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Clinical profile, risk factors, disease severity, and outcome for COVID-19 disease in patients with tuberculosis on treatment under the National Tuberculosis Elimination Program: a cohort of 1400 patients

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Abstract

COVID-19 affected millions of people worldwide, and tuberculosis (TB) continues to affect millions of people each year. The combined pandemic of COVID-19 and TB had a catastrophic effect on healthcare policies and healthcare setups around the globe. The clinical profile and factors affecting the outcome of COVID-19 disease in TB patients on treatment in field conditions have not been studied in detail. The present study attempted to study the occurrence of COVID-19 among patients on TB treatment in terms of the severity of COVID-19 disease and outcome of both COVID-19 and TB in patients at National Tuberculosis Elimination Program treatment centers over a period of one year during peak COVID-19 times. Out of 1400 TB patients enrolled, 65 (5%) suffered from COVID-19 disease. Of the 65 TB patients with COVID-19 disease, 37 (57%) were male and under 45 years old, 33 (51%) had a TB diagnosis after first receiving a COVID-19 diagnosis, 29 (45%) had a TB diagnosis first and received anti-TB treatment before receiving a COVID-19 diagnosis, and only 3 patients (5%) had a COVID-19 and TB diagnosis concurrently. The majority of 59 (91%) patients had mild COVID-19 disease. The outcome of TB treatment was available in 25 patients out of these 65 COVID-19-positive patients, with 21 (84%) patients having a favorable outcome. Out of the 65 COVID-19-positive patients, 4/25 (16%) had unfavorable outcomes, with one patient (4%) failing TB treatment and two patients (8%) dying. This is the first study from India that studied the occurrence and course of COVID-19 among a large number of TB patients taking anti-TB treatment under programmatic conditions. Due to the similarity in symptoms of TB and certain viral respiratory illnesses, a protocol should be established for healthcare workers to check patients for both illnesses.

Key words: coronavirus disease 2019, tuberculosis, treatment outcome.

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Introduction

The COVID-19 pandemic has caused a serious global health emergency. A different infectious disease pandemic, tuberculosis (TB), had its epicenter in India prior to COVID-19. An estimated 10 million illnesses and 1.3 million deaths each year make it a global health issue [1]. Because of its rapid global spread, clinical severity, high mortality rate (4 million deaths), and potential to overwhelm healthcare systems, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) pandemic has necessitated increased national and international attention and action [2]. In most countries, there has been a decrease in the number of TB patients diagnosed and treated, along with a corresponding decrease in services connected to TB. This was caused by several circumstances, including limited access to healthcare, slow diagnosis, and overburdened healthcare systems, among others. The World Health Organization research states that between 2019 and 2020, the number of TB case notifications decreased by 18%. (From 7.1 to 5.8 million cases) [3]. One estimate predicts a 20% rise in TB deaths over the following 5 years [4].

Unknown factors may contribute to the dual COVID-19/TB disease mortality, as the immune-pathological and clinical interactions between the two diseases are still unclear [5]. The Global Tuberculosis Network (GTN) published its first pilot study on 49 TB/COVID-19 co-infected patients from eight countries in 2020, and it found that, while the signs and symptoms are generally the same, TB is usually diagnosed concurrently with or after COVID-19 [6]. The dual infection may be linked to higher mortality and morbidity. In comparison to the 1-2% mortality rate reported for drug-susceptible TB and for COVID-19, a second GTN research on 69 TB/COVID-19 patients showed an overall case-fatality rate of 12.6% [7]. This study also identified older age and the presence of comorbidities as the main risk factors for mortality [7]. Later research from South Africa and the Philippines claimed that COVID-19 patients with TB had a 2.7 and 2.17 times higher risk

of mortality compared to COVID-19 patients without TB, respectively [8,9]. There is little information available regarding the clinical course of these co-infections, even though the clinical course and outcome of COVID-19 have been thoroughly reported from many parts of the world, including commentary, viewpoints, and reviews [10-13]. To date, no significant multi-country cohort of TB and COVID-19 patients has been documented.

This study was done to study the occurrence of COVID-19 among patients on TB treatment in terms of the severity of COVID-19 disease and the outcome of both COVID-19 and TB in patients at National Institute of Tuberculosis and Respiratory Diseases National Tuberculosis Elimination Programme (NITRD NTEP) treatment centers between March 2021 and June 2021.

Materials and Methods

Setting

This was a prospective questionnaire-based study done at nine NITRD treatment centers in the periphery, covering a population of 1 million. A pretested questionnaire was filled in by the health workers to gather information regarding the occurrence of COVID-19 among TB patients attending these treatment centers. Some of them could be cases where TB and COVID-19 were diagnosed together, and in some patients, COVID-19 was diagnosed while the patients were already on TB treatment, or TB was diagnosed after COVID-19. The health workers were given training to fill out the proforma accurately.

Study population

All TB patients on TB/drug-resistant TB treatment attending the TB treatment facility between March 2021 and June 2021 were contacted. Patients were either contacted on the phone or were contacted personally at the time of visit for direct observed treatment (DOT).

Ethical considerations

Ethical and research approval was obtained from the Institutional Research and Ethical Committee (office letter no. NITRD/RC/2021/6291, letter no. NITRD/EC/2021/6831, respectively).

Definitions and patient classification

COVID-19 positive: patients were labeled as confirmed cases of COVID-19 on the basis of molecular biology.

COVID-19 suspect: patients were empirically considered COVID-19 positives based on risk of exposure, contact history, and positive symptomatology.

COVID-19 and TB coinfection: this was defined as the presence of COVID-19 positivity in patients with TB. Patients were further sub-grouped based on the disease status of TB. Patients with i) newly diagnosed TB before the diagnosis of COVID-19, that is, COVID-19 was diagnosed while the patients were already on TB treatment; ii) newly diagnosed TB after the diagnosis of COVID-19, that is, they had suffered from COVID-19 disease in the past; iii) patients diagnosed with TB and COVID-19 together.

Data collection and analysis

The data was collected from the questionnaire as well as from the treatment card. The variables that were included from the Nikshay treatment card were as follows: i) initial sputum status; ii) sputum/culture conversions; iii) treatment interruption details; iv) TB treatment outcomes.

Other variables in the questionnaire were: TB disease classification, concomitant diseases, history of bacillus Calmette-Guérin (BCG) vaccination, COVID-19 status, outcome of COVID-19, and TB treatment. The data collected on the questionnaire were entered into Epi-Info version 7 for further analysis. The COVID-19 patients were classified as COVID-19 suspects and COVID-19 confirmed cases for analysis purposes.

Results

A total of 1400 TB cases were enrolled who were taking treatment under DOTS. Out of these 1400 cases, 5% were identified who had suffered from COVID-19 disease in the past. Their demographic, clinical, type of TB disease, site of TB disease in extrapulmonary TB cases, history of BCG and COVID-19 vaccination among them, along with outcome of TB treatment, are given in *Supplementary Table 1*. Out of the total 65 TB patients having COVID-19 disease, 37 (57%) were male and below 45 years of age. History of BCG vaccination was present in 34/65 (52%) in the past, with the majority [59/65 (91%)] of them having no history of TB disease in the past. Out of the total 65 COVID-19 positive patients, 33 (51%) patients had COVID-19 first, followed by diagnosis of TB, and 29 (45%) patients had TB diagnosed first and were on anti-TB treatment followed by COVID-19, and only 3 patients (5%) had both COVID-19 and TB diagnosed together. 59 (91%) patients had mild COVID-19 disease. The outcome of TB treatment was available in 25 patients out of these 65 COVID-19 positive patients, with 21 (84%) patients having a favorable outcome. 4/25 (16%) patients had having unfavorable outcome, with one (4%) patient failing TB treatment and death in 2 (8%) patients. Only 25 (38.5%) patients among the total 65 COVID-19 positive patients had received at least first dose of COVID-19 vaccination till the conclusion of the study. Various other characteristics of positive COVID-19 patients with TB are described in *Supplementary Table 2*.

Discussion

India contributes to almost one-fourth of the global burden of TB, and also ranks second globally as far as total population affected with COVID-19 disease till date [1,14]. Being the TB capital of the world, there is always fear that a person with TB, when co-infected with COVID-19, may be at more risk of poor outcomes of TB treatment or may have a severe COVID-19 disease. However, data studying the effect of one disease on the course of the other is very limited [6,7,15].

This study was done to study the occurrence of COVID-19 among patients on TB treatment in terms of the severity of COVID-19 disease and the outcome of both COVID-19 and TB in patients at NITRD NTEP treatment centers between March 2021 and June 2021. This is the period of the pandemic when COVID-19 vaccination had just begun and was in the initial stages. The low prevalence of COVID-19 (5%) in our study could be attributed to a combination of public health measures, possible immune responses, healthcare access, and underreporting. While TB patients are generally at higher risk due to pre-existing lung damage and weakened immunity, their natural precautions, close mon-

itoring by healthcare providers, and the overlap of preventive measures for both diseases likely contributed to the lower COVID-19 infection rates in this group.

In our study, the majority of TB patients enrolled were less than 45 years of age, and out of 65 TB patients also diagnosed with COVID-19, 71% were below 45 years of age. This clearly shows a higher occurrence of both these infectious diseases, TB and COVID-19, in the relatively younger and middle-aged population. This finding was also statistically significant (p=0.00001). The same thing was also seen in a meta-analysis done by Song *et al*., in which 36 studies were included. They studied 89 patients of COVID-19 and TB and found that about 53% patients were below 45 years of age who were co-infected with COVID-19 and TB [16]. One reason may be the higher mobility of the younger population for their daily work and subsequent more interaction with people, favoring the spread of these infectious diseases.

In this study, another finding was that 52% of patients with COVID-19 had a history of BCG vaccination in the past, and still, they suffered from this viral disease. Hence, protection given by the BCG vaccine against COVID-19 was not seen in our study, as hypothesized in some other studies, as per the literature. However, in all these 34 patients, the severity of COVID-19 disease was mild, and these patients recovered with symptomatic treatment. The prevalence and mortality of coronavirus disease are thought to be negatively correlated with the BCG vaccination strategy, according to several epidemiological investigations (COVID-19) [17]. BCG's limited, variable effectiveness in preventing adult TB is well known, but its effect on COVID-19 mortality remains, as of yet, at best ambiguous.

Also, it was seen that the majority (91%) of patients had mild disease and were having symptoms of acute viral illness, like fever, cough, and fatigue. They also did not require any hospitalization and were ultimately cured at home by taking symptomatic treatment and self-isolation. Only 5% of patients had moderate severity of COVID-19 and required hospitalization due to hypoxemia and oxygen supplementation. These patients ultimately recovered and were discharged. One patient who was COVID-19 positive expired; however, the death of this patient has no temporal association with COVID-19. He had extensive disease on chest X-ray due to TB and expired because of respiratory failure due to the underlying severity of tubercular disease.

From March 2021 to June 2021, the COVID-19 vaccination was only offered to a highly selective group of front-line workers, health care staff, and senior citizens or patients with comorbidities, so exact results regarding the protection offered by the vaccine cannot be deduced. However, it was evident that out of the total 65 COVID-19 patients, 40 patients had not received the COVID-19 vaccination till the end of the study.

The strength of this study is that this is the first study from India to study the occurrence of COVID-19 among a large number of TB patients taking anti-TB treatment under programmatic conditions in terms of the severity of COVID-19 disease, and also tried to study the clinical course of these patients due to the effect of one disease on another and *vice versa*.

The limitations of this study are that various factors responsible for the outcome of one disease on another and *vice versa* have not been studied. Our study's timeliness prevents us from commenting on how new SARS-CoV-2 mutations and TB may affect people differently. Laboratory data were also not collected in our study.

Conclusions

This is the first study from India which had studied the occurrence and course of COVID-19 among a large number of TB patients taking anti-TB treatment under programmatic conditions. Due to the similarity in symptoms of TB and certain viral respiratory illnesses, a protocol should be established for healthcare providers to check patients for both illnesses. Additionally, it appears clinically prudent to treat both conditions as quickly as possible in accordance with global standards to reduce morbidity and mortality. The clinical complexity of patient management is greatly impacted by the combination of COVID-19 and TB. It is still unknown how COVID-19 may affect TB patients' long-term pulmonary sequelae and whether they would require pulmonary rehabilitation. This requires further study and follow-up of such patients.

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Online supplementary material:

Supplementary Table 1. Characteristics of 1400 tuberculosis patients enrolled for the study.
Supplementary Table 2. Characteristics of 65 tuberculosis patients diagnosed with COVID-19 disease.

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