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Highlights

- We perform an observational cohort study analyzing the COVID-19/TB interaction
- TB patients appear to have a less severity of COVID-19 and a lower mortality risk
- TB patients with COVID-19 experience fatigue, with no change in taste or smell
- Patients with TB and comorbidities are at increased risk of a severity of COVID-19

Clinical characteristics of COVID-19 in TB patients and factors associated with the disease severity

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Abstract

Background: Data on COVID-19 patients who have pulmonary tuberculosis (TB) is limited. In this study we compare the clinical characteristics of COVID-19/TB and COVID-19 only patients and analyze the links between the severity of COVID-19 disease and clinical characteristics of COVID-19/TB patients.

Methods: Retrospective, anonymized, cross-sectional study of 111 patients who met inclusion criteria for analysis (75 COVID-19/TB and 36 COVID-19 patients) was conducted.

Results: Patients in both groups (COVID-19/TB vs COVID-19) mainly suffered from fever (72.0% vs 100%, $p < 0.001$), fatigue (76.0% vs 94.4%, $p = 0.018$), chest pain (72.0% vs 36.1%, $p < 0.001$), followed by cough (60.0% vs 97.2%, $p < 0.001$) and dyspnea (44.0% vs 63.9%, $p = 0.05$). In group COVID-19/TB the most frequently reported comorbidities were chronic liver disease (17 [22.7%]), cardiovascular diseases (25 [33.3%]), and diseases of the nervous system (13 [17.3%]).

Female gender, fever, dyspnea, pulmonary bilateral TB lesion, and 3 or more comorbidities have a statistic significant positive effect on severity of the disease among COVID-19/TB patients.

Conclusion: It is important to perform rapid molecular testing and CT to correctly distinguish COVID-19 and TB due to similar clinical characteristics of both diseases. Bilateral pulmonary TB lesion and comorbidity should be considered as risk factors for severe COVID-19.

Keywords: tuberculosis, COVID-19, disease severity, comorbidity, clinical characteristics, co-infection

Introduction

The global spread of COVID-19 may affect the epidemiology and clinical course of other infectious diseases such as tuberculosis (TB). Moreover, tuberculosis itself is epidemic in many parts of the world (Singh et al., 2020). The problems of co-infection can be associated with a decrease in the quality of routine medical care for patients with tuberculosis due to forced restrictive measures (McQuaid et al., 2021), as well as an increased risk of an atypical or more severe course of the disease against the background of COVID-19 (Antonio-Arques et al., 2021; Yang et al., 2020).

Currently, there is no clear understanding of the interaction between COVID-19 and TB. Most researchers regard pulmonary tuberculosis as a risk factor for the severe course of a new coronavirus infection (Chen et al., 2020; Gupta et al., 2020; Khayat et al., 2021). The reverse

negative interaction of these diseases has also been described – for example, an increased risk of a latent infection turning into an active form of tuberculosis against the background of COVID-19, due to the depletion of CD4 + T cells (Elziny et al., 2021; Starshinova et al., 2021; Visca et al., 2021). Several studies have noted an aggravation of the course of both diseases in their mutual existence due to common social, epidemiological, and clinical determinants (Mousquer et al., 2021; Ritacco and Kantor, 2020; Yang and Lu, 2020).

In addition, lung damage due to fibrosis as well as cavitation due to active tuberculosis with superimposed viral infection in COVID-19 patients lead to further deterioration of already impaired lung function (Gupta et al., 2020).

According to numerous forecasts, an increase in cases of active pulmonary tuberculosis is expected soon (Kozińska and Augustynowicz-Kopeć, 2021; Saunders and Evans, 2020; Sumner et al., 2020). While this can be considered as a consequence of the COVID-19 pandemic, it is necessary to continue studying the specifics of interaction between these diseases in order to improve prevention, diagnosis, and therapy in patients co-infected with COVID-19/tuberculosis. This study analyzed the clinical characteristics of patients with a combination of tuberculosis and COVID-19 and identified factors that determine the severity of COVID-19 in this cohort of patients.

Methodology

Study design

We performed an observational, retrospective, two-center cross-sectional study based on the original data collection to compare the clinical characteristics of COVID-19/TB and COVID-19 only and identity the links between the severity of COVID-19 disease and clinical characteristics of COVID-19/TB patients.

From October 2020 to August 2021, 134 patients were hospitalized for the treatment of either the COVID-19 and tuberculosis combination (*COVID-19/TB*; 92 patients) or COVID-19 without TB (*COVID-19*; 42 patients). Data was collected between October 15 and December 1, 2021, from TB hospitals in Khabarovsk (*COVID-19/TB; COVID-19* patients) and Moscow (*COVID-19)*, Russia.

Both hospitals had departments for newly diagnosed tuberculosis patients and separate diagnostic departments, where patients without established tuberculosis were located. During the

time at the hospitals, some patients were diagnosed with COVID-19, which allowed us to form the COVID-19/TB and COVID-19 groups. For the COVID-19/TB group, the median duration (IQR) of anti-TB treatment before the diagnosis of COVID-19 was 33 days (14-90). For the COVID-19 group, coming from the differential diagnostic department, the median duration of hospitalization before the diagnosis of COVID-19 was 13 days (6-21). Among patients in whom tuberculosis was ruled out, 14 people had fibrotic changes in the lungs and pleura, 8 people had upper lobe segmental bacterial pneumonia in the stage of incomplete resolution, 7 people had pleurisy of non-tuberculous etiology, 3 people had sarcoid intrathoracic inflammation of the nodes, 1 person had echinococcosis.

Data was collected on all available patients, and all patients were tested for HIV infection in accordance with the requirements for hospitalization in the Russian Federation. Previously, considered patients did not have TB.

A total of 23 patients (17 from COVID-19/TB group and 6 from COVID-19 group) were excluded from the study. Exclusion criteria included a diagnosis of HIV infection (7 among patients with COVID-19/TB and 3 among patients with COVID-19), other immunodeficiency conditions (4 patients receiving genetically engineered drugs - systemic lupus erythematosus, Crohn's disease; 1 - skin cancer ; 1 - invasive aspergillosis; 1 - candidiasis among patients with COVID-19 / TB and 2 patients with lung cancer among patients with COVID-19), chronic use of corticosteroids (2 patients with bronchial asthma, 1 - with COPD among patients with COVID-19 / TB and 1 among patients with COVID-19), lack of a completed course of treatment for COVID-19 in the institution (3 patients among patients with COVID-19/TB and 1 among patients with COVID-19 were transferred to another hospital due to the bed load).

Inclusion criteria were: gender, age, hospital admission, one or more comorbidities, data on the date of onset of the disease, laboratory tests at admission and discharge: erythrocytes, hemoglobin, leukocytes, neutrophils, lymphocytes, AST, ALT, creatinine, urea, C -reactive protein, fibrinogen, CT study based on a visual scale for assessing the extent of the lesion (CT0 = no lesion, CT1 < 25%, CT2 = 25-50%, CT3 = 50-75%, CT 4 > 75% involvement).

As a result, a total of 111 patients met inclusion criteria for our analysis (75 COVID-19/TB and 36 COVID-19 patients). For the summary, see Fig. 1.

All patients were examined for COVID-19 by the polymerase chain reaction (PCR) test in a tuberculosis hospital (in the department for patients with tuberculosis and in the diagnostic department). "AmpliSens® Cov-Bat-FL" RT-PCR was used to detect Sars-CoV-2 RNA in swabs from the nasal/oropharyngeal mucosa (the manufacturer is the Central Research Institute of Epidemiology of Rospotrebnadzor, Russia).

Based on the clinical picture, the presence of COVID-19 pneumonia, and test results, the patients were transferred to other departments and hospitals specialized in the combined pathology of COVID-19/TB or COVID-19 without TB. A total of 105 patients (94.6%) had a laboratory-confirmed SARS-CoV-2 infection, and the remaining patients' diagnosis of COVID-19 was based on clinical and radiological (CT) criteria.

In accordance with the classification of TB in Russia, TB cases were divided into following forms of newly diagnosed pulmonary TB: Infiltrative TB - 43 [57.3%], Disseminated TB - 15 [20.0%], Focal TB - 2 [2.7%], Tuberculomas - 9 [12.0%], Fibrous-cavernous TB - 6 [8.0%]. Infiltrative tuberculosis was characterized by pulmonary infiltrate in one lung (without a cavity or with few cavities). Disseminated tuberculosis was characterized by a bilateral pulmonary lesion (without a cavity or with few cavities). Fibrous-cavernous tuberculosis was characterized by unilateral or bilateral pulmonary lesions with one or more cavities, as well as with fibrosis.

Median SpO2 % level at admission was 97% (Q1-Q3 76-98) among patients with COVID-19/TB and 96% (Q1-Q3 90-98) among patients with COVID-19).

Study variables

The following clinical characteristics of the study groups were recorded: the severity of COVID-19 during hospitalization, the presence of confirmed close contact with a patient with COVID-19, the presence of co-morbidities and their number, the presence of symptoms of COVID-19, the results of chest CT, oxygen saturation, laboratory parameters, the presence of complications of COVID-19, ongoing oxygen therapy. The data also included additional explanatory variables such as age, sex, smoking status, temperature, shortness of breath, and the pulmonary TB status.

The severity of the condition was assessed in accordance with the "Interim Guidelines for Prevention, Diagnosis, and Treatment of the Novel Coronavirus Infection (COVID-19). Version 11 (05/07/2021)" (approved by the Ministry of Health of Russia).

A severe course of COVID-19 was defined through a complex of factors: body temperature > 38 °C; NPV > 22/min; Shortness of breath during physical exertion; Changes in CT (radiography) typical of a viral lesion; SpO2 < 95%; Serum CRP > 10 mg/l.

Statistical analysis

Demographic, clinical, and laboratory data was used to compare the groups using the independent samples t-tests. Differences clinical characteristics between the groups were analyzed using Chi-square analysis and Fisher's exact test for categorical variables. The odds ratio (OR) and its 95% confidence interval (CI) were calculated. A significance level of 5% (0.05) was used to indicate statistically significant results. The data was analyzed using SPSS software (version 22.0; IBM Corp.).

Based on the obtained data, the factors significant for the development of severe COVID-19 in patients with tuberculosis were identified. Then, a predictive model was constructed using a logistic regression to determine the likelihood of developing a severe COVID-19 condition in patients with tuberculosis, depending on the demographic and clinical characteristics of patients.

Results

The demographic and clinical characteristics of the COVID-19 with TB and COVID-19 without TB groups at the start of hospitalization are presented in Table 1. The aggregate median age was 52±16 (IQR 49–55), 28 (25.2%) were aged 65 years or older, and 71 (64.0%) patients were male. The COVID-19/TB group had younger patients, with p-value (p) < 0.001, and the number of persons aged 65 and older in this group was 14 (18.7%) compared to 14 (38.9%) in the COVID-19 group. The male/female proportions were not statistically different between the two groups (p = 0.664). In the COVID-19/TB group, a history of cigarette smoking as well as having a close contact with COVID-19 patients were more frequently observed (p < 0.001 for both variables). In the COVID-19/TB group, chronic liver disease (17 [22.7%]), cardiovascular diseases (25 [33.3%]), and diseases of the nervous system (13 [17.3%]) predominated.

In the COVID-19 group, comorbidities were dominated by cardiovascular diseases (23 [63.9%]), diabetes mellitus (12 [33.3%]), and chronic renal disease (9 [25.0%]). The COVID-19 group had more patients with 3 or more comorbidities (p < 0.001) – 21 (58%) versus 9 (12%) in the COVID-19/TB group. Overall, 88 (79.3%) were discharged from the hospital and 23 people

(20.7%) died. Among patients with COVID-19/TB, more cases of recovery (68 [90.7%] vs 20 [55.6%]) were reported. 16 (44.4%) and 7 (9.3%) patients died without TB and with TB respectively. This finding can be possibly linked to the age difference between the groups. As it was observed from the previous data of COVID-19 patients, comorbidities increase the chances of infection, and also the elderly, especially those in long-term care facilities, as well as people of any age with serious underlying medical conditions are at a greater risk of getting COVID-19 (CDC, 2020). Perhaps, the older age of patients in the COVID-19 group explains the greater number of comorbidities and death.

Signs and symptoms of the TB/COVID-19 and COVID-19 patients are summarized in Table 2.

Confirmed and reported cases of COVID-19 have a wide range of symptoms, from mild complaints, such as fever and cough, to more critical cases associated with difficulty in breathing (CDC, 2020). Some of the most common symptoms include cough, fever, chills, shortness of breath (SOB), muscle aches, sore throat, unexplained loss of taste or smell, diarrhea, and headache (Maragakis, 2020). In our study, in both groups (COVID-19/TB vs COVID-19), the main complaint on admission to the hospital was fever (72.0% vs 100%, $p < 0.001$), fatigue (76.0% vs 94.4%, $p = 0.018$), chest pain (72.0% vs 36.1%, $p < 0.001$), followed by cough (60.0% vs 97.2%, $p < 0.001$), and dyspnea (44.0% vs 63.9%, $p = 0.05$). Other symptoms noted in a minority of patients included sore throat, congestion, headache, nasal congestion, and general malaise. Loss of smell and taste disorders rarely occurred in the COVID-19/TB group (1.3% vs 52.8%, $p < 0.001$ and 1.3% vs 36.1%, $p < 0.001$).

Characteristics of pulmonary tuberculosis in individuals who fell ill with COVID-19 are given in Table 3. All of patients (n=75) had newly diagnosed TB and bacteriologically confirmed disease with pulmonary localization: Mycobacterium tuberculosis was detected in sputum by culture in 44 [59.5%] patients; more than half (57.3%) had pan-susceptible TB. MDR-TB occurred in 42 patients [56.0%], of which 10 [23.8%] patients had XDR-TB.

Pulmonary cavitary lesion were found among 36 (49.3%) patients, involvement of two segments and more in pulmonary TB – 50 (68.5%) patients. Unilateral pulmonary cavitary lesion were found among 21 patients, bilateral pulmonary cavitary lesion – 15 patients, unilateral pulmonary infiltrate (no cavities) – 30 patients, bilateral pulmonary infiltrate (no cavities) – 7 patients.

Comparing the scale of typical ground-glass opacity on CT in the two groups, it was found that during hospitalization, the scale of pulmonary lesions of more than 50% was recorded less

frequently in patients with TB (17.3% vs. 50.0%, $p < 0.001$). The extent of the lesion may have positively affected the incidence of complications in the non-TB group, which had more cases with thromboembolic syndrome (1 [1.3%] vs 13 [36.1%]), acute respiratory distress syndrome (6 [8.0%] vs. 16 [44.4%]), and respiratory failure (17 [22.7%]. vs 30 [83.3%]). Importantly, there were no cases of sepsis in the COVID-19/TB group versus 6 (16.7%) in the non-TB group. Oxygen therapy was also used less frequently in COVID-19/TB individuals (62 [82.7%] vs 16 [44.4%]).

Laboratory parameters also differed between the two groups (Table 4). Patients with TB had higher platelet counts (ME 276 vs 185, $p = 0.006$), while patients without TB had higher levels of abnormalities in urea ($p < 0.001$), creatinine ($p < 0.001$), C-reactive protein ($p < 0.001$), and ALT ($p < 0.001$).

We analyzed the need for oxygen (Table 2). 29.7% of all patients required oxygenation. At the same time, the need for oxygen therapy in patients with COVID-19/TB was significantly less compared with the group of patients without TB (62 [82.7] vs16 [44.4], <0.001).

The features of the severity of patients in both groups were analyzed (Table 5). The median age in the COVID-19/TB group was 48 years (Q1–Q3: 39–66) and 62 in the COVID-19 group (Q1–Q3: 55–68). The complication rate comparisons are: DVT/PE - 2.6% in the COVID-19/TB group vs 36.1% in the COVID-19 group ($p < 0.001$); respiratory failure - 44.7% vs 83.3% ($p < 0.001$); ARDS - 15.8% vs. 44.4% ($p=0.007$); no sepsis was recorded in the COVID-19/TB group (0%), compared to 16.7% in the COVID-19 group ($p=0.011$). In terms of the complication development, in the group of patients with COVID-19/TB, the development of DVT/PE was 20.913 times less common (OR = 0.048; 95% CI: 0.006–0.390), the development of ARDS was 4.267 times lower (OR = 0.234; 95% CI: 0.079 - 0.698), RF - 6.176 times lower (OR = 0.162; 95% CI: 0.055 - 0.479).

In the COVID-19/TB group, 26 people (52.5%) had a severity of COVID-19 with more than 2 segments of the TB process (50 people). In TB patients with pulmonary cavitary lesion, a severity of the illness was observed in 15 (41.7%) cases. Among smokers (46 people), 21 (45.7%) also had a severity of the illness. It was found that in a subgroup of patients with COVID-19/TB and a serious condition during hospitalization for COVID-19, the levels of C-reactive protein and platelets values were significantly higher (on average) than in the COVID-

19 group, where all patients had a severity – (ME 74.9 mg/l [13-213] vs ME 47 mg/l [19-106], p < 0.001) and (226x109/l [167-259] vs 185x109/l [151-231], p = 0.006), respectively.

Severity of COVID-19 patients without TB may be explained by older age of the patienth and higher rate of comorbidities (particularly cardiovascular disease).

In severe cases of COVID-19, oxygen therapy methods were used: nasal cannula - 2.6% in the COVID-19/TB group vs 8.3% in the COVID-19 group; oxygen mask - 28.9% vs 5.6%, mechanical ventilation and ECMO did not occur in the COVID-19/TB group while being used in the COVID-19 group (33.3% and 8.3%, respectively); oxygen therapy was performed in 31.6% in the COVID-19/TB group vs 53.6% in the COVID-19 group (p < 0.001).

The univariate analysis of the COVID-19/TB data revealed the following statistically significant factors influencing the severity of the disease (Table 6). The chances of developing a severe course were: 2.64 times higher in women gender (95% CI: 1.01-7.12) (p=0.05); 3.52 times higher in patients with fever (95% CI: 1.18-10.51) (p=0.020); 3.10 times higher in patients with dyspnea (95% CI: 1.19-8.09) (p=0.019); 9.931 times higher in patients having 3 or more comorbidity (95 % CI: 1.17-84.04) (p=0.013). Statistically insignificant factors were smoking, 0.63 (95% CI: 0.244-1.624) (p=0.338), disseminated tuberculosis, 2.37 (95% CI: 0.722-7.787) (p=0.148), and patient age 1.02 (95% CI: 0.99-1.06) (p=0.187).

We included these factors in a multivariate logistic regression and added 3 more control variables (disseminated TB, smoking and age). In the pathogenesis of disseminated tuberculosis, small vessels are affected that may be important in the development of lung damage in COVID-19. Smoking is an important factor influencing the development of tuberculosis in an individual. Age was selected , as many studies had shown its effect on COVID-19 outcomes.

The final multivariable logistic regression model included female gender, fever, dyspnea, disseminated TB, 3 or more comorbidities, and smoking status as independent contributors to severity. Table 6 shows the connection of each of the parameters.

The odds of a severe course increased 56.54 times (95% CI: 4.35-735.59) (p=0.002) in female patients, among patients with fever by 18.87 times (95% CI: 3.21- 111.09) (p=0.001), dyspnea by 9.21 times (95% CI: 1.90-44.45) (p=0.006), disseminated tuberculosis by 5.28 times (95% CI: 1.09 -25.50) (p=0.038), the presence of more than 3 comorbidities - by 253.55 times (95% CI: 2.52-25489.19) (p=0.019). Age and smoking were not significant, but in multivariate analysis

they influenced other factors, so we left them in the model while diabetes mellitus was not included.

The predictive model was statistically significant ($p<0.001$) based on the F-test. In accordance with the coefficient of determination R2 of Nigel Kirk, the predictors included in its composition make up only 55.8% of the factors influencing the dependent variable. The sensitivity of the developed model (1) was 78.4% (29 correct predictions out of 37 cases of severe COVID-19/TB), the specificity was 77.8% (28 correct predictions out of 36 cases of no severity in patients with COVID-19 on background of TB).

Discussion

As a result of the comparative analysis, several findings have arisen. First, TB patients appear to have a less severe course of COVID-19 and a lower risk of mortality regardless of the form of TB, even with active pulmonary TB, except for pulmonary bilateral disseminated TB. The data obtained is consistent with the results of meta-analysis (Gao et al, 2021) indicating that tuberculosis is associated with the increased risk of mortality in patients with COVID-19 (OR = 1.40, 95%CI: 0.10 to 18.93, $P = .80$; $I^2 = 31\%$). In our study, the small number of deaths did not allow us to identify factors influencing COVID-19 mortality in TB patients.

At the same time, the development of a severe course is more often observed in persons with a lung lesion of more than 2 segments, with cavities in the lungs, and smokers. Further analysis is needed to confirm this result in the future.

Identification of the relationship between tuberculosis and the severity and mortality from COVID-19 is crucial for the development of measures for the prevention and timely diagnosis of COVID-19 in patients with tuberculosis. Our study showed that the risk of developing severe COVID-19 in TB patients was associated with factors such as female gender, smoking, fever, dyspnea, disseminated TB, having 3 or more comorbidities, and patient age. When the structure of the lung tissue is affected by tuberculosis, resistance to additional infectious agents, such as viruses, decreases. In addition, it is known that tuberculosis is a secondary immunodeficiency. All this can be the basis for a more severe course of the newly emerged disease. The data obtained in the study suggest that strategies should be developed to reduce the risk of severe COVID-19 in TB patients.

The second result suggests that the clinical diagnosis of COVID-19 in TB patients should not be based on taste and smell disorders, which are rare symptoms in TB patients. Among 538 patients

in the global cohort study, they occurred in only 56 (10.4%) and 48 (8.9%) of patients (TB/COVID-19 Global Study Group, 2021), compared to 1.3% and 1.3% in our cohort, respectively. That is, these symptoms are significantly more important for the diagnosis of COVID-19 in the absence of tuberculosis. At the same time, fever and cough are important for the clinical diagnosis of COVID-19 in TB patients. The global study by the TB/COVID-19 Global Study Group (2021) found that the dominant symptoms of COVID-19 in TB patients were fever (386/538, 71.7%) and dry cough (311/538, 57.8%), compared to our observed 72.0% and 60.0%. The majority of patients in the COVID-19/TB cohort had symptoms similar to those of COVID-19 patients, making diagnosis difficult.

Thus, during the COVID-19 pandemic, TB patients should be screened regularly to prevent the spread of COVID-19/TB coinfection. At the same time, it should be remembered that COVID-19 has a rapid clinical manifestation, while TB is time-consuming, so the onset of its symptoms takes longer. This feature can help differentiate between the two diseases.

The third result is that patients with TB and comorbidities appear to be at increased risk of developing COVID-19 and having an adverse disease course. The significance of comorbidity for mortality and the development of a serious condition in TB patients with the addition of COVID-19 is widely discussed in the literature. In particular, it has been shown that old age, diabetes, and respiratory diseases are the main factors increasing the mortality in patients with COVID-19/TB coinfection (Stochino et al., 2020). In the global study by the TB/COVID-19 Global Study Group (2021), the univariate analysis of mortality showed the statistical significance having more than one comorbidity, type 2 diabetes mellitus, cardiovascular disease, chronic respiratory disease and chronic renal disease. In our study, 69.3% of patients had at least one additional disease. At the same time, in COVID-19/TB patients, as well as in patients without TB, the main comorbidity was cardiovascular disease. Assessing the significance of other comorbidities for the development of severe COVID-19 requires caution and a larger observation group.

Our study had some limitations. First, our analysis included all cases of COVID-19/TB from only TB hospitals in two regions of Russia, including cases of COVID-19. In other types of hospitals or regions of the country, different results may be obtained. Second, although the control group of patients without TB was recruited randomly, its size implies that the results should be interpreted with caution. As more data becomes available, it will be important to

identify factors that influence mortality and complications in TB patients diagnosed with COVID-19. Third, in the retrospective design of the study, analysis of symptoms was limited due to the fact, that not all symptoms could be indicated in the paper history of the disease. In addition, there was a significant age difference between the two groups.

Conclusion

In this study, we compared demographic, clinical, CT, and laboratory parameters of COVID-19/TB patients and patients without TB. Our results suggest that, in general, TB patients share the standard clinical signs and manifestations, such as COVID-19 at a younger age and have a milder course in presence of active tuberculosis. However, TB patients also show weakness and fatigue, with virtually no loss of taste or smell. Due to similar clinical characteristics, diagnostic difficulties arise, which may contribute to the development of severe COVID-19. The data analysis shows importance of rapid molecular testing and CT to diagnose COVID-19 (the ground-glass opacities).

At the same time, some evidence indicates that TB may contribute to the severe course of COVID-19. Thus, in the COVID-19/TB cohort, about half of the patients with pulmonary lesions greater than 2 segments, with cavities, and smokers had a severe course of the disease. Our results suggest that female TB patients are more likely to have a severe COVID-19, while the main indicators of severe COVID-19 likelihood in patients with TB are fever, dyspnea, disseminated tuberculosis with bilateral pulmonary TB lesion and the presence of 3 or more comorbidities. Larger multicenter studies are recommended to determine the set of factors influencing mortality and severity in the COVID-19/TB cohort, to better understand the relationship between TB and COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Approval statement

The study was approved by the local ethics committee of the National Medical Research Center for Phthisiopulmonology and Infectious Diseases by decision No. 61/4 of November 2021, which approved the retrospective collection of data from patient records with anonymization of personal data.

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Table 1 Demographic and clinical characteristics of COVID-19 patients with and without TB (at the start of hospitalization)

Characteristics	**All patients N=111 (%)**	**COVID-19/TB N=75 (%)**	**COVID-19 N=36 (%)**	**p-value**
Age (years)	52 ± 16 (49 – 55)	48±15 (45-52)	62±16 (56-66)	< 0.001
Gender (male/female)	71 (64,0)/40(36,0)	49 (65.3)/ 26 (34.7)	22 (61.1)/ 14 (38.9)	0.664
Contact with COVID-19	32 (28.8)	30 (40.0)	2 (5.6)	< 0.001
Occupation				
Unemployed	55 (49,5)	47 (62,7)	8 (22,2)	< 0,001
Employed	26 (23,5)	10 (13,3)	16 (44,5)	
Retired	30 (27,0)	18 (24,0)	12 (33,3)	
Cigarette smoking	60 (54.1)	47 (62.7)	13 (36.1)	0.009
Alcohol abuse (≥14 drinks per week in men or ≥7 drinks per week in women)	28 (25.2)	24 (32.0)	4 (11.1)	0.018
Intravenous drug user	3 (2.7)	3 (4.0)	0 (0,0)	-
Residence status				
Big town	88 (79.3)	56 (74,7)	32 (88.9)	0,047

(>50000 residents)				
Rural area	14 (12.6)	14 (18.7)	0 (0,0)	
Small town (10-49000 residents)	9(8.1)	5 (6.7)	4 (11.1)	
Comorbidities				
Cardiovascular disease	61 (55.0)	25 (33.3)	23 (63.9)	<0,001
Chronic respiratory disease	17 (15.3)	12 (16.0)	5 (13.9)	1.000
Chronic liver disease	19 (17.1)	17 (22.7)	2 (5.6)	0.025
Diabetes mellitus	20 (18.0)	8 (10.7)	12 (33.3)	0.004
Chronic renal disease	14 (12.6)	5 (6.7)	9 (25.0)	0.012
Chronic gastrointestinal tract disease	11 (9.9)	5 (6.7)	6 (16.7)	0.171
Hypothyroidism	4 (3.6)	0 (0.0)	4 (11.1)	0.010
Nervous system diseases	21 (18.9)	13 (17.3)	8 (22.2)	0.538
Comorbidity, n=3 and more (%)	30 (27.0)	9 (12%)	21 (58.0%)	< 0.001
Outcome (death/ hospital discharge)	23 (20.7)/88 (79.3)	7 (9.3)/68(90.7)	16 (44.4)/20 (55.6)	< 0.001

Table 2 Comparative analysis of signs and symptoms in the COVID-19/TB and COVID-19 groups (n/%)

Characteristics	**All patients N=111 (%)**	**COVID-19/TB N=75 (%)**	**COVID-19 N=36 (%)**	**p-value**
Severe condition at the start of hospitalization	74 (66.7)	38 (50.7)	36 (100)	< 0.001
Fever	90 (81.1)	54 (72.0)	36 (100.0)	< 0.001

Nasal congestion	25 (22.5)	5 (6.7)	20 (55.6)	< 0.001
Fatigue	91 (81.9)	57 (76.0)	34 (94.4)	0.018
Dyspnea	56 (50.5)	33 (44.0)	23 (63.9)	0.050
Cough	80 (71.7)	45 (60.0)	35 (97.2)	< 0.001
Chest pain	67 (60,4)	54 (72.0)	13 (36.1)	< 0.001
Congestion in the chest	16 (14.4)	0 (0.0)	16 (44.4)	< 0.001
Sore throat	20 (18.0)	2 (2.7)	18 (51.4)	< 0.001
Headache	20 (18.0)	10 (13.3)	10 (27.8)	0.064
General malaise	41 (36,9)	18 (24.0)	23 (63.9)	< 0.001
Olfactory disorders	20 (18.0)	1 (1.3)	19 (52.8)	< 0.001
Taste disorders	14 (12.6)	1 (1.3)	13 (36.1)	< 0.001
CT 3-4 (more than 50% of lungs damaged)	31 (27.9)	13 (17.3)	18 (50.0)	< 0.001
SpO2 %	96 (93–97)	96 (93–97)	95 (94–97)	0,272
Number of respiratory movements (per minute)	19 (18–22)	19 (18–20)	19 (18–25)	0,969
Complications				
DVT/PE (Deep Vein Thrombosis /Pulmonary Embolism)	14 (12.6)	1 (1.3)	13 (36.1)	<0,001
ARDS (Acute Respiratory Distress Syndrome)	22 (19.8)	6 (8.0)	16 (44.4)	<0,001
Respiratory failure	47 (42.3)	17 (22.7)	30 (83.3)	<0,001
Sepsis	6 (5.4)	0 (0.0)	6 (16.7)	-
Ventilation and oxygen therapy				
No ventilation	78 (70.3)	62 (82.7)	16 (44.4)	<0,001
Nasal cannula	5 (4.5)	2 (2.7)	3 (8.3)	<0,001
Oxygen mask	13 (11.7)	11 (14.7)	2 (5.6)	<0,001
Mechanical ventilation	12 (10.8)	0 (0.0)	12 (33.3)	-
ECMO	3 (2.7)	0 (0.0)	3 (8.3)	-

Table 3 Characteristics of pulmonary tuberculosis.

Pulmonary tuberculosis	**N=75 (%)**
TB lesion scale	
Less than 2 segments	23 (31.5)
More than 2 segments	50 (68.5)
Microbiology	

TB microbiology (one or more tests)	75 (100.0)
Smear microscopy	36 (48.0)
Liquid and solid culture	44 (59.5)
Drug resistance	
MDR	32 (42.7)
XDR among MDR	10 (13.3)
Radiology at TB diagnosis	
Pulmonary cavitary lesion	36 (49.3)
Disseminated TB with bilateral pulmonary lesion	15 (20.0)
Infiltrated TB without a cavity or with one or more cavities.	43 (57.3)
Tuberculoma	9 (12.0)
Focal tuberculosis	2 (2.7)
Fibrous-cavernous tuberculosis	6 (8.0)

Table 4 Laboratory results of COVID-19 patients with and without TB (at the start of hospitalization).

Laboratory indicators	**COVID-19/TB N=75**	**COVID-19 N=36**	**p-value**
	ME $Q_1 – Q_3$	ME $Q_1 – Q_3$	
Hemoglobin (g/l)	114.00 99.50–130.50	134.00 17.75–143.00	0.001
Erythrocytes ($\times 10^{12}$/l)	3.77 3.43 – 4.30	4.31 3.76–4.60	0.013
Leukocytes ($\times 10^9$/l)	6 4–9	6 5–8	0.848
Platelets ($\times 10^9$/l)	276 167–366	185 151 – 231	0.006
Neutrophils %	62 49-77	78 63–87	< 0.001
Lymphocytes (%)	30 13-40	20 14-35	0.313
Urea	5 4-7	7 5–11	< 0.001
Creatinine (µmol/l)	75 62–86	102 87–116	< 0.001
ALT (U/l)	15 9-30	28 19–47	< 0.001
AST (U/l)	29 19-45	28 20-43	0.853
C-reactive protein (mg/l)	34 6–87	47 19–106	0.171

Fibrinogen (g/l)	4 3–7	5 4–6	0.616

Table 5 Clinical characteristics of the patients with severe condition of COVID-19.

Characteristics	**COVID-19/TB N=38 (%)**	**COVID-19 N=36 (%)**	**p-value**
Gender (male/female)	21 (55,3)/ 17 (44,7)	22 (61,1)/ 14 (38,9)	0,610
Contact with COVID-19	11 (28,9)	2 (5,6)	0,013
Cigarette smoking	22 (57,9)	13 (36,1)	0,061
Signs and Symptoms			
Fever > 38 °C	32 (84,2)	36 (100,0)	0,025
Nasal congestion	3 (7,9)	20 (55,6)	< 0,001
Fatigue	12 (31,6)	23 (63,9)	0,005
Dyspnea during physical exertion	22 (57,9)	23 (63,9)	0,598
Cough	27 (71,1)	35 (97,2)	0,003
Chest pain	6 (15,8)	13 (36,1)	0,063
Congestion in the chest	0 (0,0)	16 (44,4)	< 0,001
Sore throat	1 (2,6)	18 (51,4)	< 0,001
Headache	4 (10,5)	10 (27,8)	0,077
Taste disorders	1 (2,6)	13 (36,1)	< 0,001
Olfactory disorders	1 (2,6)	19 (52,8)	< 0,001
General malaise	32 (84,2)	34 (94,4)	0,263
Rhinorrhea	0 (0,0)	1 (2,8)	0,486
Complications			
DVT/PE (Deep Vein Thrombosis /Pulmonary Embolism)	1 (2,6)	13 (36,1)	< 0,001
ARDS (Acute Respiratory Distress Syndrome)	6 (15,8)	16 (44,4)	0,007
Respiratory failure	17 (44,7)	30 (83,3)	< 0,001
Sepsis	0 (0,0)	6 (16,7)	0,011
Respiration rate	23 (22–28)	22 (20–26)	0,645
SpO_2	95 (91–97)	95 (94–97)	0,582
Serum CRP	63 (22–133)	47 (19–106)	0,523
CT			
KT1	8 (21.0)	8 (22.3)	< 0,001
KT2	17 (44,7)	10 (27,7)	
KT3	13(34,3)	7 (19,5)	
KT4	0 (0.0)	11 (30.5)	

Table 6 Logistic regression analysis to assess the relationship between demographic, clinical characteristics and severity of COVID-19 in the COVID-19/TB group (n=75).

Predictor	Univariable analysis		Multivariable analysis	
	COR (95% CI)	p-value	AOR (95% CI)	p-value
Age	1.02 (0.99-1.06)	0.187	1.05 (0.99-1.11)	0.071
Female	2. 64(1.01-7.12)	0.05	56.54 (4.35-735.59)	0.002
Fever	3.52 (1.18-10.51)	0.020	18.87 (3.21-111.09)	0.001
Dyspnea	3.10 (1.19-8.09)	0.019	9.21 (1.90-44.45)	0.006
Disseminated TB	2.37 (0.72-7.79)	0.148	5.28 (1.09-25.50)	0.038
3 or more comorbidities	9.931 (1.17-84.04)	0.013	253.55 (2.52-25489.19)	0.019
Smoking status	0.63 (0.24-1.62)	0.338	10.90 (1.15-103.33)	0.37
Diabetes mellitus	6.97 (0.79-61.07)	0.047		

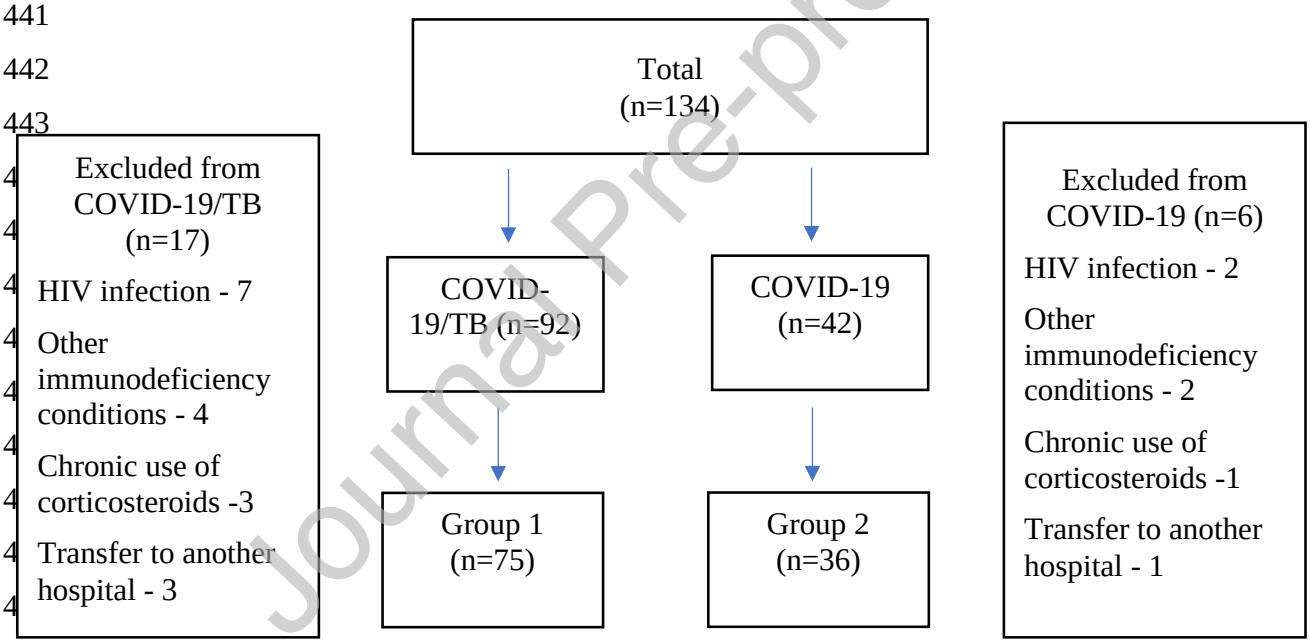

Fig.1. Patient inclusion flowchart.