Observational Study

Medicine

OPEN

Association between presence of Bacillus Calmette–Guerin vaccine scar and coronavirus disease 2019

Buket Caliskaner Ozturk, MD[a,*], Ilgim Vardaloglu[a], Deniz Ongel Harbiyeli[a], Nejdiye Gungordu[a], Gizem Senkardesler[a], Nigar Aliyeva[a], Aytan Ismayilova[a], Gunay Can[b], Ilker Inanc Balkan[c], Bilun Gemicioglu[a], Sermin Borekci[a]

Abstract

Bacillus Calmette–Guerin vaccine is administered for protection against tuberculosis and may also have beneficial effects against some viral respiratory tract infections. In this study, it was aimed to investigate the relationship between Bacillus Calmette–Guerin vaccination which is confirmed by BCG scar, and the frequency and course of Coronavirus disease 2019 (COVID-19). Among 490 patients, 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; the presence and number of Bacillus Calmette–Guerin scars were recorded by a physician. Data from groups with and without COVID-19 history were compared. 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 Bacillus Calmette–Guerin scars ($P > 0,05$). No association was found between the presence or number of BCG scars and the frequency and course of COVID-19 in individuals with Bacillus Calmette–Guerin vaccination history confirmed by the presence of Bacillus Calmette–Guerin vaccine scars. Currently, the most important protection against COVID-19 is the COVID-19 vaccine.

Abbreviations: BCG = Bacille Calmette–Guerin, BMI = body mass index, COVID-19 = coronavirus disease 2019, DM = diabetes mellitus, PAMP = pathogen-associated molecular patterns, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

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

1. Introduction

In the 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) became a 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 the prevention 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 nonspecific protection against some viruses.[4] Innate defence against viruses stimulates by pattern recognition receptors. Pattern recognition receptor, which are expressed by innate immune cells, interact with pathogen-associated molecular patterns (PAMP) of a virus and help eliminate the virus by stimulating interferons and cytokines. Thus, an innate immune response against 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 a role in trained immunity[3,7] and these cells increase the release of

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This study was previously presented at the 24th Congress of the Turkish Thoracic Society.

[a] Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul University-Cerrahpasa, Istanbul, Turkey, [b] Cerrahpasa Faculty of Medicine, Department of Public Health, Istanbul University-Cerrahpasa, Istanbul, Turkey, [c] Cerrahpasa Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul University-Cerrahpasa, Istanbul, Turkey.

** Correspondence: Buket Caliskaner Ozturk, Cerrahpasa Medical Faculty, Department of Pulmonary Diseases, Istanbul University-Cerrahpasa, Istanbul 34303, Turkey (e-mail: drbuketcaliskaner@hotmail.com).*

How to cite this article: Caliskaner Ozturk B, Vardaloglu I, Ongel Harbiyeli D, Gungordu N, Senkardesler G, Aliyeva N, Ismayilova A, Can G, Balkan Il, Gemicioglu B, Borekci S. Association between presence of Bacillus Calmette–Guerin vaccine scar and coronavirus disease 2019. Medicine 2022;101:48(e32185).

Received: 29 September 2022 / Received in final form: 14 November 2022 / Accepted: 15 November 2022

http://dx.doi.org/10.1097/MD.0000000000032185

the proinflamatuarty cytokines (Interleukin-1β, tumor necrosis factor, and interleukin-6).[8]

There are human studies that show the effects of BCG vaccination on human papillomavirus, respiratory syncytial virus, hepatitis B virus, herpes simplex viruses, and 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 intriguing 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 a BCG vaccination program.[11–16] Studies have been concentrated on this issue, while some studies shared positive 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 the 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 show the relation between the presence and the number of BCG scars and, COVID-19 prevalence and severity in patients who were admitted to the hospital.

2. Methods

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 and 01.06.2021, 400 patients who met the criteria and gave informed consent were included in the study.

2.1. Participants

Inclusion criteria; Being older than 18.

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

Variables: Patients' age, gender, body mass index (BMI), comorbidities (diabetes mellitus (DM), hypertension, coronary artery disease, chronic obstructive pulmonary disease), smoking history, tuberculosis history, the history of COVID-19 and COVID-related hospitalization, influenza vaccination history, BCG vaccination history, and 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 RNAs which isolated from nazopharyngeal swab test to be proven with polymerase chain reaction. BMI: 18–25 were considered as underweight-normal, 25–30 as overweight, and ≥ 30 as obese. The patients were investigated by dividing into 3 groups based on 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 separated 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 $P < .05$.

3. Results

3.1. 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.

3.2. Descriptive data

Of the 400 patients, 43% (n: 172) were male and 57% (n:228) were female. The mean age was 39.65 ± 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 comorbidity. (Table 1).

Table 1

Demographic features of groups according to presence of BCG vaccine scar and Coronavirus disease 2019 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	.068*
BMI	No	73	26.30	5.50	
	Yes	327	25.14	4.65	.098*
	COVID-19 history				
Age	No	212	39.18	13.35	
	Yes	188	40.16	13.75	.470*
BMI	No	212	24.87	4.15	
	Yes	188	**25.89**	**5.46**	**.036***†

* Fisher exact test,

†$P < .05$.

BCG = Bacille Calmette–Guerin, BMI = body mass index, COVID-19 = coronavirus disease 2019.

3.3. Outcomes and main data

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 ($P > .05$). Statistically higher rates of DM and coronary artery disease were noticed in the group without BCG vaccine ($P < .05$). Higher rate of tuberculosis history was found in the group without BCG scar ($P = .049$) (Table 2).

A total of 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 ($P < .05$) (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 ($P = .046$, $P = .005$ and $P = .008$) (Table 3). The COVID-19 vaccination rate was found statistically significantly higher in the group that did not have COVID-19 ($P < .001$). There was no statistically significant difference in age, presence and number of BCG scars, tuberculosis history between the groups with and without COVID-19 ($P > .05$) (Table 3).

A total of 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 ($P > .05$) (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 ($P < .05$) (Table 5). No relation was found between influenza vaccination history and COVID-19 related hospitalization, and intensive care unit admissions (Table 5).

4. Discussion

In this study, no difference was found in the frequency and severity of COVID-19 in individuals with a BCG scar compared to those without a 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 a positive relationship found between the presence of a history of influenza vaccination and the frequency 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 an issue of concern at the beginning of the COVID-19 pandemic. In an 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 5 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 nonspecific 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 a 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 each 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 our 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 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 scars.

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 a 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. Patients with a history of influenza vaccination may have better

Table 2

The distribution of the study population according to the variables and the relation between the presence of Bacille Calmette–Guerin vaccine scar and other factors.

	All patients		BCG vaccine scar				
			No		Yes		
	n	%	n	%	n	%	*P*
Sex							
Male	172	43.0	33	45.2	139	42.5	
Female	228	57.0	40	54.8	188	57.5	.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	.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	.058*
Comorbidity							
No	243	60.8	41	56.2	202	61.8	
Yes	157	39.2	32	43.8	125	38.2	.375*
COPD							
No	382	95.5	65	89.0	317	96.9	
Yes	18	4.5	**8**	**11.0**	10	3.1	**.008**†§
CAD							
No	392	98.0	70	95.9	322	98.5	
Yes	8	2.0	3	4.1	5	1.5	.164†
DM							
No	377	94.2	65	89.0	312	95.4	
Yes	23	5.8	**8**	**11.0**	15	4.6	**.048**†‡
HT							
No	368	92.0	64	87.7	304	93.0	
Yes	32	8.0	9	12.3	23	7.0	.132*
Smoking history							
Smoker	106	26.5	18	24.7	88	26.9	
Ex-smoker	72	18.0	19	26.0	53	16.2	
nonsmoker	222	55.5	36	49.3	186	56.9	.140*
COVID-19							
No	212	53.0	35	47.9	177	54.1	
Yes	188	47.0	38	52.1	150	45.9	.339*
COVID-19 hospitalization							
No	146	77.7	26	68.4	120	80.0	
Yes	42	22.3	12	31.6	30	20.0	.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	.054†
Influenza vaccine history							
No	247	61.8	49	67.1	198	60.6	
Yes	153	38.2	24	32.9	129	39.4	.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	-
Tuberculosis history							
No	388	97.0	68	93.2	320	97.9	
Yes	12	3.0	**5**	**6.8**	7	2.1	**.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	.679‡

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.

*Chi-square test,

†Fisher exact test,

‡$P < .05$,

§$P < .01$.

adhered to personal protection rules, and therefore COVID-19 may have been observed less frequently in these individuals.

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.

A limitation of this study is that since it is a prospective cross-sectional real-life study, no assessment of COVID-19 mortality could

Table 3

The relation between the presence of Coronavirus disease 2019 history or Coronavirus disease 2019-related hospitalization and other factors

	COVID-19 history					COVID-19-related hospitalization				
	No		Yes			No		Yes		
	n	%	n	%	*P*	n	%	n	%	*P*
Sex										
Male	101	47.6	71	37.8		45	30.8	**26**	**61.9**	
Female	111	52.4	**117**	**62.2**	**.046***‡	101	69.2	16	38.1	**.000** *‖
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	.674*	20	13.7	**26**	**61.9**	**.000***‖
BMI										
Underweight-Normal	115	54.2	97	51.6		88	60.3	9	21.4	
Overweight	71	33.5	46	24.5		28	19.2	**18**	**42.9**	
Obese	26	12.3	**45**	**23.9**	**.005***§	30	20.5	**15**	**35.7**	**.000***‖
Comorbidity										
No	138	65.1	105	55.9		90	61.6	15	35.7	
Yes	74	34.9	83	44.1	.059*	56	38.4	**27**	**64.3**	**.003***§
COPD										
No	201	94.8	181	96.3		143	97.9	38	90.5	
Yes	11	5.2	7	3.7	.480†	3	2.1	**4**	**9.5**	**.045**†‡
CAD										
No	210	99.1	182	96.8		145	99.3	37	88.1	
Yes	2	0.9	6	3.2	.155†	1	0.7	**5**	**11.9**	**.002**†§
DM										
No	206	97.2	171	91.0		136	93.2	35	83.3	
Yes	6	2.8	**17**	**9.0**	**.008**†§	10	6.8	7	16.7	.066†
HT										
No	199	93.9	169	89.9		136	93.2	33	78.6	
Yes	13	6.1	19	10.1	.144†	10	6.8	**9**	**21.4**	**.016**†‡
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	.627*	25	17.1	8	19.0	.249*
Tuberculosis history										
No	205	96.7	183	9.3		143	97.9	40	95.2	
Yes	7	3.3	5	2.7	.707†	3	2.1	2	4.8	.311†
COVID-19 vaccine history										
No	41	19.3	104	55.3		76	52.1	28	66.7	
Yes	**171**	**80.7**	84	44.7	**.000***‖	70	47.9	14	33.3	.093*

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.

*Chi-square test,

†Fisher exact test,

‡$P < .05$,

§$P < .01$,

‖$P < .001$.

be made. The fact that there was more history of tuberculosis in the group without a 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.

5. 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.

Author contributions

Conceptualization: Gizem Senkardesler, Gunay Can, Ilker Inanc Balkan, Bilun Gemicioglu.

Data curation: Buket Caliskaner Ozturk, Ilgim Vardaloglu, Deniz Ongel Harbiyeli, Nejdiye Gungordu, Gizem Senkardesler, Aytan Ismayilova.

Formal analysis: Buket Caliskaner Ozturk, Nejdiye Gungordu, Gunay Can.

Funding acquisition: Ilgim Vardaloglu, Gizem Senkardesler, Deniz Ongel Harbiyeli, Nigar Aliyeva, Aytan Ismayilova.

Investigation: Buket Caliskaner Ozturk, Ilgim Vardaloglu, Nejdiye Gungordu, Ilker Inanc Balkan, Bilun Gemicioglu

Methodology: Gunay Can, Bilun Gemicioglu.

Project administration: Buket Caliskaner Ozturk, Nigar Aliyeva, Sermin Borekci.

Resources: Buket Caliskaner Ozturk.

Software: Buket Caliskaner Ozturk, Nigar Aliyeva, Aytan Ismayilova.

Supervision: Bilun Gemicioglu, Sermin Borekci.

Validation: Buket Caliskaner Ozturk, Gizem Senkardesler, Ilker Inanc Balkan, Sermin Borekci.

Table 4

Relation between the presence of BCG scar with coronavirus disease 2019 frequency and severity in patients with or without comorbidity

		COVID-19 history					COVID-19-related hospitalization				
		No		Yes			No		Yes		
Comorbidity		**n**	**%**	**n**	**%**	***P***	**n**	**%**	**n**	**%**	***P***
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	.589*	13	14.4	4	26.7	.095*
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	.753*	12	21.4	4	14.8	.689*

BCG = Bacille Calmette–Guerin, COVID-19 = coronavirüs disease 2019.
*Chi-square test.

Table 5

Relation between the presence of Influenza vaccine history and history and severity of coronavirus disease 2019.

	Influenza vaccine story				
	No		Yes		
	n	**%**	**n**	**%**	***P***
COVID-19 history					
No	121	49.0	**91**	**59.5**	
Yes	126	51.0	62	40.5	**.041***‡
COVID-19 related hospitalization					
No	99	78.6	47	75.8	
Yes	27	21.4	15	24.2	.669*
COVID-19 related ICU admission					
No	118	93.7	62	100.0	
Yes	8	6.3	0	0.0	.054†

COVID-19 = coronavirus disease 2019, ICU = intensive care unit.
*Chi-square test,
†Fisher exact test,
‡$P < .05$.

Visualization: Gunay Can, Bilun Gemicioglu, Ilker Inanc Balkan, Bilun Gemicioglu, Sermin Borekci.
Writing—original draft: Buket Caliskaner Ozturk, Deniz Ongel Harbiyeli.
Writing—review and editing: Buket Caliskaner Ozturk, Deniz Ongel Harbiyeli, Sermin Borekci.

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;3:1–5.
[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;168:1964–70.
[3] Ehtesham NZ, Samal J, Ahmad F, et al. Will bacille Calmette-Guerin immunization arrest the COVID-19 pandemic? Indian J Med Res. 2020;152:16–20.
[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.
[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.
[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:e1008404. Published 2020 Apr 2.
[7] Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol. 2020;20:375–88.
[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;93:1950–66.
[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;0:1–14.
[10] Arts RJW, Moorlag SJCFM, Novakovic B, et al. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. Cell Host Microbe. 2018;23:89–100.e5.
[11] Moorlag SJCFM, Arts RJW, van Crevel R, et al. Non-specific effects of BCG vaccine on viral infections. Clin Microbiol Infect. 2019;25:1473–8.
[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 USA. 2020;117:17720–6.
[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;9:91. Published 2021 Jan 27.
[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;17:1–6.
[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;38:150–61.

[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;48:507–17.
[17] Klinger D, Blass I, Rappoport N, et al. Significantly improved COVID-19 outcomes in countries with higher BCG vaccination coverage: a multivariable analysis. Vaccines (Basel). 2020;8:378.
[18] Ozdemir C, Kucuksezer UC, Tamay ZU. Is BCG vaccination affecting the spread and severity of COVID-19? Allergy. 2020;75:1824–7.
[19] Hamiel U, Kozer E, Youngster I. SARS-CoV-2 rates in BCG-vaccinated and unvaccinated young adults. JAMA. 2020;323:2340–1.
[20] Gursel M, Gursel I. Is global BCG vaccination-induced trained immunity relevant to the progression of SARS-CoV-2 pandemic? Allergy. 2020;75:1815–9.
[21] Miller A, Reandelar MJ, Fasciglione K. Correlation between universal BCG vaccination policy and reduced mortality for COVID-19. medRxiv. 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.03.24.20042937v2.
[22] Shet A, Ray D, Malavige N. Differential COVID-19-attributable mortality and BCG vaccine use in countries. medRxiv 2020:1–10. Available at: https://www.medrxiv.org/content/10.1101/2020.04.01.20049478v1.
[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.
[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;51:650–8.
[25] Glisic S, Perovic VR, Sencanski M, et al. Biological rationale for the repurposing of BCG vaccine against SARS-CoV-2. J Proteome Res. 2020;19:4649–54.
[26] Zwerling A, Behr MA, Verma A, et al. The BCG World Atlas: a database of global BCG vaccination policies and practices. PLoS Med. 2011;8:e1001012.
[27] Riccò M, Gualerzi G, Ranzieri S, et al. Stop playing with data: there is no sound evidence that Bacille Calmette-Guérin may avoid SARS-CoV-2 infection (for now). Acta Biomed. 2020;91:207–13.
[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.
[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;71:498–505.
[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. Available at: https://www.medrxiv.org/content/10.1101/2020.06.03.20121624v1.