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Effect of Concomitant Tuberculosis Infection on COVID-19 Disease in Children: A Matched, Retrospective Cohort Study

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has had devastating effects on the health of millions globally. Patients with tuberculosis (TB) are a vulnerable population. There is paucity of data to assess association between the 2 diseases in Pediatric population.
Objective: To elucidate the effect of concomitant TB on clinical course of pediatric COVID-19 disease.
Methods: Retrospective matched cohort study was conducted at dedicated tertiary COVID-19 hospital in India. All consecutive patients aged <18 y admitted with COVID-19 were line listed. Patients with current or recently diagnosed TB were included. Consecutive age and sex matched COVID-19 patients with no history of TB were included as controls. Medical records were retrieved, clinical data entered in pre-determined proforma.
Results: During study period, 327 pediatric COVID-19 patients were admitted. Study group included 17 patients with TB. These patients, tended to be referred from other hospitals, be sicker, had lower SpO2 at arrival and higher severity of COVID-19 as compared to controls (All $P < 0.05$). They required more mechanical ventilation, had longer length of stay and worse outcome.
Conclusion: COVID-19 may secondarily affect and modify the course of TB in children. Given the high case fatality rate in this association and potentially treatable nature of TB, attention of the policy makers is drawn to this.
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KEYWORDS: SARS-CoV-2, Koch's disease, co-infection, children

INTRODUCTION

Globally, 2020–21 witnessed multiple waves of coronavirus disease 2019 (COVID-19) pandemic that had a devastating impact on lives, health and economic infrastructures across the world. In this unprecedented scenario, tuberculosis (TB) patients, who often have

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underlying comorbidities and lung damage, were particularly vulnerable to more severe COVID-19 [1]. There have been many studies from the adult world, enumerating the detrimental association of COVID-19 and TB infection [2–6]. These studies have revealed that COVID-19 patients with TB had a 2-fold increased risk of death, and were less likely to recover. Moreover, time-to-death was shorter and time-to-recovery longer as compared to patients without TB [3].

This impact has not been studied in pediatric literature, given the paucity of severe COVID-19. But given the rampant spread of COVID-19 in India and the infectivity of the disease, it is reasonable to assume that pediatric cases were also common, albeit less severe. The similarity in clinical picture between TB, childhood pneumonia and COVID-19, with all respiratory etiologies, manifesting as fever, cough and breathlessness, often makes them harder to differentiate [7]. Given the potential health system ramifications of this disease association, possibility of a third pediatric predominant wave, there exists an urgent need to identify vulnerable populations. Hence, we embarked on a study, to elucidate the effect of having TB in pediatric COVID-19 disease and studied how it impacted the outcome of pediatric patients with COVID-19.

METHODS

Study details and data collection

Adult studies show that co-infection/superinfection along with infectious diseases as TB, may contribute to increase in mortality, but similar studies are lacking from pediatric literature [2, 3, 8]. This rarity of pediatric literature is contributed by the less severity of pediatric COVID-19 necessitating hospitalization. This retrospective, single-center, matched observational cohort study was conducted in the Department of Pediatrics of a dedicated tertiary COVID-19 subspeciality referral hospital in North India, to find out the correlation of concomitant pediatric TB infection on clinical severity and outcome of COVID-19 disease.

A line listing of all consecutive patients aged < 18 y admitted with confirmed COVID-19 infection between 15 March 2020 and 31 October 2020 was prepared from the hospital admission and discharge registers.

Study definitions

Patients were diagnosed as having confirmed COVID-19 infection if they presented with symptoms suggestive of COVID-19 and had a Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test or Rapid Antigen Test (RAT) positive for COVID-19, in concordance with the Ministry of Health and Family Welfare, Government of India (MoHFW) definition [9, 10]. Patients with current or recently diagnosed (within the last 7 months) with TB, concomitantly with COVID-19 were included in the study. Only patients who had microbiological evidence in the form of either positive Cartridge Based Nucleic Acid Amplification Test (CBNAAT) or positive Acid-Fast Bacilli on microscopy were diagnosed as having TB. TB infection was subclassified into pulmonary, central nervous system (CNS), abdominal, lymphadenopathy and disseminated. Disseminated TB was defined as the presence of features suggested of TB on two or more non-contiguous sites [11]. To categorize the clinical symptomatology, the following definitions were used. Fever was categorized as temperature above 100.2°F [12]. Tachypnea was categorized as per age wise Integrated Management of Neonatal and Childhood Illnesses (IMNCI) criterion [13]. Clinical severity at admission was categorized as Government of India (GoI) clinical staging [14–16].

Study method

Consecutive age and sex matched COVID-19 patients presenting during the same period with no current or past history of diagnosis of TB were included as controls for these patients (Fig. 1). The medical records of all the subjects included were retrieved and clinical data entered in a pre-determined proforma, elucidating the sociodemographic characteristics, details of clinical severity at presentation, clinical course during stay (severity of COVID-19 infection, type of respiratory support, site of TB and duration of hospital stay) and eventual outcome.

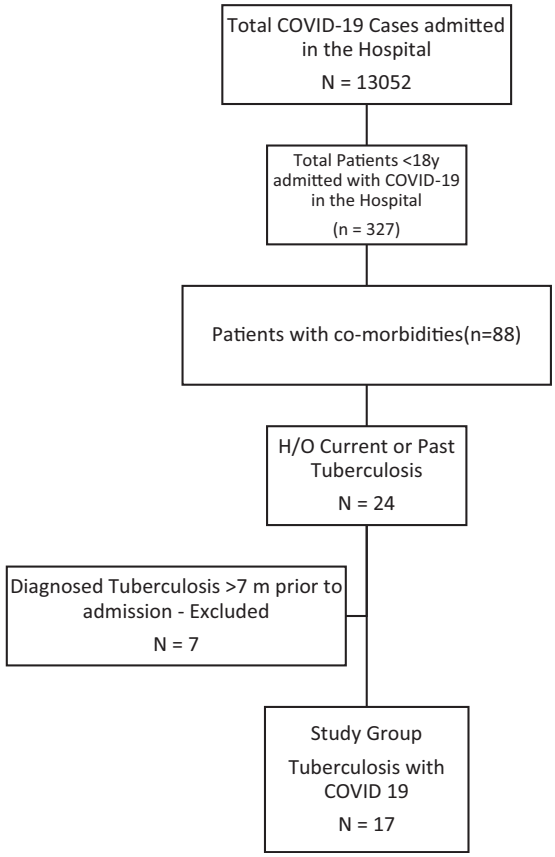

Fig. 1. Categorization of patients into the various study groups.

Statistical analysis

Categorical data were presented as counts and percentage. Normal distributions were presented as mean and standard deviation and skewed distributions were described as median and interquartile ranges. The difference in categorical variables between the groups was compared using the Chi square test or the Fischer's exact test. For normally distributed quantitative variables, difference in means was compared using the Student's *t*-test. In non-normal distribution, the samples were analyzed by the Mann–Whitney U-test. A subgroup analysis comparing the above details between COVID-19 pneumonia to pulmonary TB was also undertaken. Given the paucity of numbers and specificity of disease association (COVID-19 with pulmonary TB in pediatric age group), the controls though were matched to gender, their age matching was relaxed in this subgroup to within 24 months of the concurrent case.

Ethics

Ethical approval was taken from the institutional ethics committee and registration with the Clinical Trial Registry- India (CTRI), done prior to starting the study. The data was stored in a password protected computer, shared only between members of the clinical research team, and was anonymized to personal identification information.

RESULTS

Clinical picture at presentation

During the study period, a total of 327 patients aged <18 y were diagnosed with COVID-19 and admitted to our hospital. Of these, 88 patients had a concomitant comorbidity, which included hematological diseases, infections and congenital abnormalities (Table 1). The flow of the study and categorization of patients into the various study groups is depicted in Fig. 1. The common clinical parameters at presentation in the study and control groups are compared in Table 2.

Did TB incidence increase during COVID-19 times?

TB was the most predominant comorbidity (19%) in our presenting population. During pre-COVID-19 times, of the 9872 admissions per year in our department (2018 census), we had 457 pediatric TB (4.6%) which included 140 (1.4%) pulmonary TB patients. During COVID-19 times, we had 48 moderate–severe pediatric admissions, during the first COVID-19 wave (March–October) (excluding the asymptomatic and mild COVID-19 admissions, admitted in keeping with state and central government recommendations for quarantine purposes). Amongst these moderate–severe pediatric COVID-19 admissions, TB was present in 10.4% (5/48) patients.

Baseline clinical characteristics

In the study group, pulmonary TB was present in seven (41.2%), CNS TB in three (17.6%), lymph node and abdominal TB in one (5.9%) patient each. Disseminated TB was found in five (29.4%) patients.

Table 1. Comorbidity profile of the children who presented with pediatric COVID-19 infection

Comorbidities	Number of children (%)
Nil	239 (73.1)
Infections	35 (10.7)
• Tuberculosis	17
• Bacterial sepsis	11
• Liver abscess	7
Cancer/hematological disorder	31 (9.5)
• Hematological malignancy	14
• Other malignancy	11
• Thalassemia	5
• Sickle cell anemia	1
Congenital heart diseases	5 (1.5)
Chronic kidney disease	5 (1.5)
Central nervous system disease/seizure disorder	4 (1.2)
Others	8 (2.4)

X-rays were clinically indicated in all of the study group and four (23.5%) of the control group. Amongst those with TB and COVID-19, chest X-rays were suggestive of hilar adenopathy in four (23.5%), localized infiltrates in three (17.6%), bilateral infiltrates, pleural effusion and miliary shadows in two (11.7%) each and was normal in remaining four (23.5%) patients.

Course during stay

In the study group, four (23.5%) patients required supplemental oxygen support to maintain baseline oxygenation, as compared to nil in the control group. Out of these four patients, one each required oxygen by mask and Bilevel Positive Airway Pressure (BiPAP) support and two patients required invasive ventilation. Further during the course of stay, three patients in the study group had sepsis, one had septic shock and one had meningitis. There were no severe complications in any patient in the control group. There were four (23.5%) deaths in the study group compared to nil in the control group. The median (IQR) duration of stay in the study group was 13 (8–17) days as compared to 6 (4–10) days in the control group ($p = 0.03$). Two cases with disseminated TB expired on day 4 and day 22 of admission, one case with pulmonary TB expired on day 7 of admission and one case with CNS TB expired on day 17 of admission. We embarked on a subgroup analysis with appropriate controls (COVID-19 pneumonia) to assess the clinical course and outcome of the patients with pulmonary TB (Supplementary Table S1).

DISCUSSION

The onset of pandemic necessitated unprecedented lockdowns, movement restrictions especially in hotspot areas and closure of outpatient department (OPD) services. In India, national TB elimination program (NTEP) was strained due to diversion of resources, manpower and infrastructure [1]. The TB surveillance resources were repurposed toward national SARS-CoV-2 serosurveillance. There was a 25% decrease in TB notification in 2020, as compared to 2019 [7]. This may have led to a setback in achieving TB goals. Given the indiscriminate spread of COVID-19 in sequential waves, this affected population is particularly vulnerable to severe COVID-19 illness, with possible worse outcomes. The overlap of clinical and radiological picture complicates this scenario further [7, 17]. Current pediatric evidence for this association is limited to case reports [18, 19]. Since appropriate matched studies are lacking, we attempted to bridge this gap.

In adult studies, prevalence of TB among COVID-19 patients has been found to be 0.37–4.47% [20], but pediatric literature on the same is lacking. In our cohort, TB as a comorbidity was highly associated with moderate–severe COVID-19 disease at admission, and was detected in 10.4% of the pediatric admissions. Potentially as most young children acquire TB in their households, the lockdowns may have resulted in more exposure of children to infectious TB index cases [1].

In our study, children in the study group tended to have significantly higher duration of fever prior to presentation, which is in keeping with the chronic nature of the disease process. Children with TB also tended to have more tachypnea, increased work of breathing, worse disease severity staging (GoI) and lower oxygen saturation at presentation. This is similar to adult studies, where signs and symptoms at presentation included a similar mix of respiratory

Table 2. Clinical parameters at presentation in the study and control groups

	Pediatric COVID-19 with tuberculosis ($n = 17$)	Pediatric COVID ($n = 17$)	p value
Age[a]	137 (32)	137(32)	1
Gender	9 (52.9)	9 (52.9)	1
Facility from where arrived			**0.001**
a) Home	3	13	
b) Quarantine centre	0	1	
c) Hospital	14	3	
Admission in PICU	6	2	0.23
Fever	12 (70.6)	8 (47.1)	0.17
Cough	5	5	1
GI symptoms[b]	3	3	1
CNS symptoms[c]	2	0	0.34
Median duration of fever in days prior to presentation[d]	8 (6–25)	3 (3–4)	**0.002**
Cough	5 (29.4)	5 (29.4)	1
Coryza	1 (5.9)	5 (29.4)	0.18
Tachypnea	6 (35.3)	0	**0.02**
Increased work of breathing	6 (35.3)	0	**0.02**
SpO_2 at arrival $< 95\%$[d]	5 (29.4)	0	**0.04**
GOI staging			**0.05**
a) Mild	12 (70.6)	17 (100)	
b) Moderate	2 (11.8)	0	
c) Severe	3 (17.6)	0	

[a]All data as *n* (%) except mean (SD)/[d]median (IQR).
[b]GI symptoms included diarrhea, vomiting, pain in abdomen.
[c]CNS symptoms included headache, altered sensorium.
[d]SpO_2 on room air.
GOI, Government of India.
Bold represents statistically significant results ($p < 0.05$).

symptoms [fever (81.2%); dry cough (56.2%); dyspnea (35.4%): 49 patients across Europe] [4].

TB is associated with a 2.1-fold increased risk of severe COVID-19 disease. In addition, TB patients also tend to have comorbid or living conditions that may increase their vulnerability [20]. In our patient population as well, association of TB with COVID-19 had a 23.5% (4/17) mortality rate. We found that children, with disseminated and pulmonary TB, were more likely to succumb to severe COVID-19, with shorter survival times, as compared to other TB subtypes. The possible reason for this higher case fatality and severity of COVID-19 disease might be partially explained by studies from the adult world, which shows exaggerated humoral responses in the patients with SARS-CoV-2 infection and concomitant latent TB infection, as compared to those without latent TB infection. One study has demonstrated heightened antibody response and significantly higher inflammatory markers (C-reactive protein, vascular endothelial growth factor and transforming growth factor alpha) [21].

In our study, most of the patients having pediatric TB with COVID-19 were referred to us from some other hospital in comparison to the controls who came from their homes. The referrals were due to the fact that our institute was a dedicated tertiary COVID-19 subspeciality referral hospital and the cases had greater severity of disease. A higher number of cases required pediatric intensive care unit

(PICU) admissions even though the difference was not statistically significant. This result is of special importance in order to prepare for the possible future waves of the COVID-19 pandemic. The preparedness and streamlining of referral services will need to keep this possibility of referral of similar patients from points of first contact to dedicated health facilities with intensive care services in the future also.

The drawbacks of our study are primarily due to the single center, retrospective nature of the study, but given the paucity of severe pediatric COVID-19, getting large sample sizes prospectively to assess this association may be difficult. Also, we did not assess the Bacillus Calmette–Guerin (BCG) vaccination status of our subjects, given the current interest of BCG vaccination and impact on COVID-19 illness [22–25].

Due to the chronic course of TB, finding co-infections/superinfections of TB with COVID-19 are unusual; it is more likely that COVID-19 secondarily affects and modifies the course of TB disease in pediatrics. Given the severity of association of pediatric COVID-19 with TB, it may be reasonable to dwell upon this association. Also, administration of immunosuppressive drugs such as steroids, as a part of severe pediatric COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C) treatment, may result in reactivation of TB or potentially present as a disseminated infection or with atypical presentation [26]. Larger prospective studies are needed to understand any role played by SARS-CoV-2 in the reactivation of TB infection and atypical presentations of the disease.

To address this problem, as a public health measure, bi-directional TB-COVID screening and TB screening of Severe Acute Respiratory Infection (SARI) cases, may help in timely start of treatment, and possibly improve outcomes. Also, linkages of TB service facilities with COVID-19 isolation facilities should be established. Given the high case fatality rate in this association, the potentially treatable nature of TB, similar clinical symptomatology and radiological picture of both the disease processes and the social stigma attached with TB, attention of public health planning and resource allocation should be redirected to this subgroup, as areas with greater TB burden could have higher case fatality rates of COVID-19.

SUPPLEMENTARY DATA

Supplementary data are available at *Journal of Tropical Pediatrics* online.

REFERENCES

1. Togun T, Kampmann B, Stoker NG, *et al.* Anticipating the impact of the COVID-19 pandemic on TB patients and TB control programmes. Ann Clin Microbiol Antimicrob 2020;19:21.
2. Chen Y, Wang Y, Fleming J, *et al.* Active or latent tuberculosis increases susceptibility to COVID-19 and disease severity. medRxiv2020. https://doi.org/10.1101/2020.03.10.20033795.
3. Sy KTL, Haw NJL, Uy J. Previous and active tuberculosis increases risk of death and prolongs recovery in patients with COVID-19. Infect Dis (Lond) 2020;52:902–7.
4. Tadolini M, Codecasa LR, García-García J-M, *et al.* Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. Eur Respir J 2020;56:2001398.
5. Tadolini M, García-García J-M, Blanc F-X, *et al.* On tuberculosis and COVID-19 co-infection. Eur Respir J 2020;56:2002328.
6. Gao Y, Liu M, Chen Y, *et al.* Association between tuberculosis and COVID-19 severity and mortality: a rapid systematic review and meta-analysis. J Med Virol 2021;93:194–6.
7. India TB Report. 2021. National Tuberculosis Elimination Programme Annual report. https://tbcindia.gov.in/showfile.php?lid=3587 (22 February 2022, date last accessed).
8. Sarkar S, Khanna P, Singh AK. Impact of COVID-19 in patients with concurrent co-infections: a systematic review and meta-analyses. J Med Virol 2021;93:2385–95.
9. Clinical Management Protocol for Covid-19 Version 6. Published online May 24, 2021. https://www.mohfw.gov.in/pdf/UpdatedDetailedClinicalManagementProtocolforCOVID19adultsdated24052021.pdf (17 March 2022, date last accessed).
10. Guidelines for Management of COVID-19 in Children (below 18 years). Published online June 18, 2021. https://www.mohfw.gov.in/pdf/GuidelinesforManagementofCOVID19inCHILDREN18June2021final.pdf (17 March 2022, date last accessed).
11. Khan FY. Review of literature on disseminated tuberculosis with emphasis on the focused diagnostic workup. J Family Community Med 2019;26:83–91.
12. McCarthy PL. Fever. Pediatr Rev 1998;19:401–8.

13. Arora NK. Rational use of antibiotics for pneumonia: India Clinical Epidemiology Network (IndiaCLEN) Task Force on Pneumonia. Indian Pediatr 2010;47:11–8.
14. Global surveillance for COVID-19 caused by human infection with COVID-19 virus Interim guidance. WHO Reference No: WHO/2019-nCoV/SurveillanceGuidance/2020.6. Published online March 20, 2020. https://apps.who.int/iris/handle/10665/331506 (1 July 2022, date last accessed).
15. Government of India, Ministry of Health and Family Welfare, Directorate General of Health Services (EMR Division). Clinical Management Protocol: Covid-19. Version 4. Published online June 27, 2020. https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19dated27062020.pdf (12 March 2022, date last accessed).
16. Government of India, Ministry of Health and Family Welfare, Directorate General of Health Services (EMR Division). Clinical Management Protocol: Covid-19: Version 5. 03.07.20. https://www.mohfw.gov.in/pdf/UpdatedClinicalManagementProtocolforCOVID19dated03072020.pdf (15 March 2022, date last accessed).
17. Biswas DSS, Awal DSS, Awal DSK. COVID-19 and pulmonary tuberculosis – a diagnostic dilemma. Radiol Case Rep 2021;16:3255–9.
18. Mulale UK, Kashamba T, Strysko J, *et al.* Fatal SARS-CoV-2 and mycobacterium tuberculosis coinfection in an infant: insights from Botswana. BMJ Case Rep 2021;14:e239701.
19. Freij BJ, Gebara BM, Tariq R, *et al.* Fatal central nervous system co-infection with SARS-CoV-2 and tuberculosis in a healthy child. BMC Pediatr 2020;20:429.
20. Guidance note on Bi-directional TB-COVID screening and screening of TB among ILI/SARI cases. https://www.mohfw.gov.in/pdf/1TBCOVIDscreeningguidancenote.pdf (17 March 2022, date last accessed).
21. Rajamanickam A, Kumar NP, Padmapriyadarsini C, *et al.* Latent tuberculosis co-infection is associated with heightened levels of humoral, cytokine and acute phase responses in seropositive SARS-CoV-2 infection. J Infect 2021;83:339–46.
22. Bacille Calmette-Guérin (BCG) vaccination and COVID-19. https://www.who.int/news-room/commentaries/detail/bacille-calmette-guérin-(bcg)-vaccination-and-covid-19 (10 March 2022, date last accessed).
23. Moorlag S, van Deuren RC, van Werkhoven CH, *et al.* Safety and COVID-19 symptoms in individuals recently vaccinated with BCG: a retrospective cohort study. Cell Rep Med 2020;1:100073.
24. Murdoch Childrens Research Institute. BCG Vaccination to Reduce the Impact of COVID-19 in Healthcare Workers (BRACE) Trial. https://clinicaltrials.gov/ct2/show/NCT04327206 (5 August 2021, date last accessed).
25. Henry M. Jackson Foundation for the Advancement of Military Medicine. Novel Use of an Existing Vaccine (BCG) Alliance: The NUEVA Trial. https://clinicaltrials.gov/ct2/show/NCT04632537 (5 August 2021, date last accessed).
26. Cline JC, Davis SM. Risks of infection or reactivation of tuberculosis associated with chronic corticosteroid therapy. Ann Pharmacother 1997;31:775–6.