Research Article

Impact of BCG vaccination and metabolic risk factors on the severity of SARS-Cov-2 infection: a cross-sectional study from a tertiary care centre in northern India

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Abstract

Background and aims: We present a study on the earliest cohort of patients infected with the SARS-CoV-2 virus who were admitted to the All India Institute of Medical Sciences (AIIMS), New Delhi. The primary objective of the study was to find the difference in the rate of intensive care unit (ICU) admission with coronavirus disease 2019 (COVID-19) in patients based on BCG vaccination status. The secondary objective was to assess risk factors for ICU admission and clinical course of patients with COVID-19.

Methods: A cross-sectional observational study was done between 1 May 2020 and 30 July 2020 in AIIMS, New Delhi. Patients aged more than 14 years attending or admitted to the COVID-19 facility with suspected or confirmed SARS-CoV-2 infection were screened and 205 patients with confirmed COVID-19 were included in the study. Patients were managed as per standard protocol. The difference in ICU admission rate with COVID-19 in patients with and without metabolic risk factors was analysed.

Results: The study shows higher ICU admission in the age group ≥45-75years (n=16; 68.5%) compared to the age group 15-44 (n=10; 38.5%) which was statistically significant (p=0.01). In multivariate analysis, the age group ≥45-75 years [AOR=3.76, 95% CI (1.10,12.82), p=0.03] and diabetes mellitus [AOR=5.20, 95% CI (1.08,25.16), p=0.04] were significantly associated with higher ICU admission. Of the 26 patients admitted to ICU, 4 (15.3%) were vaccinated in contrast to 22 (84.6%) who were unvaccinated (p<0.001).

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Conclusion: Diabetes was strongly associated with ICU admission and appears to be a risk factor for severity in patients with COVID-19. BCG vaccination status is positively correlated with fewer ICU admission rates in patients with COVID-19.

Keywords: Bacillus Calmette-Guérin (BCG), Trained immunity, COVID-19, SARS-CoV-2, diabetes, metabolic syndrome

Introduction

According to the World Health Organization (WHO), emerging infectious diseases often pose a serious issue to public health. In December 2019, in Wuhan, China's Hubei province, an outbreak of viral pneumonia marked the start of the coronavirus disease 2019 pandemic and on February 11, 2020, the WHO announced that the disease was caused by a new coronavirus named "COVID-19" which is the acronym of "coronavirus disease 2019".[1] Later, experts in the International Committee on Taxonomy of Viruses (ICTV) termed it as SARS-CoV-2 virus. SARS-CoV-2 is an enveloped single-stranded RNA virus and is the seventh member of coronaviruses known to infect humans. This virus belongs to the same phylogenetic family as the 2002 SARS and 2012 MERS-CoV-2 viruses. SARS-CoV-2 is thought to have originated in bats given a remarkable (89-96%) genomic homology to bat coronaviruses.[2]

The basic reproductive number ("R0") which measures the expected number of cases that is generated from one case, is estimated to be 1.5-3.0 for SARS-CoV-2, in comparison to 0.5-1.0 and 1.5-4.0 with MERS-CoV-2 and SARS respectively.[3] The previous outbreaks of SARS and MERS-CoV-2 reported 10% and 34.4% case fatality rates respectively. The case fatality rate of SARS-CoV-2 has been estimated to be 2.3%.[4]

Similar to influenza, SARS-CoV-2 has high infectivity and a long incubation period and has all the necessary ingredients for a troubling seasonal disease. The strategy of repurposing of old vaccines that are already established in human use and do not need any safety trials in humans such as the Bacillus Calmette-Guérin (BCG) vaccine was much talked about, but subsequent studies to date have not generated enough evidence to recommend its use.[5,6] Some epidemiological studies (preprints) proposed that national differences in COVID-19 impact could be partially explained by different national policies with respect to BCG vaccination. This led to the hypothesis that the impact of routine infant BCG vaccine coverage on spread of SARS-CoV-2 infection in populations varied in accordance with national policies.[7,8] Studies have also reported on the role of BCG vaccine in prevention of acute respiratory infection in children and the elderly.[9,10]

Two immunological mechanisms, namely heterologous effects of adaptive immunity and trained innate immunity, improve the host response against COVID-19 infection. These mechanisms have been hypothesized from the immunological and epidemiological impact of BCG vaccine in the past on non-specific infections.[11] Randomized controlled trials to study the efficacy of BCG vaccination against COVID-19 are being conducted worldwide.[12,13,14,15] In earlier studies, evidence suggested that BCG vaccine effectively induces T-helper 1 (Th1) cells which secrete high levels of IFN-γ and are active against intracellular pathogens.More recently, a memory phenotype in innate immune cells, known as “trained immunity”, has been described.[16] The protective effects of BCG vaccine may be explained by trained immunity which enhances the adaptive immunity. Trained immunity enhanced pattern recognition

receptors' (PRRs) capability of conferring non-specific protection against different pathogens, inducing upregulation of PPRs and secretion of pro-inflammatory cytokines through epigenetic and metabolic reprogramming, is key to the protective effect of BCG vaccine against multiple infectious pathogens.[11,12,17]

Although there are safe and effective vaccines to curb transmission of COVID-19, the risk of severe disease remains for those with metabolic perturbations like diabetes and hypertension irrespective of the vaccination status. This study aims to determine the role of BCG vaccine in reducing this risk in patients admitted to the ICU with SARS-CoV-2 viral infection.

Methods

Study settings

The study protocol (IECPG-165/23.04.2020) was approved by the Ethics Committee, AAIMS, New Delhi. The recruitment of patients was done between 1 May 2020 and 30 July 2020 in the Department of Medicine, AAIMS, New Delhi, India.

Study cohort

Patients aged >14years, attending or admitted to the COVID-19 facility (outpatient-department and wards) with suspected or confirmed SARS-CoV-2 virus infection were screened for the cross-sectional study. All patients who tested positive for SARS-CoV-2 between 1 May 2020 and 30 July 2020 in the Department of Medicine, AIIMS, New Delhi were identified. A cohort of 205 patients with confirmed COVID-19 illness, defined as a laboratory confirmation using real time reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasopharyngeal or oropharyngeal swab specimens, irrespective of clinical signs and symptoms, were included. Those patients who were not willing to give verbal consent or not willing to follow up were excluded. Patients were stratified according to their BCG vaccination status and followed up till the outcome was achieved.

Main outcomes

The study was conducted with a primary objective to find the difference in the rate of ICU admission with COVID-19 in BCG vaccinated and unvaccinated patients. The secondary objective was to assess the risk factors for ICU admission and clinical course of patients with COVID-19.

Statistical Analysis

Data is presented in mean (SD)/Median(min-max) and frequency (%). Association of categorical variables were assessed by Fisher's exact test. Continuous variables were compared by independent t-test/Wilcoxon rank-sum test as appropriate. A stepwise logistic regression analysis was performed with a probability of entry 0.05 and a probability of removal 0.51. A p-value less than 0.05 was considered as statistically significant.

Results

In this study, 232 patients were screened for eligibility; 26 were excluded and finally 205 patients aged >14 years were enrolled. The baseline demographic characteristics are given in Table 1. In this study two age groups, 15-44 years, and 45-75 years, were evaluated.

The study showed higher ICU admission in patients aged 45-75 years (n=16; 68.5%) compared to those aged 15-44 years (n=10; 38.5%) which was statistically significant (p=0.01). The patients with history of contact with a confirmed COVID-19 case had significantly higher ICU admission (p<0.001).

Table 1. Baseline characteristics of patients infected with COVID-19

Variables	Total no. of COVID-19 cases (n=205)	Non-ICU COVID-19 cases (n=179)	ICU COVID-19 cases (n=26)	p-value[a]
Age (years), n (%)				
• 15-44	126 (61.5)	116 (64.8)	10 (38.5)	0.01
• ≥45-75	79 (38.5)	63 (35.2)	16 (61.5)	
Gender, n (%)				
• Male	157(76.5)	140(78.2)	17(65.2)	0.11
• Female	48(23.4)	39(21.7)	9(34.6)	
COVID-19 contact, n (%)				
• Lab confirmed case	61(29.8)	54 (34.2)	7 (26.9)	<0.001
• Suspected case	123(60)	121 (67.6)	2 (7.7)	
• Not known	21(10.2)	4 (2.2)	17 (65.4)	
BCG vaccine, n (%)				
• **Vaccinated**	147(71.7)	143(79.8)	4(15.3)	0.001
• **Unvaccinated**	58(28.2)	36(20.1)	22(84.6)	
Smoking, n (%)				
• Current	22(10.7)	15(8.3)	7(26.9)	0.02
• Former	4(1.9)	4(2.2)	0	
• Never	179(87.3)	160(89.3)	19(73.1)	

[a] Fisher's exact test was used

Factors associated with ICU admission

Table 2. Clinical features and comorbidities in patients infected with COVID-19 at presentation

Variables	Total no. of COVID-19 cases (n=205)	Non-ICU COVID-19 cases (n=179)	ICU COVID-19 cases (n=26)	p-value
Comorbidities, n (%)				
• Hypertension	28(13.6)	20(11.1)	8(30.7)	0.01
• Cardiovascular disease	10(4.8)	4(2.2)	6(23.1)	0.01
• Diabetes mellitus	40(19.5)	33(18.4)	7(26.9)	0.22
• Asthma	2(0.9)	0	2(7.6)	0.01
• COPD	5(2.4)	4(2.2)	1(3.8)	0.49
• Chronic kidney disease	7(3.4)	3(1.6)	4(15.3)	0.006
• Chronic liver disease	3(1.4)	1(0.5)	2(7.6)	0.04
• HIV infection	2(0.9)	2	0	0.76
• Malignancy	3(1.4)	2(1.1)	1(3.8)	0.36
• Hypothyroidism	6(2.9)	5(2.7)	1(3.8)	0.56
• Cerebrovascular disease	4(1.95)	1(0.5)	3(11.5)	0.007
Clinical feature at presentation, n (%)				
• Fever/chills	91(44.3)	75(41.9)	16(61.5)	0.04
• Sore throat	62(30.2)	58(32.4)	4(15.3)	0.05

• Cough	110(53.6)	89(49.7)	21(80.7)	0.01
• Breathlessness	52(25.3)	28(15.6)	24(92.3)	0.001
• Generalized weakness	21(10.2)	11(6.1)	10(38.4)	0.001
• Irritability/Confusion	8(3.9)	3(1.6)	5(19.2)	0.001
• Myalgia	29(14.1)	17(9.5)	12(46.1)	0.001

Abbreviations: ICU, intensive care unit; COPD, chronic obstructive lung disease.

Table 2 lists the comorbidities which were present in nearly half the patients, with hypertension (n=28; 13.6%) being the most common comorbidity, followed by diabetes mellitus (n=40; 19.5%) and cardiovascular disease (n=10; 4.8%). Of the total ICU patients, 31% had hypertension (n=8), 27% had diabetes mellitus (n=7) and 23% had cardiovascular disease (n=6). Other comorbidities included asthma (n=2; 8%), chronic kidney disease (n=4; 16%), chronic liver disease (n=2; 8%) and cerebrovascular accident (n=3; 12%).

The most common symptoms on admission were cough and fever followed by sore throat and breathlessness (Table 2). Symptoms such as breathlessness, fever, cough, myalgia, generalized weakness, and irritability/confusion were significantly higher among those admitted to the ICU.

Of the 205 patients in the study, 26 (12.6%) had ICU admission, of whom 8 patients (30.7%) died during hospitalization. Of these 26 patients with severe COVID-19, 16 (61.5%) required invasive mechanical ventilation, of whom 8 (50%)] died. Pneumonia (n=33; 15%) was the most frequently observed complication, followed by acute respiratory distress syndrome (ARDS) (n=15; 7.2%), acute kidney injury (n=10; 4.8%), and heart failure (n=2; 0.8%). Of the patients admitted to the ICU, 81% (n=21) were not BCG vaccinated, while 20% (n=5) of the non-ICU patients were not BCG vaccinated.

Table 3. Clinical features associated with increased risk of ICU admission in COVID-19 patient at presentation

Variables	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	p-value
BCG Vaccination • Yes • No	0.04(0.01,0.14)	0.1(0.02,0.38)	0.001
Breathlessness • Yes • No	60.8(13.6,4,271)	46.4(8.2.4,261.70)	0.0001
Myalgia • Yes • No	8.16(3.25,20.47)	12.3(1.93,79.39.)	0.008

Adjusted variables:- Age >45 years , fever, sore throat, breathlessness, headache, cough, myalgia,

As shown in Table 3, breathlessness [adjusted odds ratio (AOR)=46.4, 95% CI (8.24,261.70), p=0.0001] was significantly associated with higher ICU admission. Myalgia [AOR=8.16, 95% CI (1.93,79.39), p=0.008] also had higher odds of admission into ICU but was not statistically significant. BCG vaccination [AOR=0.1, 95% CI (0.024,0.38), p=0.001] was significantly associated with lesser ICU admission.

The risk of ICU admission was higher in patients aged 45-75 years. Diabetes mellitus and chronic kidney disease were associated with increased risk of ICU admission. As shown in Table 4, patients aged 45-75 years [AOR=3.76, 95% CI (1.10,12.82), p=0.03] and those with diabetes mellitus [AOR=5.20, 95% CI (1.08,25.16), p=0.04] were significantly associated with higher ICU admissions and BCG vaccinated individuals [AOR=0.038, 95% CI (0.009,0.148), p<0.001] were significantly associated with fewer ICU admissions.

Table 4. Comorbidities associated with increased risk of ICU admission in COVID-19 patients at presentation

Variables	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	p-value
BCG Vaccination • Yes • No	0.04(0.01,0.14)	0.03(0.01,0.11)	< 0.001
Diabetes mellitus • Yes • No	1.66(0.65,4.28)	0.21(0.04,0.97)	0.04
Hypertension • Yes • No	3.60(1.39,9.34)	9.2(2.0,42.0)	0.004

Adjusted variables:- Hypertension, chronic liver disease, chronic renal disease, diabetes mellitus

Multiple studies have been done so far to assess the role of metabolic derangements in COVID-19 outcome. Table 5 describes different studies done on association of metabolic factors and COVID-19.

Table 5: Studies on impact of metabolic factors in COVID-19 severity

Author	Title	Type of study	Citation/Country	Outcome
Yanai H[18]	Metabolic Syndrome and COVID-19	Systematic Review	Cardiol Res. 2020 11(6):360-365.Japan	Enhanced ACE2 expression, procoagulant state play a crucial role for development of severe COVID-19.
Stefan N et al[19]	Global pandemics interconnected - obesity, impaired metabolic health and COVID-19	Review	Nat Rev Endocrinol. 2021; 17(3):135-149. USA	In studies using multivariate adjustment, obesity emerged as a strong and independent determinant of increased risk of morbidity and mortality in patients infected with SARS-CoV-2
Ghoneim S et al[20]	The incidence of COVID-19 in patients with metabolic syndrome and non-alcoholic steatohepatitis:	A population-based study	Metabol Open. 2020 Dec.USA	NASH had the strongest association with COVID-19.
Mechanick JI et al[21]	Clinical Nutrition Research and the COVID-19 Pandemic: A Scoping Review of the ASPEN COVID-19 Task Force on Nutrition Research.	Review	JPEN J Parenter Enteral Nutr. 2021 Jan.USA	The research gaps corresponding to food insecurity/societal infrastructure and transcultural factors (pre–COVID-19); obesity and cardiometabolic-based chronic disease were addressed
Guisado-Vasco P et al[22]	COVID-19 and Metabolic Syndrome: NF-κB Activation. Crossroads	Hypothesis	Trends Endocrinol Metab. 2020 Nov. Spain	The deregulation of NF-κB activation could cause the aberrant T-cell activation, which is associated with the autoimmune and inflammatory response
Abu-Farha M et al[23]	Impact of Diabetes in Patients Diagnosed With COVID-19.	Review	Front Immunol. 2020 Dec.Kuwait	The risk seen among people with diabetes may be due to insulin resistance, inflammation, or hypercoagulation, or owed to underlying obesity

Schiffrin EL et al [24]	Hypertension and COVID-19.	Review	Am J Hypertens. 2020.Canada	Unclear whether uncontrolled blood pressure is a risk factor for acquiring COVID-19
Tadic M et al [25]	COVID-19, hypertension and cardiovascular diseases: Should we change the therapy?	Review	Pharmacol Res. 2020. Italy	Hypertension and CVD, adjusted primarily for age, did not remain independent predictors of the lethal outcome in COVID-19 patients.

Discussion

In this cohort of a Northern Indian population aged 15-75 years, the presence of diabetes mellitus was found to be a risk factor for higher rates of ICU admission in patients with COVID-19. According to a narrative review published by Bansal et al, diabetes mellitus enhances COVID-19 severity by multiple mechanisms, notably by increased expression of ACE receptors in lungs, pancreas and also by increased presence of circulating furin. Furin is an intracellular protease which cleaves S1 and S2 domain of the spike protein and facilitates its entry.[26]

Patients aged 45-75 years had a higher ICU admission rate compared to the younger age group of 14-44 years. According to a study by Loukman Omarjee et al[27], the inflammaging or inflammation associated with aging is responsible for the increased severity of disease in COVID-19 which is similar to our study. Table 5 provides a summary of different studies done on association of metabolic factors and COVID- 19. Yanai et al suggest that enhanced angiotensin receptor expression is associated with severe outcome in COVID-19 in patients with metabolic diseases.[18] A few other studies also discuss the increased association of metabolic risk factors such as obesity, non-alcoholic steatohepatitis and also food insecurity with COVID-19.[19,20,21] Nuclear factor kappa beta activation in metabolic diseases was discussed as a cause of T cell activation leading to severe disease in COVID-19 infection.[22] Our study found hypertension to be a risk factor for ICU admission unlike studies done previously where hypertension adjusted for factors like age could not be established as a risk factor for severe disease in COVID-19 infection.[23,24,25] Breathlessness and myalgia on presentation were also found to be significantly associated with ICU admission.

BCG vaccination in early years of life was significantly associated ($p<0.001$) with a lower rate of ICU admission in adult COVID-19 patients compared with unvaccinated individuals. The Japanese study suggests that routine infant BCG vaccine showed a protective effect against local COVID-19.[28] However, a study published from Israel showed no difference in COVID-19 positivity in BCG vaccinated and unvaccinated patients.[29] Our study is one of its kind which assessed the protective role of BCG vaccine in an Indian population which included asymptomatic to severe COVID-19 cases. A study reported by Mohamed Hussein et al[30] evaluated the effect of BCG vaccine on COVID-19 infection rate, mortality levels, prevalence of serious/critical cases, and case fatality rates in 183 countries (which included countries which had never included BCG vaccine in their national immunization program (NIP), countries which had included the vaccine in the past but not at present, and countries who currently have BCG vaccine included in their NIP). The study concluded that the BCG vaccine correlated with reduced COVID-19 mortality rates and probably offered protection against severe COVID-19 similar to our results.[30] This further adds to the evidence of the protective effects of BCG vaccine due to trained immunity which enhances adaptive immunity.

The training of innate immune cells conferred by BCG could be playing a fundamental role in helping vaccinated individuals to respond to a wide variety of pathogens. Utilizing this concept, researchers worldwide have been keen on understanding any such beneficial effect of BCG vaccine on SARS-CoV-2.[11,12] Existing published studies have shown mixed results. Some are of the opinion that the protective effect is a mere chance finding subject to confounders whereas others believe that it has a protective role, especially against severe forms of SARS-CoV-2 infection. WHO in its last updated information on this issue on 12th April, 2020 stated that there is no protective effect of BCG against SARS-CoV-2 infection.[31] However, it is worth mentioning here that this document was updated during a period when the pandemic was still in a phase where many aspects of its dynamics were yet to be explored. As we have entered into the 9th month since this pandemic began, newer evidence has evolved which needs to be taken into consideration.

The first two randomised controlled trials (RCT) that were designed are the BRACE trial, Australia, BADAS trial, United States, and later the BCG-CORONA trial, Netherlands which are all phase-3 RCTs still in the phase of recruitment and the results are expected by March, 2022.[13-15] The aim of these three studies was to look for the protective effects of BCG vaccine in health care workers.

Our study looked at the differences in the rate of ICU admissions in BCG vaccinated and unvaccinated patients. The first study in this regard was published by Cevdet Ozdemir et al in April 2020.[32] They showed hemispheric as well as BCG vaccination status related differences in incidence and mortality. However, the researchers agreed that this study could be subject to bias. Soon after, in July 2020, another study was published from the United States by Escobar et al.[33] They showed the differences in incidence and severity in socially similar European countries with those having lower BCG coverage experiencing higher number of cases and increased severity due to SARS-CoV-2 infection compared to countries with higher BCG vaccination coverage. The current study looked at the association of SARS-CoV-2 with various comorbidities like cardiovascular diseases, hypertension, diabetes mellitus, chronic lung diseases, chronic kidney diseases and heart diseases, and demonstrated significant ICU admission in patients with diabetes mellitus and chronic kidney disease which is similar to previous reports.[34,35,36]

Studies by the Indian Council of Medical Research (ICMR) are underway to determine the effect of BCG vaccine on SARS-CoV-2 infection dynamics in the Indian population.[37] Until the results of well-designed RCTs are available, it is not recommended to vaccinate or revaccinate the susceptible adult population with BCG vaccine to protect against COVID-19 although the theoretical explanations seem quite convincing to date.

Conclusion

The presence of metabolic risk factors like diabetes, age >45 years and chronic kidney disease has been found to be strongly associated with severe outcomes including ICU admission in patients infected with COVID-19 in our study. As the study was done at a time when vaccines were not available, more well designed prospective trials are required to know whether diabetes, older age, chronic kidney disease are still risk factors for severe outcomes in vaccinated individuals as well.

Clinical features like breathlessness and myalgia at presentation had a higher odds of ICU admission (AOR 100.49, 9.63; p<0.001, 95% CI). BCG vaccination may offer a certain degree of protection against COVID-19 as shown in this study. BCG vaccination in childhood was associated with fewer ICU admissions due to COVID-19 and probably offers protection against severe cases of COVID-19. Currently, there is no data to validate the role of BCG vaccine for immune prophylaxis in high-risk populations against SARS-CoV-2. Well-designed randomised control trials, a couple of which are underway, to determine BCG-induced protective immune response against COVID-19 could be the answer to this burning question in the COVID-19 era.

Declarations

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Author contributions:
Nazneen Nahar Begam and Gaurav Gupta conceptualized the study and wrote the manuscript. Soumyadip Chatterji, Ananthu Narayan, Shalini Tomar, Sanjeev Sinha contributed in results and discussion part including literature search. Shivam Pandey contributed to statistical analysis.

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