COVID-19 And Tuberculosis: Convergence Of Two Pandemics Requiring A Change In Outlook

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ABSTRACT
This review article has tried to cover the similarities and differences between the two diseases. The immune dysregulation during COVID-19 and Corticosteroid (CST) therapy poses a significant risk for new secondary infections or reactivation of existing quiescent infections, such as LTBI. The convergence of these two infections, especially in the developing world, is raising an alarm bell among health authorities. Can COVID-19 flare up Tuberculosis (TB)? Will the use of CST in the treatment of COVID-19 can cause a resurgence of TB? Do we need to change our outlook and use our resources in smart and diligent ways to minimize the impact of both diseases on our population? These are the questions that have been addressed in this article. Only time will tell how much success we have achieved in this regard; till then, let us work smartly.

KEYWORDS: COVID-19, Tuberculosis (TB), Corticosteroid.

1. INTRODUCTION

South Asia is getting ready to battle the new wave of COVID-19. In India, it has led to lots of damage to lives and livelihood [1]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes Coronavirus disease 2019 (COVID-19), a member of the Coronaviridae family, which also includes SARS-CoV and MERS-CoV [2], while Mycobacterium TB causes TB. In third-world countries, including the South Asian region, there is concern that it may lead to the flaring up and convergence of these two leading infectious diseases in the world [3]. TB is the leading cause of death worldwide from adult infectious diseases and has been considered a global public health emergency for the past 25 years [4]. While according to WHO, COVID-19 has caused 6,190,349 deaths globally [5]. COVID-19 and TB primarily affect the respiratory system, including the lungs, and the disease can disseminate to other organs [6].

2. SIMILARITIES BETWEEN TB AND COVID-19

Table 1

Critical aspects	COVID-19	TB
Epidemiologically	A significant burden to society	A significant burden to society
Transmission	Droplet	Droplet
High-risk groups	Type 2 DM, Immunocompromised states, chronic lung disease, HIV, obesity, heart conditions	Type 2 DM, Immunocompromised states, chronic lung disease, HIV, malnourishment
Diagnostics	Available in the form of rapid antigen test, RT-PCR, chest radiography	Available in the form of sputum microscopy, chest radiography, CBNAAT
Social stigma	Huge	Huge
Stress on health care	Huge	Huge

Adapted from: Visca *et al*. [7]

3. DIFFERENCES BETWEEN TB AND COVID-19

Table 2

Critical aspects	COVID-19	TB
Progression	Acute	Chronic
Treatment	Still under research though few antivirals and monoclonal antibodies are available, effectiveness is debatable	Drugs are available for treatment, but further research is needed for Isoniazid and rifampicin-resistant strains
Case Definition	Still under development	Well established
Policy Development	Rapid	Slow
Resource Allocation	Rapid	Slow
Economic Impact	Huge and rapid	Huge and slow

Adapted from: Visca *et al.* [7]

4. CLINICAL PHASES OF SARS-COV-2 INFECTION

Based on current practice, COVID-19 is classified into three clinical phases:

a) An initial phase with symptoms, such as cough, fever, pneumonia, and chest radiology (computed tomography or CT) impressions prominently "ground-glass" appearance of lungs with infiltrates. It is also known as mild to moderate disease.
b) In the second phase, COVID-19 cases show symptoms, including oxygen saturation deficit with a spatial oxygen pressure (SpO_2) below 96%. It is also known as severe disease.
c) The third phase of COVID-19 includes acute respiratory distress syndrome (ARDS) associated with multi-organ dysfunction. It is also known as a critical disease [8-10].

5. IMMUNOLOGICAL AND PATHOLOGICAL FEATURES IN PATIENTS SEVERELY INFECTED WITH SARS-COV-2

Patients with severe and critical COVID-19 present with high systemic levels of interleukins (IL-2, IL-6, IL-10), interferon- γ (IFN-γ), inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP-1), granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor-alpha (TNF-α) with lymphopenia. Elevated immune cell infiltrations in the lungs lead to severe inflammation, cellular immune response failure, and finally, the onset of a "cytokine storm" in patients infected with COVID-19 [8,9,11].

6. TREATMENTS AVAILABLE FOR SARS-COV-2

So, the primary objective in treating COVID-19 is to decrease inflammation. Anti-inflammatory drugs, such as corticosteroids (CST), including dexamethasone, prednisone, methylprednisone, and hydrocortisone, play a huge and significant role in it [12]. A prospective metanalysis was conducted to evaluate the usefulness of CST therapy for severe or critically ill patients across five continents, which compared seven clinical trials [13] (DEXA-COVID-19, CoDEX, RECOVERY, CAPE COVID, COVID STEROID, REMAP-CAP). Results of these trials conclusively showed the benefits of CST therapy in reducing the mortality among COVID-19 patients that required mechanical ventilation and hospitalization [13]. Certain therapeutic interventions available for the incubation and early stages of SARS-CoV-2 infection; include specific antivirals like remdesivir and casirivimab/imdevimab antibody cocktail, and bamlanivimab, some of which have already been approved by US Food and Drug Administration [14,15].

7. CLINICAL FEATURES OF TB

The typical clinical manifestations of pulmonary TB include:

(a) Cough lasting for longer than 2 weeks
(b) Hemoptysis,

(c) Weight loss,
(d) Fever, and night sweats [16].

A variety of diagnostic tests are available to diagnose TB, such as sputum microscopy, Xpert MTB, and CT chest, and it is diagnosed as a bacteriologically confirmed TB case and a bacteriologically confirmed TB case. A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture, or the WHO-approved rapid diagnostics (such as Xpert MTB/RIF). A clinically diagnosed TB case does not fulfill the criteria for bacteriological confirmation. However, it has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of treatment for TB. This definition includes cases diagnosed based on X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation [17].

8. IMMUNOLOGICAL AND PATHOLOGICAL FEATURES IN TB

Upon infection, MTB is thought to be phagocytosed by innate immune cells, such as the alveolar macrophages and dendritic cells, with the help of pattern recognition receptors (PRRs), predominantly toll-like receptors expressed on their surface to interact with the pathogen-associated molecular patterns (PAMPs) of the pathogen. Following MTB engulfment, the phagocytes produce a lot of proinflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-12, IL-18, IL-23, and IFN-γ, and chemokines. The cytokine/chemokine milieu attracts more immune cells from the circulation to the infection site and starts forming the granuloma [18,19].

9. USE OF CORTICOSTEROID THERAPY IN TB

The American Thoracic Society (ATS) and, US-CDC, the Canadian Lung Association (CLA) have said MTB-infected individuals receiving >15 mg/day of CST for 2–4 weeks are at a higher risk of developing active TB [20]. A systematic review study on the use of corticosteroids to improve the clinical outcome of TB showed a clinically significant beneficial effect of steroid therapy for TB meningitis cases only [21]. WHO has advised on the cautious use of CSTs for people with diabetes and indicated an under-representation of individuals with active or LTBI in most trials [22].

10. PULMONARY TB AND COVID-19 - A DOUBLE MAYHEM

A meta-analysis of six studies from China on a few patients concluded that TB prevalence was between 0.47% to 4.47% in COVID patients. The prevalence of TB was higher among patients with severe COVID-19 [23]. A cohort involving patients from 8 countries reported an 11.6% fatality rate in 8 out of 69 confirmed cases of COVID-19 and TB. However, it was suggested that TB might not be a major determinant of mortality. The migrants experienced lower mortality, probably due to their younger age and lower number of co-morbidities. In comparison, mortality was more in the elderly population due to more co-morbidities [24]. In a clinical study from cohorts of patients from countries like Belgium, Brazil, France, Italy, Russia, Singapore, Spain, and Switzerland, TB and COVID-19 were studied in 49 patients during the initial wave of the pandemic [25], and the results showed that COVID-19 could occur at any stage of TB. However, the role of TB sequelae in COVID-19 evolution was unclear. Hence, its potentiality in being a risk factor for worsening outcomes and the role of COVID-19 in the development of active TB from LTBI or a new TB infection is still to be concluded. A study from South Africa showed that TB (both drug-susceptible and drug-resistant) increased the risk of COVID-19 death by 2.7 times. However, in those with a previous TB, it was 1.51 [26]. As of today, the Global TB Network (GTN) is coordinating a global study on TB and COVID patients, with support from the World Health Organization (WHO), to improve the knowledge of the interaction between the two diseases, involving 36 Countries/Regions [1]. This study will help us with a better understanding of both diseases and will answer several questions such as:

1. Whether COVID-19 increases the risk of f developing TB disease in individuals with LTBI.
2. Determinants of mortality in TB−COVID-19 co-infected patients
3. Is there a different management strategy for TB/COVID-19 co-infected patients
4. Are post-TB sequelae a high-risk group for COVID? Is there increased mortality or delayed cure in these patients
5. The impact of COVID-19 on TB services over the coming years, whether our services will need remodeling to meet the needs of society.

11. IMPACT OF COVID-19 PANDEMIC ON TB MANAGEMENT PROGRAMS AND HOW CAN WE MODIFY THEM FOR PEOPLE'S BENEFIT

With the advent of the COVID-19 pandemic, another danger that looms in INDIA is the management and diagnosis of a disease that we are already dealing with. It will lead to delay in diagnosis and management of TB, leading to further aggravation of complicated cases and deaths and hamper our target to eliminate it from India by 2030 [1]. The indiscriminate use of steroids and other immunosuppressive therapies in COVID-19 may further suppress the immune system and may lead to the reactivation of Latent cases. Population-based case-control studies in many different parts of the world have shown a strong association between increased active TB cases and CST use, which may be attributable to CST's immunosuppressive effects [27-29]. A case report said that sputum testing was done for intubated COVID-19 patients with ARDS, chest consolidation, and fever who failed to respond to steroid therapy. Upon diagnosis of TB, the patient received

anti-TB therapy, which led to an improved clinical outcome [30]. In another case study, the patient without co-morbidities with severe COVID-19, the use of single-dose Tocilizumab (TCZ) led to the development of symptomatic TB [31]. So, reactivation of dormant or latent TB infection (LTBI), especially among those recovering from COVID-19, can occur with the irrational use of steroids and other immunosuppressive drugs [1].

Another important aspect to be considered in this regard is the effect of the pandemic on TB management programs due to the huge impact of COVID-19 on an already stressed health care system. The resources were suddenly diverted to deal with the pandemic, leading to less availability of resources. Due to sudden nationwide lockdowns, many patients may not be able to access health care services in the time leading to delays in their diagnosis. Even after diagnosis, timely initiation of therapy and adherence to it play an important role in management. An African study showed a significant drop in diagnosed TB cases in the first 4 months of 2020, suggesting how this pandemic has hit hard on TB management programs in the third world [32].

According to the GTN global study majority of the centers involved in the study in the first 4 months of 2020 had a low rate of newly diagnosed cases of active TB, the total active TB outpatient visits, and the new LTBI diagnosed. In some centers, due to a shortage of workforce, people working as TB services were re-assigned to COVID-19. In the community, due to fear of exposure to COVID-19, there was decreased attendance to TB. Due to national lockdowns, there was also disruption of door-to-door TB services [33,34].

12. NEED TO THINK DIFFERENTLY AND COHERENTLY

Between 2020 and 2025, it is estimated that there may be additional 6.3 million cases of TB globally and an extra 1.4 million death due to COVID [35]. Due to the lockdowns, we expect increased transmission in home clusters and decreased transmission in social circumstances for TB [25]. Increasing awareness about TB along with COVID should be a new way forward. Wearing masks, social distancing, and avoiding large gatherings have to be reemphasized on every occasion to reduce the transmission of both diseases. TB programs are to be modified so that we can have good diagnostic and treatment facilities for patients in government and private settings. To avoid exposure of vulnerable TB patients to COVID, we should have mobile vans equipped with mobile chest x-rays and drugs so that these patients could avail of this facility at home. During COVID vaccination, we should prioritize high-risk groups for both diseases for vaccinations [1].

According to a GTN study, national lockdowns favored the increased use of telemedicine in Australia, Russia, India, and the United Kingdom. Telehealth service use increased, which can be further used for surveillance of these two diseases [34]. We can create opportunities, such as contact tracing among the general population and public health units, to engage more in core epidemiologic surveillance and infectious disease control for the follow-up of patients for COVID-19 and TB [36]. Genomic surveillance should be conducted across the country regularly to monitor further drug resistance to TB and new variants in COVID-19 in the wake of any further pandemic or “third” wave [1].

Due to accelerated COVID research, many TB research programs are affected by the sudden diversion of funds, which should not happen. We should utilize the newly developed laboratories for COVID research to find new aspects in TB research so that we can obtain the best results with our limited means [37].

13. CONCLUSION

With the advent of a new pandemic, the oldest pandemic in the world should not be ignored. As we embrace the new normal ways of life, we should always look forward to new avenues in both diseases. Due to COVID, there is a renewed interest in scientific research and its implementation in public life by means of new public health programs. We can use this opportunity to modify existing programs as well as the behavior of society to infectious diseases so that not only the scientific community but society as a whole can reap fruits.

CONFLICT OF INTEREST

There is no conflict of interest.

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