Original Article

Co-infection of COVID-19 and Tuberculosis

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Abstract

OBJECTIVE: Tuberculosis and COVID-19 diseases occur more frequently in people with similar risk factors. This study aimed to share the data on active tuberculosis patients during the severe acute respiratory syndrome coronavirus 2 pandemic.

MATERIAL AND METHODS: The registration information of TB outpatient clinic between November 1, 2019, and April 20, 2020, was screened. A 7-question survey was administered to the patients who were diagnosed with active tuberculosis and who were agreed to participate in the study.

RESULTS: A total of 309 patients with active tuberculosis were evaluated, the average age of the patients was 42.5 ± 18.5 years, and 70% were male. The percentage of having at least 1 comorbidity was 30.4%. The percentage of coronavirus disease 2019 disease in our study population was 1.9%; none of the patients of coronavirus disease 2019 were taken into the intensive care unit or dead due to clinical deterioration and/or respiratory failure. On the other hand, in this process it was announced that 146 457 cases were diagnosed with coronavirus disease 2019 throughout the country, of which 72% had inpatient treatment, 2% died, and 944 patients were still being treated in the intensive care unit, of which 490 were intubated. The positivity ratio of the reverse transcription-polymerase chain reaction test was 20.0% in the study group, while 20.3% in the İstanbul population.

CONCLUSION: Tuberculosis patients might be more disadvantageous than the normal population in terms of the risk of exposure to severe acute respiratory syndrome coronavirus 2, but this does not cause an increase in the frequency and severity of coronavirus disease 2019 disease in active tuberculosis patients.

KEYWORDS: Coronavirus, pandemic, rifampicin, SARS-CoV-2, treatment
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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The disease, which was first identified in the Wuhan province of China's Hubei region, in 2019, has since spread rapidly, evolving into the COVID-19 pandemic.[2] To date, no effective vaccine against the virus and/or a drug with proven efficacy in the treatment of the disease has been found, so the virus continues to adversely affect the world and to be the cause of death for increasing numbers of people. Moreover, the treatments to reduce the severity of the infection are mostly limited to supportive strategies to prevent complications from coronavirus infection.[3] Negative results and death are more common in the elderly and those with accompanying comorbidity (50%-75% of fatal cases).[4,5] It is important to identify the risk factors to prevent the development of serious or critical COVID-19 forms in people considered to be at high risk, and further data are needed to clarify its relationship with other diseases besides the known risk factors and to reduce the severity of the disease.

To date, only a few studies have been conducted investigating the association of tuberculosis (TB) with COVID-19.[6,7] A recently published study reported that *Mycobacterium tuberculosis* infection (MTB) is a risk factor for SARS-CoV-2 infection and severe COVID-19 pneumonia.[8] Emphasizing the importance of the coexistence of these 2 diseases, World Health Organization (WHO) recommended to routinely check MTB infection status in patients with COVID-19.[9] TB is caused by *M. tuberculosis*, a type of bacteria, while COVID-19 is caused by a coronavirus. However, the primary target organ of both is the lungs, and they are similar in symptoms (i.e., cough, fever, weakness, and dyspnea).[10-12] The fact that diseases caused by both occur more frequently in people with similar living conditions (such as crowded population and poor ventilation[13]) and risk factors (malnutrition,[14] immunosuppressive drug use,[15] cancer,[16] diabetes,[17] kidney disease,[18] and chronic obstructive respiratory disease[19]) supports this idea. Especially, it seems reasonable to think that TB might be a risk factor for severe COVID-19 pneumonia during the active disease period (where the person's immune system is the weakest).

Tuberculosis remains to be 1 of the top 10 causes of deaths worldwide. In the 2019 TB report, the WHO reported that about 10 million people were infected with TB, and 1.5 million died.[20] This indicates the importance of clarifying TB's

relationship with SARS-CoV-2 infection. According to the last statistics published by the General Directorate of Public Health in 2018, of 11 786 patients diagnosed with TB in all Turkey (2018 country population 82 003 882, incidence rate 14.1 per 100 thousand), 30% (n = 3528) were living in İstanbul (2018 İstanbul population 15 067 724, incidence rate 23.4 per 100 thousand).[21]

The purpose of this study is to examine the status of active TB patients under therapy in the pandemic and to investigate the effect of TB on the severity of COVID-19 disease.

MATERIAL AND METHODS

The registration information of the patients who applied to our TB Outpatient Clinic between November 1, 2019 and April 20, 2020, was screened. Patients who were diagnosed with active TB and under first-line drug therapy were identified, regardless of the location of the disease (lung, pleura, or lymph node) (Figure 1), and patients were interviewed using the phone number obtained from the hospital information system. The starting date of the phone call was set as April 30, and the deadline was May 15. A 7-question survey was administered to the patients in addition to age, gender, history of smoking, and comorbidities. In our country, for COVID-19 disease rates, the number of cases declared by the Ministry of Health on May 15, 2020, was taken as reference.

The study was approved by the Clinical Research Ethics Committee of the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Training and Research Hospital of Health Education University (No: 2260, May 8, 2020). Since the study was carried out by phone call, the written informed consent was omitted due to the nature of the study, and verbal consent was taken because it was inconvenient for patients to come to the hospital due to the risk of transmission.

Inclusion Criteria
Male and female patients over 15 years of age; Patients whose first-line anti-TB treatment was continuing during the COVID-19 pandemic; Patients who agreed to answer questions by phone.

Exclusion Criteria: Patients found to have no active TB in their microbiological, clinical, and radiological examinations; Patients receiving anti-TB drug treatment other than first-line drugs due to drug resistance; Patients who have completed TB treatment and applied only for control.

Questions Addressed to Patients
First of all, patients' verbal consent was taken, and those who agreed to participate in the clinical research were asked to answer the following questions.

1. When was your TB treatment started?
2. Do you use your TB drugs regularly?
3. Did you and/or any of your family members travel abroad? Or have you met someone from your immediate surroundings who have traveled to these countries?
4. Did you have close contact with someone suspected or proven to be SARS-CoV-2 infected?
5. Has the COVID-19 test been performed to you or your immediate surroundings? If so, why?
6. Did you or any of your family members apply to a healthcare facility with the symptoms seen in COVID-19 disease (fever, cough, weakness, shortness of breath, loss of sense of taste, and/or smell, etc.)? If any treatment was started, was it applied in an outpatient or inpatient setting?
7. Do you have any disease other than TB?

Statistical Analysis
The Statistical Package for Social Sciences, version 15.0 software (SPSS Inc.; Chicago,IL, USA). Descriptive statistics were given as numbers and percentages for categorical variables, as mean, standard deviation, minimum, and maximum for numerical variables. The data were not normally distributed; thus, the Mann-Whitney U-test was used in the comparison of numerical variables in independent groups. The numbers in the groups were compared by chi-square analysis. The significance level was taken as $P < .05$.

RESULTS

In total, 653 patients who applied to the TB outpatient clinic, 541 were diagnosed with active TB and under first-line drug therapy; of these, 309 patients who could have been reached by telephone constituted the patient population of the study. The reasons for excluding the patients (n = 232) from the study were shown in the chart (Figure 1).

The average age of the patients included in the study was 42.5 ± 18.5 (16-91) years, 70% were male; the age of 21% was ≥60 (Table 1). The average duration of TB treatment was 135.9 ± 49.5 (15-240) days (until the day of the interview with patients) and history of smoking 31.7%.

The percentage of having at least 1 comorbidity was 30.4% (n = 94) (Table 1); 14.9% had diabetes, 9.7% had hypertension, 11% had chronic obstructive pulmonary disease (COPD or asthma), 4.9% had heart disease, and 2.6% had malignancy.

MAIN POINTS

*   In order to prevent the development of severe coronavirus disease 2019 (COVID-19) forms, it is needed to clarify the relationship with other diseases as well as to determine the risk factors.
*   Experience providing information on the simultaneous course of tuberculosis (TB) and COVID-19 is extremely limited.
*   *Mycobacterium tuberculosis* and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occur more frequently in people with similar living conditions and risk factors.
*   Tuberculosis (TB) patients might be more disadvantageous than the normal population in terms of the risk of exposure to SARS-CoV-2. In spite of that, this did not cause an increase in the frequency and severity of COVID-19 disease in active TB patients under first-line drug therapy.
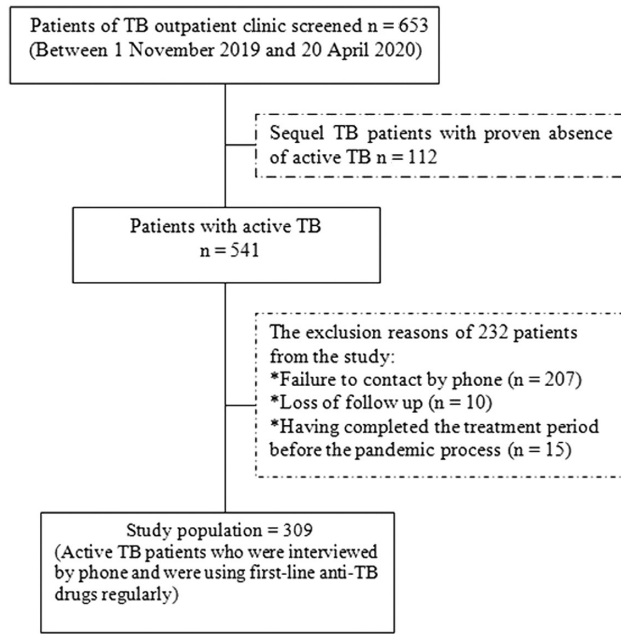
Figure 1. Study flowchart.

The number of patients diagnosed with COVID-19 was 6 (1.9%), of which 4 had positive test results. Two other patients with negative test results were clinically and radiologically diagnosed with COVID-19 pneumonia. The average age of these patients, 1 female and 5 male, was 38 ± 13.5 years (23-66 years). In descending order, COVID-19 symptoms were cough (83.3%), fatigue (66.6%), fever (50%), myalgia/arthralgia (50%), and hypoxemia (16.6%) (Table 1). One of 6 patients had inpatient treatment because of being hypoxemic; the others had outpatient treatment. After the treatment, the reverse transcription-polymerase chain reaction (RT-PCR) test of the patients was found to be negative on 2 occasions.

Regarding the 6 patients diagnosed with COVID-19, the severity of the disease was not worsened, and no intensive care treatment or death was observed. Only 1 patient had been hospitalized for COVID-19 pneumonia because of coursing with hypoxia. Whereas, according to the report of the Ministry of Health dated May 15, 2020, indicate that there were 146 457 confirmed cases in Turkey, of which 106 133 (72%) had inpatient treatment, 944 patients were still being treated in the intensive care unit, of which 490 were intubated and 4055 (2%) people lost their lives because of COVID-19.[22] Considering the number of cases verified by RT-PCR test as a reference, the positivity ratio of the tests performed was 20% in the study group, while in the same period, it was 20.3% in the İstanbul province (number of people tested 468 268, number of positive people 95 211) and 9.5% in overall Turkey (total number of tests 1 547 389, with a positive of 146 457).[22]

The total number of patients with COVID-19 radiological findings was 3 (50%); of them, one's RT-PCR test was positive, and the other two's tests were negative. Seventeen of the TB patients who underwent RT-PCR tests had a long-term history of close contact with people at risk of infection (living in the same house or meeting with others). No statistically significant

Table 1. Demographic and Clinical Characteristics of 309 Active Tuberculosis Patients

	Mean ± SD (Min-Max)	
Duration of TB treatment	135.9 ± 49.5 (15-240)	
Age	42.5 ± 18.5 (16-91)	
	n	%
Gender		
Male	216	69.9
Female	93	30.1
Smoking	98	31.7
Comorbidity	97	31.4
HT	30	9.7
DM	46	14.9
COPD/asthma	34	11.0
Heart disease	15	4.9
Malignancy	8	2.6
Received COVID-19 treatment	6	1.9
COVID-19 symptoms	5	83.3
Weakness	4	66.6
Cough	5	83.3
Fever	3	50
Myalgia/arthralgia	3	50
Hypoxemia	1	16.6
COVID-19 radiological finding	3	50
Contact with people at risk of infection	17	5.5
RT-PCR test	20	6.5
Positive	4	20.0
Negative	16	80.0

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HT, hypertension; RT-PCR, reverse transcription polymerase chain reaction.

difference was observed in co-infected COVID-19 patients' characteristics according to age, whereas 5 of 6 patients diagnosed with COVID-19 were under 60 years old (as shown in Table 2). Regarding the occurrence of comorbidities, it was statistically significantly higher in ≥60 patients for all diseases (*P* < .001) (as shown in Table 2).

DISCUSSION

To the best of our knowledge, this is the first report examining the relationship between active TB patients under first-line drug therapy with COVID-19. In spite of the number of cases in our study is small, the results of the this study are important as it shows that TB does not cause an increase in the risk of COVID-19 compared to the normal population and does not cause severe and/or fatal forms of COVID-19.

Although both infectious diseases are more common in people with similar risk factors, COVID-19 co-infection was

Table 2. Characteristics of 6 COVID-19 Patients According to Age

| | <60 Years | | ≥60 Years | | |
| | Mean ± SD (Min-Max) | | Mean ± SD (Min-Max) | | |
	n	%	n	%	P
Gender					
Male	173	70.9	43	66.2	.458
Female	71	29.1	22	33.8	
Smoking	2	0.8	0	0.0	
Comorbidity	51	20.9	43	66.2	<.001
HT	14	5.7	16	24.6	<.001
DM	33	13.5	13	20.0	.192
COPD/asthma	12	4.9	22	33.8	<.001
Heart disease	2	0.8	13	20.0	<.001
Malignancy	4	1.6	4	6.2	.064
Received COVID-19 treatment	5	2.0	1	1.5	1.000
COVID-19 symptom	4	1.6	1	1.5	1.000
COVID-19 radiology	3	1.2	0	0.0	
Contact with people at risk of infection	11	4.5	6	9.2	.115
RT-PCR test					
Positive	3	15	1	5	
Negative	9	3.7	7	10.8	

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HT, hypertension; RT-PCR, reverse transcription polymerase chain reaction.

observed in only 1.9% of the study population. In addition, none of the patients diagnosed with COVID-19 were taken into the intensive care unit or died due to clinical deterioration and/or respiratory failure. But according to the report of the Ministry of Health dated May 15, 2020, 944 patients were still being treated in the intensive care unit, of which 490 were intubated and 4.055 (2%) people lost their lives because of COVID-19.[22] Although these data show the situation in the country, it was announced by the Ministry of Health that 60% belongs to İstanbul.[22] Besides, in the research conducted by the professional and scientific association of Turkey's thoracic diseases specialists, the Turkish Thoracic Society, deaths in İstanbul and Trabzon have been shown to increase significantly in 2020. According to the said research, 10% weekly increase in the number of deaths in Istanbul was observed in April, 2020.[23] On the contrary, some researchers claimed that TB causes an increased risk of COVID-19 and disease severity.[8] Yu Chen et al[8] suggested that TB infection increases susceptibility to SARS-CoV-2 and can cause severe COVID-19 by causing the symptoms to develop faster and suggested that TB infection as an important risk factor for COVID-19. The results of the current study are important because we show that TB does not cause an increase in COVID-19 risk compared to the normal population. Besides, the COVID-19 disease seen in TB patients was not as severe as expected.

The positivity of the RT-PCR test result of the study group was higher than the value reported for Turkey (20% vs 9.5%); however, considering the outcomes of the city of Istanbul, where the sample of the study lives, there was no actual difference (20% vs 20.3%), and the numbers were similar.

İstanbul, a major metropolitan city, has been the city with the highest number of TB cases in our country, as well as being the city most affected by the pandemic since its announcement in our country (March 11, 2020).[21,22]

In our study, 4 of 17 people with a history of contact with people at risk of infection were patients diagnosed with COVID-19 (RT-PCR results of 3 patients were positive, 1 had clinical and radiological diagnosis); for the remaining 13 cases, it was interesting that they did not get sick although they had close contact with people diagnosed with COVID-19 in their immediate vicinity and they were at risk of becoming infected.

Individuals of any age can experience SARS-CoV-2 infection, but middle-aged and older adults are most frequently affected, and older adults are more likely to develop serious illness.[24] In this study, the younger age of the cases with COVID-19 (38 ± 13.5 years, 23-66 years) can be explained by the prevalence of TB in the young population.[10] During the preparation of this study, another study was published reporting some data supporting the result of our study.[25] In this study, Yamini et al[25] reported their research results of a comprehensive literature review to discover commercially available Food and Drug Administration-approved drug compounds for human therapeutic applications with antiviral properties. This study is important to show that some drugs approved to treat other viral or bacterial infections might be promising drug candidates and can be re-purposed to treat COVID-19. This study suggested that rifampicin as the most promising drug showing a very good binding energy. All of

the patients in our study were under anti-TB drug therapy containing rifampicin, but it is not possible to associate our findings with rifampicin due to the limitations of the results of our study, such as being a single center, lack of a control group, and the small number of patients.

As a result, TB patients might be more disadvantageous than the normal population in terms of the risk of exposure to SARS-CoV-2. In spite of that, this did not cause an increase in the frequency and severity of COVID-19 disease in active TB patients under first-line drug therapy. However, it should be noted that clinical studies in a wider population are needed.

Ethics Committee Approval: This study was approved by Ethics committee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, (Approval No: 2260).

Informed Consent: Verbal informed consent was obtained from the patient on the phone call (because of pandemic precaution).

Peer-review: Externally peer-reviewed.

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