Pathogens and Global Health

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ypgh20

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To cite this article: Serife Torun, Sevket Ozkaya, Nazan Şen, Fikret Kanat, Irem Karaman, Sebnem Yosunkaya, Ozlem Sengoren Dikis, Ali Asan, Selma Aydogan Eroglu, Sefa Semih Atal, Omer Ayten, Nimet Aksel, Hilal Ermiş, Neslihan Özçelik, Meryem Demirelli, Iskender Kara, Sua Sümer, Kamile Marakoğlu, Fatih Üzer, Yasin Uyar, Tuba Çiçek, Zuhal E Ünsal, Husamettin Vatansev, Berna Botan Yildirim, Tuba Kuruoğlu, Aynur Atilla, Yasemin Ersoy, Bahar Kandemir, Yasemin Durduran, Fatma Goksin Cihan, Nur Demirbaş, Fatma Yıldırım, Dursun Tatar & M Sule Akcay (2021) The Relationship between COVID-19 Severity and Bacillus Calmette-Guérin (BCG)/ *Mycobacterium tuberculosis* exposure history in healthcare workers: a multi-center study, Pathogens and Global Health, 115:6, 405-411, DOI: 10.1080/20477724.2021.1927605

To link to this article: https://doi.org/10.1080/20477724.2021.1927605

Published online: 20 May 2021.

PATHOGENS AND GLOBAL HEALTH
2021, VOL. 115, NO. 6, 405–411
https://doi.org/10.1080/20477724.2021.1927605

The Relationship between COVID-19 Severity and Bacillus Calmette-Guérin (BCG)/ *Mycobacterium tuberculosis* exposure history in healthcare workers: a multi-center study

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ABSTRACT

The COVID-19 pandemic has brought countries' health services into sharp focus. It was drawn to our group's attention that healthcare workers (HCWs) had a lower mortality rate against higher COVID-19 incidence compared to the general population in Turkey. Since risk of exposure to tuberculosis bacillus among healthcare workers are higher than the population, we aimed to investigate if there is a relationship between BCG and *Mycobacterium tuberculosis* exposure history with COVID-19 severity in infected HCWs. This study was conducted with 465 infected HCWs from thirty-three hospitals to assess the relationship between COVID-19 severity (according to their hospitalization status and the presence of radiological pneumonia) and BCG and *Mycobacterium tuberculosis* exposure history. HCWs who required hospital admission had significantly higher rates of chronic diseases, radiological pneumonia, and longer working hours in the clinics. Higher rates of history of contact and care to tuberculosis patients, history of tuberculosis, and BCG vaccine were observed in hospitalized HCWs. HCWs who had radiological pneumonia had a significantly increased ratio of history of care to tuberculosis patients and a higher family history of tuberculosis. The findings from our study suggest that the lower mortality rate despite the more severe disease course seen in infected HCWs might be due to frequent exposure to tuberculosis bacillus and the mortality-reducing effects of the BCG vaccine.

KEYWORDS

COVID-19; tuberculosis; BCG; healthcare workers; pneumonia; mortality

Introduction

The novel coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China, in late December 2019 [1]. On 30 January 2020, the World Health Organization (WHO) declared a global public health emergency for the novel COVID-19 disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. Since then, the entire world has been battling with COVID-19 which can be lethal in high-risk populations. One of the most concerning aspects of COVID-19 is the seven-fold increased risk of severe disease among

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healthcare workers (HCWs), probably due to increased viral load [3].

Since the beginning of the pandemic, all efforts have been made to generate a specific and effective vaccine against SARS-CoV-2. To date, several reports have been published on the immuno-stimulant and protective role of Bacillus Calmette-Guérin (BCG) vaccine against COVID-19 [2,4,5]. Data regarding the number of patients with COVID-19 from countries with universal BCG vaccination and those who discontinued vaccination showed that the disease mortality was significantly lower in countries with universal BCG vaccination policies [4,5] Likewise, the excess mortality rates (comparison of the all-cause mortality of 2020 with the average mortality rates of the previous five years) in countries with BCG vaccination policy (such as Ireland,Portugal, Hungary) was significantly lower than countries without universal BCG policy (such as Italy, the Netherlands, Belgium,) [6,7].

As of 28 March 2021 3.8% of Turkish population had COVID-19, with the mortality rate of COVID-19 was reported to be 0.96%, compared to the 2.18% global mortality rate [5]. According to a recent report, 14.3% of confirmed COVID-19 cases in Turkey were HCWs with a case fatality rate of 0.18 [8]. It was drawn to our group's attention that HCWs had a lower mortality rate compared to the general population in Turkey, despite the higher COVID-19 incidence in this group. However, data regarding the characteristics of infected frontline HCWs are limited to draw conclusions. On the other hand, several studies analyzed the impact of BCG vaccination in COVID-19 severity, and only few studies investigated the effect of *Mycobacterium tuberculosis* exposure history. Therefore, we aimed to report the characteristics of infected HCWs and investigate the relationship between *M. tuberculosis* exposure history and BCG vaccination with COVID-19 severity in an infected HCW population. In addition, this study aimed to investigate if the *M. tuberculosis* exposure history has a similar effect on COVID-19 severity as with the BCG vaccine.

Material and methods

This study included 465 SARS-CoV-2 positive HCWs diagnosed between March 2020 – October 2020 from thirty-three hospitals to assess the correlation between COVID-19 severity and BCG and *M. tuberculosis* exposure history. Hospitalized HCWs had either severe COVID-19 which was characterized by significant hypoxia ($SpO2 < 94\%$ on room air) or more than 50% radiological lung infiltrations or hemodynamic instability [9]. Informed consent was obtained from each participant prior to participation. This protocol was approved by the relevant institutional review boards/ethical committees of Baskent University, Ankara, Turkey; approval number: [KA20/171-20/64, 1 July 2020] with respect to its scientific content. Confidentiality of the participants' information was maintained by making the information anonymous to encourage the participants to provide honest answers. In general, HCWs received their positive SARS-CoV-2 result three days after the beginning of the COVID-19 symptoms such as fever, cough, and dyspnea. HCWs with severe COVID-19 were hospitalized between day 5–7. As part of the public policy of Turkish Ministry of Health, recovered HCWs returned to work 14 day after a positive SARS-CoV-2 result.

An online platform was used to create an online questionnaire that was automatically hosted via a unique URL. The online questionnaire were applied between June 2020 – October 2020. Questions regarding demographic characteristics, medical history, family history, tuberculosis contact history, and COVID-19 course (hospitalization status and the presence of radiological pneumonia) were directed to each HCW. Password protected access to the URL link and a unique study ID gave patients around the clock access from anywhere in Turkey. Unique study ID ensured confidentiality of all self-reported data. Responses were secured using a 'Cloud' database where the data was automatically sorted, scaled, and scored using custom Excel formulas. Researchers downloaded real-time questionnaire responses in multiple formats, which were then analyzed with Statistical Package for Social Sciences (SPSS) version 17.0 . Data are reported as numbers (percentages) for binary/categorical variables and means with standard deviations for continuous variables. Chi-Square test was used to analyze the differences between categorical parameters. Mann-Whitney U test was used to analyze the differences between nonparametric scale parameters. Spearman's rho correlation analysis was used to investigate the relationship between working hours and tuberculosis related parameters. A p value < 0.05 for confidence interval (CI) of 95% was considered as statistically significant.

Results

A total of 465 SARS-CoV-2 positive HCWs completed the online questionnaire and were included in the study. The demographic characteristics of the patients according to their hospitalization status are shown in Table 1. 59% percent of the patients who were hospitalized and 53.9% of the patients who did not require hospitalization were women. The mean age of the non-hospitalized patients (34.66 years) was lower than the mean age of the hospitalized patients (39.59 years); however, the difference was not statistically significant ($p > 0.05$). Average working hours in the clinics was significantly higher in the hospitalized group ($p < 0.05$). Hospitalized HCWs reported

Table 1. Demographic characteristics of the patients according to their hospitalization status.

	Admission to hospital due to COVID-19		
	No (n = 248; % 53.3)	Yes (n = 217; % 46.7)	p
Gender, n (%)			
Female	146 (58.9)	117 (53.9)	0.282[a]
Male	102 (41.1)	100 (46.1)	
Age(Mean ± SD)	34.66 ± 8.93	39.59 ± 46.17	0.056[b]
Average time spent in the working unit(Mean ± SD)	6.42 ± 5.64	8.15 ± 7.49	0.046[b]
Workplace, n (%)			
Inpatient service	63 (25.4)	76 (35.0)	
Outpatient clinic	29 (11.7)	27 (12.4)	
Intensive care unit	33 (13.3)	34 (15.7)	0.097[a]
Emergency	16 (6.5)	13 (6.0)	
Other	34 (13.7)	25 (11.5)	
More than one unit	73 (29.4)	42 (19.4)	
Job, n (%)			
Doctor	92 (37.1)	70 (32.3)	
Nurse	95 (38.3)	84 (38.7)	0.441[a]
Other	61 (24.6)	63 (29.0)	
Presence of chronic diseases, n (%)			
No	203 (81.9)	154 (70.9)	0.007[a]
Yes	45 (18.1)	63 [29]	

a. Chi-square test, b. Mann Whitney U Test, SD: Standard Deviation

significantly higher rates of chronic diseases (29%) than patients who were treated at home (18.1%) ($p < 0.05$).

The relationship between *M. tuberculosis* exposure history and characteristics of the patients according to hospitalization status is described in Table 2. The difference between the hospitalized and non-hospitalized groups (Table 2), in terms of the presence of tuberculosis units in the institution, presence of a first-degree family member who had a history of tuberculosis, and the purified protein derivative (PPD) results were not statistically significant ($p > 0.05$). Higher rates of history of contact and care of tuberculosis patients, history of tuberculosis, and BCG vaccine were observed in hospitalized HCWs ($p < 0.05$). HCWs who required hospital admission had significantly higher rates of radiological pneumonia ($p < 0.05$). Although not significant, non-hospitalized HCWs had higher mean PPD result than hospitalized HCWs.

The difference between the patients who presented with or without radiological pneumonia (Table 3), in terms of the presence of tuberculosis unit in the institution, a history of tuberculosis, BCG scar, and PPD results was not statistically significant ($p > 0.05$). Conversely, HCWs with radiological pneumonia had a significantly increased ratio of history of care to tuberculosis patients and a higher family history of tuberculosis ($p < 0.05$). We noted that only one HCW (0.2%) died due to COVID-19.

Spearman's rho correlation analysis was applied to better understand the stratified effect of working hours, which was significantly higher among hospitalized HCWs, on tuberculosis-related parameters and COVID-19 severity (Table 4). Analysis results showed

Table 2. The relationship between *M. tuberculosis* exposure history and characteristics of the patients according to hospitalization status.

	Admission to hospital due to COVID-19*		
	No (n = 248; % 53.3)	Yes (n = 217; % 46.7)	p
Patient with tuberculosis in the institution, n (%)			
No	78 (35.5)	65 (34.0)	0.763[a]
Yes	142 (64.5)	126 (66.0)	
Tuberculosis unit in the institution, n (%)			
No	96 (41.6)	95 (47.0)	0.253[a]
Yes	135 (58.4)	107 (53.0)	
History of direct care to a tuberculosis patient, n (%)			
No	174 (75.3)	127 (64.5)	0.014[a]
Yes	57 (24.7)	70 (35.5)	
History of direct contact to a tuberculosis patient, n (%)			
No	157 (72.4)	118 (62.8)	0.039[a]
Yes	60 (27.6)	70 (37.2)	
History of tuberculosis, n (%)			
No	74 (100.0)	58 (93.5)	0.027[a]
Yes	-	4 (6.5)	
Presence of BCG Scar, n (%)			
No	32 (12.9)	12 (5.5)	0.007[a]
Yes	216 (87.1)	205 (94.5)	
History of PPD positivity, n (%)			
No	191 (77.0)	178 (82.0)	0.183[a]
Yes	57 (23.0)	39 (18.0)	
Presence of a first-degree family member who had tuberculosis, n (%)			
No	209 (88.9)	162 (82.7)	0.061[a]
Yes	26 (11.1)	34 (17.3)	
Existence of radiological pneumonia, n (%)			
No	194 (89.8)	69 (37.3)	0.001[a]
Yes	22 (10.2)	116 (62.7)	
PPD Result, Mean ± SD	10.32 ± 9.59	8.88 ± 6.95	0.477[b]

*a. Chi-square test *Since tuberculosis contact history was missing in some HCW, the tuberculosis contact history rates are given according to the ones whose information can be accessed.*

that there was a significant positive correlation between working hours and TB patients in the institution ($r = 0.133$; $p < 0.01$), history of direct care to TB patients ($r = 0.147$; $p < 0.01$), and history of direct contact with TB patients ($r = 0.144$; $p < 0.01$). A significant positive correlation was found between working hours and admission to hospital due to COVID-19 ($r = 0.094$; $p < 0.05$) and presence of radiological pneumonia ($r = 0.216$; $p < 0.01$).

Discussion

Today, the COVID-19 pandemic has brought countries' health services into sharp focus. HCWs are at an increased risk of being exposed to the SARS-CoV-2 and potentially transmit the virus to themselves and others. Turkey has one of the largest population of HCWs with 127 HCWs per 10,000 people, compared to 162 HCWs per 10,000 people in UK [10].

Data from several countries, including the UK, USA, Netherlands, and China, reported that frontline HCWs had an increased risk of reporting a positive hospital-

Table 3. The relationship between *M. tuberculosis* exposure history and characteristics of the patients according to presence of radiological pneumonia.

	Radiological pneumonia*		
	No (n = 263; % 65.6)	Yes (n = 138; % 29.7)	p
Patient with tuberculosis in the institution, n (%)			
No	81 (35.1)	39 (32.5)	0.631[a]
Yes	150 (64.9)	81 (67.5)	
Tuberculosis unit in the institution, n (%)			
No	113 (45.9)	62 (47.0)	0.847[a]
Yes	133 (54.1)	70 (53.0)	
History of direct care to a tuberculosis patient, n (%)			
No	175 (72.9)	79 (60.8)	0.016[a]
Yes	65 (27.1)	51 (39.2)	
History of direct contact to a tuberculosis patient, n (%)			
No	153 (69.5)	73 (57.9)	0.029[a]
Yes	67 (30.5)	53 (42.1)	
History of tuberculosis, n (%)			
No	71 (98.6)	40 (93.0)	0.114[a]
Yes	1 (1.4)	3 (7.0)	
Presence of BCG Scar, n (%)			
No	31 (11.8)	8 (5.8)	0.054[a]
Yes	232 (88.2)	130 (94.2)	
History of PPD positivity, n (%)			
No	205 (77.9)	108 (78.3)	0.942[a]
Yes	58 (22.1)	30 (21.7)	
Presence of a first-degree family member who had tuberculosis, n (%)			
No	221 (89.5)	97 (77.6)	0.002[a]
Yes	26 (10.5)	28 (22.4)	
Number of BCG Scar, Mean ± SD	1.37 ± 0.64	1.46 ± 0.65	0.079[b]
PPD Result, Mean ± SD	9.51 ± 7.87	10.31 ± 9.33	0.835[b]

**Since radiological pneumonia information was not available in 13.8% of the patients, the rates are given according to the ones whose information can be accessed.*

Table 4. Spearman's rho correlation analysis between working hours and tuberculosis related parameters.

	r	p
Patient with tuberculosis in the institution	0.133	0.008**
Tuberculosis unit in the institution	−0.053	0.278
History of direct care to a tuberculosis patient	0.147	0.003**
History of direct contact to a tuberculosis patient	0.144	0.004**
History of tuberculosis	−0.085	0.325
Presence of a first-degree family member who had tuberculosis	0.024	0.626
Admission to hospital due to COVID-19	0.094	0.046*
Presence of radiological pneumonia	0.216	0.000**

$*p < 0.05$ $**p < 0.01$

acquired COVID-19 test and asymptomatic SARS-CoV-2 infection [11–15]. A study of more than 72,000 patients with COVID-19 by the Chinese Center for Disease Control and Prevention showed that by early February, around 3,000 HCWs had become infected, accounting for 3.8% of all cases of COVID-19 with a case fatality ratio of 0.3%. This was approximately one sixth of the overall case fatality rate (2.3%) [16]. Similar to the results from the world, by December, more than 120,000 HCWs had become infected in Turkey, accounting for approximately 14% of all cases of COVID-19 in Turkey, with a case fatality rate of 0.18%, which was approximately one fifth of the overall case fatality rate in Turkey [8], The reasons behind the lower incidence of COVID-19 and higher mortality rate in the public population, and the lower mortality rate against the higher incidence declared in HCWs remain to be determined.

The BCG vaccine has been shown to have a strong protective effect against both upper and lower acute respiratory tract infections including COVID-19, lethal influenza A virus, and pandemic influenza (H1N1) [17], Neonatal BCG vaccine has been implemented compulsorily after 1951 in Turkey. BCG has been applied as four doses until 1997, two-doses until 2006 and one dose after 2006 [18]. The protective effect of BCG have been attributed to its role in educating the innate immune system to build a more effective immune response against related and unrelated infections. The underlying biological mechanism for this protection is consisted of epigenetic and metabolic reprogramming of innate immune system, which is known as 'trained immunity'. Independent from the adaptive immunity, BCG-induced trained immunity have been shown to prevent not only M. tuberculosis infection, but also infection with unrelated pathogens such as *Candida albicans* and *Staphylococcus aureus* [19]. Likewise, Joosten et. al. showed that *M. tuberculosis* itself can induce trained immunity, which was demonstrated by presence of CXCR3 ligands in circulating monocytes after mycobacterial infection [20]. On the contrary, Khan et al.showed that M. tuberculosis reprograms hematopoietic stem cells which impairs trained immunity response via type I interferon response [21].

On the other side, Urban et al.identified that cross-reactive heterologous cell-mediated adaptive immunity may exist between BCG-Pasteur strain proteome and peptides of SARS-CoV-2 [22]. Singh et al.brought a different perspective into the topic of "trained immunity" from Mycobacterium spp. exposure or BCG vaccination and COVID-19 outcomes, and suggested that the prevalence of tuberculin immunoreactivity – a measure of cell-mediated immunity persistence as a result of Mycobacterium spp. (including BCG vaccine) exposure of the populations – was consistently negatively correlated with COVID-19 infections and mortality [23]. They also suggested that not the countries' BCG policies but their cell-mediated tuberculin immunoreactivity prevalence should be argued when assessing the functional potentially protective trained immunity and cell-mediated immunity of a population [23]. These studies together show that immunological responses produced by tuberculosis infection and exposure to *M. tuberculosis* bacillus without an active infection (including BCG) can be different, and sometime opposite. While infection with tuberculosis bacillus might have inhibitory effects on trained immunity, tuberculin immunoreactivity as a result of *Mycobacterium* spp. (including BCG vaccine) exposure stimulates it. Therefore, the impact of *M. tuberculosis* exposure on trained and adaptive immunity and its effect on COVID-19 severity remains to be determined.

Increased exposure to an infectious tuberculosis patient might develop neither active infection nor latent tuberculosis infection, also known as early clearance (resistance to infection by innate protection). Several immune mechanisms that functionally reprogram innate immunity such as unconventional T-cell responses, higher levels of T helper type 17 cytokines which are involved in the orchestration of neutrophil responses have been implicated in the early clearers [19]. Kooken et al.suggested that trained immunity can be responsible for eliminating the mycobacteria and inducing early clearance. Likewise, we hypothesized that different parameters that increase the exposure to *M. tuberculosis* bacillus such as presence of tuberculosis unit in the hospital, direct care and contact to infectious tuberculosis patients might have an impact on functional programming of innate immunity into trained immunity through early clearance mechanisms.

Starting from this, we hypothesized that the lower mortality rate observed among HCWs might be explained by the fact that HCWs are more frequently exposed to bacterial and viral agents, such as *Mycobacterium tuberculosis*, than the general public. In addition, several reports published about the protective role of BCG against COVID-19 raised our idea if *M. tuberculosis* exposure history and BCG have similar effects on COVID-19 severity [24]. Therefore, we investigated the relationship between COVID-19 severity and *M. tuberculosis* exposure and BCG history.

Our investigation showed that hospitalized HCWs reported significantly higher rates of history of direct care and direct contact with patients with tuberculosis, history of tuberculosis, and BCG scar. In addition, although not significant, non-hospitalized HCWs had higher mean PPD result than hospitalized HCWs. Patients with radiological pneumonia also reported significantly higher rates of history of direct care and direct contact with patients with tuberculosis and a family history of tuberculosis. Although those parameters such as history of direct care and contact with tuberculosis patients, or having a family history of tuberculosis might not imply an actual immune response to *Mycobacterium tuberculosis*, they might indicate a mechanism for trained immunity triggered by early clearance.

Here, we concluded that not a history of tuberculosis, but a history of contact with tuberculosis patients is associated with increased hospital admission, increased rates of radiological infiltrations and increased severity of the COVID-19 course, possibly due to overstimulation of trained immunity that was gained through early clearance phenomenon. Similarly, BCG-induced trained immunity was associated with increased hospitalization rate and radiological infiltrations in HCWs with COVID-19. Therefore, the theoretical possibility of induction of trained immmunity might have deleterious effects by boosting or inhibiting innate immune responses needs to be considered in those patients [25]. Here, the observation of potential increased severity of COVID-19 course with lower mortality is paradoxical, however, it might be related with the context of trained immunity. While trained immunity improves the anti-viral host defense, it may also strongly induce inflammatory Th1/Th17 response and lead to systemic inflammation, which is associated with severe COVID-19 course [25].

Several contradictory studies have been published about the potential association between the incidence and severity of COVID-19 and BCG and *M. tuberculosis* exposure history. This might be in part due to different impacts of BCG and tuberculosis infection on trained immunity. Liu et al.reported that a history of tuberculosis affects susceptibility to the SARS-CoV-2 and can increase disease severity [26]. A comprehensive meta-analysis by Gao et al.revealed that the prevalence of tuberculosis history may be a risk factor for disease progression and that patients with preexisting tuberculosis have a higher chance of developing serious complications from COVID-19 [27]. Another recent study by Rivas et al.concluded that a history of BCG vaccination is associated with decreased frequency of SARS-CoV-2 infection, decreased 'self-report' of COVID-19 related symptoms and diagnosis; however, it was also found to be associated with decreased anti-SARS-CoV-2 IgG seroprevelance, which might explain the increased disease severity seen in this population [28]. In a small cohort from Rhode Island, USA, C-H Weng et al.reported that individuals with BCG vaccination were less likely to require hospital admission during the COVID-19 course, supporting the potential of BCG in preventing more severe COVID-19 [29]. M. Levi et al.stated that mass screening interventions for SARS-CoV-2 infections among HCWs revealed an inverse association between being an HCW and the risk of developing a severe form of COVID-19. They demonstrated that BCG vaccination might provide protection against severe forms of COVID-19; however, they also suggested that being an HCW should be considered as an effect modifier for the association between BCG vaccination and COVID-19 outcomes [30]. In this study, we have concluded that increased frequency of contact with patients with tuberculosis, as well as previous tuberculosis infection might result in a similar effect with BCG vaccination, which induces trained immunity and produces stronger response upon restimulation by nonspecific boosters.

To the best of our knowledge, this is the first clinical study to investigate the characteristics and relationship between *M. tuberculosis* exposure history and COVID-19 severity among infected HCWs. However, we are aware that this observational study is limited to fully support the aforementioned conclusion. In our study, important biases related to observational studies exist, such as different working hours and working units of HCWs, compared to randomized clinical trials. It seems paradoxical that BCG and a history of exposure in a tuberculosis unit may increase the requirement for hospitalization on one side, but reduce the mortality on the other. Some hypotheses that can explain why HCWs have a lower case fatality ratio against a higher incidence includes easier access to testing, increased use of personal protective equipment (PPE), and smaller infection dose related to the increased use of PPE. Additional biases in healthcare workers that can account for a diminished severity compared to general population include a lower age (working population vs general population), health status, and increased accessibility to healthcare. On the other hand,the finding that average working hours in clinics was significantly higher in the hospitalized group suggests that the viral load and exposure intensity can be related to COVID-19 severity, which is a confounder in this context. Another limitation of this study is the absence of a sub-analysis with different age groups in order to minimize the effect of different BCG vaccination rates in different age groups as a confounder. In addition, the duration of work life as a HCW might influence the chance and rate of exposure to tuberculosis bacillus during their work life, since hospitalized HCWs were on average 5 years older and had about a 33.6% higher chance of exposure than those who did not require hospitalization. Therefore, further in-depth studies and sub-analysis are needed to provide stronger evidence for such an association.

In conclusion, although COVID-19 risk and incidence are higher among HCWs compared to the normal population, the lower mortality rate and increased severity of disease course (characterized by increased hospitalization rates and radiological pneumonia) seen in infected HCWs might be due to frequent exposure to tuberculosis bacillus and the mortality-reducing effects of the BCG vaccine. Further large scale descriptive research might help documenting this potential association.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

Data Availability

The research article data that used to support the findings of this study is available from the corresponding author upon request.

Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the author(s).

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