ORIGINAL ARTICLE - PUBLIC HEALTH

SARS COV-2 AND TB CO-INFECTION AMONG CURRENT TB PATIENTS IN CHENNAI, NIRT, INDIA

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Abstract

ABSTRACT: During the COVID-19 pandemic, bidirectional screening of patients was recommended among TB and COVID-19 patients owing to the overlap of the respiratory symptoms. In this study, we studied the co-existence of COVID-19 along with TB among the TB patients who visited NTEP clinics in Chennai. Of the 384 bacteriologically confirmed TB cases, 22 of them were tested positive for SARS-CoV2 by Standard Q COVID-19 Antigen test. In this study, we also compared the treatment outcomes for both co-infected and only TB groups along with comparison of their baseline characteristics. Among the limited cases of TB-COVID-19 co-infection, we did not observe any significant differences between the two groups in treatment outcomes and/or clinical characteristics. As a high TB burden country with infant BCG vaccination program in place, more studies are required to validate the effect of COVID-19 infection among bacteriologically confirmed TB cases.

INTRODUCTION

Before the arrival of the COVID-19 pandemic, tuberculosis (TB) continued its rank as the primary cause of death with contagious conditions everywhere.[1] The development of the novel corona virus (COVID-19) has bestowed a significant challenge in the 21st century, developing weak impacts on health, demographics, and public aspects.[2] The symptoms of COVID-19 closely resemble those of TB and other extensive infections. Consequently, co-infection of SARS-CoV-2 with other viruses, bacteria, and fungi frequently complicates the prevention, diagnosis, and control strategies for COVID-19. Both COVID-19 and TB primarily affect the human respiratory tract, specifically the bronchi, and are transmitted through aerosol droplets from an infected person to a healthy individual.[3,4] COVID-19 pandemic, resulting from the novel corona virus SARS-CoV-2, varies from a mild cold to more severe cases such as pneumonia.[5,6] Human-to-human transmission primarily occurs through droplet infections, either by inhaling respiratory droplets or touching surfaces contaminated with the virus.

Tuberculosis (TB) continues to be widespread in various regions worldwide, standing as a significant contributor to mortality in India.[7] India grapples with the simultaneous challenges posed by both COVID-19 and TB. The concern lies in the possibility that, as attention and resources are diverted to address the immediate health crisis of COVID-19, there could be a setback in the treatment of TB patients. This setback might lead to a surge in TB cases once lockdown restrictions are eased. It is imperative to effectively manage the response to the COVID-19 pandemic while ensuring the uninterrupted continuity of essential national TB programmes.[8]

The World Health Organization (WHO) has issued recommendations on managing the effects of COVID-19 on tuberculosis (TB).[9] WHO proposes utilizing the capabilities of National TB Elimination Programme (NTEP) to promptly conduct testing and contact tracing in response to COVID-19. Additionally, WHO advocates for the adoption of digital technologies to provide remote care and assistance to individuals with TB. In 2018, the United Nations pledged to eradicate the global tuberculosis (TB) epidemic by 2030 through the "End TB" strategy. This initiative aimed at an 80% reduction in TB incidence, a 90% decrease in deaths, and the elimination of catastrophic costs for households affected by TB. India declared its commitment to achieving

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TB elimination within its borders by 2025, surpassing the UN's target by five years.[10] Lockdowns and periods of elevated COVID-19 prevalence and hospital strain have been associated with a decline in the case notification ratio. This ratio represents the primary and immediate impact of the spread of COVID-19 on tuberculosis (TB) transmission dynamics.[11] To control the spread of SARS-CoV-2, countries worldwide enforced lockdowns, mandating people to stay indoors. This resulted in several repercussions. The similarity in symptoms between TB and COVID-19 might have led to a delay in considering TB, as many individuals could have linked comparable symptoms to COVID-19 and chosen to wait it out. Moreover, the existing stigma associated with TB, combined with the additional stigma surrounding COVID-19, and could have discouraged people from seeking testing, even when experiencing symptoms shared by both diseases.[12,13] The present study will carry out SARS-CoV-2 screening among TB patients in sputum samples transported to ICMR-NIRT as part of TB diagnostics.

METHODOLOGY

STUDY DESIGN: Anonymized, non-interventional study on TB and SARS-CoV-2 co-infection.

STUDY POPULATION: Stored sputum samples for a period of three months (February 2021 to April 2021) were included in the study form the NTEP sites under ICMR-NIRT. Our study examines the impact of COVID-19 on tuberculosis (TB) in Tamil Nadu, specifically focusing on five districts of Chennai.

ELIGIBILITY CRITERIA: All sputum samples received at ICMR-NIRT as part of NTEP algorithm for TB diagnostics. (Fig: 1)

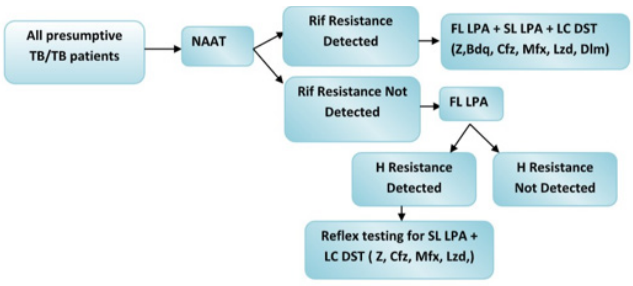

Figure 1: NTEP algorithm for TB diagnostics.

Diagnostic laboratories for tuberculosis (TB) are being upgraded to NAAT. This enhancement enables the provision of NAAT for all individuals suspected of having TB right from the initial diagnostic stage. Based on the NAAT result subsequent tests will be conducted to gather additional information or refine the diagnostic process as needed.

TB: Tuberculosis, NAAT: Nucleic Acid Amplification Test, Rif: Rifampicin, FL LPA: First Line -Line Probe Assay, SL LPA: Second Line –Line Probe Assay, LC DST: Liquid Culture Drug Susceptibility Test, Z: Pyrazinamide, Bdq: Bedaquiline, Cfx: Clofazimine, Mfx: Moxifloxacin, Lzd: Linezolid, Dlm: Delamanid, H: Isoniazid

STUDY PROCEDURES: All newly diagnosed TB patients were tested for SARS-CoV-2 infection(Fig:2). The data relating to date of TB diagnosis and Nikshay number was recorded for the request form.

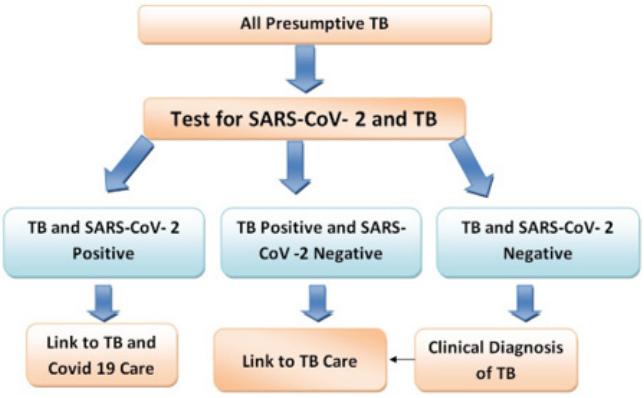

Figure 2: Algorithm for testing of SARS-CoV-2 among TB patients in NIRT Chennai, India.

STANDARD Q COVID-19 Ag Test was used in the study for screening sputum samples for the SARS-CoV-2 infection. STANDARD Q COVID-19 Ag Test is a rapid chromatographic immunoassay for the qualitative detection of specific antigens of SARS-CoV-2 present in human nasopharyngeal specimens. This product is intended for healthcare professionals at the clinical setup and point of care sites, as an aid to early diagnosis of SARS- CoV-2 infection in patient with clinical symptoms of SARS-CoV-2 infection. It provides only an initial screening test result. STANDARD Q COVID-19 Ag Test has two pre-coated lines, “C” Control line, “T” Test line on the surface of the nitrocellulose membrane. Both the control line and test line in the result window are not visible before applying any specimens. Mouse mono-clonal anti-SARS-CoV-2 antibody is coated on the test line region and mouse mono-clonal anti-Chicken IgG antibody is coated on the control line region. Mouse mono-clonal anti-SARS- CoV-2 antibody conjugated with color particles are used as detectors for SARS-CoV-2 antigen device. During the test, SARS-CoV-2 antigen in the specimen interacts with mono-clonal anti-SARS-CoV-2 antibody conjugated with color particles making antigen-antibody color particle complex. This complex migrates on the membrane via capillary action until the test line, where it

will be captured by the mouse monoclonal anti-SARS-CoV-2 antibody. A colored test line would be visible in the result window if SARS-CoV-2 antigens are present in the specimen. The intensity of colored test line will vary depending upon the amount of SARS-CoV-2 antigen present in the specimen. If SARS- CoV-2 antigens are not present in the specimen, then no color appears in the test line. The control line is used for procedural control and should always appear if the test procedure is performed properly and the test reagents of the control line are working. All positive and faint bands with the screening test were tested by RT- PCR as a gold standard test for comparison.

STATISTICAL CONSIDERATIONS

Sample size: The study population consists of all TB positive sputum samples received from 2021 February to April and stored at ICMR-NIRT, Chennai. We will collect basic demographic, epidemiological, microbiological and clinical information (including outcomes) on TB and COVID-19 patients during the study period from available NTEP database. The prevalence of TB among Covid-19 patients has been found to be 0.37 - 4.47 % among different studies. Considering this reference and assuming that 95% confidence level and 20% relative precision, a minimum sample size required would be 384 TB positive patients.

Data collection and Analysis: We have included all reported TB cases in the samples sent to us and stored from February 2021 to April 2021. COVID-19 cases were confirmed with positive real-time reverse transcription polymerase chain reaction (RT-PCR) from ICMR certified laboratory. Information on TB confirmed cases was collected from Nikshay and filled out electronically in an Excel sheet.

Ethical considerations: This protocol was submitted for review and approval to the ICMR-NIRT Ethical Review Committee for ethical clearance and started once the approval was in place (NIRT-IEC: 2021 030). This was laboratory study and was carried out on the de-identified by name.

RESULTS

Of these 384 patients (i.e., 88 females, 296 males), the population of men was almost three times that of women. Except for patients whose mean age was not reported (8 patients) and non-adult ones (4 patients), the mean age of adult patients was 53.59 years for the TB-Covid group and 45.36 years for the only TB group (Table 1).

All the samples were tested by Gene Xpert and were included if positive, no rifampicin resistance was detected, INH resistance was seen in one TB with Covid. In the TB alone group 19 patients had rifampicin resistance was detected (11 MDR-TB and 8 Mono Rif resistance-TB), INH mono resistance was seen 19 patients.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Characteristics		Tuberculosis and COVID-19 (22)	Tuberculosis (362)
Age (Mean/Median)		53.59/53	45.36/47
Height		45.13/48	46.6/45
Weight		156.59/156	155.38/155
Gender	Male	18 (81.8%)	278 (76.8%)
	Female	4 (18.2%)	84 (23.2%)
Socio-economic status	APL	0.0	4 (1.1%)
	BPL	16 (72.7%)	285 (78.7%)
	Unknown	6 (27.3%)	73 (20.2%)
Diabetes	Diabetic	11 (50%)	135 (37.3%)
	Non-Diabetic	11 (50%)	221 (61.0%)
	Unknown	0.0	6 (1.65%)
Smoking	Smoker	7 (31.8%)	94 (26.0%)
	Non-Smoker	15 (68.2%)	232 (64.1%)
	Unknown	0.0	36 (9.9 %)
Alcohol	Alcoholic	9 (40.9%)	119 (32.9%)
	Non-Alcoholic	13 (59.1%)	199 (54.9%)
	Unknown	0.0	44 (12.2%)
HIV Status	Non-Reactive	22 (100%)	335 (92.5%)
	Reactive	0.0	6 (1.7%)
	Unknown	0.0	21 (5.8%)

Data is presented both in number and percentage as indicated. APL: Above Poverty Level BPL: Below Poverty Level, HIV: Human Immunodeficiency Virus

OUTCOME BASED ANALYSIS: A total of 17 (77.27%) patients were cured in the TB with covid patient group and 5 patients show unfavorable outcome ranging from death (2, 9.1%), lost to follow up (2, 9.1%), and treatment changes due to development of resistance (1, 4.5%). The distribution of diabetic patients in the TB with covid patient group was diabetic (8, 47.05%) and non-diabetic (9, 52.9%) among the cured patients and there was no association of diabetic patients with unfavorable outcome as both the patient died of TB was nondiabetic.

A total of 230 (63.2%) patients were cured in the only TB patient group and 132 patients show unfavorable outcome ranging from death (31, 8.5%), lost to follow up (35, 9.6%), treatment changes due to development of resistance (23, 6.3%) and not traceable (43, 11.8%). (Fig:3) The distribution of diabetic patients in the only TB patient group was diabetic (135, 37.3%) and non-diabetic (221, 61.0%) among the patients with unfavorable outcome (132, 36.5%) and there was no association of diabetic patients with unfavorable outcome (Death 31, 8.5%) as both the diabetic (12, 3.2%) and non-diabetic (18, 4.9%) has no significant difference.

The TB-COVID-19 patients with higher rate of coinfection were seen in male, belonged to older age groups and with more co-morbidity. These determinants of death are similar to those described for mono-disease TB.

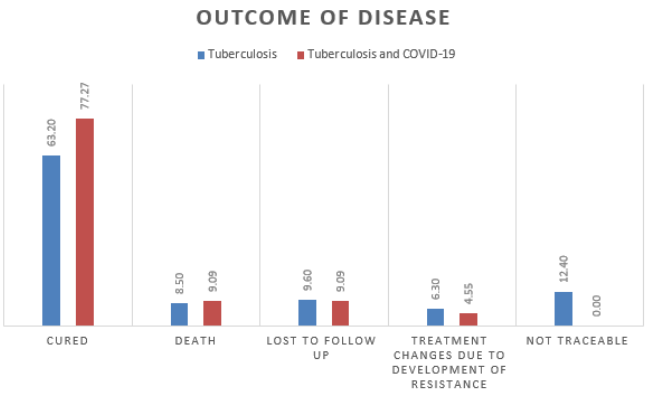

Figure 3: Shows outcome of the Tuberculosis group alone and Tuberculosis and COVID-19 group.

DISCUSSION

The data on the impact of COVID-19 severity on treatment outcome of TB is unclear and literature reports are often conflicting. The management of co-infected patients is complicated as there are pharmacokinetic interactions between several drugs used for the therapy of SARS-CoV-2 infection and the treatment of TB.[14] There is a moderate level of evidence indicating that individuals co-infected with COVID-19 and TB are at a higher risk of experiencing severe disease or mortality compared to those solely affected by COVID-19. As a precautionary measure, it may be advisable to incorporate routine screening for TB among suspected or confirmed cases of COVID-19 in countries facing a high burden of TB.[15]

Various research studies have delved into the consequences of the COVID-19 pandemic on tuberculosis (TB). According to a previous report, the shock triggered by COVID-19 may significantly influence the occurrence and mortality associated with tuberculosis, with a prolonged timeline for a return to normalcy in these aspects.[16] Changes in blood cell parameters are linked to an adverse treatment outcome. COVID-19/TB co-infection is correlated with a higher mortality rate, particularly among individuals of older age, those with a history of smoking or current smokers, individuals with a history of drug abuse, and those with co-existing non-communicable diseases.[17]

Our study observed 22 cases of TB-COVID-19 co-infection among 384 TB patients with symptoms who were tested positive by NAAT. A lower incidence of COVID-19 was observed in regions with higher tuberculosis (TB) incidence and widespread Bacillus Calmette-Guérin (BCG) vaccine coverage. This finding encourages additional exploration into the pathogenesis and immune response of COVID-19.[18] While combating the COVID-19 pandemic, it is crucial not to overlook the importance of vigilance and proper management of tuberculosis (TB). TB remains a significant infectious cause of mortality globally, and addressing it appropriately is imperative.[19] In a previous study, an annual decline of approximately 2% in the prevalence and incidence of tuberculosis (TB) from 2020 to 2025, both in the presence and absence of COVID-19. While an overall reduction is observed, it lacks statistical significance, suggesting that COVID-19 has not significantly influenced TB in Tamil Nadu.[20]

Our study compared the gender, age, co-morbidities, social habits, socioeconomic status between the two groups but we did not find any significant differences. This could be due to the limited co-infection cases observed in our study. Statistically significant factors contributing to the severity of disease in patients with COVID-19/TB include female gender, presence of fever, dyspnea, pulmonary bilateral TB lesions, and the presence of three or more co-morbidities. To accurately differentiate between COVID-19 and TB, it is crucial to conduct rapid molecular testing and computed tomography, especially given the similar clinical characteristics of both diseases. Additionally, bilateral pulmonary TB lesions and the presence of co-morbidities should be recognized as risk factors for the development of severe COVID-19.[21]

Concerning the risk of morbidity and mortality, various risk scores for COVID-19, as well as independent risk factors for tuberculosis (TB), have been identified. These factors include, age, poverty, malnutrition, and co-morbidities such as HIV co-infection and diabetes. Ongoing global TB/COVID-19 studies are anticipated to furnish additional evidence and insights into the interplay of these factors, further contributing to our understanding of the risks associated with these diseases.[22] Research findings indicate that common symptoms in COVID-19/TB co-infection include fever, cough, hypotension, altered blood cell count, and abnormal liver enzymes, along with lower hemoglobin levels. Unfavorable treatment outcomes are associated with alterations in blood cell parameters. However, no significant differences in treatment outcomes were observed in the TB-COVID-19 co-infection group in comparison to only TB group. In previous study, a higher death rate was observed COVID-19/TB co-infection, particularly among individuals of older age, those with a history of smoking, drug abuse, and co-morbidity of non-communicable diseases. Conversely, HIV patients exhibit a lower death rate, possibly attributed to the impact of antiviral drugs. Further investigations into immune cell function in HIV patients are warranted for a comprehensive understanding.[17]

Individuals at a heightened risk of experiencing severe COVID-19 or facing a higher likelihood of mortality often share specific characteristics. These include advanced age, male sex, and the presence of underlying health issues like cardiovascular disease (CVD), obesity, and either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM).[23, 24] Diabetes Mellitus elevates the risk of contracting Tuberculosis (TB) disease by approximately threefold, doubling the likelihood of death during TB treatment and contributing to other unfavorable treatment outcomes. Additionally, diabetes may heighten the risk of latent infection with Mycobacterium tuberculosis (LTBI).[25] In contrast to other research, our study reveals no statistically significant association between co morbidities and SARS-CoV-2 or tuberculosis (TB).

CONCLUSION

The study showed a rate of co-infection with COVID-19 and tuberculosis to be 5.7%, there was no significant difference in the favorable treatment outcome of patient with TB alone and TB plus COVID-19 group.

As patients reported similar symptoms, it advisable for health services to screen patients for both diseases whenever possible, taking advantage of the possibility to obtain imaging rapidly and stimulating adoption of rapid molecular testing for TB and COVID-19. Although our study does not provide specific data on this, it seems clinically advisable to treat both conditions as soon as possible following international recommendations.

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