

Tuberculosis and Coronavirus Disease 2019 (COVID-19) from A Clinical Perspective: A Systematic Review

Klinik Perspektiften Tüberküloz ve 2019 Koronavirüs Hastalığı (COVID-19): Sistemik Bir İnceleme

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ABSTRACT

The aim of this review is to examine the effects of COVID-19 on Tuberculosis (TB) management and to highlight evidence of the extent of TB and COVID-19 co-infection. Current findings on TB and COVID-19 have been identified using six databases: Pubmed, Science Direct, Pubmed Central, MedXRiv, Wiley, and Google Scholar. This search in literature was conducted up to 8 May 2020. We included five studies that met the selection criteria. These selected studies have been performed in regions having various demographic characteristics including developed and developing countries, mainly China. The total number of participants in each study ranged from 24 to 203. The case fatality rate of patients with TB and COVID-19 co-infection was found to be high (6/49; 12.3 percent) while a combined diagnosis of TB and COVID-19 was found in 9/49 patients. This condition is linked to several complications, manifested as the need for ex novo oxygen supply, pneumothorax, and extreme hypoxia. Researches on BCG vaccination have shown that countries without vaccination policy are more likely to be seriously affected than those with BCG vaccination programs. COVID-19 infection in patients with TB or the lack of sufficient BCG vaccination may be associated with higher detrimental consequences, including mortality.

Keywords: BCG vaccine, COVID-19, tuberculosis

ÖZ

Bu incelemenin amacı, COVID-19'un Tüberküloz (TB) yönetimi üzerindeki etkilerini incelemek ve TB ile COVID-19 ko-enfeksiyonunun kapsamına ilişkin kanıtları vurgulamaktır. TB ve COVID-19 ile ilgili mevcut bulgular altı veri tabanı kullanılarak tanımlanmıştır: Pubmed, Science Direct, Pubmed Central, MedXRiv, Wiley ve Google Scholar. Bu kaynaklardan 8 Mayıs 2020 tarihine kadar literatür taraması yapılmıştır. Seçim kriterlerine uyan beş çalışma seçilmiştir. Bu seçilmiş çalışmalar, başta Çin olmak üzere, gelişmiş ve gelişmekte olan ülkeler dahil olmak üzere çeşitli demografik özelliklere sahip bölgelerde gerçekleştirilmiştir. Çalışmalardaki katılımcı sayıları ise 24 ile 203 arasında değişmiştir. Kombine TB ve COVID-19 tanısı 9/49 oranında hastada bulunurken, TB ve COVID-19 ko-enfeksiyonu olan vakaların ölüm oranı yüksek (6/49; %12,3) bulunmuştur. Bu durum ex novo oksijen kaynağı ihtiyacı, pnömotoraks ve aşırı hipoksi olarak ortaya çıkan çeşitli komplikasyonlarla bağlantılıdır. BCG aşılması üzerine yapılan araştırmalar, aşılama politikası olmayan ülkelerin etkilenme olasılığının aşılama programları olan ülkelere göre ciddi şekilde daha yüksek olduğunu göstermiştir. TB hastalarında COVID-19 enfeksiyonu bulunması veya yeterli BCG aşısının olmaması, mortalite dahil daha yüksek zararlı sonuçlarla ilişkili olabilir.

Anahtar kelimeler: BCG aşısı, COVID-19, tüberküloz

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INTRODUCTION

The World Health Organization (WHO) confirmed a new form of pneumonia with an unclear cause on 31 December 2019 in Wuhan, China. After the first outbreak, the disease has spread exponentially across the globe. The rise made it possible for the WHO to issue a statement claiming that the epidemic is a public health emergency of international concern. Since February 12, 2020, COVID-19 (coronavirus disease 2019) has been used as the official name of the disease replacing 2019 n-CoV (coronavirus novel 2019). SARS-CoV-2 is known as the pathogen responsible for this infection^{1,2}.

COVID-19 has a person-to-person transmission that is mostly induced by droplets and close contact, distinct from other respiratory pathogens such as tuberculosis (TB) that spreads airborne. Fomites are major sources of the infection and SARS-CoV-2 can survive in the open environment for three hours. Virus transmitted by the infected person's droplets can stick to the surface and cause transmission if the individual touches on the contaminated surface; and also touches on the eye, nose, and mouth without adequate hygiene precautions¹.

Major clinical symptoms of COVID-19 include fever, cough, and trouble breathing. Less common symptoms may include fatigue, myalgia, and gastrointestinal symptoms such as diarrhea. It is believed that SARS-CoV-2 has been transmitted first from animals to humans, and eventually among human beings. Asymptomatic transmission can occur with COVID-19. The incubation period of the disease is from one to 14 days, with an average of three to seven days⁴.

TB is an ancient disease that has been described as a major problem worldwide. One third portion of the world's population (about 1.7 billion) have been afflicted with *Mycobacterium tuberculosis*⁵. By 2018, 87% of new TB cases occurred in the 30

high TB burden countries. Constituting two-thirds of the new cases of TB, there are eight major contributors, including India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. Southeast Asia, followed by Africa and the Western Pacific, are the key geographical areas impacted by this situation⁶.

According to the study model, if the COVID-19 pandemic triggers a 3-month decrease in the TB detection rate (a reasonable prediction given the TB detection issue in many countries) there would be a rise of 13 percent in TB deaths, leading to the TB mortality rate like five years ago⁷. This calculation is very conservative and does not take into account certain impacts of this pandemic on the incidence of TB.

Therefore, we conduct a systematic review to assess the evidence of TB and COVID-19, especially from clinical perspective. This study may help to examine the impact of COVID-19 on TB management and to highlight the evidence on severity of co-infection with TB and COVID-19.

MATERIAL and METHODS

We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria for the preparation of manuscripts. The inclusion criteria comprised of researches relating to our goal (they must be explanatory about TB or BCG, and its association with COVID-19). Studies must be conducted in English and include observational studies (cross-sectional, case-control, and cohort design). The full text of the studies must also be available. The exclusion parameters related to the characteristics of studies were also determined. Articles, thoughts, critiques, editorials, case reports and case series, observational research, and those with an experimental design were not included in our review. We have two objectives: (i) to evaluate the prevalence of TB in COVID-19 patients; (ii) to assess the effect of TB on the clinical course of COVID-19.

The databases of MEDLINE/PubMed, Pubmed Central (PMC), Science Direct, Wiley, MedXriv, and Google Scholar were scanned using the keywords given in Table I. Then selected studies were reviewed for their titles and abstracts by reviewers and balanced with inclusion and exclusion criteria. Literature search was conducted up to May 8, 2020. After screening, the qualifying studies have been downloaded and the full texts were further read by reviewers. Thereafter, they reached a consensus on which studies would be included for review.

RESULTS

Our search strategies have listed a total of 1914 potentially relevant articles. We recognized 11 papers after screening by their titles and abstracts. We eventually agreed that five studies should be included in our systematic review after a careful reading of the full text and removing studies that

did not apply to our goal. There is only one article referring to our second objective. Due to the lack of available TB literature and COVID-19, we decided to include BCG studies in our analysis because they are related to TB and might potentially disclose the effect of TB on COVID-19. The flow of our sample collection is described following the PRISMA Statement (Figure 1).

Table 2 summarizes the features of six studies arranged by the first author's names. Three studies were of cross-sectional design, two with retrospective cohort design, and one study used case-control design. Two of the studies were conducted in China, one from US (through the Internet source), one from Italy, and the last one was a multi-centered study. Total number of participants in each study ranged from 24 to 203.

One research revealed that the co-infection of TB and COVID-19 resulted in a high case fatal-

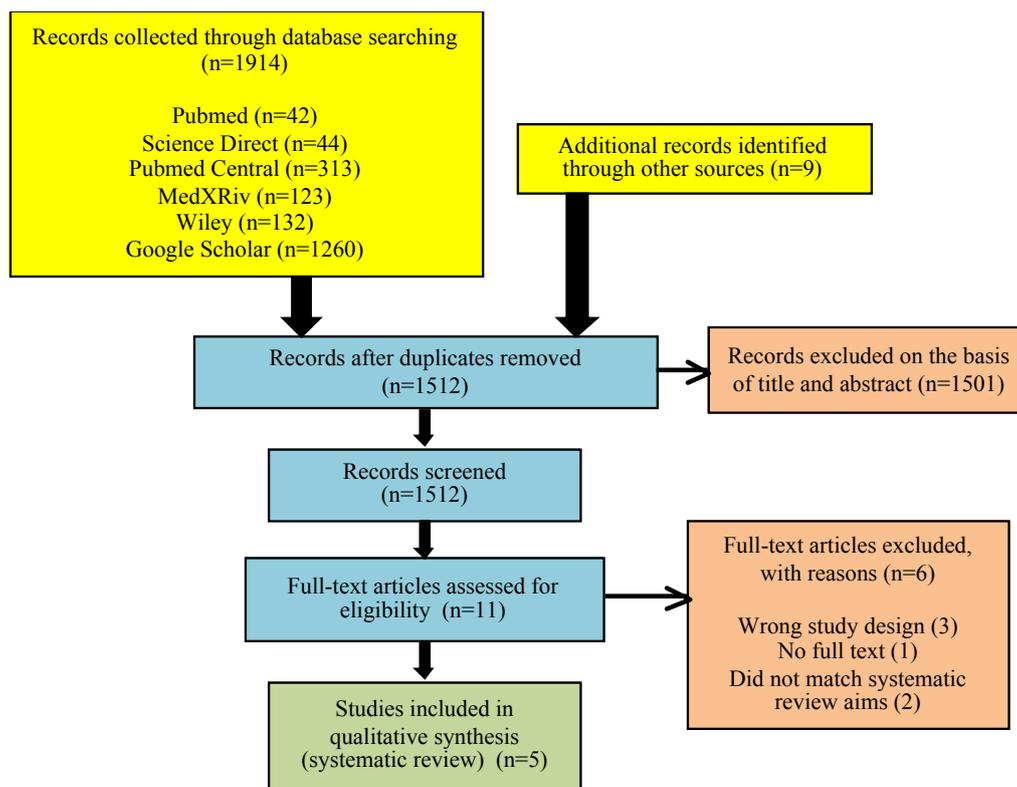


Figure 1. Diagram for the identification and exclusion of study in systematic review process.

Table 1. Terminology used in search queries.

Location	Terminology	Hits	Selected
Pubmed	[tuberculosis OR TB] AND [SARS-Cov-2]	42	0
Sciencedirect	[tuberculosis OR TB] AND SARS-Cov-2] AND characteristic	44	0
PMC	[tuberculosis OR TB] AND SARS-Cov-2]	313	2
MedXriv	[tuberculosis OR TB] AND SARS-Cov-2] AND clinical characteristic	123	1
Wiley	[tuberculosis OR TB] AND SARS-Cov-2] AND clinical characteristic	132	0
Google Scholar	[“tuberculosis” OR TB] AND SARS-Cov-2] AND clinical characteristic AND Risk factor AND Clinical features	1260	3

Table 2. Summary and important results of five included studies.

Studies	Sample size	Country	Age range	Gender	Data Collection	Study design	Results
Tadolini et al ⁸	n=49	Belgium, Brazil, France, Italy, Russia, Singapore, Spain, Switzerland	28.0-63.0	Male and Female	Medical records	Retrospective cohort Cross sectional Case control Retrospective cohort Ecological study	There were high case fatality rate on TB patient (5/49,10,2%). 5/6 were >60 years old and all of them had ≥ comorbidities (4 COPD; 1 HIV coinfection plus liver and kidney diseases, hypertension and cancer in different combination) Simultaneous diagnosis of TB and COVID-19 was found in 9/49 patients) Protective effects of BCG (bacillus Calmette–Guérin) vaccination is inconclusive
Stochino et al ⁹	n=24	Italy	27-46	Male and Female	Medical records and primary clinical data		Among 24 patients diagnosed with active TB, 19 patients had COVID-19. During hospitalization, three patients required ex novo oxygen supply due to low saturation, among them two had respiratory complications (pneumothorax) and one elderly patients with severe pulmonary TB developed severe hypoxia
Chen et al ¹⁰	n=36	China	25-79	Male and Female	Medical records		TB infection is linked with disease severity (78% of critical cases vs 22% of mild/moderate cases, p value=0,049). TB infection is also found more common than other comorbidities
Chen et al ²⁰	n=203	China	41-68	Male and Female	Medical records		TB was present in 4 patients out of 203 patients. one patient diagnosed with TB died after admission.
Miller et al ¹¹	n=60 countries (BCG World Atlas)	United States of America	N/A	N/A	BCG World Atlas and Google COVID-19 Map		Countries without BCG policy is more severely affected compared to countries with BCG vaccination policy

ity rate (10.2 %), in addition to some concurrent findings for diagnosis of TB and COVID-19 in 9/49 patients⁸. Another research found a higher proportion of joint TB-COVID-19 infection (19/24 patients)⁹ which was also linked to higher number of complications in these patients¹⁰. In a country with a wide BCG implementation, our quest for BCG vaccination found that it was correlated with a milder COVID-19 event¹¹.

DISCUSSION

Co-infection of TB and SARS-CoV-2

COVID-19 pandemic has a major effect on the prevalence of TB in healthcare facilities. Access to diagnostic tools may decrease because of limited human and material resources and social stigma attached to TB patients due to cough as a sign. This stigma has always existed for TB but has

worsened as a result of the COVID-19 pandemic, and it may lead individuals to conceal their condition from others and to postpone visits to health facilities¹². The World Health Organization has estimated that about one third of the people living with TB are now undiagnosed, untreated, and underreported. COVID-19 pandemic may increase the number of “missing” people and become a major source of transmission that lead to high morbidity and mortality¹³.

While SARS-CoV-2 pathophysiology has not yet been completely understood, the virus appears to have the same pathophysiology as SARS-CoV-1. Strong evidence of SARS-CoV-2 infection can cause severe inflammation by increasing expressions of cytokines such as interleukin-1 β (IL-1 β), interferon- Δ (IFN- Δ), tumor necrosis factor-5-007 (TNF-5-007), interleukin-2 (IL-2), interleukin-4 (IL-4), and interleukin-10 (IL-10) associated with an increase in the severity of the disease due to the cytokine storm¹⁴.

Since SARS-CoV-2 was first detected in December 2019, there is very little research to determine TB co-infection. Nevertheless, it was found from the available data that the TB status played a significant part in progressive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The incidence of TB and COVID-19 coinfection was found to be 0.45 % in India on January 21, 2020. According to these results, TB may increase the risk of death for COVID-19 (2.27% for non-TB vs 100% for TB)¹⁵. A study in China also found that TB is the most prevalent coinfection as opposed to other comorbid conditions such as hypertension, coronary artery disease or COPD. It means that TB is a common risk factor for infection with SARS-CoV-2. The research also showed that co-infection of TB would lead to a faster development of the disease, three days earlier in comparison to a non-TB patient¹⁰.

Treatment of patients diagnosed with TB can also be affected, particularly in drug-resistant TB due

to issues in medication manufacturing and transport, lack of nutritional and mental support, inadequate access to healthcare facilities, and insufficient treatment of drug reactions and comorbid diseases such as HIV, diabetes, and cancer¹⁶. In addition, treatment of comorbid diseases can have a major effect on the progression of latent TB to active TB. Preventive measures against TB among populations will lose their vigor due to the allocation of healthcare services to COVID-19 patients, and consequently non-emergency visits to healthcare facilities are not recommended¹⁶. This is particularly worrisome because TB transmission to household members may increase with COVID-19, and also by higher exposure to TB for the patient family during quarantine period^{17,18}.

BCG Vaccine and SARS-CoV-2

Vaccination is the most effective way to avoid illness caused by pathogens such as bacteria or viruses. After the discovery of SARS, several attempts have been made to find an effective vaccine to prevent the occurrence of the disease. Several vaccine ideas have been created, such as inactivated or live-attenuated, DNA-based vaccines, recombinant proteins, virus-like particles, etc. but none has been accepted. Recent research has shown that the SARS-CoV-2 genome is 80 % similar to SARS-CoV-1 and 50 % similar to MERS-CoV, therefore studies on the safety of the SARS-CoV-1 immune response could be helpful in developing the SARS-CoV-2 vaccine^{11,19}.

The TB vaccine is also one of the vaccines considered to prevent COVID-19 since no approved vaccine has yet been developed. The TB vaccine has been used widely and BCG-vaccinated neonates have been shown to have a threefold lower mortality rate compared to those who did not. Recent studies have shown an inverse association between BCG vaccination and the incidence and mortality rate of COVID-19. BCG has shown to help avoid SARS-CoV-2 via an innate immune response that is beneficial to respiratory viruses similar to SARS-CoV-2^{11,19}.

Our analysis has a range of limitations. First, several areas such as Africa and Australia, have not entered our quest area. It may be because published literature from these regions is not included in the five search engines that we used. Potential studies should provide a source of literature for local areas. Second, we have not been just looking for TB, we have also used BCG, trying to scan as much literature as possible, but related literature is still sparse, and the findings are only a few. Third, the recovered papers have a small number of samples, making it difficult to make generalizations.

This analysis also has a range of strengths. In the first instance, this research has been performed in both developing and developed countries. Second, it relates to the broad characteristics of the clinical aspects of TB and COVID-19 patients.

Conclusion

While the data are sparse, TB could be one of the risk factors for a rise in the mortality rate of COVID-19. In one study, TB is shown to be more severe than other comorbid medications such as hypertension, coronary artery disease, and COPD. TB can be a common risk factor for infection with SARS-CoV-2. Further research on the inter-relationship between TB and SARS-CoV-2 infection with a more diverse demographics is required to boost global coverage to draw a solid conclusion on this phenomenon.

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