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

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## Summary

**Background: The impact of countries' bacillus Calmette–Guérin (BCG) vaccination policies on the course of coronavirus disease (COVID-19) outbreak is a curiosity. In this study, the relationship between BCG vaccination status and severity of COVID-19 pneumonia and the factors affecting disease severity were investigated.**

**Methods: A retrospective cross-sectional study was conducted between March and June 2020 in patients diagnosed with COVID-19 pneumonia, confirmed by severe acute respiratory syndrome coronavirus-2 polymerase chain reaction positivity in a nasopharyngeal sample and pulmonary infiltrates in computed chest tomography, in a state hospital in Istanbul, Turkey. Socio-demographic features, body mass index, smoking status, concomitant diseases, income rates and BCG vaccination status of subjects were analyzed.**

**Result: The study population comprised 123 adults with COVID-19 pneumonia [mean age = 49·7 years, standard deviation = 13·3 years; 82 (66·7%) male]. While the rate of cases vaccinated with BCG is lower (68·5 *versus* 88·2%, $P = 0·026$), mean age (54·0 ± 11·5 years *versus* 38·3 ± 10·7 years; $P < 0·001$), diabetes (32·6 *versus* 5·9%, $P = 0·002$) and low income (84·3 *versus* 52·9%, $P < 0·001$) are higher in patients with severe disease compared to those with mild disease. According to multivariate analysis increasing age [odds ratio (OR) = 1·119; 95% confidence interval (CI) = 1·062–1·178, $P < 0·001$] and low income (OR = 3·209; 95% CI = 1·008–10·222, $P = 0·049$) are associated with severe disease in COVID-19 pneumonia.**

**Conclusion: This study reveals that BCG vaccination is not associated with disease severity in COVID-19 pneumonia. Age and low income are the main determinants of severe COVID-19 pneumonia.**

**Keywords:** bacillus Calmette–Guérin, COVID-19, diabetes mellitus, hypertension, income, SARS-CoV-2, severity, smoking

## Introduction

The epidemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in Wuhan, China in December 2019 was identified in February 2020 by the World Health Organization (WHO) as coronavirus 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 treatment research into the coronavirus pandemic continues globally, the group of patients with a high probability of severe disease is still to be determined.

COVID-19 mortality and morbidity rates differ disproportionately between countries regarding the level of measures and restrictions taken by them. It is possible that the socio-cultural or lifestyle differences of citizens


 

and differences in the health policies of countries are vastly different in COVID-19 epidemiology in different countries. Accordingly, factors underlying the severe epidemic in some countries need 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 a high level of social isolation measures, whereas countries with an immunization policy, such as Japan, were slightly affected by the outbreak, even though they did not take a 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 are investigated in a country that has been running a national BCG vaccination programme for nearly 70 years.

## Materials and methods

### Study population and data collection

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

Socio-demographic characteristics, body mass index, smoking history, co-morbid diseases and symptoms were recorded from the patients' files. Subjects earning a minimum wage (monthly income approximately less than $US355) were defined as low income. BCG vaccination history was determined based on subjects' self-declaration, together with observation of the vaccine scar by consultant pulmonologist.

### Outcomes and measures

The main outcome of the study is comparison of BCG-vaccination status between severe and mild subjects with COVID-19 pneumonia. Secondly, socio-demographic 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 comparison, independent Student's *t*-test and the $\chi^2$-test were used for continuous and categorical variables, respectively. Binomial logistic regression was performed to assess the association between disease severity and study parameters. All statistical tests were two-sided, and a $P$-value < 0·05 was considered statistically significant. The analyses were performed using the Statistical Package for the Social Sciences® version 22.

### Standard protocol approvals

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

## Results

The study population comprised 123 adults aged 19–87 years who received a diagnosis of COVID-19 pneumonia in a state hospital in Istanbul, Turkey. Among the study population, 34 (27·6%) subjects had mild pneumonia and 89 (72·4%) had severe pneumonia. Ninety-one (74·0%) patients were vaccinated with BCG. Socio-demographic, smoke-related and co-morbidities 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. The severe disease rate was significantly higher in BCG-unvaccinated subjects compared to BCG-vaccinated subjects (87·5 *versus* 67·0%; $P$ = 0·026) (Table 2). Mean age, rate of diabetes, low income and BCG-vaccination status parameters differed

**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) |
| Current 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.
BCG = bacille Calmette–Guérin; 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 | < 0·001 |
| Male gender | 23 (71·9) | 59 (64·8) | 0·467 |
| Body mass index; kg/m$^2$ (mean ± SD) | 26·6 ± 2·6 | 27·3 ± 4·7 | 0·437 |
| Low income | 31 (96·9) | 62 (68·1) | 0·001 |
| Current smoker | 3 (9·4) | 11 (12·1) | 0·678 |
| Diabetes | 10 (31·3) | 21 (23·1) | 0·360 |
| Hypertension | 9 (28·1) | 14 (15·4) | 0·112 |
| Coronary artery disease | 1 (3·1) | 3 (3·3) | n.a.† |
| Severe clinical condition | 28 (87·5) | 61 (67·0) | 0·026 |

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

†Statistical analysis could not be performed due to the small number of subjects.

BCG = bacillus Calmette–Guérin; n.a. = not available.

**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 | < 0·001 |
| Male gender | 22 (64·7) | 60 (67·4) | 0·776 |
| Body mass index, kg/m$^2$ (mean ± SD) | 26·8 ± 5·3 | 27·2 ± 3·7 | 0·601 |
| Low income | 18 (52·9) | 75 (84·3) | < 0·001 |
| BCG-vaccinated | 30 (88·2) | 61 (68·5) | 0·026 |
| Current smoker | 3 (8·8) | 11 (12·4) | 0·756 |
| Diabetes | 2 (5·9) | 29 (32·6) | 0·002 |
| Hypertension | 3 (8·8) | 20 (22·5) | 0·083 |
| Coronary artery disease | 1 (2·9) | 3 (3·4) | n.a.† |

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

†Statistical analysis could not be performed due to the small number of subjects.

BCG = bacillus Calmette–Guérin; SD = standard deviation.

**Table 4.** Results of binomial logistic regression

| | Exp (B) | 95% CI for Exp(B) | $P$ |
|---|---|---|---|
| Increased age | 1·119 | 1·062–1·178 | < 0·001 |
| Gender | 0·510 | 0·164–1·591 | 0·246 |
| Low income | 3·209 | 1·008–10·222 | 0·049 |
| BCG-unvaccinated | 0·995 | 0·224–4·417 | 0·994 |
| Smoking | 2·777 | 0·533–14·478 | 0·225 |
| Diabetes | 0·287 | 0·052–1·577 | 0·151 |
| Hypertension | 2·227 | 0·441–11·237 | 0·332 |

BCG = bacillus Calmette–Guérin; CI = confidence interval.

significantly between mild and severe COVID-19 pneumonia patients (Table 3). The effects of age, gender, income, BCG-vaccination status, smoking, diabetes and hypertension on the likelihood of severe COVID-19 pneumonia were examined by binary logistic regression analysis. According to the Hosmer and Lemeshow test, the intended model was found significant by including independent variables in the initial model, in which the constant term was included ($\chi^2$ = 15.397, $P$ = 0·052). As a result of the analysis, 58·8% of patients with mild COVID-19 pneumonia and 92·1% of patients with severe COVID-19 pneumonia were accurately estimated. In total, the predictive power of the model was found to be 82·9%. When independent variables are included in the analysis, the Nagelkerke $R^2$ value explains 47·3% of the change in disease severity. In the model where the dependent variable is COVID-19 pneumonia, severity odds ratio values and significance levels are given in Table 4. The analysis revealed that increased age and low income independently predict severe disease among COVID-19 pneumonia patients. In contrast, BCG-vaccination status is not associated with the severity of COVID-19 pneumonia.

## Discussion

In this study, conducted in patients with COVID-19 pneumonia, the characteristics of subjects with severe and mild disease were investigated. 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 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]. As well as immunization against tuberculosis, BCG vaccine provides an improved immune response against some viral pathogens, including respiratory syncytial virus, influenza A virus and herpes simplex virus type 2. These non-specific immune effects, known as trained immunity, occur via epigenetic reprogramming of monocytes and production of interleukin (IL)-1β, tumour necrosis factor (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 the 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 are 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 the 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, the national BCG immunization 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 the presence of diabetes and hypertension. However, they were significantly different in terms of age and income; for instance, the BCG-unvaccinated group was significantly older compared to the BCG-vaccinated group and almost all subjects in BCG-unvaccinated group were in the low-income group. A possible explanation for the low income of people without BCG vaccination is migration from rural to urban areas in search of employment and earning a 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 was the uneven distribution of income between the unvaccinated and the vaccinated groups. 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 our knowledge, to evaluate the 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 that a 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 and the non-vaccinated groups [15]. In Brazil, which has been carrying out the BCG vaccination programme since 1920, the morbidity and mortality rates of COVID-19 disease have reached today's distressing levels, and also question any protective role of BCG vaccination in the COVID-19 outbreak.

A 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 has been reported as the 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 from the United States were most affected, especially in 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 socio-economic inequalities rather than racial and ethnic differences [24,25]. In line with previous reports on the importance of socio-economic inequalities in COVID-19, in the present study low income was an independent predictor of severe disease.

Most prevalent co-morbidities 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 patients [17]. However, data from different countries may vary for vatious reasons, such as health policies implemented, the proportion of the elderly population, the prevalance of concomitant diseases and whether or not co-morbidities are under control. The prompt measures taken by the Turkish government early in the epidemic may be the reason why co-morbid 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 the public and private sectors.

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 a national BCG vaccination policy. Another strength of the study is that all patients were evaluated in a single centre, providing homogeneity in the clinical evaluation of patients. The main limitation of the study is the relatively low number of subjects. However, as BCG vaccine is administered regularly in the country, the number of individuals who have not been vaccinated is limited. Secondly, data on the clinical follow-up of patients, such as clinical recovery time, admission to the intensive care unit and mortality rate, were not evaluated because they were outside the scope of the study.

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## Disclosures

Authors have no conflicts of interest regarding the submitted work. K. A. reports personal fees from Novartis, personal fees from Astra Zeneca, personal fees from Chiesi, personal fees from Sandoz, personal fees from GlaxoSmithKline, personal fees from İbrahim Etem and personal fees from Abdi İbrahim, outside the submitted work. T. N. and P. Ö have nothing to disclose for the 3-year period prior to the date of submission. The data set used and/or analyzed during the present study is available upon reasonable request.

## Author contributions

K. A. and T. N. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. K. A. constructed the research hypothesis; K. A., T. N. and P. Ö. contributed substantially to the study design; T. N. and P. Ö. contributed substantially to data collection; K. A. and T. N. performed data analysis and interpretation. K. A, T, N. and P. Ö. substantially contributed to the writing of the manuscript. K. A., T. N. and P. Ö. approved the final manuscript.

## References

1 Phelan AL, Katz R, Gostin LO. The novel coronavirus originating in Wuhan, China: challenges for global health governance. JAMA 2020. https://doi.org/10.1001/jama.2020.1097.

2 Chan JW, Ng CK, Chan YH *et al*. Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS). Thorax 2003; **58**:686–9.

3 Chen N, Zhou M, Dong X *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; **395**:507–13.

4 Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. BioRxiv 2020. https://doi.org/10.1101/2020.03.24.20042937.

5 COVID-19 guide. Available at: https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf. (accessed 20 May 2020).

6 Summary of the WHO Position Paper on BCG vaccines: WHO position paper – February, 2018. Available at: https://www.who.int/immunization/policy/position_papers/PP_BCG_summary_2018.pdf (accessed 20 May 2020).

7 O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? Nat Rev Immunol 2020; **20**:335–7.

8 Stensballe LG, Nante E, Jensen IP *et al*. Acute lower respiratory tract infections and respiratory syncytial virus in infants in Guinea-Bissau: a beneficial effect of BCG vaccination for girls community based case–control study. Vaccine 2005; **23**:1251–7.

9 Nemes E, Geldenhuys H, Rozot V *et al*. Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination. N Engl J Med 2018; **379**:138–49.

10 Berg MK, Yu Q, Salvador CE, Melani I, Kitayama S. Mandated bacillus CalmetteGuérin (BCG) vaccination predicts flattened curves for the spread of COVID-19. MedRxiv 2020. https://doi.org/10.1101/2020.04.05.20054163.

11 Singh BR, Gandharva R, Karthikeyan R *et al*. Epidemiological determinants of acute respiratory syndrome coronavirus-2 disease pandemic and the role of the bacille-Calmette–Guerin vaccine in reducing morbidity and mortality. J Pure Appl Microbiol 2020; **14**:6224.

12 Hizel K, Maral I, Karakus R, Aktas F. The influence of BCG immunisation on tuberculin reactivity and booster effect in adults in a country with a high prevalence of tuberculosis. Clin Microbiol Infect 2004; **10**:980–3.

13 Eskiocak M, Marangoz B. Status of immunization services in Turkey. http://www.ttb.org.tr/kutuphane/turkiyede_bagisiklama.pdf. (accessed 20 May 2020).

14 Hensel J, McAndrews KM, McGrail DJ, Dowlatshahi DP, LeBleu VS, Kalluri R. Exercising caution in correlating COVID-19 incidence and mortality rates with BCG vaccination policies due to variable rates of SARS CoV-2 testing. MedRxiv 2020. https://doi.org/10.1101/2020.04.08.20056051.

15 Hamiel U, Kozer E, Youngster I. SARS-CoV-2 rates in BCG-vaccinated and unvaccinated young adults. JAMA 2020; **323**:2340–1.

16 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020. https://doi.org/10.1001/jama.2020.2648.

17 CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 - United States, February 12–March 28, 2020. Morb Mortal Wkly Rep 2020; **69**:382–6.

18 Chen T, Wu D, Chen H *et al*. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;**368**:m1091.

19 Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020. https://doi.org/10.1001/jama.2020.4683.

20 Wang D, Hu B, Hu C *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;**323**:1061–9.

21 Chen N, Zhou M, Dong X *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; **395**:507–13.

22 Verity R, Okell LC, Dorigatti I *et al*. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis 2020. https://doi.org/10.1016/S1473-3099(20)30243-7S1473-3099(20)30243-7.

23 CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) – United States, February 12–March 16, 2020. Morb Mortal Wkly Rep 2020; **69**:343–6.

24 Gold JAW, Wong KK, Szablewski CM *et al*. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19 – Georgia, March 2020. Morb Mortal Wkly Rep 2020; **69**:545–50.

25 Garg S, Kim L, Whitaker M *et al*. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019-COVID-NET, 14 States, March 1–30, 2020. Morb Mortal Wkly Rep 2020; **69**:458–64.