



## Tuberculosis Incidence and COVID-19-Related Mortality Rates in 20 Countries: An ecological study

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### ABSTRACT

**Background:** On 31<sup>st</sup> December 2019, the China Country Office of the World Health Organization (WHO) reported cases of pneumonia of unknown etiology in the city of Wuhan in the province of Hubei. On 7<sup>th</sup> January, 2020, the agent was described as a novel coronavirus (SARS-CoV-2) not previously detected in humans. **Objectives:** The aim of this study was to investigate the difference in the severity of the disease among various countries, in terms of the mechanism caused by SARS-CoV-2 in cellular immunity. **Method:** Countries with the highest numbers of coronavirus disease 2019 (COVID-19) cases as of July 2020 according to WHO data (USA, Brazil, India, Russia, the United Kingdom, Peru, Chile, Spain, Mexico, Iran, Pakistan, Italy, South Africa, Saudi Arabia, Turkey, Germany, France, Bangladesh, Colombia, and Canada) were included in the study. The average incidence of tuberculosis (TB) in the previous five years in these countries were then correlated with COVID-19-related mortality rates. **Results:** Correlation analysis revealed a negative, moderate relationship between COVID-19-related mortality and TB rates in the general population and in individuals over the age of 65 ( $r=-0.466$ ,  $p=0.038$  and  $r=-0.521$ ,  $p=0.018$ , respectively). **Conclusions:** COVID-19-related mortality rates were low in those countries in which the incidence of TB was high, thus highlighting the importance of investigating the immunology of the virus in determining the severity of the disease.

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### INTRODUCTION

When some pneumonia cases, the origin of which could not be identified, occurred in the city of Wuhan in China in December 2019, samples were taken and it was confirmed that this infection originated from a novel coronavirus which had been detected neither in humans nor in animals before. Later, this novel coronavirus was named as 2019 coronavirus disease (COVID-19) by WHO.<sup>1</sup> As of the end of July 2020, it caused more than thirteen million cases and over

570 thousand deaths worldwide.<sup>2</sup> According to WHO COVID-19 report on People's Republic of China, deaths were observed in individuals in older ages or with concomitant systemic diseases (hypertension, diabetes, cardiovascular diseases, cancer, and other immunosuppressive cases, particularly chronic lung diseases).<sup>1</sup> The different number of cases and differing rates of mortality in almost all countries has made it necessary to identify the source of such differences.

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Pneumonia cases of unknown origin first began appearing in the city of Wuhan in China in December 2019. Samples were collected, and analysis confirmed that this infection originated from a novel coronavirus not previously detected in animals or humans. This novel coronavirus was subsequently named 2019 coronavirus disease (COVID-19) by the World Health Organization (WHO).<sup>1</sup> By the end of July 2020, it had resulted in more than 13 million cases and over 570,000 deaths worldwide.<sup>2</sup> According to a WHO COVID-19 report on the People's Republic of China, deaths were observed in older individuals or with concomitant systemic diseases (hypertension, diabetes, cardiovascular diseases, cancer, and other immunosuppressive cases, particularly chronic lung diseases).<sup>1</sup> The differing numbers of cases and mortality rates in almost all countries has made it essential to identify the source of this variation.

Tuberculosis (TB) is an intracellular infection which can be controlled through the cellular immune response. Cellular immunity is provided by macrophages, dendritic cells, cytokines, and T lymphocytes.<sup>3</sup> The intracellular immune response in TB starts with the presentation of antigens belonging to *M. tuberculosis* to T lymphocytes over major histocompatibility complex (MHC)-I/II or cluster of designation (CD) molecules of macrophages or dendritic cells. It develops by means of lymphocytes recognizing specific antigens, proliferating, and differentiating as effector cells.<sup>4,5</sup> Innate and adaptive immune responses can be triggered by SARS-CoV-2 infection. However, both local and systemic tissue damage can result from uncontrolled inflammatory innate responses and impaired adaptive immune responses. In contrast to patients with mild COVID-19, lymphopenia characterized by drastically reduced numbers of CD4<sup>+</sup>T cells (helper T cells), CD8<sup>+</sup>T cells (CD8 T lymphocytes), B cells (B lymphocytes), and natural killer (NK) cells in addition to diminished proportions of monocytes, eosinophils and basophils is commonly observed in patients with severe Covid-19.<sup>6,7</sup>

In addition, exhaustion markers, such as natural killer (NK) cell receptor NKG2A on cytotoxic lymphocytes, including NK cells and CD8<sup>+</sup>T cells, are upregulated in patients with COVID-19. The numbers of CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, B cells, and NK cells and markers of exhaustion on cytotoxic lymphocytes subsequently normalize in recovered or convalescing patients.

Direct cytopathic effects and host immune responses caused by SARS-CoV-2 virus are thought to play a significant role in the severity of the disease.<sup>8</sup> The differentiation of naïve CD4<sup>+</sup>T cells into effector and memory subtypes is one of the essential aspects of immunity mediated by T cells.<sup>9</sup> The balance between naïve and memory CD4<sup>+</sup>T cells is critical for the maintenance of an effective immune response.

TB and COVID-19 infections which share a common pathway with cellular immunity are believed to affect the severity of the other through various mechanisms. This study was planned in the light of the differences in the rate of COVID-19-related deaths and the differences between TB incidences in different countries. The purpose of this study was to examine the relationship between TB incidences and COVID-19-related mortality in different countries.

## METHOD

The countries with the highest numbers of COVID-19 cases as of July 2020 based on WHO data (USA, Brazil, India, Russia, the United Kingdom, Peru, Chile, Spain, Mexico, Iran, Pakistan, Italy, South Africa, Saudi Arabia, Turkey, Germany, France, Bangladesh, Colombia, and Canada) were included in this ecological study. The average incidences of tuberculosis (TB) in the previous five years in these countries were then correlated with COVID-19 related mortality rates.

COVID-19-related mortality rates at the time of writing of this paper were obtained from <https://covid19info.live/>.<sup>11</sup>

The TB incidences in the countries included in the study were retrieved from <https://www.who.int/TB/country/data/profiles>, on which the WHO publishes global TB reports.<sup>12</sup> The average incidences of TB in the previous five years in the countries included in the study were correlated with their COVID-19-related mortality rates.

## Statistical Analysis

Statistical analysis was performed on SPSS 23.0 software. Spearman's correlation test was applied to measure relationships between values.

## Results

TB incidences, TB incidences in individuals over the age of 65, the average TB incidence in the previous five years, and COVID-19-related mortality rates in the 20 countries included in the study (USA, Brazil, India, Russia, the United Kingdom, Peru, Chile, Spain, Mexico, Iran, Pakistan, Italy, South Africa, Saudi Arabia, Turkey, Germany, France, Bangladesh, Colombia, and Canada) are presented in Table 1.

**Table 1: Countries’ tuberculosis incidences and rates and mortality rates associated with COVID-19 (rate per 100,000 population per year)**

Country	2018 TB rate	2017 TB rate	2016 TB rate	2015 TB rate	2014 TB rate	TB incidence over the age of 65 in 2018	Average incidence of TB in the last 5 years	Mortality rate related to COVID-19
USA	3	3.1	3.1	3.2	3.2	4.86	3.12	4.1
Brazil	45	44	42	41	44	50.29	43.2	3.9
India	199	204	211	217	167	275.14	199.6	2.6
Russia	54	60	66	80	84	26.6	68.8	1.6
Untd. Kingdom	8	8.9	9.9	10	12	6.8	9.76	13.9
Peru	123	116	117	119	120	197.1	119	3.6
Chile	2.2	17	16	16	16	319.5	13.44	2.2
Spain	9.4	10	10	12	12	10.83	10.68	9.6
Mexico	23	22	22	21	21	881.04	21.8	11.8
Iran	14	14	14	16	22	58.8	16	5
Pakistan	265	267	268	270	270	1070.7	268	2.1
Italy	7	6.9	6.1	5.8	6	5.3	6.36	3.6
South Africa	520	567	781	834	834	819.9	707.2	1.5
Saudi Arabia	10	10	10	12	12	471.99	10.8	1
Turkey	16	17	18	18	20	38.66	17.8	2.5
Germany	7.3	7.4	8	8	6.1	5.62	7.36	4.6
France	8.9	8	7.7	8.2	8.7	7.6	8.3	15.1
Bangladesh	221	221	221	221	221	684.81	221	1.3
Colombia	33	33	32	31	33	72.51	32.4	3.6
Canada	5.6	5.6	5.5	5.2	5.1	8.3	5.4	8.1

**Table 2: Relationships between COVID-19 mortality rates and average incidences of TB in the previous five years and the incidence in individuals over 65**

	COVID-19 mortality rate
Tuberculosis rate*	r= -0.654 p=0.002
Tuberculosis rate over 65 years of age	r= -0.627 p=0.003

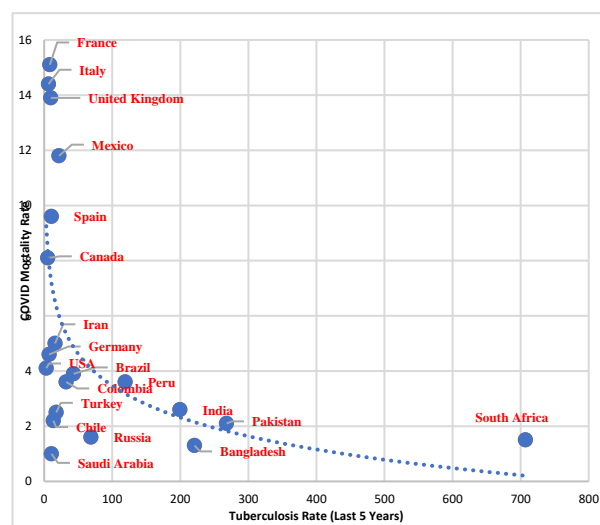
\*: average TB rate in the last 5 years

Examination of the figure showing the distribution of COVID-19 mortality rates and TB rates in the previous years revealed high TB rates in South Africa and Pakistan, while France and Italy had high COVID-19 mortality rates.

The relationship between the average TB incidences and COVID-19-related mortality rates in the different countries is shown in Table 2. A negative moderate relationship was determined between COVID-19-related mortality rates and TB rates and with TB rates in individuals over 65 (r=-0.654, p=0.002; r=-0.627, p=0.003, respectively). The distribution of COVID-19 related mortality rates and TB incidences is presented in Figure 1.

**DISCUSSION**

This study was planned in the light of the differences observed in mortality rates related to the COVID-19 pandemic. Cytopathic effects caused by the SARS-CoV-2 virus and the effectiveness of the host cellular



**Figure 1: Countries’ COVID-19 mortality rates and distribution of average TB incidences in the previous five years**

immune response play a significant role in the severity of the disease.<sup>13</sup> Moderate negative correlation was observed in the present study between the average TB incidence in the previous five years and COVID-19-related mortality rates in the 20 countries with populations exceeding 10 million with the highest numbers of COVID-19 cases worldwide.

As micro bacteria proliferate, macrophage and dendritic cells infected with M. tuberculosis secrete cytokines and chemokines, such as tumor necrosis factor a (TNF-a) and interleukin (IL)-1, IL-12, and IL-

18 that permit migration of phagocytes and T lymphocytes to the infected site and cause granuloma to form, thereby developing a specific inflammatory response and activating further macrophages and dendritic cells.

Macrophages and dendritic cells recognize *M. tuberculosis* through Toll-like receptors (TLRs) and pathogen recognition receptors such as nucleotide-binding oligomerization domain-containing protein 2 (NOD2). After antigens belonging to *M. tuberculosis* are presented to CD4<sup>+</sup>TH or CD8<sup>+</sup>Tc lymphocytes by macrophages or dendritic cells, as a result of interferon gamma (IFN- $\gamma$ ) generation and adaptive immunity, a tuberculin-induced delayed-type hypersensitivity reaction that can be detected with tuberculin test and cellular immunity also develops.

Immune system suppressing follicular helper T cells (THF-B) and IL-10, immune system protecting tumor necrosis factor B (TNF-b), IL-12, IL-2, TNF-a, natural killer (NK) cells and cytokines activating CD8 are secreted from macrophages infected with *M. tuberculosis*. Of the secreted cytokines, tumor growth factor B (TGF-B), IL-6, and IL-23 trigger the differentiation of CD4 cells into Th17 and the secretion of IL-17, IL-21, and IL-22. In contrast, IL-12 and IL-18 trigger Th1 formation and IFN- $\gamma$ , TNF-a, IL-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF) secretion.<sup>14</sup> These mediators acquired after recovery from TB infection can provide protection against the development of new infections.

In addition, "trained immunity", a subject of particular interest in recent years, is induced after primary infection or inoculation. T / B cells provide protection against secondary infection through mechanisms independent of adaptive responses. Macrophages and NK cells are involved in this type of immunity, and since its pathogen recognition system is not as specific as acquired immunity, it has been suggested that it can provide protection against cross-infections.<sup>15</sup>

The negative relationship identified in this study can be considered from a different perspective with Bacillus Calmette-Guérin (BCG) vaccine. The immunological response of the vaccine obtained from a live strain of *Mycobacterium bovis* is similar to that of the TB bacillus.<sup>16</sup> Important evidence showing that BCG protects the host against certain viral pathogens has been elicited by experimental studies showing that BCG provides protection against DNA and RNA viruses, including herpes and influenza. It has been argued that BCG mediates

these effects through the induction of innate immunity memory and heterologous lymphocyte activation, and that this mechanism causes an increase in cytokine production, macrophage activity, T cell responses, and antibody titers.<sup>17</sup>

Ritz et al. compared geometric mean concentrations of Anti-HBs IgG in newborns inoculated and not inoculated with BCG. Those authors concluded that BCG vaccination at birth positively affected antibody responses to routine vaccinations applied in later periods of infancy.<sup>18</sup>

Lymphopenia, CD4<sup>+</sup>T cells, CD8<sup>+</sup>T cells, B cells and NK cells have been reported to decrease significantly in patients with severe Covid-19 disease (the percentages of monocytes, eosinophils, and basophils also decreased.) An increase in neutrophil numbers and the neutrophil-lymphocyte ratio generally indicates a high severity of disease and poor clinical outcomes. Increased exhaustion indicators such as NKG2A on cytotoxic lymphocytes including NK cells and CD8<sup>+</sup>T cells have also been determined in COVID-19 patients. A significant increase in serum levels of pro-inflammatory cytokines including IL-6, IL-1 $\beta$ , IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, monocyte chemoattractant protein-1 (MCP1), methylisopropyllysergamide (MIPl), and TNF is observed in the majority of patients with severe Covid-19. C-reactive protein and D-dimer elevation have also been seen.<sup>19</sup>

Cytotoxic lymphocytes such as T lymphocytes and NK cells are essential for controlling viral infection, and the functional exhaustion of cytotoxic lymphocytes is associated with the progression of the disease. The function of NK and CD8<sup>+</sup>T cells is exhausted by increased NKG2A expression in COVID-19 patients. A comparison of the amount of NKG2A synthesis in patients infected with SARS CoV2 with that in healthy adults revealed a significant increase on NK and CD8<sup>+</sup>T cells. This strongly suggests that NKG2A expression may be associated with functional exhaustion in the early stages of COVID-19 and during the progression of the disease.<sup>20</sup>

A comparison of COVID-19 related mortality rates in the 20 countries with the highest numbers of cases to date with the global TB report issued by the WHO including TB incidences in those countries in the previous five years shows that our study is consistent and realistic.

Prognostic bio-indicators for patients at risk of developing acute respiratory distress syndrome (ARDS) and multiple organ failure need to be identified in the fight against COVID-19. Age (65

years and above) has emerged as an independent risk factor for severe disease, and this has led to concerns about the feasibility of developing a strong vaccine capable of inducing effective cellular and humoral responses in this population.<sup>19</sup> Identification of immunopathology in determining the severity of the disease and better understanding of SARS-CoV-2 immunity-avoidance mechanisms may provide clues to the clinical management of severe cases.

**Limitations:** Since this research was an ecological study, other factors affecting mortality rates due to COVID-19 were not included in the analysis.

## CONCLUSION

The differences in the severity of the disease among countries during the current pandemic can be explained in terms of the mechanisms created by SARS-CoV-2 in cellular immunity. The similarities of these mechanisms with the TB bacillus shed light on the present study. Our finding that COVID-19 related mortality rates are low in those countries in which TB incidences are high emphasizes the importance of investigating the immunopathology of the virus in determining the severity of the disease.

## Ethical Approval

Approval for this study was granted by the Ethics Committee of the Recep Tayyip Erdogan University Faculty of Medicine under protocol number 2020/67.

## Conflict of Interest

None declared by the authors.

## Financial Disclosure

None declared by the authors.

## Data Availability Statement

The data sets that were created and examined during the current study are available on request from the corresponding author.

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