DOI: 10.7860/JCDR/2024/64633.18879

Original Article

Public Health Section

Impact of COVID-19 Vaccines on Mortality Rates among Adult COVID-19 Patients

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ABSTRACT

Introduction: The Coronavirus Disease 2019 (COVID-19) pandemic has been a public health concern since 2019. Multiple strategies have been implemented to flatten the curve of cases, including isolating active cases, contact tracing, quarantines, lockdowns, hand hygiene, face mask usage, and sanitisation. Vaccination has been used as a tool to reduce morbidity and mortality due to COVID-19.

Aim: To analyse the impact of COVID-19 vaccines on mortality rates among COVID-19 patients, with a secondary objective of studying the association between age, time since vaccination, and mortality rates.

Materials and Methods: The present cohort study was conducted in the Department of Forsenic Medicine at All India Institute of Medical Sciences (AIIMS), Nagpur, Maharashtra,India, with a sample size of 60 cases, out of which 30 were included. Data was collected over a six month period from January 1, 2022, to June 30, 2022. The study included adult COVID-19 patients who were admitted to AIIMS Nagpur and subsequently died. Data on vaccine type, dose, and time since vaccination were also collected.

Results: The mean age of patients was 53 years. Of the patients, 63.3% (n=57) were males and 36.6% (n=33) were females. Among the patients, 60% were vaccinated, while 40% were unvaccinated. Among the vaccinated patients, 14.8% received Covaxin, while 85.1% received Covishield. Regarding the vaccination dosage, 9.2% of the patients received a single dose, while 90.7% received two doses. All the patients who survived COVID-19 had been vaccinated for more than one month.

Conclusion: Vaccination resulted in a 93.1% reduction in the odds of death among vaccinated patients. Among the unvaccinated patients, 80% died due to COVID-19. After adjusting for age and co-morbidities, vaccination was found to be independently associated with a lower risk of mortality ($p<0.001$). Furthermore, 73.3% of the deceased cases had co-morbidities ($p<0.001$). The study demonstrates the protective effect of vaccination with either Covishield or Covaxin, which should hopefully address any misconceptions among the general public.

Keywords: Coronavirus disease 2019, Mortality decline, Potency of vaccine

INTRODUCTION

Coronavirus Disease-19 (COVID-19) is a highly contagious disease caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). It is known worldwide due to the ongoing COVID-19 pandemic and has raised concerns among health authorities since 2019. India diagnosed its first case in January 2020 [1]. By January 2022, the pandemic had caused around 44 million cases and five lakh deaths [2]. The COVID-19 pandemic followed a wave pattern globally, with the first wave in September 2020, the second wave in April-May 2021, and the third wave in December 2021-January 2022 [3].

Multiple strategies were implemented to flatten the curve of cases, including the isolation of active cases, contact tracing, quarantines, lockdowns, following hand hygiene, wearing face masks, and sanitisation, among others. The development of vaccines had the potential to prevent severe diseases and decrease mortality.

In India, vaccination began on January 16, 2021, with the use of Covishield (AstraZeneca) and Covaxin (Bharat Biotech) for the mass vaccination program. Covishield is the non replicating chimpanzee Adenovirus Vaccine Vector ChAdOx1, manufactured by the Serum Institute of India in collaboration with the University of Oxford and AstraZeneca, while Covaxin is the inactivated-virus vaccine BBV152, developed by Bharat Biotech International [4]. The vaccination drive was implemented in a phased manner. Untill September 22, 80% of administered vaccine doses were Covishield, 35% Covaxin, and 4% Corbevax [5]. In October 2022, India administered over 2.19 billion doses, including first, second, and booster doses [6]. Since then, the mortality curve has flattened to a great extent. Several Indian studies were conducted to evaluate Vaccine Effectiveness (VE) in preventing virus infection, reducing hospital stay, severe COVID-19 disease, or mortality. Ghosh S et al., conducted a cohort study on the Indian population to check the effectiveness of the Covishield vaccine and claimed that the vaccine provided 93% protection against COVID-19 and a 98% reduction in mortality [7]. Another multicentric hospital-based case-control study conducted by the Indian Council of Medical Research (ICMR) to evaluate the effectiveness of Covishield and Covaxin showed that the VE of complete vaccination was 85% (95% CI: 79-89%) and 71% (95% CI: 57-81%), respectively [8]. In a case-control study at JIPMER, VE following any number of vaccine doses was found to be 95% (44%-100%) in preventing moderately severe disease [9].

Comparative analysis of mortality due to COVID-19 in vaccinated subjects who have received either the first dose of the vaccine or are fully vaccinated is not well reported, particularly regarding its association with factors such as age group or co-morbidities. The present study aims to examine the impact of COVID-19 vaccination in preventing deaths due to COVID-19. Secondary objectives of present study are to investigate the association of age, co-morbidities, and time since vaccination with mortality rates due to COVID-19 in vaccinated and unvaccinated patients.

MATERIALS AND METHODS

This was a cohort study conducted at AIIMS Nagpur, Maharashtra India over a period of six months, from January 1, 2022, to June 30, 2022. The study commenced after obtaining approval from the Institutional Ethics Committee (IEC), AIIMS Nagpur (EC/NEW/INST/2020/548).

Sample size calculation: Based on previous literature and assuming a vaccination proportion of 56.1% in the control group and 28.7% in the cases [8], with a study power of 80%, a case-to-control ratio of 1:2, and a two-sided confidence interval (1-α) of 95, the calculated sample size was 37 cases and 74 controls. However, considering the feasibility of a hospital-based study, the sample size was considered as 30 cases and 60 controls. Therefore, 30 deaths that occurred at AIIMS Nagpur hospital due to COVID-19 were included as cases, while 60 cases that were admitted due to COVID-19 but recovered were included as controls. A consecutive sampling technique was used for sampling.

Inclusion criteria: The study included deaths occurring due to COVID-19 or its complications in adult patients admitted to the hospital.

Exclusion criteria: Deaths occurring due to unnatural causes in COVID-19 patients and patients for whom vaccination details were not provided were excluded.

Study Procedure

Data was collected from the Medical Certificate of Cause of Death (MCCD) issued for deaths due to COVID-19 at AIIMS Nagpur. The data included age, gender, existing co-morbidities, and duration of hospital stay. A predesigned study proforma was used for data collection. Information on the vaccination status of the patients (first/second dose, Covaxin/Covishield, and time since receiving the dose of the vaccine) was collected from the treatment file of the patients admitted at AIIMS Nagpur. The admission criteria for these patients were determined by the institute's policy, which included patients with at least two of the following symptoms: fever (temperature ≥38°C), chills, myalgia, headache, sore throat, or new olfactory or taste disorder, or those who had at least one respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic evidence of pneumonia) and at least one Severse Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Polymerase Chain Reaction (PCR)-positive nasopharyngeal swab. The post-dose period was categorised as 0-31 days and more than 31 days.

STATISTICAL ANALYSIS

The data was collated in MS Excel, and descriptive statistics were used for analysis. VE was calculated as (1-Odds ratio) × 100% [9]. The qualitative data were evaluated using Pearson's Chi-square test or Fisher's-exact test. Matched pair analysis was conducted, and multivariable conditional logistic regression was performed to calculate the adjusted odds ratio. The factors used for adjustment were vaccination status, presence of comorbidity, and age.

RESULTS

The present was a cohort study that enrolled 30 deaths due to COVID-19 as cases and 60 survivors of COVID-19 infection as controls. The mean age of the participants was 53 years. Among the patients, 63.3% (n=57) were males, while 36.6% (n=33) were females [Table/Fig-1].

Variables	Deaths n (%)	Survivors n (%)	Total n (%)	p-value (Pearson's Chi-square)
Age (years)				
18-39	5 (16.6)	25 (41.6)	30 (33.3)	
40-59	3 (10)	20 (33.3)	23 (25.5)	
60-90	22 (73.3)	15 (25)	37 (41.1)	
Gender				
Male	20 (66.6)	37 (61.6)	57 (63.3)	
Female	10 (33.3)	23 (38.3)	33 (36.6)	
Vaccination status#				
Unvaccinated	24 (80)	12 (20)	36 (40)	<001
Vaccinated	6 (20)	48 (80)	54 (60)	
Co-morbidities##				
Absent	8 (26.6)	39 (65)	47 (52.2)	<0.001
Present	22 (73.3)	21 (35)	43 (47.7)	

[Table/Fig-1]: Distribution of patients according to age, gender, vaccination status and co-morbidities.
#The odds ratio is 0.063, CI (95 %, 0.021-0.187), while the adjusted odds ratio is 0.069, CI (0.020-0.237). The adjustment was done for age and co-morbidities. VE was 93.1%
##An odds ratio is 5.10, CI (95%, 1.94-13.4)

Among the vaccinated patients, 14.8% were vaccinated with Covaxin, while 85.1% were vaccinated with Covishield [Table/Fig-2]. There was a 93.1% reduction in the odds of deaths in vaccinated patients. Among the unvaccinated patients, 80% died due to COVID-19, while among the vaccinated patients, 80% survived (p<0.01). Regarding the vaccination status, 9.2% of the patients had received a single dose of vaccination, while 90.7% of patients had received two doses of vaccination [Table/Fig-2]. All the patients who survived the COVID-19 infection were found to be vaccinated for more than one month [Table/Fig-3]. Of the patients, 52.2% had no comorbidity, while 47.7% of cases had co-morbidities. However, 73.3% of cases who died due to COVID-19 had co-morbidities (p<0.001).

Parameters	Deaths n (%)	Survivors n (%)	Total n (%)	
Vaccine type				
Covaxin	0	8 (16.6)	8 (14.8)	p-value=0.575
Covishield	6 (100)	40 (83.3)	46 (85.1)	
Vaccine dose*				
1st	2 (33.3)	3 (6.2)	5 (9.2)	p-value=0.089
2nd	4 (66.6)	45 (93.7)	49 (90.7)	
Time since vaccination				
Upto 1 month	1 (16.6)	0	1 (1.8)	p-value=0.111
More than 1 month	5 (83.3)	48 (100)	53 (98.1)	

[Table/Fig-2]: Distribution of cases according to the type of vaccine, vaccine dose and time since vaccination.
*The odds ratio is 0.133 CI (95%, 0.017-1.047)

Vaccine dose	Time since vaccination	Covaxin		Covishield		Total
		Survivors	Deaths	Survivors	Deaths	
1st	Upto 1 month	0	0	0	0	0
	More than 1 month	0	0	3	2	5
2nd	Upto 1 month	0	0	0	1	1
	More than 1 month	8	0	37	3	48
Total		8	0	40	6	54

[Table/Fig-3]: Distribution of cases according to their vaccination details.

Multivariate regression analysis of independent parameters such as vaccination, co-morbidities, and age showed that the adjusted odds ratio for vaccination was significant with a p-value <0.001 [Table/Fig-4].

Parameters	Exposure level	Odds ratio	Confidence interval	p-value
Vaccine	No	1	-	-
	Yes	0.069	0.020-0.237	0.001
Co-morbidities	No	1	-	-
	Yes	2.842	0.656-12.305	0.162
Age	Yes	0.251	0.037-1.695	0.156

[Table/Fig-4]: Multivariate analysis showing independent predictors for mortality among COVID-19 patients.

DISCUSSION

The results of present case-control study indicate that vaccination significantly reduced the risk of mortality among COVID-19 patients aged 18 years and above who were admitted to the hospital. There

was a 93.1% reduction in the odds of deaths in vaccinated patients. Among the unvaccinated patients, 80% died due to COVID-19, while among the vaccinated patients, 80% survived. The VE was calculated to be 93.1% (1-adjusted odds ratio).

It is important to note that all cases and controls included in present study were above 18 years of age. While 18 years of age was considered as the benchmark, the current vaccination program in India includes individuals above 12 years of age. Additionally, there were no deaths reported in the hospital statistics for patients between 12 to 18 years of age. Lopez Bernal J et al., included individuals above 70 years in their study [10], while Bhatnagar T et al., conducted a case-control study on patients above 45 years of age [8], and Desai A et al., included patients above 18 years of age [4].

In the present study, 63.3% (n=57) of the patients were males, while 36.6% (n=33) were females. The higher representation of male patients in the study may be attributed to their higher engagement in outdoor activities, which may increase the risk of acquiring COVID-19 infection. It is important to note that the VIN-WIN study [7] included only male participants. Therefore, the results of the VIN-WIN study cannot be directly compared to the findings of the present study in terms of gender.

Vaccination Status

The present study is unique as it is a cohort study where both cases and controls were individuals suffering from COVID-19 and admitted to the hospital. In contrast, studies by Lopez Bernal J et al., and Dagan N et al., which also investigated mortality as an outcome, considered vaccinated patients as cases and unvaccinated patients as controls [10,11]. Lopez Bernal J et al., found that vaccination with one dose significantly reduced symptomatic COVID-19 in older adults and provided further protection against severe disease [10]. Dagan N et al., studied vaccine efficacy and reported higher effectiveness for more serious outcomes such as hospitalisation, severe illness, and death [11]. On the other hand, studies by Bhatnagar T et al., and Pramod S et al., considered COVID-19 positive cases and COVID-19 negative individuals as controls [8,9]. The present study directly measures the reduction in odds of mortality in vaccinated patients. The odds ratio is 0.063, with a 95% confidence interval (0.021-0.187), while the adjusted odds ratio is 0.069, with a confidence interval of (0.020-0.237). The adjustment was done for age and co-morbidities. The study showed a 93.1% reduction in the odds of deaths in vaccinated patients. Among the unvaccinated patients, 80% died due to COVID-19, while among the vaccinated patients, 80% survived. The VE was calculated to be 93.1%. In India, deaths due to COVID-19 account for 1.18% of all cases, but this constitutes 5,29,008 deaths nationwide as of October 2022 [12].

Vaccine Efficacy/Effectiveness Studies

Various studies have been conducted to report vaccine efficacy/effectiveness. The vaccination trial results of Covaxin showed 93% efficacy against severe COVID-19 [13]. Real-world estimates of VE should take into account various factors such as storage and cold chain maintenance, incomplete delivery of doses, and emerging variants of the virus. Real-world studies have been conducted to evaluate the impact of vaccines on preventing breakthrough infections [9,14], hospital stay [4,15], severity of disease [8], and mortality outcomes [7,10,11]. These studies are summarised in [Table/Fig-5] [7,8,10,15].

In the present study, the VE {(VE) (1-adjusted odds ratio)×100} was found to be 93.1%, and there was a 93.1% reduction in the odds of deaths in vaccinated patients. Among the unvaccinated patients, 80% died due to COVID-19. These findings are comparable to other studies. Ghosh S et al., reported a VE of 98.53% (95% CI, 0.00-99.99) [7], while Dagan N et al., reported it as 92% (95% CI, 75 to 100) [11].

The impact of the vaccine also depends on the number of doses administered and the time since vaccination. Studies by Desai A et al., and Lopez Bernal J et al., evaluated the impact of vaccines after a single dose of vaccination [4,10]. However, other studies evaluated the impact of vaccines after the first dose and subsequently after the second dose [7-9]. The evidence from the present study aligns with the observations of Bhatnagar T et al., where the efficacy of vaccines was found to be 85% (95% CI: 79-89%) with Covishield and 71% (95% CI: 57-81%) with Covaxin [8]. Regarding the mortality outcome, Dagan N et al., reported a vaccine efficacy of 72% (95% CI, 19 to 100) after the first dose of the vaccine, which improved to 92% (95% CI, 75 to 100) after the second dose of vaccination [11].

In the present study, it was found that all the patients who survived the COVID-19 infection had been vaccinated for more than one month. Bhatnagar T et al., reported that VE was highest between 6-8 weeks after the administration of Covishield (94%, 95% CI: 86-97%) and Covaxin (93%, 95% CI: 34-99%) [8]. Similarly, Dagan N et al., observed an increase in vaccine efficacy with an increase in the duration since vaccination [11]. In the present study, an arbitrary limit for the time since vaccination (<1 month or >1 month) was decided based on the findings of Ghosh S et al., where the mean duration between the first and second dose in cases who subsequently tested positive was 31.43 days [7].

In the present study, 54 patients (60%) were vaccinated. Among them, 46 patients (85.1%) received Covishield, while eight patients (14.8%) received Covaxin. These proportions corresponded with the national vaccination database, where Covishield constituted 80%, Covaxin accounted for 16%, and other vaccines constituted 4% [6]. No deaths were recorded among the patients who received Covaxin. Of the patients who received Covishield, 83% survived, while 17% succumbed to COVID-19. Although our analysis did show protection against mortality after vaccination with Covishield/Covaxin, the numbers for each type of vaccine were too few to draw any statistical conclusions.

Multivariate regression analysis was performed to investigate whether significant differences in independent parameters could obscure an association with COVID-19 mortality. After adjusting for age and co-morbidities, vaccination was found to be independently associated with a lower risk of mortality (p<0.001), with an adjusted odds ratio of 0.069 (95% CI, 0.020-0.237). This finding was consistent with the observations of Desai A et al., [4].

The present study provides evidence of the impact of vaccines in preventing deaths due to COVID-19. It will help establish vaccines as effective tools in the fight against COVID-19 in future waves and variants. The findings of present study can contribute to public

Parameters	Present study	Ghosh S et al., [7]	Lopez Bernal J et al., [10]	Vasileiou E et al., [15]	Bhatnagar T et al., [8]
Samples	Age >18 years	Males	Age >70 years	Mean age 65 years	Age >45 years
Type of study	Cohort	VIN-WIN cohort	Case-control	Cohort	Case-control
Outcomes	Deaths Vaccine Effectiveness (VE)	Cases Deaths Vaccine Effectiveness (VE)	Cases Hospitalisation Vaccine Effectiveness (VE)	Hospitalisation after 1 dose Vaccine Effectiveness (VE)	Cases Vaccine Effectiveness (VE)
Results	Reduced odds of 93.1% in deaths in vaccinated patients	Reduction of 95.4 % in cases	Reduced odds of 73% in cases	Reduction of hospitalisation by 88%	VE 94% is for Covishield and 93% for Covaxin

[Table/Fig-5]: Vaccine efficacy/effectiveness studies [7,8,10,15].

education and awareness campaigns about the importance of vaccination.

Limitation(s)

Authors did not consider whether the patients admitted to the hospital were experiencing reinfection of COVID-19, and this is particularly significant in drawing conclusions for unvaccinated patients. Another limitation of the present study is the smaller sample size.

CONCLUSION(S)

Vaccination resulted in a 93.1% reduction in the odds of death in vaccinated patients, leading to a VE of 93.1% for COVID-19 mortality. Among unvaccinated patients, 80% died due to COVID-19. Although the results demonstrate protection against mortality after vaccination with Covishield/Covaxin, the numbers for each type of vaccine are insufficient to draw statistical conclusions. After adjusting for age and co-morbidities, vaccination was found to be independently associated with a lower risk of mortality ($p<0.001$). Among the cases who died due to COVID-19, 73.3% had co-morbidities ($p<0.001$).

The findings of present study will help alleviate fears or misconceptions about vaccines among the general population. The data generated by present study will also contribute to further research on mortality patterns in vaccinated or unvaccinated COVID-19 patients.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Apr 14, 2023
- Manual Googling: Nov 08, 2023
- iThenticate Software: Nov 10, 2023 (8%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Apr 11, 2023**
Date of Peer Review: **Jul 18, 2023**
Date of Acceptance: **Nov 14, 2023**
Date of Publishing: **Jan 01, 2024**