Association Between Presence of Bacillus Calmette-Guerin Vaccine Scar and Coronavirus Disease 2019

Buket Caliskaner Ozturk[1], Ilgim Vardaloglu[1], Deniz Öngel[1], Nejdiye Mazican[1], Gizem Senkardesler[1], Nigar Aliyeva[1], Aytan Ismayilova[1], Gunay Can[1], Ilker Inanc Balkan[1], Bilun Gemicioglu[1], and Sermin Borekci[1]

[1]Istanbul Universitesi-Cerrahpasa Cerrahpasa Tip Fakultesi

April 16, 2024

Abstract

Objective: Bacillus Calmette-Guerin (BCG) vaccine is administered for protection against tuberculosis and may also have beneficial effects against some viral respiratory tract infections. The low incidence and mortality of coronavirus disease (COVID-19) in countries that have BCG vaccination program is impressive, and some studies have shared contradictory results. In this study, it was aimed to investigate the relationship between BCG vaccination which is confirmed by BCG scar, and the frequency and course of COVID-19. **Methods:** Among 490 patients who applied to the outpatient clinic for Pulmonary and Enfectious Diseases between March 2021 and June 2021, 400 patients who accepted to participate in the study were included. After the consent of patients; age, gender, body mass index, comorbidities, smoking, history and the progress of COVID-19 of these patients were investigated; presence and number of BCG scar were recorded by physician. Data from groups with and without COVID-19 history were compared. **Results:** Of the 400 patients 228 (57%) were female. Mean age was 39.65 ± 13.53. 188 (47%) patients had a history of COVID-19. There was no relation between presence and number of the BCG scar and COVID-19 related hospitalization and intensive care unit admission. When groups with and without COVID-19 history compared, no statistically significant difference was found with the presence and number of BCG scars (p>0,05). **Conclusion:** No association was found between the presence or number of BCG scars and the frequency and course of COVID-19 in individuals with BCG vaccination history confirmed by the presence of BCG vaccine scars.

Association Between Presence of Bacillus Calmette-Guerin Vaccine Scar and Coronavirus Disease 2019

Short title: Association Between BCG Scar and COVID-19

Buket Caliskaner Ozturk[1], Ilgim Vardaloglu[1], Deniz Ongel Harbiyeli[1], Nejdiye Mazican[1], Gizem Senkardesler[1], Nigar Aliyeva[1], Aytan Ismayilova[1], Gunay Can[2], Ilker Inanc Balkan[3], Bilun Gemicioglu[1], Sermin Borekci [1]

[1]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul, Turkey

[2]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Public Health, Istanbul, Turkey

[3]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

Authors

Buket Caliskaner Ozturk, MD

ORCID-ID: 0000-0001-5514-1108

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul-Turkey

E-mail:drbuketcaliskaner@hotmail.com

Ilgim Vardaloglu, MD

ORCID-ID: 0000-0003-1839-0951

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul-Turkey

E-mail: ilgimvardaloglu@gmail.com

Deniz Ongel Harbiyeli, MD

ORCID-ID: 0000-0002-6531-8883

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul-Turkey

E-mail: denizong@gmail.com

Nejdiye Mazican, MD

ORCID-ID: 0000-0002-4058-3154

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul-Turkey

E-mail: nejdiyegungordu@gmail.com

Gizem Senkardesler, MD

ORCID-ID: 0000 0001 7204 2830

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul-Turkey

E-mail: drgizemsenkardesler@gmail.com

Nigar Aliyeva, MD

ORCID-ID: 0000-0002-1957-2362

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul-Turkey

E-mail: nigaralijev@gmail.com

Aytan Ismayilova, MD

ORCID-ID: 0000-0002-9936-639X

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul-Turkey

E-mail: ismayilaytan@gmail.com

Gunay Can, MD

ORCID-ID: 0000-0001-5815-6700

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Public Health, Istanbul, Turkey

E-mail: gunaycan09@yahoo.fr

Ilker Inanc Balkan, MD

ORCID-ID: 0000-0002-8977-5931

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

E-mail: ilkerinancbalkan@hotmail.com

Bilun Gemicioglu, MD, PhD

ORCID-ID: 0000-0001-5953-4881

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul-Turkey

E-mail: bilung@gmail.com

Sermin Borekci, MD

ORCID-ID: 0000-0002-0089-1312

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul-Turkey

E-mail: borekcisermin@gmail.com

Corresponding Author: Buket Caliskaner Ozturk, MD

Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Pulmonary Diseases, postal code:34303, Istanbul-Turkey

Adress**:** IU-C Cerrahpaşa Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı 34098 Fatih-İstanbul/Türkiye

E-mail: drbuketcaliskaner@hotmail.com

Contact phone number: 90-212 414 32 06

Fax Number: 90-0212 351 24 09

Abstract

Objective: Bacillus Calmette-Guerin (BCG) vaccine is administered for protection against tuberculosis and may also have beneficial effects against some viral respiratory tract infections. The low incidence and mortality of coronavirus disease (COVID-19) in countries that have BCG vaccination program is impressive, and some studies have shared contradictory results. In this study, it was aimed to investigate the relationship between BCG vaccination which is confirmed by BCG scar, and the frequency and course of COVID-19.

Methods: Among 490 patients who applied to the outpatient clinic for Pulmonary and Enfectious Diseases between March 2021 and June 2021, 400 patients who accepted to participate in the study were included. After the consent of patients; age, gender, body mass index, comorbidities, smoking, history and the progress of COVID-19 of these patients were investigated; presence and number of BCG scar were recorded by physician. Data from groups with and without COVID-19 history were compared.

Results: Of the 400 patients 228 (57%) were female. Mean age was 39.65 ± 13.53. 188 (47%) patients had a history of COVID-19. There was no relation between presence and number of the BCG scar and COVID-19 related hospitalization and intensive care unit admission. When groups with and without COVID-19

history compared, no statistically significant difference was found with the presence and number of BCG scars (p>0,05).

Conclusion: No association was found between the presence or number of BCG scars and the frequency and course of COVID-19 in individuals with BCG vaccination history confirmed by the presence of BCG vaccine scars.

Keywords: BCG, BCG scar, BCG vaccine scar, COVID-19, SARS-CoV-2

INTRODUCTION

In last months of 2019, Coronavirus disease 2019 (COVID-19) caused by a novel human coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become worldwide threat. Host immunity is significantly important for the elimination of viruses and the prevention of disease progression. Hence, as vaccine studies for COVID-19 are beginning, factors affecting host immunity are being investigated in order to control and prevent the disease.

Bacille Calmette-Guerin (BCG) is a live, attenuated strain of Mycobacterium Bovis which has been used for preventation of tuberculosis caused by Mycobacterium tuberculosis. It provides a protective effect against tuberculosis infection in children and adults. Although it has been applied for tuberculosis, different efficacy areas of the vaccine have been shown.[1-3] There are studies pointing that BCG vaccination strengthens the immune response to other pediatric vaccines.[1] It is also an agent that has been used for its immunological effect in the treatment of bladder cancer.[2]

In previous studies, it is shown that BCG provides non-specific protection against some virus.[4] Innate defence against viruses stimulates by Pattern Recognition Receptors (PRR). PRR which are expressed by innate immune cells; interact with pathogen-associated molecular patterns (PAMP) of virüs and help eliminating virus by stimulating interferons and cytokines. Thus, an innate immune response against to viral pathogens begins.[3,5] BCG vaccination can stimulate "trained immunity" (innate immune memory).[3,6] Innate immune cells (monocytes, macrophages, natural killer cells) which are prepared by microbial PAMPs for a secondary exposure; play role in trained immunity[3,7] and these cells increase the release of the proinflamatuarty cytokines (Interleukin-1β , tumour necrosis factor and Interleukin-6).[8]

There are human studies show the effects of BCG vaccination on human papillomavirus (HPV), respiratory syncytial virus (RSV), hepatitis B virus (HBV), herpes simplex viruses (HSV), influenza A virus subtype H1N1.[9] Lower viremia levels with yellow fever virus strain has been determined in human volunteers who were vaccinated with BCG and BCG dependent protection has been reported to be associated with increased interleukin-1β production.[10] It is considered that the immune response against BCG can cross-reactivate virus related PAMPs, which create an immune response to these infections.[11]

Therefore, in SARS-CoV-2 pandemic with high mortality and morbidity, whether BCG has protection against COVID-19 has been an intruiging topic and several studies have been initiated at the beginning of pandemic. Among first data, lower rates of COVID-19 associated deaths have been noticed in countries which have BCG vaccination program.[11-16] Studies have been concentrated on this issue, while some studies shared postive results[17,18], some studies have reported no efficiency of BCG. [19]

It is not clear whether the BCG vaccine is protective against COVID-19. However, in most of these studies, BCG vaccine evidence is based on vaccination rates of population. Also, there may be a possibility of absence of scar presence in people with BCG vaccination. On the other hand, the presence of BCG scars can be considered as indirect evidence of vaccination.

In this study; in a population which BCG vaccination is mandatory, we aimed to showthe relation between the presence and the number of BCG scars and, COVID-19 prevalence and severity in patients who admitted to hospital.

MATERIAL AND METHOD

Study Design: It is a prospective, cross sectional, real-life study. Approval was obtained from the ethics committee of the university, dated on 24.04.2021 and numbered E-23786442-604.01.01-16448.

Setting: Among the first 490 patients who applied to the Pulmonary Diseases and Infectious diseases outpatient clinic between 01.03.2021 - 01.06.2021, 400 patients who met the criteria and gave informed consent were included in the study.

Participant:

Inclusion criterias; Being older than 18.

Exclusion criterias; Refusing to sign informed consent document, presence of an immun-suppressive disease or treatment.

Variables: Patients' age, gender, body-mass index (BMI), comorbidities (diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD)), smoking history, tuberculosis history, the history of COVID-19 and COVID-related hospitalization, influenza vaccination history, BCG vaccination history, COVID-19 vaccination history were questioned by physicians. Additionally, the presence and number of BCG scars were evaluated and recorded by the physicians. COVID-19 history required viral ribonucleic acids (RNA) which isolated from nasopharynial swab test to be proven with PCR. BMI: 18-25 were considered as underweight-normal, 25-30 as overweight, and [?]30 as obese. The patients investigated by dividing into three groups as age <30, 30-49 and [?]50.

Study size: Between the specified dates, 400 patients who met the criteria and gave informed consent were included in the study. Patients were seperated into groups according to the presence of BCG scars, COVID-19 history and COVID-19 related hospitalization and results were evaluated.

Statistics: IBM SPSS 22 program was used to analyze the study data. Qualitative data were evaluated using the Chi-squared test and Fisher's exact test. In the comparison of quantitative data, Student's t test was used for data with normal distribution and Mann-Whitney U test was used for data that did not fit normal distribution. The significance level was accepted as $p < 0.05$.

RESULTS

Participants

Among the 490 patients who applied between the specified dates; 41 patients did not give informed consent, 13 patients were excluded because of the presence of immunosuppressive disease and 36 patients were excluded because of receiving immunosuppressive treatment. The remaining 400 patients were included in the study.

Descriptive Data

Of the 400 patients, 43% (n: 172) were male and 57% (n:228) were female. The mean age was 39.65 $\pm$ 13.53. BCG scar was not observed in 18.2% (n:73), 1 scar was observed in 63.5%, [?]2 scars were observed in 18.2% of participants. 212 (53%) patients did not have COVID-19 history, and 188 (47%) patients had. 22.3% (n:42) of the patients who had COVID-19 were followed up in the hospital and 8 of these patients were followed up in the intensive care unit. In our study, 157 (39.2%) patients had a comorbidity, while 243 (60.8%) had no comorbidty. (Table 1).

Outcomes and main datas

BCG scar was observed in 81.7% (n:327) of all patients. The mean age of the patients with BCG scar was 39.06 +- 13.18, 57.5% (n=188) were women. The mean BMI in the group with BCG scar was 25.14 +- 4.65 (Table 1).

When the groups with and without BCG scar were compared, no statistically significant difference was found between age, gender, BMI, smoking history, history of COVID-19, COVID-19 related hospitalization or intensive care unit admission, and Influenza vaccine history (p>0.05). Statistically higher rates of DM

and CAD were noticed in the group without BCG vaccine ($p<0.05$). Higher rate of tuberculosis history was found in the group without BCG scar ($p=0.049$) (Table 2).

47% (n:188) of all patients had COVID-19 history. The mean age of patients with COVID-19 was 40.16 +- 13.75, and the mean BMI was 25.89 +- 5.46. 62.2% (n:117) of the patients who had COVID-19 were female ($p<0.05$) (Table 3).

When the groups with and without COVID-19 were compared, female gender, obesity and presence of DM were found statistically significantly higher in the group that had COVID-19 ($p=0.046$, $p=0.005$ and $p=0.008$) (Table 3). The COVID-19 vaccination rate was found statistically significantly higher in the group that did not have COVID-19 ($p<0.001$). There was no statistically significant difference in age, presence and number of BCG scars, tuberculosis history between the groups with and without COVID-19 ($p>0.05$) (Table 3).

22.3% (n:42) of the patients who had COVID-19 received inpatient treatment. Male gender, [?]50 age, overweight and obesity, and presence of additional disease were found statistically significantly higher in patients who received inpatient treatment than the outpatients (Table 3). When the outpatient and inpatient groups were compared with each other, no statistically significant difference was found between the presence and number of BCG scars, tuberculosis history, and COVID-19 vaccination ($p>0.05$) (Table 3).

No correlation was found between the presence of BCG scar and the history of COVID-19 or COVID-19 related hospitalization in patient groups with and without comorbidity (Table 4).

Among the patients, 153 (38.3%) had been vaccinated with influenza vaccine at least once before, 247 (61.7%) had not been vaccinated with influenza vaccine before. COVID-19 story occurred less frequently in people with influenza vaccination history ($p<0.05$) (Table 3). No relation was found between influenza vaccination history and COVID-19 related hospitalization, and intensive care unit admissions (Table 5).

DISCUSSION

In this study, no difference was found in the frequency and severity of COVID-19 in individuals with BCG scar compared to those without BCG scar. No correlation was found between the number of BCG scars and the history and severity of COVID-19. It was observed that patients without BCG scar had more history of tuberculosis. There was no relationship found between the presence of a history of influenza vaccination and the frequency and severity of COVID-19. Compared with the patients who have a history of COVID-19, vaccination rates with the COVID-19 vaccine were found to be statistically significantly higher in patients who did not have had COVID-19.

Since it is known that BCG vaccine has an innate immunity activating effect against some viruses [3-5]; the effect of BCG against SARS-CoV-2 was a issue of concern at the beginning of the COVID-19 pandemic, In a earlier study conducted in 55 countries, positive results were reported regarding COVID-19 infection among persons vaccinated with BCG.[17] In the first observations, it was stated that there were fewer COVID-19 cases and fewer deaths in populations that received BCG vaccine in childhood.[18,20-24] Therewith, many clinical and laboratory studies on the subject began.

In a study, Glisic et al. identified five BCG antigens corresponding to Rv9034, Rv3763, Rv3875 and Rv2997 Mycobacterium tuberculosis proteins that can cross-react with the S-protein of SARS-CoV 2.[25] In a molecular study, it was also shown that BCG vaccination is protective against SARS-CoV-2 by non-specific ways.[8]

In ecological studies, there are many results indicating that the frequency of COVID-19 and the mortality and morbidity associated with the disease are low in countries that have BCG vaccination program.[18,20-24] In another study in countries where BCG vaccination is part of the immunization schedule, it was observed that the rates of COVID-19 cases in the population were almost similar to those in countries that did not receive BCG vaccination, while deaths from COVID-19 were significantly lower in countries that received BCG vaccination.[26] All of these studies evaluated BCG vaccination based on population vaccination rates. Again in all 13 articles reviewed by Ricco et al., BCG vaccination rates of countries are presented as evidence

of BCG.[27] The positive results found between BCG and COVID-19 in such studies where community-based evaluations are made; it may be considered less reliable due to multiple potential confounders such as stage differences of the epidemic between countries, how the pandemic is managed in respective country, underreporting of deaths related to COVID-19, genetic and environmental factors. Conversely, in our study no correlation was found between the frequency and severity of COVID-19 and BCG scar. Also differently, scar tissue was taken as evidence for BCG vaccination and the relationship between BCG and COVID-19 was examined individually in ur study.

In another study conducted on healthcare workers, the presence of a history of BCG vaccination was found to be associated with a decrease in anti-SARS-CoV-2 immunoglobulin G (IgG) seroprevalence.[3] However, in our study no relationship was found between BCG scar and the frequency of COVID-19.

In a cohort study of BCG-vaccinated individuals, it was reported that the hospitalization requirements of these patients were low.[28] Conversely, in our study no relationship was found between the history of COVID-19 hospitalization and the presence of BCG scar.

In a study conducted by Hamiel et al. on young patients, no significant difference was found in COVID-19 frequency and mortality in BCG-vaccinated and unvaccinated individuals.[19] Similar to this study, no correlation was found between the frequency and severity of COVID-19 and the presence of BCG scar in our study.

A study conducted in Ecuador was concluded that the time elapsed after BCG vaccination increased the prevalence of COVID-19.[13] This indirectly means that the prevalence of COVID-19 increases with age, and it is already known that COVID-19 is more severe depending on variables such as advanced age and comorbidity. On the other hand Wassenaar et al., in their study of patients over 70 years of age with variable vaccination dates in 18 countries, found no correlation between the time of BCG vaccination and the results of COVID-19.[29] In our study, a significant relationship was found between advanced age and COVID-19 hospitalizations; however, this relationship cannot be attributed to the time elapsed since BCG vaccination alone, as variables such as advanced age and increased comorbidity with age may also have an effect on this relationship.

There is no study in the literature examining the relationship between BCG vaccination and COVID-19 in patients with comorbidities. Our study is the first in this respect, and no relationship was found between BCG scarring and the frequency and course of COVID-19 in the patient group with comorbidities.

In another study comparing influenza, pneumococcal and BCG vaccines, the presence of BCG was associated with low mortality in COVID-19.[30] Differently, we found related results with influenza but conversely, unrelated with BCG.

The strength of our study is that it evaluated BCG vaccination by confirming it with a *scar* , unlike studies conducted so far on the effect of BCG on COVID-19. In addition, there is no study in the literature investigating the effect of childhood BCG vaccine on the frequency and mortality of COVID-19 in patients with comorbidities, our study is also valuable in this respect.

Our limitation is that since it is a prospective cross-sectional real-life study, no assessment of COVID-19 mortality could be made. The fact that there was more history of tuberculosis in the group without BCG scar strengthens the possibility of these patients being unvaccinated with BCG, but in the group without BCG scar; There may also be cases that do not develop a scar despite vaccination. Another limitation of our study is that we did not question when the influenza vaccination was done.

Conclusion

As a result no association was found between the presence or the number of BCG scars and the frequency and course of COVID-19 in individuals with a BCG vaccination history confirmed by the presence of a BCG vaccination scar. Currently, the most important protection against COVID-19 is the COVID-19 vaccine.

Tables

Table 1. Demographic features of groups according to presence of BCG vaccine scar and COVID-19 history

			n	Mean	Std. Deviation	p
Age				39.65	13.53	
BMI				25.35	4.83	
Smoking history (pack-year)				6.89	13.86	
		BCG vaccine scar presence				
Age		No	73	42.26	14.81	
		Yes	327	39.06	13.18	0.068 ?
BMI		No	73	26.30	5.50	
		Yes	327	25.14	4.65	0.098 ?
		COVID-19 history				
Age		No	212	39.18	13.35	
		Yes	188	40.16	13.75	0.470 ?
BMI		No	212	24.87	4.15	
		Yes	188	**25.89**	**5.46**	**0.036** ? *
? Fisher Exact test, *p<0.05	? Fisher Exact test, *p<0.05	? Fisher Exact test, *p<0.05	? Fisher Exact test, *p<0.05	? Fisher Exact test, *p<0.05	? Fisher Exact test, *p<0.05	? Fisher Exact test, *p<0.05

BCG: Bacille Calmette-Guerin, BMI: Body-mass index, COVID-19: Coronavirüs disease 2019

Table 2. The distribution of the study population according to the variables and the relation between the presence of BCG vaccine scar and other factors

	All patients	**All patients**	**BCG vaccine scar**	**BCG vaccine scar**	**BCG vaccine scar**	**BCG vaccine scar**	**BCG vaccine scar**
	n	**%**	**No n**	**No %**	**Yes n**	**Yes %**	**p**
Sex							
Male	172	43.0	33	45.2	139	42.5	
Female	228	57.0	40	54.8	188	57.5	0.674
Age							
<30	133	33.2	20	27.4	113	34.6	
30-49	177	44.2	31	42.5	146	44.6	
[?]50	90	22.5	22	30.1	68	20.8	0.192
BMI							
Underweight-Normal	212	53.0	34	46.6	178	54.4	
Overweight	117	29.2	19	26.0	98	30.0	
Obese	71	17.8	20	27.4	51	15.6	0.058
Comorbidity							

	All patients	**All patients**	**BCG vaccine scar**	**BCG vaccine scar**	**BCG vaccine scar**	**BCG vaccine scar**	**BCG vaccine scar**
No	243	60.8	41	56.2	202	61.8	
Yes	157	39.2	32	43.8	125	38.2	0.375
COPD							
No	382	95.5	65	89.0	317	96.9	
Yes	18	4.5	**8**	**11.0**	10	3.1	**0.008** ? **
CAD							
No	392	98.0	70	95.9	322	98.5	
Yes	8	2.0	3	4.1	5	1.5	0.164 ?
DM							
No	377	94.2	65	89.0	312	95.4	
Yes	23	5.8	**8**	**11.0**	15	4.6	**0.048** ? *
HT							
No	368	92.0	64	87.7	304	93.0	
Yes	32	8.0	9	12.3	23	7.0	0.132
Smoking history							
Smoker	106	26.5	18	24.7	88	26.9	
Ex-smoker	72	18.0	19	26.0	53	16.2	
Non-smoker	222	55.5	36	49.3	186	56.9	0.140
COVID-19							
No	212	53.0	35	47.9	177	54.1	
Yes	188	47.0	38	52.1	150	45.9	0.339
COVID-19 hospitalization							
No	146	77.7	26	68.4	120	80.0	
Yes	42	22.3	12	31.6	30	20.0	0.126
COVID-19 related ICU admission							
No	180	95.7	34	89.5	146	97.3	
Yes	8	4.3	4	10.5	4	2.7	0.054 ?
Influenza vaccine history							
No	247	61.8	49	67.1	198	60.6	
Yes	153	38.2	24	32.9	129	39.4	0.296
BCG vaccine scar							
0	73	18.2	73	100.0	0	0.0	
1	254	63.5	0	0.0	254	77.7	
[?]2	73	18.2	0	0.0	73	22.3	-

	All patients	All patients	BCG vaccine scar	BCG vaccine scar	BCG vaccine scar	BCG vaccine scar	BCG vaccine scar
Tuberculosis history							
No	388	97.0	68	93.2	320	97.9	
Yes	12	3.0	**5**	**6.8**	7	2.1	**0.049** ? *
COVID-19 vaccine history							
No	145	36.2	28	38.4	117	35.8	
Yes	255	63.7	45	61.6	210	64.2	0.679
Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01

BCG: Bacille Calmette-Guerin, BMI: Body-mass index, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, COVID-19: Coronavirus disease 2019, DM: Diabetes mellitus, HT: Hypertension, ICU: Intensive care unit

Table 3. The relation between the presence of COVID-19 history or COVID-19 related hospitalization and other factors

	COVID-19 history	COVID-19 history	COVID-19 history	COVID-19 history	COVID-19 history	COVID-19 related hospitalization	COVID-19 related hospitalization	COVID-19 related hospitalization	COVID-19 related hospitalization
	No n	**No %**	**Yes n**	**Yes %**	**p**	**No n**	**No %**	**Yes n**	**Yes %**
Sex									
Male	101	47.6	71	37.8		45	30.8	**26**	**61.9**
Female	111	52.4	**117**	**62.2**	**0.046 ***	101	69.2	16	38.1
Age									
<30	72	34.0	61	32.4		58	39.7	3	7,1
30-49	96	45.3	81	43.1		68	46.6	13	31.0
[?] 50	44	20.8	46	24.5	0.674	20	13.7	**26**	**61.9**
BMI									
Underweight Normal	115	54.2	97	51.6		88	60.3	9	21.4

	COVID-19 history	**COVID-19 history**	**COVID-19 history**	**COVID-19 history**	**COVID-19 history**	**COVID-19 related hospitalization**	**COVID-19 related hospitalization**	**COVID-19 related hospitalization**	**COVID-19 related hospitalization**
Overweight	71	33.5	46	24.5		28	19.2	**18**	**42.9**
Obese	26	12.3	**45**	**23.9**	**0.005 ******	30	20.5	**15**	**35.7**
Comorbidity									
No	138	65.1	105	55.9		90	61.6	15	35.7
Yes	74	34.9	83	44.1	0.059	56	38.4	**27**	**64.3**
COPD									
No	201	94.8	181	96.3		143	97.9	38	90.5
Yes	11	5.2	7	3.7	0.480 ?	3	2.1	**4**	**9.5**
CAD									
No	210	99.1	182	96.8		145	99.3	37	88.1
Yes	2	0.9	6	3.2	0.155 ?	1	0.7	**5**	**11.9**
DM									
No	206	97.2	171	91.0		136	93.2	35	83.3
Yes	6	2.8	**17**	**9.0**	**0.008 ? ******	10	6.8	7	16.7
HT									
No	199	93.9	169	89.9		136	93.2	33	78.6
Yes	13	6.1	19	10.1	0.144 ?	10	6.8	**9**	**21.4**
BCG vaccine scar									
0	35	16.5	38	20.2		26	17.8	12	28.6
1	137	64.6	117	62.2		95	65.1	22	52.4
[?]2	40	18.9	33	17.6	0.627	25	17.1	8	19.0
Tuberculosis history									
No	205	96.7	183	9.3		143	97.9	40	95.2
Yes	7	3.3	5	2.7	0.707 ?	3	2.1	2	4.8
COVID-19 vaccine history									
No	41	19.3	104	55.3		76	52.1	28	66.7
Yes	**171**	**80.7**	84	44.7	**0.000 *** **	70	47.9	14	33.3

	COVID-19 history	**COVID-19 history**	**COVID-19 history**	**COVID-19 history**	**COVID-19 history**	**COVID-19 related hospitalization**	**COVID-19 related hospitalization**	**COVID-19 related hospitalization**	**COVID-19 related hospitalization**
Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01, ***p<0.001	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01, ***p<0.001	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01, ***p<0.001	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01, ***p<0.001	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01, ***p<0.001	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01, ***p<0.001	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01, ***p<0.001	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01, ***p<0.001	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01, ***p<0.001	Chi-square test, ? Fisher Exact test, *p<0.05, **p<0.01, ***p<0.001

BCG: Bacille Calmette-Guerin, BMI: Body-mass index, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, COVID-19: Coronavirus disease 2019, DM: Diabetes mellitus, HT: Hypertension

Table 4. Relation between the presence of BCG scar with COVID-19 frequency and severity in patients with or without comorbidity

		COVID-19 history	**COVID-19 history**	**COVID-19 history**	**COVID-19 history**	**COVID-19 history**	**COVID-19 related hospitalization**	**COVID-19 related hospitalization**	**COVID-19 related hospitalization**	**COVID-19 related hospitalization**
Comorbidity		**No n**	**No %**	**Yes n**	**Yes %**	**p**	**No n**	**No %**	**Yes n**	**Yes %**
No	**BCG Scar**									
	0	21	15.2	20	19.0		15	16.7	5	33.3
	1	89	64.5	69	64.8		62	68.9	6	40.0
	[?]2	28	20.3	17	16.2	0.589	13	14.4	4	26.7
Yes	**BCG Scar**									
	0	14	18.9	18	21.7		11	19.6	7	25.9
	1	48	64.9	49	59.0		33	58.9	16	59.3
	[?]2	12	16.2	16	19.3	0.753	12	21.4	4	14.8
Chi-square test	Chi-square test	Chi-square test	Chi-square test	Chi-square test	Chi-square test	Chi-square test	Chi-square test	Chi-square test	Chi-square test	Chi-square test

BCG: Bacille Calmette-Guerin, COVID-19: Coronavirüs disease 2019

Table 5. Relation between the presence of Influenza vaccine history and history and severity of COVID-19

	Influenza vaccine story	**Influenza vaccine story**	**Influenza vaccine story**	**Influenza vaccine story**	**Influenza vaccine story**
	No	**No**	**Yes**	**Yes**	
	n	**%**	**n**	**%**	**p**
COVID-19 history					
No	121	49.0	**91**	**59.5**	
Yes	126	51.0	62	40.5	**0.041 ***
COVID-19 related hospitalization					
No	99	78.6	47	75.8	
Yes	27	21.4	15	24.2	0.669
COVID-19 related ICU admission					
No	118	93.7	62	100.0	
Yes	8	6.3	0	0.0	0.054 ?
Chi-square test, ? Fisher Exact test, *p<0.05	Chi-square test, ? Fisher Exact test, *p<0.05	Chi-square test, ? Fisher Exact test, *p<0.05	Chi-square test, ? Fisher Exact test, *p<0.05	Chi-square test, ? Fisher Exact test, *p<0.05	Chi-square test, ? Fisher Exact test, *p<0.05

COVID-19: Coronavirüs disease 2019, ICU: Intensive care unit

References

1. Libraty DH, Zhang L, Woda M, et al. Neonatal BCG vaccination is associated with enhanced T-helper 1 immune responses to heterologous infant vaccines. *Trials Vaccinol.* 2014;3(1):1–5. doi.org/10.1016/j.trivac.2013.11.004

2. Sylvester RJ, van der MEIJDEN AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol* . 2002;168(5):1964-1970. doi:10.1097/01.ju.0000034450.80198.1c

3. Ehtesham NZ, Samal J, Ahmad F, et al. Will bacille Calmette-Guerin immunization arrest the COVID-19 pandemic?. *Indian J Med Res* . 2020;152(1 & 2):16-20. doi:10.4103/ijmr.IJMR_1563_20.

4. Uthayakumar D, Paris S, Chapat L, et al. Non-specific Effects of Vaccines Illustrated Through the BCG Example: From Observations to Demonstrations. *Front Immunol* . 2018;9:2869. Published 2018 Dec 4. doi:10.3389/fimmu.2018.02869

5. Weber M, Weber F. Monitoring activation of the antiviral pattern recognition receptors RIG-I and PKR by limited protease digestion and native PAGE. *J Vis Exp* . 2014;(89):e51415. Published 2014 Jul 29. doi:10.3791/51415

6. Tarancón R, Domínguez-Andrés J, Uranga S, et al. New live attenuated tuberculosis vaccine MTBVAC induces trained immunity and confers protection against experimental lethal pneumonia. *PLoS Pathog* . 2020;16(4):e1008404. Published 2020 Apr 2. doi:10.1371/journal.ppat.1008404

7. Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol* . 2020;20(6):375-388. doi:10.1038/s41577-020-0285-6

8. Toraih EA, Sedhom JA, Dokunmu TM, et al. Hidden in plain sight: The effects of BCG vaccination in the COVID-19 pandemic. *J Med Virol* . 2021;93(4):1950-1966. doi:10.1002/jmv.26707

9. Aspatwar A, Gong W, Wang S, et al. Tuberculosis vaccine BCG: the magical effect of the old vaccine in the fight against the COVID-19 pandemic. *Int Rev Immunol.* 2021;0(0):1–14. doi.org/10.1080/08830185.2021.1922685

10. Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang SY, Oosting M, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. *Cell Host Microbe* . 2018;23(1):89-100.e5. doi.org/10.1016/j.chom.2017.12.010

11. Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. *Clin Microbiol Infect* . 2019;25(12):1473-1478. doi:10.1016/j.cmi.2019.04.020

12. Escobar LE, Molina-Cruz A, Barillas-Mury C. BCG vaccine protection from severe coronavirus disease 2019 (COVID-19) [published correction appears in Proc Natl Acad Sci U S A. 2020 Nov 3;117(44):27741-27742]. *Proc Natl Acad Sci U S A* . 2020;117(30):17720-17726. doi:10.1073/pnas.2008410117

13. Garzon-Chavez D, Rivas-Condo J, Echeverria A, et al. COVID-19 Infection and Previous BCG Vaccination Coverage in the Ecuadorian Population. *Vaccines (Basel)* . 2021;9(2):91. Published 2021 Jan 27. doi:10.3390/vaccines9020091

14. Sharquie IK. BCG is a good immunotherapeutic agent for viral and autoimmune diseases: Is it a new weapon against coronavirus (COVID-19)?*Electron J Gen Med* . 2020;17(6).

15. Charoenlap S, Piromsopa K, Charoenlap C. Potential role of Bacillus Calmette-Guérin (BCG) vaccination in COVID-19 pandemic mortality: Epidemiological and Immunological aspects. *Asian Pac J Allergy Immunol* . 2020;38(3):150-161. doi:10.12932/AP-310520-0863

16. Sharma AR, Batra G, Kumar M, et al. BCG as a game-changer to prevent the infection and severity of COVID-19 pandemic?. *Allergol Immunopathol (Madr)* . 2020;48(5):507-517. doi:10.1016/j.aller.2020.05.002.

17. Klinger D, Blass I, Rappoport N, Linial M. Significantly Improved COVID-19 Outcomes in Countries with Higher BCG Vaccination Coverage: A Multivariable Analysis. *Vaccines (Basel)* . 2020;8(3):378. Published 2020 Jul 11. doi:10.3390/vaccines8030378

18. Ozdemir C, Kucuksezer UC, Tamay ZU. Is BCG vaccination affecting the spread and severity of COVID-19?. *Allergy* . 2020;75(7):1824-1827. doi:10.1111/all.14344

19. Hamiel U, Kozer E, Youngster I. SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults. *JAMA* . 2020;323(22):2340-2341. doi:10.1001/jama.2020.8189

20. Gursel M, Gursel I. Is global BCG vaccination-induced trained immunity relevant to the progression of SARS-CoV-2 pandemic?. *Allergy* . 2020;75(7):1815-1819. doi:10.1111/all.14345

21. Miller A, Reandelar MJ, Fasciglione K, et al. Correlation between universal BCG vaccination policy and reduced mortality for COVID-19.*medRxiv* . 2020. doi.org/10.1101/2020.03.24.20042937

22. Shet A, Ray D, Malavige N, et al. Differential COVID-19-attributable mortality and BCG vaccine use in countries. *medRxiv.* 2020;1–10. doi.org/10.1101/2020.04.01.20049478

23. Sala G, Miyakawa T. Association of BCG vaccination policy with prevalence and mortality of COVID-19 [Internet]. Huntington, NY:*medRxiv* . Cold Spring Harbor Laboratory; 2020. doi.org/10.1101/2020.03.30.20048165

24. Khade SM, Yabaji SM, Srivastava J. An update on COVID-19: SARS-CoV-2 life cycle, immunopathology, and BCG vaccination. *Prep Biochem Biotechnol* . 2021;51(7):650-658. doi:10.1080/10826068.2020.1848869

25. Glisic S, Perovic VR, Sencanski M, Paessler S, Veljkovic V. Biological Rationale for the Repurposing of BCG Vaccine against SARS-CoV-2. *J Proteome Res* . 2020;19(11):4649-4654. doi:10.1021/acs.jproteome.0c00410

26. Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. *PLoS Med* . 2011;8(3):e1001012. doi:10.1371/journal.pmed.1001012

27. Riccò M, Gualerzi G, Ranzieri S, Bragazzi NL. Stop playing with data: there is no sound evidence that Bacille Calmette-Guérin may avoid SARS-CoV-2 infection (for now). *Acta Biomed* . 2020;91(2):207-213. Published 2020 May 11. doi:10.23750/abm.v91i2.9700

28. Weng CH, Saal A, Butt WW, et al. Bacillus Calmette-Guérin vaccination and clinical characteristics and outcomes of COVID-19 in Rhode Island, United States: a cohort study. *Epidemiol Infect* . 2020;148:e140. Published 2020 Jul 9. doi:10.1017/S0950268820001569

29. Wassenaar TM, Buzard GS, Newman DJ. BCG vaccination early in life does not improve COVID-19 outcome of elderly populations, based on nationally reported data. *Lett Appl Microbiol* . 2020;71(5):498-505. doi:10.1111/lam.13365

30. Gallagher J, Watson C, Ledwidge M. Association of Bacille Calmette-Guérin (BCG), adult pneumococcal and adult seasonal influenza vaccines with Covid-19 adjusted mortality rates in level 4 European countries. *medRxiv.* 2020. doi.org/10.1101/2020.06.03.20121624