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Relationship between Covid-19 infection and its severity and receiving the BCG vaccine

Abstract

Because the Coronavirus is highly cont, this research investigates the relationship between the BCG vaccine and the infection of Covid-19 and its severity so that if it is positive, this vaccine can be used to control it.
agious, and as a pandemic, it has affected the world, it is essential to find new ways to fight and develop a vaccine against the disease. The plan of martyr Haj Qassem Soleimani was widely implemented. During correspondence with Kohgiluyeh and Boyar Ahmed University of Medical Sciences, we received the list of people tested for Covid-19. The cases were positive for one of the mentioned tests (rapid test, PCR, CT scan). The control group was those who had negative tests. After completing the collection, the questionnaires were analyzed using SPSS 16.1 statistical software. There was a significant difference in the covid-19 severity between people with a history of the underlying disease and others. Based on univariate models, the probability of contracting Covid-19 is significantly 2.913 times higher in people who have not received the BCG vaccine. The incidence of covid-19 for patients with the underlying disease is 1.845 times higher than for patients without a history of underlying disease. According to the results, it can be said that the BCG vaccine can be effective in preventing the severity of virus 19. This disease is seen in people with underlying conditions more than other people.

Keywords: *Covid-19, BCG vaccine, incidence, severity, case-control*

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Introduction

While the whole world is fighting the Coronavirus (COVID-19), which (SARS-CoV- 2) (Severe Acute Respiratory Syndrome Coronavirus) causes and is a significant threat to the economy and health worldwide, the new virus is spread mainly through physical/close contact or respiratory droplets. The new Coronavirus has an irregular and uneven developmental pattern. For this reason, the first three months of the disease outbreak caused the death and infection of many people worldwide (1). SARS-CoV-2 belongs to the family Coronaviridae, has a single-stranded RNA genome, is approximately 30 KB long, and has 29,903 nucleotides (2-4).

The new Coronavirus has posed many challenges. Scientists are working hard to overcome the obstacles ahead to destroy or disable the virus. Therefore, the research to find an effective treatment or vaccine against the new Coronavirus continues, and numerous experiments are being performed in different parts of the world. Unfortunately, the attempts have had no definite progress on this front so far. Of course, this does not mean all hopes disappear (5). Vaccines are one of the most successful and cost-effective public health tools that have greatly helped destroy or control several severe diseases in the last century (6).

For this reason, in addition to effective public health measures, such as social distancing, use of masks, hand washing, avoiding crowded enclosed spaces, and educating the public, effective vaccination is essential to reduce disease and prevent mortality. However, despite the safety and effectiveness of immunization measures, skepticism about vaccination has become an emerging global issue, and the World Health Organization (WHO) has identified it as one of the top 10 threats to global health in 2019 (7). The BCG vaccine (Bacille Calmette-Guérin) was first used in humans in 1921 (8) and remained the most widely used vaccine worldwide (5). Nowadays, several types of BCG vaccines are prepared and used worldwide, and each is different in terms of the quality and ratio of living cells in each dose (9). Animal and human studies have shown that BCG vaccine strains effectively immunize against mycobacteria. As stated in some recent articles, in countries with massive BCG vaccination, the incidence of Covid-19 and respiratory infections has been lower than in countries without BCG vaccination (10, 11). Although BCG vaccination to prevent COVID-19 has not been approvable, further researches in this area are not without merit. Therefore, in this project, we further investigated the effect of the BCG vaccine on the incidence and severity of Covid-19 disease by preparing and distributing a questionnaire and statistical studies. We design a study to find answers to research questions as follows.

- What is the frequency of BCG vaccination in COVID-19 case and control groups?
- What is the ratio of catching Covid-19 in terms of receiving age- and gender-adjusted BCG vaccine, using a logistic regression model?
- What is the ratio of catching severe Covid-19 in terms of age and gender, according to the receiving BCG vaccine?

McIntosh (10) conducted research entitled "Role of trust in receiving or not receiving the Covid-19 vaccine". Among the

respondents, those with higher confidence in the vaccine, the manufacturers, the government, and health officials received the vaccine, which shows the importance of trust in vaccination. Therefore, it is necessary to pay attention to the options of trust and reduce the tools of distrust in society for the success of national immunization.

Mortazavi et al. (5) conducted research entitled "Effect of attenuated live vaccines on corona inhibition." Recent studies by scientists and researchers show that attenuated live vaccines in various forms, including polio, tuberculosis, MMR, hepatitis C, and even diphtheria and pertussis, routinely injected into children under 6 years of age, provide probably temporary protection against Covid-19 disease. Therefore, stimulating the natural immune system by attenuating live vaccines can increase resistance to infection through the SARS coronavirus; it is usable for the vulnerable population against the new Coronavirus. The results, published in a medical journal (Science), show that available attenuated live vaccines can help prevent Covid-19 disease.

Materials and Methods

The project of Martyr Haj Ghasem Soleimani was widely implemented. Through correspondence with the Deputy of Health and the Deputy of Treatment of Kohgiloyeh and Boyerahmad (KB) University of Medical Sciences, we received the list of all those who had performed rapid PCR (PCR) test or CT scan, registered in the systems of Health Integrated System in Iran (SIB), the portal of the Ministry of Health or MCMC. We obtained the information, including identity card, contact number, hospital history, occupation, gender, underlying disease, national code, and place of residence. In this project, the cases were positive for one of the mentioned tests (rapid test, PCR, CT scan). The controls were those who had negative tests. Then we designed, uploaded, and published an online questionnaire in the link. However, due to the incomplete completion of all questionnaires by individuals, it was completed again by telephone and in person. After collecting the questionnaires, we analyzed their databased using SPSS statistical software. In this study, the inclusion criteria for entering the project were having literacy, the ability to use the Internet and registering national code, and the exclusion criterion for leaving the project was the answer to an incomplete questionnaire. Due to the unavailability of similar studies, we calculated the sample size after selecting 50 samples from each case and control group.

Furthermore, we continued the study until the calculated sample size was completed. We analyzed the collected data through SPSS 16.1 statistical software. We investigated the normality of data distribution through the Kolmogorov-Smirnov test, descriptive statistics on the incidence of Covid-19 infection and BCG vaccine injection, Leven test on equality of variance. Hence, we used the logistic regression model to calculate the raw odds and adjusted odds ratios.

Results

The primary study was performed on 200 people, including 106 women and 94 men. The mean age of women was 63.2, and for men was 62.8 years. In terms of the type of disease, among the case group, the most frequently mentioned disease was diabetes, and in the controls, blood pressure was high. Still, there was no significant difference between the case and control groups regarding the type of disease (p-value = 0.189). Table 1 shows the baseline characteristics and history of the tuberculosis vaccine and the history of cases and control groups.

In this study, there were more female participants in the case group (52.8%), and there was an equal number of participants in terms of gender in the control group. There was no significant difference in terms of gender between the two groups (p-value = 0.395) (Table 2).

As for the job, the most frequent job in both groups was housekeeping, with the highest percentage of participants without significant difference (p-value = 0.159).

Among all participants, 8 had a history of tuberculosis. There was no significant difference between the case and control groups. 5 cases and three controls had tuberculosis (p-value = 0.470).

Moreover, the history of BCG vaccine injection was significantly higher in the control group than in the case group (p-value = 0.001).

In both groups of participants with a history of vaccine injection, the highest number of BCG injections was over five years old. There was no significant difference between the case group and controls in the age of vaccine injection (p-value = 0.460)

According to Table 3, the difference between the two groups of case and control in the household dimension is insignificant (p-value = 0.54).

According to Table 3, the total number of participants with a history of underlying disease was significantly higher in the case group than in the control group (p-value = .033).

In terms of the type of underlying disease, diabetes was the most common among the case group, and the blood pressure was high in the controls. However, in general, there was no significant difference between the case and the control group concerning the type of disease (p-value = 0.189).

According to the hospitalization criteria in the ICU and the need for a ventilator, we considered (*Yes or No*) to determine the Covid-19 severity. Those who answered no were considered mild

According to Table 4, there was a significant difference only in the severity of catching Covid-19 disease between people with a history of the underlying disease and people who did not have the underlying condition (P = 0.006).

According to Table 5, based on univariate models, the chance of catching Covid-19 in people who have not taken vaccine BCG is significantly (P = 0.002) 2.913 times higher than those who have taken it. The chance of catching Covid-19 for patients with the underlying disease is 1.845 times higher than for patients with no history of underlying disease (P = 0.034).

According to multivariate models with age and gender adjustment, the chance of catching Covid-19 in people who have not taken vaccine BCG is significantly (P = 0.001) 3.294 times higher than those who have taken it. The chance of catching Covid-19 in patients with the underlying disease is significantly (P = 0.03) 1.935 times more than in patients without a history of underlying disease.

According to Table 6, based on univariate models, severe Covid-19 involvement for people with the underlying disease was significantly (P = 0.008) 4.03 times higher than those without a history of underlying disease.

Based on multivariate models with age and gender adjustment, severe Covid-19 involvement for people with the underlying disease was significantly (P = 0.004) 4.84 times higher than those without a history of underlying disease.

Discussion

In this study, among the case group, there were more female participants (52.8%), and in the control group, there was an equal number of participants. There was no significant difference in terms of gender between the two groups. Regarding occupation, the most abundant job in both groups was housekeeping, with the highest percentage of participants. Five of the cases and three of the controls had tuberculosis. The rate of BCG vaccine injection in the control group was higher than in the case group. In both groups of participants with a history of vaccine injection, the highest number of BCG injections was over five years. There was no significant difference between the case group and controls in the age of vaccine injection. In terms of the history of underlying disease, the case group was significantly more than the control group. In terms of the type of disease, among the case groups, the most frequently mentioned disease was diabetes; in the controls, it was high blood pressure.

Nonetheless, there was no significant difference between the case and control groups in terms of disease type. We considered and determined the severity of Covid-19 according to the criteria of hospitalization in the ICU and the need for a ventilator (as *Yes or No*). There is a significant difference in the severity of Covid-19 disease between people with a history of underlying disease compared to people who do not have an underlying illness. According to univariate models, the chance of catching Covid-19 is significantly 2.913 times higher in people who have not taken vaccine BCG. The possibility of contracting Covid-19 for patients with the underlying disease was 1.845 times higher than for those with no underlying disease history. According to multivariate models with age and gender adjustment (P = 0.001), the chance of catching Covid-19 in people who had not taken vaccine BCG was 3.294 times higher than in those who had taken it. The possibility of contracting Covid-19 in patients with the underlying disease was 1.935 times higher than in patients with no underlying disease history. According to multivariate models with age and gender adjustment, the probability of catching severe Covid-19 for people with the underlying disease was significantly (P = 0.004) 4.84 times higher than for those without a history of underlying disease.

According to the results, we can say that the BCG vaccine can be effective in preventing severe Covid-19. The severity of this disease in people with the underlying illness is higher than in others who need prevention to catch it by observing the health protocols such as reducing attendance in assemblies, maintaining proper physical distance, masking, strengthening the immune system, etc.

Most importantly, without solid evidence from randomized controlled trials, we cannot conclude that BCG vaccination can prevent COVID-19 or reduce COVID-19-related mortality. Therefore, evidence from well-conducted observational studies can reinforce the evidence. Although we cannot conclude that BCG vaccination provides protection against COVID-19 or reduces mortality, evidence from many studies confirms this hypothesis.

Conclusion

According to the results, it can be said that the BCG vaccine can be effective in preventing the severity of the virus 19. Similarly, the severity of this disease is more in people with underlying conditions than other people, which requires prevention to prevent these people from getting infected by following more accurate health protocols, including reducing attendance in gatherings, maintaining proper physical distance, wearing masks, strengthening the immune system, etc. Hence, it is necessary to reduce the incidence and cases of death. Therefore, evidence from well-conducted observational studies can strengthen the evidence. Although it cannot be concluded that BCG vaccination provides protection against COVID-19 or reduced mortality, evidence from many studies supports this hypothesis.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical statement

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Table 1. The majority of covid-19 cases were diagnosed by the method of Polymerase _ Chain Reaction (PCR) 62%.

	Group	**Infected = 100n**
Variable		Number (%)
Method of diagnosis of the disease	PCR (polymerase chain reaction)	62(62)
	Ct (CT scan)	20(20)
	Rapid (rapid test)	13 (13)
	Clinical diagnosis	5 (5)
	Total	100 (100)

Table 2. Baseline characteristics in case and control groups.

	Group	**Case group (n=100)**		**Control group (n=100)**		**Chi-square**	**p-value**
Variable		No	%	No	%		
Gender	Female	56	52.8	50	47.2	0.723	0.395
	Man	44	46.2	50	53.2		
Job	housewife	26	43	34	56.7	6.59	0.159
	Employee	25	61	16	39		
	Free	9	56.2	7	43.8		
	Military	11	35.5	20	64.5		
	Other	29	55.8	23	44.2		
History of tuberculosis	Yes	5	62.5	3	37.5	0.521	0.470
	No	95	50.5	97	49.5		
History of BCG vaccine injection	Yes	61	42.7	82	57.3	81.10	.001
	No	39	68.4	18	31.6		
Age of BCG vaccine injection	From the birth	16	51.6	15	48.4	1.55	0.460
	1-5 years	21	42.9	28	57.1		
	>5	24	38.1	39	61.9		

Table 3. History of other diseases and type of disease among the participants in the study according to the group of patients with Covid-19 and patients without it.

Group	**Case group (n=100)**	**Control group (n=100)**	**Chi-**	**p-value**

Variable		No	%	No	%	square	
History of other diseases	Yes	52	58.4	37	41.6	4.55	0.033
	No	48	43.2	63	56.8		
Type of Disease	blood pressure	10	43.5	13	65.5	6.13	0.189
	Diabetes	15	55.6	12	44.4		
	Asthma	13	65	7	35		
	Cancer	8	88.9	1	11.1		
	Other	7	63.6	4	36.4		

Table 4. Primary characteristics of Covid-19 patients by the severity of Covid-19 in the case group (N = 100).

Variable	Not sever covid-19		Sever Covid-19				p-value
			Sever		Mild		
Age	62.66 ± 6.03		61.16 ± 6.37		62.10 ± 6.37		0.46
Gender	N0	%	No	%	No	%	
Male	44	44	11	25	33	75	
Female	56	56	14	25	42	75	1
History of tuberculosis							
Yes	5	5	3	60	2	40	
No	95	95	22	23.2	73	76.8	0.06
History of BCG vaccine injection							
Yes	61	61	19	31.1	42	68.9	
No	39	39	6	15.4	33	84.6	0.076
Underlying disease							
Yes	52	52	19	36.5	33	63.5	
No	48	48	6	12.5	42	87.5	0.006

* Significance level of 5% test

Table 5. Odds ratio for catching Covid-19 in univariate and multivariate logistic regression.

Variable	Model 1		Model 2	
	OR (95%CI)	P-value	OR (95%CI)	P-value
History of BCG vaccine injection[1]	-5.576 2.913(1.521)	0.002*	- 6.598) 3.294(1.644	0.001*
Underlying disease[2]	1.845(1.049-3.244)	0.034*	1.935(1.067- 3.508	0.03*

1 Reference level for BCG vaccine injection history: Yes

2 Reference level for underlying diseases: No.

* Significance level of 5% test, Model 1: Univariate logistic regression (raw model), Model 2: Adjusted logistic regression based on age and gender, Odds ratio = OR, 95% confidence interval: CI

Table 6. Odds ratio of catching severe Covid-19 in univariate and multivariate logistic regression.

Variable	Model 1	Model 2

	OR (95%CI)	P-value	OR (95%CI)	P-value
History of BCG vaccine injection[1]	0.402 (0.144-1.12)	0.08	0.412 (0.143-1.183)	0.09
Underlying disease[2]	4.03 (1.446-1.231)	0.008*	4.84 (-14.162-1.662)	0.004*

1 Reference level for BCG vaccine injection history: Yes

2 Reference level for underlying diseases: No.

*Significance level of 5% test, Model 1: Univariate logistic regression (raw model), Model 2: Adjusted logistic regression based on age and gender, Odds ratio = OR, 95% confidence interval: CI