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Tuberculosis and COVID-19: A combined global threat to human civilization

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ABSTRACT

A new era has begun with the discovery of SARS-CoV-2 in a seafood market in Wuhan, China. The SARS-CoV-2 outbreak has wreaked havoc on health systems and generated worldwide attention. The world's attention was diverted from the treatment of the leading chronic infectious illness, *Mycobacterium tuberculosis*. The similarities in the performance of the two infectious species had obvious repercussions. Administrative efforts to combat SARS-CoV-2 have weakened the tuberculosis control chain. As a result, progress against tuberculosis has slowed. Thus, the goal of this review is to examine the impact of SARS- CoV-2 on a chronic public health issue: tuberculosis.

1. Introduction

The coronavirus has spread worldwide since the end of December 2019. The 2019 pandemic Coronavirus disease is expected to be our generation's largest worldwide health disaster.[1] While Wuhan had the first incidence of Coronavirus induced disease in China (SARS-CoV-2), it also moved to and expanded around the Republic of Thailand, Japan, USA, Philippines, Vietnam, including our country, India and spread all over the world. All other ancient epidemics that cause persistent lung illness and immunosuppression should not be eclipsed by this horrible epidemic. Tuberculosis, for example, was a long-ago disease before COVID-19 became a global epidemic.[2] It is a very old disease that has plagued humanity since the beginning of time. Tuberculosis symptoms have been discovered even in Egyptian skeletons.[3,4] Ancient India and China are the origins of the first literary accounts of TB. The pathogen *Mycobacterium tuberculosis* is the cause of this disease and the contagious nature of it makes people more vulnerable to it. MTB first appeared as a human pathogen in Africa some 70,000 years ago, then spread across the continent as a result of human migration and became a global Pandemic.[5]

Tuberculosis has a long-term course and necessitates long-term therapy. The World Health Organization advises multi-drug therapy because of the increased proclivity of the tuberculosis mycobacterium to become drug-resistant. Every year, over 2 lakh folks in India are affected by TB and on average around 20,000 people are infected every month in each state.[3] In 2018, approximately 10 million folks were globally contaminated with TB. Many TB patients who have a major risk of COVID-19 are not being diagnosed and treated promptly. SARS-CoV-2 is produced by the β-coronavirus genus from the Coronaviridae family's -Coronavirus genus. Over a hundred million infections and more than 2 million deaths, which are still rising, have been caused by this fatal virus. Various studies done by Indian Council for Medical Research have found that the third wave might have hit India by February 2022 with the new variant Omicron. But experts suggested that it will be less severe than the second wave.[6] However, a deeper look at COVID-19 data shows that India has already experienced the third wave. In 2020, the prompt nationwide lockdown may have helped to slow the virus from spreading and the country was exempted from the worst effects.

COVID-19 disease doubles the growth of tuberculosis in people. Several studies have shown that the cases of TB in COVID-19 patients are

Abbreviations: SARS-CoV-2:, Severe acute respiratory syndrome coronavirus-2; MTB:, *Mycobacterium tuberculosis*; MDT:, Multi-drug therapy; ICMR:, Indian Council for Medical Research; TB:, Tuberculosis; WHO:, World Health Organization; COVID-19:, Coronavirus Disease-19; AFB:, Acid-Fast Bacilli; CRP:, C-Reactive Protein; RT-PCR:, Reverse Transcription Polymerase Chain Reaction; HRCT:, High-resolution Computed Tomography; BCG:, Bacillus Calmette–Guérin; COPD:, Chronic Obstructive Pulmonary Disease; ELISA:, Enzyme Linked Immunosorbent Assay; BMI:, Body mass index; LTBI:, Latent Tuberculosis Infection.

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0.37–4.47%. Specialists and scientists have predicted that Tuberculosis intensifies the action of COVID-19. Both TB and COVID-19 harm the lungs, which is a terrible concern in the COVID-19 pandemic. There is worldwide proof that patients with chronic respiratory diseases like TB have a risk of serious sickness and death from COVID-19. When COVID-19 or TB patients breathe out, they can discharge pathogens into the air.[7] Also, the poor immune system because of COVID-19 infection can make a person more susceptible to an active infectious disease like TB. There are some similarities between the symptoms of coronavirus disease and TB, For example, cough, difficulty breathing, fever, etc. According to Faramarz Valafar Lab, the TB bacterium remains dormant until immunity is impaired in COVID-19 disease and causes chronic lung disease and low immune system.[8] It's not unusual for people with severe lung disease like tuberculosis or those who have TB-related lung damage to perform poorly if they get another acute respiratory infection like COVID-19. However, both COVID-19 and TB have similar risk factors for poor outcomes, particularly diabetes, and older age. The burst of COVID-19 diseases drew worldwide attention; practically all healthcare services were diverted to handle this situation.

2. Global scenario and Indian aspects

The COVID-19 disease has had a devastating impact all over the world, where people have been struggling with TB for a long time. Numerous individuals have perished as a result of the financial crisis that has gripped many countries.[9]

COVID-19 has ceased 12 years of global progress against tuberculosis and influenced it severely, making the situation worse than initially thought.[10] However, the global impact of COVID-19 is worse than the TB epidemic. The COVID-19 was devastating in the first four-month of 2020 (January–April 2020). TB-related hospital discharges decreased during the countrywide lockdown mode in the first four months of 2020. It includes newly diagnosed instances of active TB cases. The total active TB visits to the surrounding areas and new latent TB infections were diagnosed.[10]

According to WHO preliminary statistics collated from 84 countries, an estimated 1.4 million fewer persons received tuberculosis treatment in 2020 (when the novel coronavirus was reported) than in 2019, a 21% decline from 2019. As per the modelling research predicted in the report, there could potentially be somewhere between 200,000 and 400,000 extra TB deaths worldwide by 2020.[11]

In 2020, India saw a 26% decrease in tuberculosis notifications compared to 2019. In March 2021, the country saw a major wave of recurring COVID-19 infections.[9] According to government statistics, India currently has approximately 27 lakh Tb cases, with over 2 lakh deaths annually. According to a health ministry review, COVID-19 reduced TB detection by 25% in India by 2020.[12] In 2019, 24.04 lakh instances of tuberculosis were registered in India, according to the study.[13] In 2020, the year of COVID-19, which was distinguished by a lockdown and measures to prevent the pandemic, the registered instances dropped by 25% to 18.02 lakh.

The COVID-19 pandemic has reversed the achievements in worldwide tuberculosis management and control achieved in the 12 years. Since 1997, the World Health Organization has published a Global Tuberculosis Report, which provides an up-to-date assessment of the global TB situation. It now includes information on how the COVID-19 may disrupt TB health care, treatment, and prevention activities.[14] However, even before the COVID-19 pandemic, worldwide TB control efforts were on the track, but the numerical disparity between the projected number of persons with TB globally and the numbers reported to health officials remained large (Fig. 1).

3. TB types

Infectious tuberculosis affects the lungs, but it can also affect other body parts. Extrapulmonary TB refers to TB that occurs outside of the lung as opposed to pulmonary TB, which affects the lungs. There are two stages to the disease, when a person has latent TB, they have bacteria in their body but no symptoms of the disease, and when they have active TB, they have signs and symptoms of an active TB infection.[15] In patients with COVID-19, pulmonary (73%) and extrapulmonary TB (17%) have both been reported. There have been reports of extrapulmonary TB in the lymph nodes, bone, larynx, and CNS in COVID-19 patients as well as in the digestive tract, genitourinary, pleural, and spinal regions.[16]

4. How are COVID-19 and tuberculosis alike and different?

Nowadays the problems of TB patients are increasing as a result of covid-19. The similarities and differences between covid-19 and TB are discussed here. Tuberculosis and COVID-19 share comparable clinical symptoms and manifestations, including fever, shortness of breath, etc [Table 1].[17] There are delicate distinctions between TB and COVID-19, although COVID-19 infection develops faster than Tuberculosis [Table 2].[17,18]

5. The challenges for managing tuberculosis during the COVID-19 pandemic

5.1. Methods of detection of COVID-19 and tuberculosis

The current COVID-19 outbreak has wreaked havoc on tuberculosis sufferers.[17] Due to the epidemic, identifying TB in the presence of

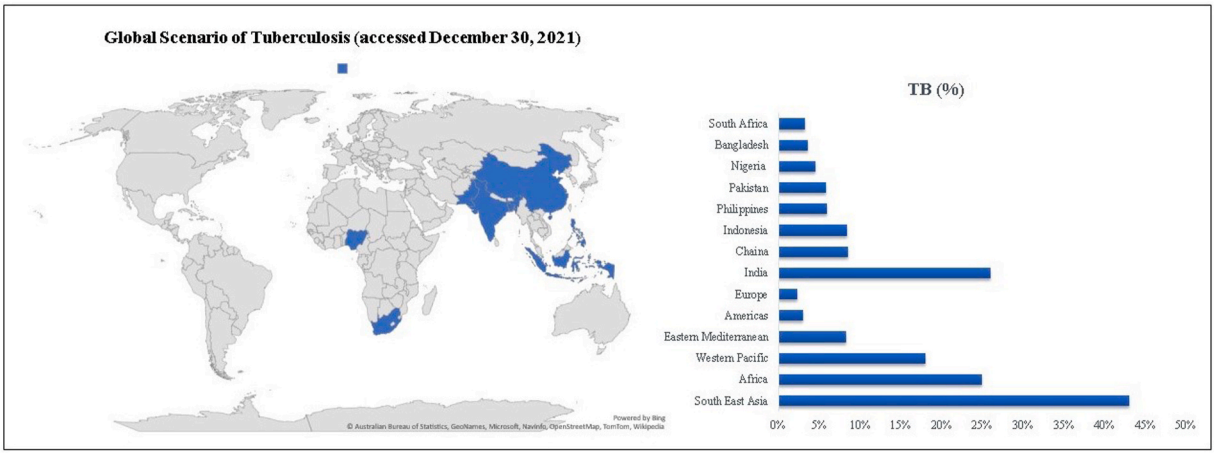

Fig. 1. Graphical representation of trends notification of people diagnosed with tuberculosis in the era of COVID-19.

Table 1
Similarities between COVID-19 and tuberculosis.[17]

Characters	Tuberculosis	COVID-19
Affected Organs	Lung, but can affect any region of the body	Lung
Symptoms	Cough (Sometimes blood-tingling), fever, night sweats, weight loss	Cough, fever, breathing difficulty, chest pain, smell, and taste go away. Headache, tiredness is also seen. In some cases, vomiting and diarrhea occur.
Immediate diagnosis	Required	Required
Disease type	Airborne infectious disease	Airborne infectious disease
Death rate	High	High
Public Consciousness	When people avoid social distancing and are in close contact.	When people avoid social distancing and are in close contact.
Affected Age Group	This disease is affecting people of all ages.	In old age, this is an active disease. Though it affects people of all ages.

Table 2
Dissimilarities between COVID-19 and tuberculosis.[17,18]

Characters	Tuberculosis	COVID-19
Pathogen	*Mycobacterium tuberculosis*	Severe Acute Respiratory Syndrome Coronavirus −2
Nature of Pathogen	Bacteria	Virus
Affected Host	Only Human	Animals (Including-Bats and Human)
Incubation Period	Longer	Shorter (in between 7 and 14 days)
Diagnostic Test	Mantoux Test, AFB Smear and Culture Test, Chest X-Ray, TB Skin Test, Blood Test, etc.	Rapid Diagnostic Test, RT-PCR Test, Sometimes CRP Test, HRCT
Treatment	BCG Vaccine and Rifampin Antibiotic	Evidence Specific Drugs like Remdesivir, Lopinavir/ritonavir, Nafamostat, Camostat, Famotidine, Ivermectin, Tocilizumab, Sarilumab, and Vaccines like Sputnik-V, AZD1222, Ad5-nCoV, BNT162b1, mRNA-1273, NVX-CoV2373, BBV152, Corona Vac etc.
Chances of Recovery	Possible and can be completely cured	Complete cure may or may not happen

COVID-19 is difficult. Several potential constraints include the absence of technology in a given area to test for both COVID and TB, the health system's insufficiency to do both, a lack of appropriate health equipment, and transport barriers that could cause both illnesses to be misdiagnosed.[19] Because TB and COVID-19 have identical signs and symptoms (cough and fever), stigma may cause one of the diseases to be missed.[20] Diagnostic testing is, therefore, a vital step in the prevention and monitoring of diseases such as COVID-19 and tuberculosis. Parallel or combined testing is extremely important for persons who are at increased risk for developing one or both disorders including older populations and people with comorbidities like diabetes mellitus and chronic obstructive pulmonary disease [21] [Table 3].[18,22–24]

Table 3
Various methods of detection of COVID-19 and tuberculosis.[18,22–24]

Name of the Techniques	COVID-19	Tuberculosis
NAAT	RT-PCR	Xpert MTB/RIF Ultra assay
Smear Microscopy	Not Applicable	ZN Stain/AR stain
Antigen-based Test	This test is also known as COVID-19 lateral flow tests or LFTs. These are rapid antigen tests used to detect SARS-COV-2 infection.	Not Applicable
Serological Blood Test	ELISA based test	Sero-diagnostic Test (Anda-TB IgG)
Other Tests	RT-LAMP Test, CRISPR based Test	Skin Test, Chest X-Ray Test, Sputum Test

5.2. TB control actions

TB control tactics are being challenged as a result of resource divergence and an unavoidable shift in the objectives of the health system, resulting in poorer TB care quality and outcomes. The threat posed by COVID-19 could increase not just diagnostic ambiguity, but also stigmatisation of tuberculosis patients, particularly in low- and middle-income countries.[25] To minimize such effects, digital health technology, programs through improved communication, counselling, therapy might be used to assist patients. Also, respiratory physicians, vascular technicians of all levels can provide instructions for patients with pulmonary complications due to this COVID-19.[26]

5.3. BCG and COVID-19

The BCG vaccine is used to protect children from tuberculosis.[27] But after the COVID-19 pandemic, immunization services were suspended, which could lead to vaccine-preventable disease occurrence having a big cost on health systems.[17] In addition to protecting children against miliary TB and tuberculous meningitis, WHO highly advocates worldwide vaccination of BCG to ensure consistent vaccine availability worldwide.[28] Unexpectedly, new evidence suggests that BCG also boosts the immune system's antiviral response despite its projected selectivity for *Mycobacterium tuberculosis*. It has been claimed that COVID-19 mortality rates have decreased as a result of national BCG immunization efforts.[28] Even though it is yet unknown whether BCG prevents COVID-19 in adults. The long-term safety of this technique is yet to be proved.[28]

5.4. Risk factor

COVID-19 and TB share an imbalance of immune responses based on the individual immunological mechanism. It suggests co-infection may increase the risk of disease progression in both diseases.[29] Chronic lung disease, diabetes mellitus, smoking, and liver failure are only a few of the medical factors that increase the risk of severe sickness and the requirement for critical care units or mechanical ventilation associated with COVID-19. When tuberculosis is present in the body, smoking raises the chances of inadequate therapy resulting in delayed sputum cultivation and treatment. There is growing evidence of an increased probability of COVID-19 in people with diabetes that may lead to hospitalization, organ failure, and premature mortality.[30] In TB patients and COVID-19 patients, the combination of malnutrition and low BMI is a major risk factor for early mortality.[31]

5.5. Clinical features

Fever, productive cough and constitutional symptoms are present in pulmonary TB patients. In sub-sets of COVID-19 patients with TB

symptoms, they remain identical to patients without TB at the time of the occurrence. In contrast to solitary COVID-19 individuals, the majority of the coinfected patients described are symptomatic. This could be due to the selection bias in the recruitment of solely symptomatic patients. The most prevalent symptoms include fever, dry cough, and dyspnoea. Other signs of chest tightness, chest pain, and diarrhea have been recorded. Hypoxia needing oxygen supplementation was also found among symptomatic patients. COVID-19 can appear in tuberculosis patients before or after the disease's emergence, which has a significant negative impact on patients' clinical image.[16]

5.6. Imaging

The features of pulmonary activity have been detected using HRCT and chest X-rays. In more than 40% of patients, HRCT has been the primary imaging mode. In tuberculosis patients who develop COVID-19, the development of multiple bilateral ground-glass opacity and air bronchogram consolidation have been recorded.[32]

5.7. Some major challenges that affected India

The population is the main obstacle in India's fight against the epidemic situation. In town slums, where population density can be high, social distancing becomes impossible leading to a potentially disastrous circumstance. Unfortunately, the attitude and actions of a few individuals have been a serious stumbling block in India's fight against COVID-19; there have been claims of civilians misrepresenting their travel history in order to avoid quarantine and people attending otherwise prohibited large gatherings.[32] The COVID-19 breakout has also hampered the control of tuberculosis and its related services severely. There is evidence that coronavirus infection exacerbates tuberculosis by causing lung tissue damage. Public transport is one of the severely affected services due to the COVID-19 epidemic. As a result, the TB patients suffered from a lack of transportation which in turn resulted in the rise of the death rate of the country. The lockdown to reduce the spread of COVID-19 has left many people jobless and led to a major financial crisis in India.[33] Economic decline has had a significant impact on people from lower socio-economic backgrounds throughout this pandemic. The purpose of knowing the major challenges in advance is to be able to fight against such a pandemic situation in the future.[34]

5.8. Coinfection

It is possible to develop active or non-progressive tuberculosis when infected with *Mycobacterium tuberculosis*. Latent Tuberculosis Infection can reactivate into symptomatic TB when the host's immune system is weakened. As a result, people with active tuberculosis or long-term tuberculosis are more susceptible to SARS-CoV-2 infection. It was found after detailed inspection that the immune system got worsened for the Mtb patients who had both SARS-CoV-2 and Mtb symptoms making their condition even worse. Additional to this, SARS-COV-2 infection of LTBI sufferers may result in future reinfection.[35]

6. Molecular interaction between COVID-19 and tuberculosis

The molecular connections between tuberculosis and COVID-19 in the context of co-infection are still a mystery. There has been very little research in this area, and the findings are summarised here.

Dormant *Mycobacterium tuberculosis* was reactivated by altruistic defense mechanism of the stem cell in mice coronavirus model system. This result shows increase in tuberculosis in synergism with COVID-19.[36] There is an assumption made from study done in a cohort of 49 patients that SARS-CoV-2 infection helps in active Tuberculosis development, although not confirmed due to lack of follow up studies.[37]

The development of SARS-CoV-2 coinfection, on the other hand, appears to be linked to tuberculosis.[38] SARS-CoV-2 specific immunity was impaired by Tuberculosis, according to immunological research.[39] Many factors should be considered while acquiring Tuberculosis, SARS-CoV-2, or both at the same time, such as overcrowding, poor cleanliness, the existence of autoimmune illnesses, and so on.[40,41] At the molecular level, Fig. 2 depicts the possible mechanism and synergistic effects of SARS-CoV-2 and MTB.

7. Future strategies

The COVID-19 epidemic has underlined the importance of ensuring continued treatment and concern for TB-affected patients. Communication between patients and medical providers became difficult due to circumstances such as worldwide lockdown, TB service disruption, and social isolation. Patients may benefit from the use of digital technologies and virtual care. The proper classification of TB and COVID-19 patients should be included in future clinical studies. All features, such as clinical appearance, laboratory assessment, and test results, should be described in detail for future scientists.[16] A uniform treatment regimen and a consistent treatment protocol for both infections should be included in future research studies. Multiple drug interactions, as well as detrimental drug occurrences, must be recorded. Following the physician's advice based on susceptibility pattern, the multidrug antitubercular treatment can be safely used. In symptomatic patients, COVID-19 regimens should be utilized according to available medical reports, instructions, and guidelines. Now, strict control measures are needed for all patients admitted to the hospital (especially for those who are at higher risk, including the aged and patients with co-morbidities like tuberculosis). International scientific collaboration and government assistance are essential to the cumulative influence of infections among non-hospitalized TB patients in various aspects. These aspects include social insulation, patient training, availability of rapid testing, and patient support.[16,42]

8. Conclusion

The COVID-19 epidemic has had a negative influence on and disrupted the lives of people in a number of countries. Since both viral respiratory infections and tuberculosis impair the host's immune response, it's reasonable to assume that their lethal combination will have far more severe repercussions than they would have had separately. A stronger management strategy is required as a result of the risk that delaying TB treatment will exacerbate the patient's condition. As a result, diseases like COVID-19 and tuberculosis should be diagnosed and treated as soon as possible. In the case of Tuberculosis, patients should be identified and treated as soon as possible. Patients with tuberculosis and COVID-19 could be better monitored and treated if they were able to consult with one another through teleconference. Numerous effects, such as economic instability, healthcare worker sickness and resignation, and overwhelmed health facilities, have been highlighted as a result of the COVID-19 pandemic in the context of pre-existing endemic diseases, such as tuberculosis. All of these factors have the potential to impair the delivery of health care services, either directly or indirectly. To avoid this trouble, we need to do more research on this disease and find proper medicine that we can be aware of and deal with such epidemic situations in the future. Here our review sheds light on a long-standing infectious disease Tuberculosis and its correlation, molecular interaction, and its effects in different countries in midst of the COVID-19 pandemic.

Authors' contributions

Conceptualization: [Dhriti Ghose], [Joy Sarkar]; Formal analysis and investigation: [Kanika Patra], [Sovona Batabyal, [Kashmira Mandal]; Writing – original draft preparation: [Sovona Batabyal], [Kanika Patra], [Kashmira Mandal]; Image Preparation: [Kanika Patra], [Sovona Batabyal]; Writing – review and editing: [Dhriti Ghose], [Joy Sarkar];

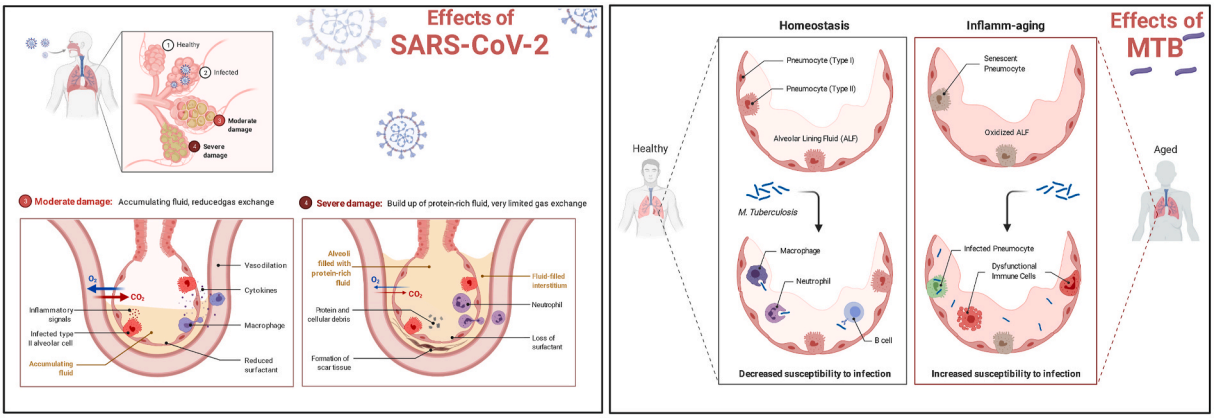

Fig. 2. Graphical representation of the possible mechanism and synergistic effects of SARS-CoV-2 (a) and MTB (b).

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Consent to participate

All the authors mutually agree to participate in this work.

Consent for publication

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Declaration of competing interest

On behalf of all listed authors, the corresponding authors declare that there is not any sort of financial and non-financial conflict of interest in the subject materials mentioned in this manuscript.

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