73%)
Total no patients with co-morbidities	69 (67.64%)	51 (69.86%)

[Table/Fig-3]: Number of patients with different co-morbidities (p-value=0.86). A p-value <0.05 was considered to be significant

groups using the unpaired T-test. Serum ferritin levels were significantly higher in the unvaccinated group, indicating a higher inflammatory response.

DISCUSSION

The main aim of the study was to compare the severity of the disease, oxygen requirement, and mortality between vaccinated and unvaccinated patients. This study revealed an increase in severe COVID-19, oxygen requirement, and increased mortality in the unvaccinated group. Also, it was observed that there was an increase in serum ferritin levels in the unvaccinated population. Unvaccinated patients with co-morbidities have shown an increase in mortality. The severity of the disease was higher in unvaccinated patients. These findings correlated with a study done by Tenforde MW et al., in which vaccination was associated with a decrease in disease progression and mechanical ventilation or death [13].

The need for oxygen requirement, either high flow or mechanical ventilation was higher in unvaccinated patients. In an Israeli study by Rinott E et al., there was a decrease in the number of vaccinated patients requiring mechanical ventilation comparable to this study [14].

Mortality was found to be significantly higher in the unvaccinated group. This correlated with the study by Alsaffar WA et al., in which a significant reduction in mortality and the complicated course was observed [15].

Co-morbidities observed in this study were: diabetes mellitus, hypertension, cardiac disease, Chronic Kidney Disease (CKD), and chronic pulmonary disease (other than COVID). Diabetes was the most common (52.5%) co-morbidity followed by hypertension (46.6%) which was similar to a study done by Varma M et al. To understand the effect of co-morbidity on poorer outcomes in unvaccinated, compared to the vaccinated group, the odds of overall mortality rate in patients with co-morbidity were assessed [16]. There was a statistically significant increase in mortality with OR 3.55 (p-value=0.03) in unvaccinated patients when compared to vaccinated patients. Similar findings were observed in studies by Lechien JR et al., [17], and Bianca de Almeida-Pititto [18]. In the former study, pre-existing chronic lung disease, cardiovascular disease, chronic kidney disease, diabetes mellitus, hypertension, obesity (BMI >30) and immunosuppression, sickle cell disease, cancer, age, sex, and pregnancy have been found to predispose to higher intubation rates and death/severity in unvaccinated individuals. Ali H et al., showed a strong antibody response to COVID-19 vaccination in diabetics although the titres were low when compared to non diabetics. The presence of hypertension did not show any variation in the immune response to COVID-19 vaccination [19]. In a study by Sanders JF et al., immune response to COVID-19 vaccination in CKD and dialysis patients was comparable to those without chronic kidney disease [20]. Hence, all patients with co-morbidities are advised to receive the vaccination.

Biochemical parameters studied include serum ferritin, CRP, and D dimer. Serum ferritin levels were significantly higher in the unvaccinated population indicating a higher inflammatory response. So far no article

could be found that compared ferritin levels between vaccinated and unvaccinated COVID-19 patients to the best of our knowledge.

The CT chest was done in 97 patients. CT severity index in the unvaccinated group was higher (13.82±5.4) than in the vaccinated group (11.58±5.49) although statistically not significant (p-value=0.08). In a study by Lee JE et al., proportion of patients without CT pneumonia was significantly higher in a vaccinated group but CT severity scores were not compared between the vaccinated and unvaccinated in their study [21].

Limitation(s)

This is a retrospective analysis done from a single institute. Prospective studies from multiple centres and a higher number of patients are required to substantiate the above findings.

CONCLUSION(S)

This study has shown that COVID-19 vaccination has a significant impact on decreasing the severity of the disease, the need for high flow oxygen or mechanical ventilation, and mortality, especially in patients with co-morbidities. Unvaccinated patients constituted 3/4th of severe COVID-19 disease. The odds of mortality in unvaccinated patients with co-morbidity were observed to be 3.55 (1.1-11.4; p=0.03). Most of the deaths (80%) in this study occurred in unvaccinated patients. Serum ferritin levels were significantly lower in vaccinated individuals. Head-to-head comparison between similar vaccines (i.e between mRNA vaccines) and efficacy against different variants of COVID-19 is needed.

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