BCG Vaccination in COVID-19 Patients Admitted to the Emergency Department of a Low-Middle-Income Country: A Cross-Sectional Study.

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ABSTRACT:

Objective: To determine the severity and outcome of covid-19 patients who are vaccinated with BCG in our setup.

Methodology: This cross-sectional study was conducted, from 20th February 2021 to 30th August 2021, at emergency department, Aga Khan University Hospital, Data of interest from 93 covid-19 cases was recorded on predesign proforma. A total of 93 covid 19 positive patients who were included in this study. Effect modifiers were controlled by stratification. Chi-square test was applied post stratification to calculate the expected value and p-value ≤0.05 was considered as significant.

Results: The mean age of the patients was 47.36 years. Most patients were managed at special care unit for covid-19. We did not observe statistically significant association between BCG vaccinated patients (73.11%) and the age, gender, length of hospital stay, or patient disposition in this sample. (Observed p values were above 0.05)

Conclusion: Most cases of covid-19 were BCG vaccinated but there were no statistically significant differences between vaccinated and non-vaccinated individuals in term of age, gender and length of hospital stay.

Keywords: COVID 19, length of hospital stay and BCG vaccination.

Introduction:

In December 2019, an unusual outbreak of pneumonia with an unknown cause was reported in Wuhan, Hubei province, China. The World Health Organization (WHO) later identified a novel coronavirus as the responsible agent, which was subsequently named Covid-19.[1] The reported incubation period varies between 1 to 14 days and a mortality of 3.2%. [2] Various treatment modalities are emerging and clinical trials are underway. Bacillus Calmette-Guérin (BCG), a vaccine against tuberculosis developed at Institute Pasteur at the beginning of the twentieth century as a vaccine to prevent tuberculosis.[3] It also induces protective heterologous effects against infections and malignancies. Studies have shown its ability to induce potent protection against other infectious diseases, the so-called non-specific effects (NSEs). [4] BCG vaccine has been shown to reduce the severity of infections by other viruses with that structure in controlled trials. For example, the BCG vaccine reduced yellow fever vaccine viraemia by 71% (95% CI 6-91) in volunteers in the Netherlands and it markedly reduced the severity of mengovirus (encephalomyocarditis virus) infection in two studies in mice.[5] Randomized controlled trials have provided evidence that the BCG vaccine's immunomodulatory properties can protect against respiratory infections.[6] In Guinea-Bissau, a high-mortality setting, BCG-Danish reduced all cause neonatal mortality by 38% (95% CI 17-54), mainly because there were fewer deaths from pneumonia. [7]

Many of the mechanisms underlying the beneficial off-target effects of the BCG vaccine are now understood.[8] The BCG vaccine and some other live vaccines induce metabolic and epigenetic changes that enhance the innate immune response to subsequent infections, a process termed trained immunity.[9] The BCG vaccine might therefore reduce viremia after SARS-COV-2 exposure, with consequent less severe COVID-19 and more rapid recovery.[10] There are currently 8 randomized clinical trials are undergoing aiming to asses efficacy of BCG vaccine and covid 19 Incidence/severity among different subsets of population. [11] Based on available evidences/benefits of BCG vaccine, we want to conduct a study aiming to assess the frequency of BCG vaccine with COVID 19 incidence in our set of population and also, we want to see to the outcomes among such patients.

Methodology:

This was a cross sectional study involved patients who presented to emergency department Aga Khan University Hospital and were positive for Covid19 PCR test. It was conducted from 20th February 2021 to 30th August 2021. Sample size of 93 patients was calculated by taking prevalence of BCG vaccinated to be 11.7% among a positive case of COVID-19.[12] Data was collected either directly from the patients or from parents/ guardian via a pre designed questionnaire, comprising of basic demographic data and BCG vaccination status. Ethical approval was obtained from ethics review committee before starting the study.

BCG (Bacillus Calmette – Guerin) vaccination status was labeled as those who received a single dose of Intradermal BCG vaccine at birth, as part of the EPI (Expanded programme immunization WHO) Schedule, confirmed either by asking patient/guardian or presence of scar over deltoid region (if unable to recall). Whereas, COVID 19 infection was labelled positive by nasal swab PCR testing (polymerase Chain reaction). Paediatric population (From day 0 and below 18 years) and patient who refuses to consent were excluded.

Data was entered and analysed by using SPSS statistical package version 22 software. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges. Chi square Test will be applied in compar-

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ing BCG vaccine among different study characteristics. All statistical analysis will be presented in terms of tables, charts and graphs. P-value of < 0.05 will be taken as significant.

Results:

The study included 93 participants, with a majority being male (72%). The age distribution showed that 76.3% were between 20-45 years old, while 23.7% were between 46-70 years old. The mean age was 47.36 years with a standard deviation of 17.50 years. Regarding the length of hospital stay, 40.9% stayed for 7 days or less, and 59.1% stayed for more than 7 days. Disposition outcomes revealed that 31.2% of participants were treated in the ward, 50.5% in the special care unit (SCU), and 18.3% in the intensive care unit (ICU). In terms of final outcomes, 71% of the participants were discharged, 9.7% left against medical advice (LAMA), and 19.4% expired. A significant proportion (73.1%) of participants had received BCG vaccination.

In the stratification of variables across BCG vaccination status, among those vaccinated, 70.4% were aged 20-45 years, and 81.8% were aged 46-70 years. For non-vaccinated participants, the respective percentages were 29.6% and 18.2%. Among males, 70.1% were vaccinated, compared to 29.9% who were not. Among females, 80.8% were vaccinated, while 19.2% were not. The length of hospital stay was 7 days or less for 76.3% of vaccinated participants and 23.7% of non-vaccinated participants. For those staying longer than 7 days, the percentages were 70.9% for vaccinated and 29.1% for non-vaccinated. Disposition in the ward was more common among vaccinated participants (86.2%) compared to non-vaccinated (13.8%). In the SCU, 68.1% of vaccinated participants were present versus 31.9% non-vaccinated. In the ICU, 64.7% of vaccinated participants were present compared to 35.3% non-vaccinated. Regarding outcomes, 77.3% of vaccinated participants were discharged compared to 22.7% non-vaccinated. Among those who left against medical advice, 55.6% were vaccinated, and 44.4% were non-vaccinated. Finally, among those who expired, 66.7% were vaccinated compared to 33.3% non-vaccinated. Statistical analysis revealed no significant differences between the vaccinated and non-vaccinated groups across these variables, with p-values above 0.05 for all comparisons.

Table No 1: Baseline characteristics and outcomes of the study participants.

Characteristics		(n)	(%)
Sex	Male	67	72%
	Female	26	28%
Age (years)	20-45	71	76.3%
	46-70	22	23.7%
Age (years)	Mean ±SD	47.36 ± 17.50	
LOHS	≤ 7 Days	38	40.9%
	> 7 Days	55	59.1%
Disposition	Ward	29	31.2%
	SCU	47	50.5%
	ICU	17	18.3%
Outcome	Discharged	6	71%
	LAMA	09	9.7%
	Expired	18	19.4%
BCG vaccination	Yes	68	73.1%
	No	25	26.9%

Table No 2: Stratification of variables across the BCG vaccination.

BCG VACCINATION				
Variables		Yes (n%)	No (n%)	p value
Age	20-45 Years	50 (70.4%)	21 (29.6%)	0.29
	46-70 Years	18 (81.8%)	04 (18.2%)	
Sex	Males	47 (70.1%)	20 (29.9%)	0.30
	Females	21 (80.8%)	05 (19.2%)	
LOHS	≤ 7 days	29 (76.3%)	09 (23.7%)	0.14
	> 7 days	39 (70.9%)	16 (29.1%)	
Disposition	Ward	25 (86.2%)	04 (13.8%)	0.40
	SCU	32 (68.1%)	15 (31.9%)	
	ICU	11 (64.7%)	06 (35.3%)	
Outcome	Discharged	51 (77.3%)	15 (22.7%)	0.42
	LAMA	05 (55.6%)	04 (44.4%)	
	Expired	12 (66.7%)	06 (33.3%)	

Discussion:

The liver is the has very minor, The observed trends suggest that BCG vaccination may have a protective effect, potentially leading to shorter hospital stays and less severe outcomes, yet despite the high number of BCG-vaccinated participants (73.1%) for this current study we found statistically insignificant differences between vaccinated and non-vaccinated with respect to age, length of hospital stay, and mortality rates. A higher proportion of vaccinated individuals were treated in the general ward (86.2%) compared to non-vaccinated individuals (13.8%). Conversely, a larger proportion of non-vaccinated individuals required intensive care (35.3% in ICU). This suggests a possible trend where BCG-vaccinated patients might experience less severe illness, requiring less intensive care, however differences were statistically insignificant (p = 0.40). A higher proportion of BCG-vaccinated patients were discharged (77.3%) compared to non-vaccinated patients (22.7%), suggesting that BCG vaccination may be associated with more favorable outcomes. These results suggest that BCG might offer some protection in reducing disease severity, but further research is needed to confirm any causal relationship, as the p-value of 0.42 indicates no significant difference. These results are consistent with published research, that has shown mixed outcomes regarding the protective effect of BCG against COVID-19.[13-15] The relatively small sample size (n = 93) and the specific context of this study may explain the lack of significant results. Still, the observed trends, particularly in relation to shorter hospital stays and less severe outcomes for vaccinated participants, suggest the need for additional research.

Earlier research has suggested that BCG vaccination might provide broader immune protection, potentially lessening the severity of COVID-19 by enhancing the body's innate immunity through the process of trained immunity. [13-15] Although currently most widely held opinion is that the BCG vaccination help to prevent COVID-19 infection, this study did not find a significant protective effects. Nevertheless, the higher proportion of vaccinated individuals being discharged (77.3%) compared to those who were not vaccinated (22.7%) aligns with previous research that indicates BCG might contribute to reducing disease severity. This study also touches on the crucial role of vaccine acceptance and sociocultural factors in shaping public health responses, specially in low- and middle-income countries (LMICs). Bono et al.[16] and Patwary et al.[17] have shown that vaccine acceptance in LMICs is affected by levels of trust in healthcare systems, access to vaccines, and the spread of misinformation. This points to the need for targeted communication strategies that enhance vaccine uptake, especially in areas where vaccine hesitancy poses a significant challenge.[16-17] The absence of statistically significant findings in this study might reflect broader systemic issues in LMICs, such as limited healthcare access, socio-economic difficulties, and misinformation, all of which can obscure the potential benefits of vaccines. Future research should take into account these sociocultural factors when examining vaccine uptake and related outcomes.

Although the association between BCG vaccination and relatively better outcome after COVID-19 infection remains unclear, prior vaccinations could still play a key role in shaping immune responses. The published studies [18-20] have demonstrated that previous vaccinations, including mRNA vaccines, significantly reduced hospitalizations during the Delta and Omicron outbreaks. This is particularly important in LMICs, where healthcare systems might struggle to manage large-scale hospitalizations. The possibility that BCG vaccination enhances innate immunity through trained immunity is a promising area for further study, especially as more data from randomized clinical trials become available.

Several studies [21-23] are being conducted globally to investigate the potential protective effects of BCG vaccination against COVID-19. Early research found that countries with established BCG vaccination programs reported fewer COVID-19 cases and deaths per capita. This suggests that vaccines that induce trained immunity could offer some level of protection while awaiting the development of a COVID-19-specific vaccine. [21-23] In contrast, some studies have found that BCG vaccination in childhood does not provide protective effects against COVID-19 in adulthood. 23 Another study 24 adjusted for factors like healthcare access, education, and COVID-19 epidemic stages, finding a strong correlation between BCG vaccination policies and reduced COVID-19 morbidity and mortality in European countries. A 10% increase in the BCG index was linked to a 10.4% decrease in mortality. [24] The immunomodulatory effects of the BCG vaccine have been demonstrated in randomized controlled studies to provide protection against respiratory infections. BCG-Danish decreased newborn mortality in Guinea-Bissau, a high-mortality area, by 38%. This was mostly because fewer babies died from sepsis and pneumonia. Similarly, BCG-Danish reduced adolescent respiratory infections by 73% in South Africa.[24]

Furthermore, several studies, such as those conducted in 4 European countries and across 175 countries, observed a reduction in both infection rates and deaths, suggesting BCG's potential protective effect. Cohort studies demonstrated that BCG vaccination may prevent severe COVID-19 outcomes, while large-scale cross-sectional and multivariable analyses showed that countries with established BCG policies had lower COVID-19 incidence and mortality. Additionally, studies among healthcare workers found that BCG was associated with decreased clinical symptoms. A notable result from multiple regression analyses indicated a 30-fold decrease in COVID-19-related mortality in countries with BCG programs. Although the trends across these studies point to a potential protective effect of BCG through trained immunity, further controlled research is necessary to establish a definitive causal relationship.[25-33]

This study and the literature highlight several knowledge gaps. More extensive, multi-center cross-sectional studies are needed to assess the frequency and outcomes of BCG vaccination among COVID-19 patients in different LMICs. These studies could determine if the trends seen here—such as shorter hospital stays and less severe disease among vaccinated participants—are consistent in larger, more diverse populations. [34-40]

Additionally, a deeper exploration of sociocultural factors influencing vaccine acceptance is necessary, especially in communities with long-standing BCG vaccination programs. Understanding these factors is critical for developing effective public health strategies that improve vaccine coverage and mitigate the effects of future pandemics. Lastly, longitudinal studies are essential to evaluate the long-term protective effects of BCG and other vaccines in the context of COVID-19. As the effectiveness of some vaccines, like mRNA vaccines, decreases over time, continuous monitoring of vaccine performance across various populations is crucial. [41-48]

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