



## BCG VACCINATION STATUS AND EARLY OUTCOME OF COVID 19 : AN OBSERVATIONAL STUDY

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**ABSTRACT** **BACKGROUND AND OBJECTIVES:** Hypothesis regarding the protective effect of BCG vaccine on Covid 19 has been proposed since the start of the SARS CoV2 pandemic. BCG vaccination seems to have non- specific beneficial effects against other viral infections like RSV, HSV2, Yellow fever and Influenza. The aim was to find out significant association between childhood BCG vaccination and the outcome of COVID 19 in a sample of adult patients who were admitted during the peak of the infection in India.

**METHODS:** We enrolled 370 adult patients by complete enumeration method, admitted in our hospital in July 2020. We looked for the presence of BCG scar and studied the clinical profile of every patient. All of them were followed up till discharge or death and their outcomes were categorised as favourable or unfavourable. The clinical data and the significance of the presence of scar on the outcome was analysed.

**RESULTS:** 87% patients had a favourable outcome. 25% patients had comorbidities like Hypertension, Diabetes Mellitus, Chronic lung disease and Chronic kidney disease. BCG scar was present in 73% of all patients. 75.78% of the patients who had favourable outcome had evidence of the vaccination as compared to the 24.22% without the scar (p value=0.001). This result was however not seen in patients with hypertension and diabetes mellitus suggesting that they could be confounding variables in the study and independent risk factors of poorer outcome.

**CONCLUSIONS:** Adults vaccinated with BCG in childhood seem to have better progression and outcome of Covid 19. Prospective clinical trials would help confirm these results.

**KEYWORDS :** COVID-19, BCG Vaccine, Innate Immunity

### INTRODUCTION

SARS-CoV-2 pandemic, is one of the worst to have shaken our world since the 1918 Spanish flu and is the third serious Coronavirus outbreak following SARS in 2002–2003 and MERS in 2012.<sup>1</sup>

At the start of the pandemic, it was expected that developing nations such as India would face higher case fatalities due to the deprived health infrastructure and huge population density.<sup>2</sup> Though there was an increasing trend in number of incident cases in India the severity of the disease and mortality was less as compared to some developed nations. The host immune response is speculated to be responsible for this inter-regional disparity in the clinical severity of COVID-19.<sup>2</sup> BCG vaccine may have a role to play in this immune response too.<sup>3</sup>

The bacille Calmette-Guérin (BCG) vaccine has existed for more than 90 years. It is a live attenuated Danish 1331 strain of *Mycobacterium bovis*.<sup>4</sup> Although the protection offered by BCG vaccination against pulmonary Tuberculosis (TB) is low, it does protect against severe forms of childhood TB like TB meningitis and miliary TB.<sup>5,6,7</sup> The national coverage of the vaccine was initiated in many nations towards the middle of the twentieth century but as the prevalence of TB decreased, some countries in Europe stopped mass vaccination of children and countries like the United states of America limited vaccination to the high-risk population.<sup>8</sup>

BCG vaccination was included in Expanded Programme of Immunization of India since 1978 and till date is given to every child at birth or as early as possible till the first year of life.<sup>9,10</sup> Administered as intradermal injection in left upper arm with a dose of 0.1ml, the usual response to the vaccine is development of a papule followed by healing with scar formation by 6 weeks at the site of the injection.<sup>11</sup> The BCG scar has been quoted to be a sensitive indicator of successful vaccination.<sup>12</sup> Studies have suggested that children with BCG scar have better survival in early childhood in developing countries.<sup>13,14</sup> There has been evidence from developed countries too where BCG vaccination reduced hospital admission due to respiratory infections in children through heterologous protection.<sup>15</sup>

BCG vaccination has broad protective effects that are not limited to M. Tuberculosis infection.<sup>16</sup> There are studies done on animals that demonstrate the protective effects of BCG vaccination against viral pathogens such as Herpes and Influenza viruses.<sup>17</sup>

BCG vaccination induces nonspecific effects of immune responses. These effects are accompanied by transcriptional, epigenetic and metabolic reprogramming of the myeloid cells in the BCG- vaccinated individuals. The changes that induce memory in the innate immune system after vaccination is termed trained immunity.<sup>18,19</sup> It has been hypothesized that induction of trained immunity is partially the mechanism through which BCG vaccination induces its beneficial effects.<sup>20</sup>

Clinical trials results are expected from trials that assess whether BCG vaccination reduces health care workers absenteeism and reduces hospital admission among the elderly during the COVID-19 pandemic.<sup>21</sup>

Our study was conducted in a tertiary care referral centre for Covid 19 cases with the aim of establishing a correlation between BCG vaccination status and the clinical outcome in a sample of adult patients who were admitted with the dreaded viral disease. The study was done in July-August 2020, during the peak of the pandemic in India. We hope to add to the literature of the protective effects of BCG vaccine and demonstrate the hypothesis on its possible beneficial role in COVID 19 outcome.

### METHODS

#### Study design and participants

A cross sectional study was done in the Covid 19 wards and ICU of MGM medical college, New Mumbai, Maharashtra, the second most populous state of India. The study was performed in accordance with the Declaration of Helsinki and was approved by The Institutional Ethics Committee of MGM Medical College, Navi Mumbai, India.

**Approval number:** N-EC/2020/07/22. All participants were adults

and provided written informed consent to participate in this study. Legally accepted relatives gave consent for patients who were on the ventilator.

**Inclusion Criteria**

1. Adult patients tested positive for SARS CoV2 disease by RT-PCR of nasopharyngeal swab.

**Exclusion Criteria**

1. Patients or legally accepted relatives who refused to give consent to participate.
2. Pregnant patients
3. Patients with severe psychiatric illness

370 patients were enrolled from 10<sup>th</sup> July to 30<sup>th</sup> July 2020 and each of these patients was followed up for a maximum of 20 days after admission.

**Procedures**

Upon admission the patients were subjected to the following.

1. Clinical assessment- Patients were categorized into mild, moderate, severe and critical disease as per WHO guidelines<sup>27</sup>. No modifications were done to the investigations or treatment of any of the patients by the investigator or the co-investigator of this study.
2. As evidence of vaccination, presence of BCG scar over the left or right deltoid area was looked for in all the patients who fit into the inclusive criteria.
3. Patients were followed up daily to see the progression or resolution of the disease.
4. The outcome was categorized as favorable or unfavorable.

**Favorable outcome in a subject denoted that the patient at the end of the study was either:**

- a. Discharged
- b. A moderate disease resolved to mild disease, or became better clinically. A severe or critical case mellowed down to a moderate or mild case.

**An unfavourable outcome was given to the patients who either:**

- a. Died
- b. Were mild cases during admission but they progressed to moderate or severe disease by the end of the study.
- c. Were moderately ill patients who worsened clinically needing ICU admission during or by the end of the study.

**Statistical Analysis**

The data was entered and analysed using Microsoft Excel version 2019. The data was summarised using frequency, percentage, mean and standard deviation. The results are presented in tables and bar diagrams. Two tiered tests, Chi square test and unpaired t test were used as tests of significance, with p value less than 0.05.

**RESULTS**

The demographic and clinical profile of the patients is tabulated (Table no. 1). 65% patients were male, 67% were under the age of 55.

**Table No.1- Demographic And Clinical Parameters Of The Patients**

	Frequency (n=370)	Percentage (%)
<b>Age group</b>		
<55 years	248	67
>55 years	122	33
<b>Gender</b>		
Male	240	65
Female	130	35
<b>Symptoms</b>		
Fever	295	79.7
Cough	219	59
Breathlessness	182	49
Malaise	171	46
Sore throat	153	41
Headache	79	21
Chest pain	79	21
Sneezing & rhinorrhea	56	15
<b>Comorbidities</b>		
Hypertension	94	25.4

Diabetes mellitus	76	20.5
Chronic lung disease	39	10.5
Chronic kidney disease	14	3.8
Coronary artery disease	12	3.2
<b>Stage of presentation</b>		
Mild	203	55
Moderate	132	35.6
Severe	18	4.8
Critical	17	4.6
<b>Outcome</b>		
Favourable	322	87
Non favourable	48	13
<b>BCG scar</b>		
Present	269	73
Absent	101	27
<b>Active Tuberculosis</b>	3	0.8

Hypertension and Diabetes mellitus were the most common associated comorbidities.

55% of the patients presented with mild disease. 35.7% patients had moderate disease, 4.9% had severe disease requiring high flow oxygen or NIV and 4.6% of the patients presented in a critical state requiring endotracheal intubation with mechanical ventilation.

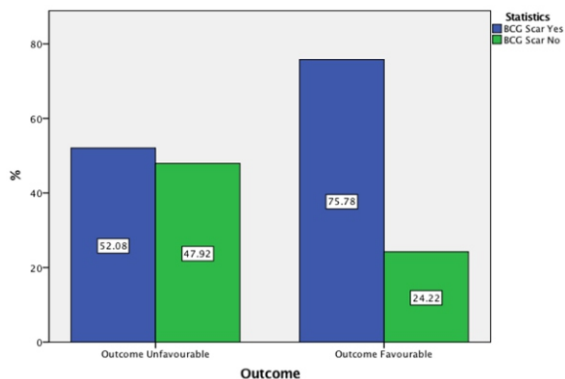
Out of the 370 patients 322 (87%) had a favourable outcome of the disease. 13% had an unfavourable outcome suggesting that they either worsened to severe disease by the end of the study or died. The mean age of patients having unfavourable outcome was 55.3 years.

Age over 55 years was a risk factor for poorer outcome in our study as was associated comorbidities namely Hypertension, Diabetes mellitus, Chronic lung disease and chronic kidney disease.

There was no statistical difference in the clinical outcome of the disease in both sexes. (p value = 0.319, Pearson Chi-square test)

BCG scar was present in 269 out of the 370 patients, corresponding to 72.7% . There was no evidence of BCG scar nor a clear BCG vaccination history in the rest 27.3% of the cases. The BCG scar was present in almost equal percentage (72%) in both sexes.

The association of BCG scar with outcome was statistically significant when tested with Chi square test using p value significance of less than 0.05. Patients with the scar had a higher percentage of favourable outcome of Covid 19 as compared to the those without the scar.(graph 1, Table 2)



**Graph No.1- Association Of Bcg Scar Status With Disease Outcome**

**Table 2: association Of Bcg Scar Status With Outcome**

		Outcome		Total
		Unfavourable	Favourable	
BCG Scar	Yes	25 (52.1%)	244 (75.8%)	269 (72.7%)
	No	23 (47.9%)	78 (24.2%)	101 (27.3%)
Total		48 (100%)	322 (100%)	370 (100%)
<b>Chi-Square Tests</b>				
		Value	Df	p Value
Pearson Chi-Square		11.816	1	0.001

We analysed the progression of the disease in patients with respect to those with and without the BCG scar. Harboursing the BCG scar had no significant difference on the final outcome of patients with mild and critical disease.

However, vaccinated patients with moderate and severe disease had better progression to milder disease as compared to their counterparts who didn't have the BCG scar, by the end of the study.(Table 3)

**Table 3: Progression Of Stage Of Disease In Patients From Start To End Of The Study In Patients With And Without Bcg Scar**

BCG Scar	Stage at the end of study		Outcome				Total
			CRITICAL	MILD	MODERATE	SEVERE	
Yes	Stage of disease at start of study	CRITICAL	12 (85.7%)	1(7.1%)	1 (7.1%)	---	14 (100.0%)
		MILD	0 ( 0.0%)	166 (99.4%)	1 (0.6%)	---	167 (100.0%)
		MODERATE	10 (13.0%)	67 (87.0%)	0 (0.0%)	---	77 (100.0%)
		SEVERE	2 (18.2%)	9 (81.8%)	0 (0.0%)	---	11 (100.0%)
	Total		24 (8.9%)	243 (90.3%)	2 (0.7%)	---	269 (100.0%)
No	Stage of disease at start of study	CRITICAL	1 (33.3%)	2 (66.7%)	---	---	3 (100%)
		MILD	1 (2.8%)	35 (97.2%)	---	0	36 (100.0%)
		MODERATE	16 (29.1%)	38 (69.1%)	---	1 (1.8%)	55 (100.0%)
		SEVERE	3 (42.9%)	4 (57.1%)	---	0	7 (100%)
	Total		21 (20.8%)	79 (78.2%)	---	1 (1.0%)	101 (100%)

In patients with comorbidities namely Hypertension, Diabetes Mellitus, having a BCG vaccination scar does not confer positive association with outcome (table 4 shows the correlation in hypertensives with p values). However, patients who harboured

the scar but didn't have any of these coexistent diseases had statistically significant positive difference in the outcomes than those patients without the scar.

**Table 4: Association Of Hypertension And Outcome With Presence Of Scar**

Hypertension			Outcome		Total
Yes	BCG Scar	Yes	Unfavourable	Favourable	72 (76.6%)
		No	6 (60.0%)	66 (78.6%)	
Total			10 (100.0%)	84 (100.0%)	94 (100.0%)
No	BCG Scar	Yes	19 (50.0%)	178 (74.8%)	197 (71.4%)
		No	19 (50.0%)	60 (25.2%)	79 (28.6%)
Total			38 (100.0%)	238 (100.0%)	276 (100.0%)

**Chi-Square Tests**

Hypertension		Value	Df	p Value
Yes	Fischer Exact Test	—	—	.190
No	Pearson Chi-Square	9.857	1	.002

Older age group (more than 55 years) was associated with unfavourable outcome as compared to lower age group ( Pearson Chi square at p value = 0.006).

other studies<sup>23,25,28</sup>. Kui found a female preponderance of 65% in 137 patients studied in Hubei province of China<sup>29</sup>. The outcome with regard to the gender was equal in our study but some places found percentage of female patients admitted in ICU to be lesser than males.<sup>25</sup>

BCG vaccination has an advantage in older patients in terms of outcome status. 74.5% patients above the age of 55 years with BCG scar had favourable outcome whereas 50% patients over 55 years who did not harbour a scar showed a favourable outcome (p value of 0.014 for > 55 years and p value of 0.036 for < 55 years with Chi square test).The mean duration of stay in hospital in patients with BCG scar was 13.06 days and in patients without the scar it was 14.80 Older age group (more than 55 years ) was associated with unfavourable outcome as compared to lower age group ( Pearson Chi square at p value = 0.006).

Fever and cough are common symptoms of this disease as seen in patients of this study as well as other studies done in India and abroad.<sup>23,30,31</sup>. Complaint of breathlessness was reported by almost 50 % of our patients whereas other researchers have quoted a lower percentage of patients presenting with this complaint.<sup>26,28,30</sup>

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In our study population 25% of the patients had at least one comorbid condition. Saluja et al found comorbidities in 19% of 406 patients in their study<sup>24</sup>. Fei Zhou et al saw 48% comorbidities in a sample of 191 patients in two hospitals in China<sup>27</sup>. Cardiovascular complications including Hypertension followed by Diabetes Mellitus was most frequently seen in patients of Covid 19 in this study as well as others.<sup>24,25,27,31</sup>

It is worthwhile mentioning that during the study 3 patients of the 370 cases had active Tuberculosis along with COVID 19 disease and all 3 cases recovered.

From a meta-analysis of 16 different studies worldwide by Nandy et al it was inferred that the presence of Cardiovascular disease, Diabetes mellitus, chronic lung disease and chronic kidney disease led to more adverse outcomes in the patients.<sup>32</sup>

**DISCUSSION**

The demographic data of this study is similar to other studies done in the past months of the pandemic.

The mortality rate for Covid pts varied from centre to centre. We had a mortality rate of 12% at our hospital and this was higher than some studies in India.<sup>24,28</sup> It could have been because our hospital was a referral institute for serious Covid 19 cases in the Raigad district of the state of Maharashtra and many of our patients delayed getting admitted as they lived-in far-off villages.

The median age of presentation was 45.56 years in our study. Bhandari et al reported a median age of presentation to be 43.5 years<sup>23</sup>, Saluja et al quoted an average age of 36 years +/- 15 in a sample of 406 patients<sup>24</sup>. Richardson et al carried out a case series of patients admitted in various hospitals in New York City where the median age of presentation was 63 years.<sup>25</sup> Guan W- jie analysed a large pool of data from China and reported the mean age of presentation to be 49 years<sup>26</sup> Advanced age is a risk factor for worsor outcome.<sup>25,27</sup>

This study gives validation to the theory that prior BCG vaccination may reduce the morbidity of COVID 19 disease. As shown in our results BCG has protective role in terms of progression of disease in all adult age groups including the elderly, it reduced hospital stay and improved overall outcome. There seems to be no benefit of BCG vaccination status in patients with coexistent comorbid diseases like Hypertension, Diabetes Mellitus. These diseases are independent risk factors associated with unfavourable outcomes in SARS CoV2 patients as other studies also suggest.<sup>32</sup>

Males patients outnumbered female ones in this study similar to most

A retrospective cohort study done by Moorlag et al evaluating individuals who had vaccination with BCG in adult population in the

Netherlands give evidence to the fact that recent vaccination with BCG is safe and is associated with reduced illness and symptoms like fatigue in patients with COVID 19.<sup>33</sup>

In an ongoing trial by Indian council of medical research (ICMR) elderly individuals were vaccinated with BCG and being compared with subjects who weren't vaccinated, for their immune response.<sup>34</sup> The results of these studies may add more information to our hypothesis on the beneficial effects of BCG vaccination on COVID 19.

Our study had some limitations. Due to the small sample size and short duration of study we cannot extrapolate the results to the community. A multicentric study would be ideal to get more results. Secondly, there are speculations on the non-specific effects of BCG on the immune system waning off by adulthood.<sup>35</sup> An analysis was done by Chaisemartin on a population of middle-aged swedes who were born before and after 1975, the year BCG vaccination in new born was stopped in Sweden. They commented that receiving BCG at birth doesn't have statistically significant protective effects against Covid 19 occurrence on these patients<sup>36</sup>.

Our data throws light on the prospect of BCG vaccination offering some protection in terms of early Covid 19 outcome. It also emphasizes the importance of routine vaccination of BCG to infants and children.

**Acknowledgements:** The authors are grateful to Dr. Dipak Patil (Associate Professor, Dept. of Community Medicine) for help with statistics and also to the Dean and the Medical superintendent of our institute for their support and guidance during this study period.

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