Factors determining COVID-19 pneumonia severity in a country with routine BCG vaccination

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Abstract

Background: Bacillus Calmette-Guérin (BCG) vaccination policies of countries are postulated to have effect on the course of coronavirus disease 2019 (COVID-19) pandemic. Methods: Retrospective cross-sectional study was conducted between March 11-June 10, 2020 in a chest clinic in a state hospital in Istanbul,Turkey. Adults with diagnosis of COVID-19 pneumonia confirmed with severe acute respiratory syndrome coronavirus 2 polymerase chain reaction positivity in a nasopharyngeal sample and pulmonary infiltrates in computed chest tomography were included consecutively. Sociodemographic characteristics, body-mass index, smoking status, comorbid diseases, income rates, and BCG-vaccination status were compared between severe and mild patients with COVID-19 pneumonia. Results: Study population consisted of 123 adults (mean age, 49.7 years [standard deviation, 13.3 years]; 82 (66.7%) male). The proportion of BCG-vaccinated cases was significantly lower among severe patients than mild patients with COVID-19 pneumonia (68.5% vs 88.2%; p=.026). Mean age (54.0 $\pm$ 11.5 years vs 38.3 $\pm$10.7 years; p <.001), diabetes rate (32.6% vs 5.9%; p=.002) and low-income (84.3% vs 52.9% p<.001) are higher in patients with severe COVID-19 pneumonia than in patients with mild COVID-19 pneumonia. Multivariate logistic regression analysis showed that increasing age (odds ratio [OR], 1.112; 95% confidence interval [CI], 1.058 – 1.169; p<.001) and low income (OR, 3.369; 95% CI, 1.074 – 10.570; p =.037) are associated with severe COVID-19 pneumonia. Conclusion: Clinical data does not support that being vaccinated with BCG is associated with disease severity in COVID-19 pneumonia. Age and low-income are the major predictors for disease severity.

Introduction

The epidemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in Wuhan, China in December 2019 was identified in February 2020 by World Health Organization (WHO) as corona virus disease 2019 (COVID-19).[1,2] SARS-CoV-2 infection may appear asymptomatic or may present as mild upper respiratory tract disease, however viral pneumonia may also lead to respiratory failure.[3] While the treatment research against coronavirus pandemic continues all over the world, the group of patients with high probability of severe disease is tried to be determined.

COVID-19 mortality and morbidity rates differ disproportionately between countries to the level of measures and restrictions taken by them. It is possible that the sociocultural or lifestyle differences of citizens and the differences in the health policies of countries make surprising differences in COVID-19 epidemiology in different countries. Accordingly, factors underlying the severe epidemic in some countries are tried to be clarified. It has recently been suggested that countries' Bacillus Calmette-Guérin (BCG) vaccination policies can affect the epidemiology of COVID-19.[4] This hypothesis is mainly based on the fact that countries such as Italy, who do not have a BCG-vaccination policy, are severely affected by the COVID-19 outbreak despite implementing high-level of social isolation measures, whereas countries with immunization policy, such as Japan, were slightly affected by the outbreak, even though they did not take high level of measures.[4]

In the present study, the severity of COVID-19 pneumonia in BCG vaccinated and unvaccinated people is compared and factors associated with the severity of the disease is investigated in a country that has been running national BCG vaccination program for nearly 70 years.

Methods

Study population and data collection

This retrospective cross-sectional study was conducted in subjects who were diagnosed with COVID-19 pneumonia based on positive SARS-CoV-2 polymerase chain reaction result in combined nasal-throat swab sample and pulmonary infiltrates in computed chest tomography in a state hospital in Istanbul, Turkey between 11 March and 10 June, 2020. Study population was grouped according to severity of COVID-19 pneumonia according to Turkish Ministry of Health COVID-19 guide; 1) subjects with severe clinical condition with tachypnea ([?]30 / minute), oxygen saturation below 90% breathing room air together with bilateral diffuse pulmonary infiltrates and hospitalized, 2) subjects with mild clinical condition followed up on an outpatient basis.[5]

Sociodemographic characteristics, body-mass index, smoking history, comorbid diseases, and symptoms were recorded from the patients' files. Subjects earning minimum wage (monthly income approximately less than 355 U.S. dollar) were defined as low income. BCG vaccination history was determined based on subjects' self-declaration together with observation of vaccine scar by consultant pulmonologist.

Outcomes and measures

Main outcome of the study is comparison of BCG-vaccination status between severe and mild subjects with COVID-19 pneumonia. Secondly, sociodemographic and clinical factors that are determinant for severe COVID-19 pneumonia are evaluated.

Statistical analysis

Continuous variables were expressed as mean +- standard deviation (SD) and categorical variables were expressed as numbers (percentages). For comparisons independent Student's t-test and χ2-test were used for continuous and categorical variables, respectively. Binomial logistic regression was performed to assess association between disease severity and study parameters. All statistical tests were two-sided and a p value <.05 was considered statistically significant. The analyses were performed using Statistical Package for the Social Sciences® version 22.

Standard Protocol Approvals

The study was approved by Kartal Dr. Lütfi Kırdar Education and Research Hospital Ethics Comittee (13 May, 2020 - 2020/514/177/35).

Results

Study population consists of 123 adults aged 19-87 years, who received diagnosis of COVID-19 pneumonia in a state hospital in Istanbul, Turkey. Among study population 34 (27.6%) subjects had mild pneumonia whereas 89 (72.4%) had severe pneumonia. The number of patients vaccinated with BCG was 91 (74.0%). Sociodemographic, smoke-related, and comorbidities of subjects are summarized in Table 1. Comparison of characteristics of BCG-vaccinated and -unvaccinated COVID-19 pneumonia patients revealed that, mean age and low income rate were significantly higher in BCG-unvaccinated subjects compared to BCG-vaccinated subjects. Severe disease rate was significantly higher in BCG-unvaccinated subjects compared to BCG-vaccinated subjects (87.5% vs 67.0%; p=0.026) (Table 2). Mean age, rate of diabetes, low-income and BCG-vaccination status were the parameters differed significantly between mild and severe COVID-19 pneumonia patients (Table 3). Effects of age, gender, income, BCG-vaccination status, diabetes and hypertension on the likelihood of severe COVID-19 pneumonia were assessed with logistic regression. The logistic regression model is statistically significant, $\chi2(8) = 7.072$, p =.529 and it explains 46.0% (Nagelkerke R^2) of the variance severe disease and correctly classifies 84.6% of cases. The analysis revealed that increased age and

low-income independently predict severe disease among COVID-19 pneumonia patients. On the contrary, BCG-vaccination status is not associated with severity of COVID-19 pneumonia (Table 4).

Discussion

This is a descriptive study which aimed to investigate the characteristics of subjects with severe and mild COVID-19 pneumonia. According to the study results, BCG vaccination status is not related to clinical condition in COVID-19 pneumonia, whereas, increasing age and low-income are the factors associated with severe COVID-19 pneumonia.

BCG vaccine, a live attenuated bacterial vaccine derived from Mycobacterium bovis, is recommended in countries with a high incidence of tuberculosis.[6] Beyond immunisation against tuberculosis, BCG vaccine provides improved immune response against some viral pathogens including respiratory syncytial virus, influenza A virus and herpes simplex virus type 2. These nonspecific immune effects, known as trained immunity, occur via epigenetic reprogramming of monocytes and production of IL-1β, TNF and IL-6 during subsequent viral infection.[7] Observational studies on clinical reflection of the immunopathogenesis of BCG vaccine report that BCG vaccination and presence of a BCG scar among infants reduce the risk of respiratory tract infections.[8,9]

Countries' vaccination policies gained importance during the COVID-19 pandemic. Analyses of the relationship between countries' BCG vaccination databases and their COVID-19 statistics suggest that BCG vaccination significantly reduces COVID-19 mortality rates, and that the earlier a country establishes a BCG vaccination policy, the lower COVID-19 deaths per million inhabitants. National BCG vaccination policies are also thought to be related to flattened COVID-19 growth curves.[4,10] Another report which analyzed data of 210 countries and territories have shown that BCG-vaccination policy was associated with lower COVID-19 morbidity and mortality rates, but not with case-fatality rate. High median age, low per capita gross domestic production adjusted to purchasing power and high per capita health expenditure were found to be related to higher morbidity and mortality rates in COVID-19.[11] In Turkey, national BCG-immunisation programme has been implemented since 1953 for control of tuberculosis. BCG vaccination rates reached 94.4% in 2013.[12,13]

The study population consisted of BCG-vaccinated and -unvaccinated COVID-19 pneumonia cases in order to compare the severity of the disease in the two groups. BCG-vaccinated and -unvaccinated groups were similar in terms of body-mass index, gender distribution, smoking status and presence of diabetes and hypertension. However they were significantly different in terms of age and income; such as, BCG-unvaccinated group was significantly older compared to BCG-vaccinated group and nearly all subjects in BCG-unvaccinated group were low-income. A possible explanation for low income of people without BCG vaccination is people migrating from rural to urban areas in search of employment and earn living. As the major outcome of the study, in severe COVID-19 pneumonia patients, the rate of cases not vaccinated with BCG was significantly higher than in patients with mild COVID-19 pneumonia. However, the most important confounding factor in the study was the uneven distribution of income between the unvaccinated group and the vaccinated group. Accordingly, logistic analysis revealed that increasing age and low income level were predictive of severe disease, whereas BCG vaccination status is not related to the severity of COVID-19 pneumonia.

This is the first study to evaluate severity of clinical condition with BCG-vaccination status in COVID-19 pneumonia patients. Previous reports are based on analysis of COVID-19 statistics and countries' national BCG vaccination policies. However, international comparisons of COVID-19 epidemiology are difficult because the ways in which countries record COVID-19 cases and deaths are different depending on the polymerase chain reaction results or clinical decision. Population characteristics of countries such as population density, median age, and urban population and mainly SARS-CoV-2 test rates are major confounders that may lead to misjudgement of BCG vaccination policy is beneficial.[14] According to a report published very recently, there was no statistically significant difference in the SARS-CoV-2 positive test results between the BCG-vaccinated group and the non-vaccinated group.[15] Also in Brazil, which has been carrying out the BCG vaccination program since 1920, the morbidity and mortality rates of COVID-19 disease have reached

today's distressing levels, also questions any protective role of BCG vaccination in the COVID-19 outbreak.

Second most important finding of the present study is that increasing age and low-income are the predictors of severe disease in COVID-19 pneumonia. Age is reported as main risk factor for disease severity and mortality in COVID-19 since the beginning of the outbreak.[16-23] The relationship between low-income and serious COVID-19 emerged mainly after news that low-income minority residents were most affected, from the USA, especially New York City. According to various reports from different states non-Hispanic black patients were disproportionately hospitalized with diagnosis of COVID-19. However, the absence of any difference in intensive care unit admission and mortality rates in black patients suggests that the distinction in SARS-CoV-2 infection rates is due to socioeconomic inequalities rather than racial and ethnic differences.[24,25] In line with previous reports on the importance of socioeconomic inequalities in COVID-19, in the present study, low income was an independent predictor of severe disease.

Most prevalent comorbidities reported in serious or critically ill subjects with COVID-19 are diabetes mellitus, chronic lung disease and cardiovascular disease.[16-18,20,21] The percentage of COVID-19 cases with at least one underlying health condition was higher among those hospitalized compared to non-hospitalized.[17] Yet, data from countries may vary for different reasons, like health policies implemented in the countries, proportion of elderly population, prevalance of concomitant diseases and whether or not comorbidities are under control. Prompt measures taken by Turkish Government early in the epidemic may be the reason why comorbid disease rates were not an independent predictor of severe COVID-19 pneumonia in the present study. Because immediately after the first COVID-19 case was detected in Turkey, people with chronic illness were considered on leave in public and private sector.

The major strength of the present study is that severity of COVID-19 pneumonia is assessed in BCG vaccinated and unvaccinated inhabitants of the same country, which implements national BCG vaccination policy. Another strength of the study is that all patients are evaluated in a single center, providing homogeneity in clinical evaluation of patients. Main limitation of the study is the relatively low number of subjects. However, since BCG vaccine is administered regularly in the country, the number of individuals who have not been vaccinated is limited in the country.

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Table 1. Study population characteristics (n=123)

Age;years (mean ±SD)	49.7 ± 13.3
Gender (Male)	82 (66.7)
Body-mass index; kg/m^2 (mean ±SD)	27.1 ± 4.2
Low-income	93 (75.6)
BCG scar present	91 (74.0)
Active smoker	14 (11.4)
Comorbidities	
Diabetes mellitus	31 (25.2)
Hypertension	23 (18.7)
Coronary artery disease	4 (3.3)

Data are expressed as n (%), unless otherwise stated. SD; standard deviation.

Table 2. Comparison of characteristics of BCG-vaccinated and -unvaccinated cases with COVID-19 pneumonia (n=123)

	BCG-unvaccinated cases (n=32)	BCG-vaccinated cases (n=91)	P
Age; years (mean ±SD)	58.2 ±13.2	46.7 ± 12.1	<.001
Male gender	23 (71.9)	59 (64.8)	.467
Body-mass index; kg/m^2 (mean ±SD)	26.6 ± 2.6	27.3 ± 4.7	.437
Low income	31 (96.9)	62 (68.1)	.001
Current smoker	3 (9.4)	11 (12.1)	.678
Diabetes	10 (31.3)	21 (23.1)	.360
Hypertension	9 (28.1)	14 (15.4)	.112
Severe clinical condition	28 (87.5)	61 (67.0)	0.026

Data are expressed as n (%), unless otherwise stated. BCG; Bacillus Calmette-Guerinn.

Table 3. Comparison of characteristics of COVID-19 subjects with mild and severe disease (n=123)

	Mild (n=34)	Severe (n=89)	P
Age; years (mean ±SD)	38.3 ±10.7	54.0 ± 11.5	<.001
Male gender	22 (64.7)	60 (67.4)	.776
Body-mass index; kg/m^2 (mean ±SD)	26.8 ± 5.3	27.2 ± 3.7	.601
Low income	18 (52.9)	75 (84.3)	<.001
BCG-vaccinated	30 (88.2)	61 (68.5)	.026
Current smoker	3 (8.8)	11 (12.4)	.756
Diabetes	2 (5.9)	29 (32.6)	.002
Hypertension	3 (8.8)	20 (22.5)	.083

Data are expressed as n (%), unless otherwise stated.

Table 4. Results of Binomial Logistic Regression

	Exp (B)	95% CI for Exp (B)	P
Increased age	1.112	1.058 – 1.169	<.001
Gender	.474	.156-1.440	.188
Low income	3.369	1.074 – 10.570	.037
BCG-unvaccinated	1.024	.233 – 4.511	.975
Diabetes	.276	.050 - 1.509	.137
Hypertension	2.230	.447 – 11.111	.328

BCG; Bacillus Calmette-Guerinn.