ORIGINAL ARTICLE

COVID-19 and Tuberculosis Coinfection: An Observational Study

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Abstract

Background: COVID-19 is a highly infectious disease with a wide range of symptoms, from asymptomatic to acute respiratory distress syndrome that may even lead to death. Tuberculosis also is one of the deadliest respiratory infections. There is still a lack of literature about coinfection of these diseases in both adults and children.

Materials and methods: This retrospective study was performed in a tertiary care hospital in Mumbai, in which children with TB and those without a TB diagnosis were enrolled. All patients were tested for COVID-19 infection. Variables significantly associated with COVID-19 positivity, in children with TB were assessed and analyzed. Treatment protocols for COVID-19 were compared in children with TB and those without.

Results: No variable was significantly associated with COVID-19 positivity in children with TB. The mean duration of hospital stay for COVID-19 was not significantly different between the TB and non-TB groups. COVID-19 treatment did not differ in children with TB compared to those without. In both groups, children who succumbed to COVID-19 were the ones who required invasive ventilation along with steroids and had significant lesions on their chest radiology. Symptomatic treatment was all that was needed for the vast majority of the milder cases.

Conclusion: The management of COVID-19 is unrelated to the status of TB infection. We must fight new pandemics while ensuring that those in need of attention from ongoing illnesses like TB are provided with uninterrupted health care. We should not forget to suspect and manage TB appropriately (in the case of coinfection), as it is still one of the leading infectious causes of death worldwide.

Keywords: Coinfection, COVID-19, Tuberculosis.

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Introduction

Coronavirus disease 2019 is a highly infectious disease with a wide range of symptoms, from asymptomatic to severe respiratory distress syndrome, that may even lead to death.[1] Around 35 million individuals have been impacted by COVID-19 in India, with children accounting for 8.5% of them.[2–4] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coinfection with other microbes seems to provide a substantial barrier for COVID-19 infected individuals' care and prognosis. One such connection is coinfection with *Mycobacterium tuberculosis*.[5]

Tuberculosis was the leading cause of mortality from any single infectious illness in 2020, with India accounting for 26% of worldwide TB cases.[6] Children aged 15 years accounted for 16% of all TB cases worldwide.[6] In high-TB burden nations, there are a significant number of individuals with post-TB lung sequelae, and the prognosis of COVID-19 in such patients is not known.[7] Because viral respiratory infections and TB both impair the host's immune responses, their fatal synergism may lead to more severe clinical evolution. Despite the fast-increasing number of cases, the evidence required to forecast the impact of the COVID-19 on individuals with latent TB and TB sequelae is still lacking.[8]

To our knowledge, there is no research done to date that has shown a link between TB and COVID-19 except a study by Tadolini et al.[9]; that too was on the adult population. It is critical to accurately estimate the relationship between TB and COVID-19 severity and outcomes to develop effective treatment options for all age groups, including children. In this paper, we looked at how COVID-19 infection affected children and adolescents with TB, factors associated with COVID-19 positive status in TB, duration of hospital stay in COVID-19 patients with TB, and treatment of COVID-19 in TB.

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Materials and Methods

Study Design

A retrospective observational study was done at a tertiary care hospital in Mumbai, India. Children with TB and those without TB were enrolled in the study. According to National Tuberculosis Elimination Programme of India guidelines dated September 2020,[10] all patients diagnosed (both new and ongoing treatment) with TB must be checked for COVID-19 and vice versa. We enrolled all patients visiting inpatient and outpatient departments from

May 2020 to September 2021. COVID-19 testing was performed in all patients using reverse transcription-polymerase chain reaction (RT-PCR). Those who tested negative for RT-PCR were investigated for COVID-19 antibodies. Because children and adolescents up to the age of 18 years in India were not vaccinated throughout the time of this research, a positive antibody titer in serum suggested a subclinical exposure to COVID-19 in these children. This article is associated with our another article from the same research.[11]

Data Collection

The data collection started after the approval from the Institutional Ethics Committee. The demographics, anthropometry, history, vaccination status, investigations, and outcomes were recorded from medical records using a predesigned pro forma, along with the history of close contact with a confirmed COVID-19 positive index case. Complete blood counts, liver and kidney profile, chest X-ray, and sputum/gastric aspirate for cartridge-based nucleic acid amplification test were done for all TB patients as per hospital protocols. Additionally, mycobacteria growth indicator tube cultures and line probe assay for drug resistance testing and phenotypic drug sensitivity testing were done wherever applicable. All these data were taken from the hospital's electronic medical records.

Coronavirus Disease 2019 Diagnosis

The diagnosis of COVID-19 was confirmed by nasopharyngeal RT-PCR.

Severe acute respiratory syndrome coronavirus 2 nucleocapsid antibody levels in serum were done for children whose RT-PCR was negative. The antibody test was done by enhanced chemiluminescence immunoassay. It is a qualitative detection of total high-affinity antibodies (including IgG) that uses a recombinant protein representing the nucleocapsid (N) protein of SARS-CoV-2.

Data Collection and Analysis

Data were collated and analyzed in a Microsoft Excel spreadsheet. The results were presented in tabular form.

Statistical Analysis

Qualitative data were reported in frequencies and percentages. Median and interquartile ranges (IQR) were expressed for quantitative data. For testing the association between categorical variables, the Chi-squared test was used. Kolmogorov-Smirnov was used to test the normality of the data. If the normality was rejected, then nonparametric tests for significance were used. For factors associated with COVID-19 positive status in children with TB, bivariate logistic regression analysis was applied while adjusting for potential confounders. A *p*-value less than 0.05 was considered statistically significant. All the statistical calculation was done with IBM Statistical Package for the Social Sciences Software (SPSS) v26.

Results

Demographic Characteristics

A total of 140 and 154 children were enrolled in the TB and non-TB groups, respectively. Three children were excluded from the analysis in the TB group because of incomplete data. The median age of patients in the TB group was 11 (6) years, while that of the non-TB group was 4.5 (7) years. Forty-eight (35%) and 91 (59.1%) participants were males in TB and non-TB groups, respectively. Eighty-nine (65%) and 63 (40.9%) of the participants were female in the TB and non-TB groups, respectively. Among those with TB, 44 (32.1%) had pulmonary TB, 47 (34.3%) had extrapulmonary, and 46 (33.6%) had disseminated TB. There were 39 (28.5%) cases of drug-sensitive (DS) TB, 53 (38.7%) cases of multidrug-resistant (MDR) TB, 35 (25.5%) cases of pre-extensively drug-resistant (XDR) TB, six (4.4%) cases of extensively drug-resistant (XDR) TB. Four (2.9%) patients were isoniazid monoresistant. Six (4.3%) and 111 (79.28%) children were RT-PCR positive in TB group and non-TB group, respectively; whereas 102 (74.45%) and 11 (7.69%) children were COVID-19 antibody positive in TB and non-TB groups, respectively (Table 1).

Factors Associated with COVID-19 Positive Status in TB

On bivariate logistic regression analysis, no variable was found to be significantly associated with COVID-19 positivity in children with TB, results of which are depicted in Table 2. Neither the site of TB disease nor the resistance pattern of TB was associated with an increased likelihood of contracting COVID-19 infection in children on treatment for TB.

Comparison of Duration of Hospital Stay in COVID-19 Patients

The mean duration of hospital stay for COVID-19 was not significantly different in the TB and non-TB groups ($p = 0.166$) (Table 3).

Treatment of COVID-19 in TB and Non-TB Group

Coronavirus disease 2019 patients were treated with recommended therapies according to the appropriate guidelines. COVID-19 treatment did not differ in children with TB compared to those without. In both groups, children who succumbed to COVID-19 were the ones who required invasive ventilation along with steroids and had significant lesions on their chest radiology. The majority of the mild cases recovered only with symptomatic treatment (Table 4).

Discussion

The 21st century has witnessed three deadly pandemics, including SARS, Middle East respiratory syndrome (MERS), and COVID-19, whereas TB has been around in India for 3300 years.[12,13] A person infected with TB has a 5–15% lifetime risk of developing active disease and can infect 10–15 people per year.[12] It was crucial to study the association between COVID-19 and TB, as no research to our knowledge has been published on the pediatric population. However, we found no evidence to support the concept that TB COVID-19 coinfection affects the course and/or treatment of one another.

Tuberculosis and COVID-19 can exist in the same person, augmenting the effects of each other. A transient decrease in cellular immunity may lead to a new infection (COVID-19) or

Table 1: Demographic characteristics of the patients

	TB group n (%)	*Non-TB group n (%)*
Gender		
Male	48 (35)	91 (59.1)
Female	89 (65)	63 (40.9)
Age median (IQR)	11 (6)	4.5 (7)
Nature of treatment received		
Inpatient	26 (19)	71 (46)
Outpatient	111 (81)	83 (54)

Table 2: Bivariate logistic regression model showing the variables explaining COVID-19 positivity in children

							95% CI for OR	
	B	*SE*	*Wald*	*Df*	*Sig.*	*OR*	*Lower*	*Upper*
Outpatients	–0.548	0.623	0.776	1	0.378	0.578	0.171	1.958
Age	0.063	0.061	1.079	1	0.299	1.066	0.945	1.201
Type of TB (congenital)			1.254	3	0.740			
Type of TB (pulmonary)	–0.230	0.566	0.165	1	0.685	0.795	0.262	2.411
Type of TB (extrapulmonary)	19.534	40192.969	0.000	1	1.000	304563768.337	0.000	
Type of TB (disseminated)	–0.574	0.523	1.204	1	0.272	0.563	0.202	1.570
Resistance pattern in TB (DS)			3.317	4	0.506			
Resistance pattern in TB (DR)	–0.940	1.351	0.484	1	0.487	0.391	0.028	5.520
Resistance pattern in TB (pre-XDR)	0.913	1.021	0.801	1	0.371	2.492	0.337	18.422
Resistance pattern in TB (MDR)	0.825	0.977	0.712	1	0.399	2.281	0.336	15.473
Resistance pattern in TB (XDR)	0.626	0.963	0.422	1	0.516	1.870	0.283	12.345
Constant	0.628	1.302	0.233	1	0.629	1.875		

Forward Stepwise Logistic Regression

Table 3: Duration of hospital stay for patients with COVID-19

	TB group	*Non-TB group*	*Mann-Whitney test statistic*	*p-value (Mann-Whitney U test)*
Duration of hospital stay for hospitalized COVID-19 patients	10 (5) days	10 (3) days	524.500	0.166

Table 4: Treatment of COVID-19 in TB and non-TB group

	TB group		*Non-TB group*	
	Recovered (n = 106)	*Died (n = 2)*	*Recovered (n = 118)*	*Died (n = 4)*
Symptomatic treatment	102	0	108	0
Oxygen	4	2	10	4
Ventilation	0	2	0	4
Ionotropic	1	2	5	4
Steroids	0	2	3	4
Remdesivir	0	1	0	1
Antibiotic	4	2	10	4

lead to the reactivation of latent TB infection. Another factor is that TB and COVID-19 share host and environmental factors for transmission, such as overcrowding, poverty, pollution, advanced age, diabetes, malnutrition, immunosuppression, and other chronic respiratory illnesses.[7] A study by Pathak et al. on mouse models, where activation of a stem cell defense mechanism accelerated the activation of dormant TB, indicates a potential increase in active TB post-COVID-19 infection.[14]

In a study by Tadolini et al. in 2020,[9] 43 (87.8%) patients with TB and COVID-19 were hospitalized, and, provisionally, the overall median (IQR) number of hospital admission days was 15 (8–27). Our study had a hospitalization time of 10 (5) days for the TB group. In their study, six patients needed noninvasive ventilation, and 14 needed oxygen supply, which is much more than ours. Hydroxychloroquine, anti-HIV protease inhibitor, azithromycin, and other drugs were administered in these patients, while in our study, patients were on symptomatic treatments.

Regardless of the potential temporal link between COVID-19 and TB, both infectious illnesses may have a synergistic influence on global social and economic impact. Most children with TB who had evidence of COVID-19 exposure were on antitubercular drugs for their disease. Whether these drugs could have been responsible for the attenuation of COVID-19 manifestations in these children is a research domain that needs to be explored. Another postulate is that many of those with disseminated or neuro-TB were on oral steroids, which may have suppressed active COVID-19 in these patients.

Coinfection most certainly affects both sides of these individuals, causing SARS and an increased risk of TB reactivation. As a result of earlier outbreaks, hospitalization for TB patients should be confined to severe cases to minimize the transmission of SARS-CoV-2 in TB cases. Despite the rapidly rising number of cases, the data required to forecast the impact of the COVID-19 pandemic on patients with latent TB and TB sequelae and advise care in this specific setting need to be collected.

Limitations

It may be possible that COVID-19 has most likely only shown some of the modest active TB cases responsible for concealed transmission in the broader population. We did SARS-CoV-2 nucleocapsid

antibody tests, which was an indirect marker of the infection, while the patient may have had COVID-19 in the remote past and not concurrently with TB. Though the titer levels may predict the time of infection, further research can be done based on these findings. Another significant limitation is that we encountered patients in different stages of antitubercular treatment (i.e., intensive and continuation phases). Analysis with this parameter-wise stratification with an appropriate sample size may help answer this question.

Conclusion

Coronavirus disease 2019 is a relatively new disease for us with no specific treatment; however, TB is curable and preventable with timely management, airborne infection control measures, and treatment of latent TB infection. We must fight new pandemics while ensuring that those in need of attention from ongoing illnesses like TB are provided with uninterrupted health care. From the results, we can say that the active TB infection did not affect the length of hospital stay or the treatment of COVID-19. Neither any specific factor of TB patients predicted the occurrence of COVID-19. The management of COVID-19 is unrelated to the status of TB infection. It is also essential to understand from this analysis that in the fight against the COVID-19 pandemic, we should not forget to suspect and manage TB appropriately as usual (in the case of coinfection), which is still one of the leading infectious causes of death worldwide.

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Ethics Approval

Obtained, IEC/Pharm/RP/570/Sep/2021 from IEC, Grant Government Medical College, Mumbai.

Authors' Contributions

SM, JJ, MP, GIK, NY, AW, MKA, and RC: Concept and designed the study, collected and analyzed data, and drafted, revised the manuscript. All authors approve the present version for publication.

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