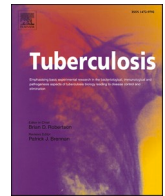




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Pathology of TB/COVID-19 Co-Infection: The phantom menace

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ABSTRACT

Tuberculosis (TB) and coronavirus disease 2019 (COVID-19) are currently the two main causes of death among infectious diseases. There is an increasing number of studies trying to elucidate the interactions between *Mycobacterium tuberculosis* and SARS-CoV-2. Some of the first case reports point to a worsening of respiratory symptoms in co-infected TB/COVID-19 individuals. However, data from the cohort studies has shown some conflicting results. This study proposes to conduct a systematic review on the current literature on TB/COVID-19 co-infection cohorts, evaluating clinical and epidemiological data, focusing on its implications to the immune system. From an immunological perspective, the TB/COVID-19 co-infection has the potential to converge in a "perfect storm". The disorders induced by each pathogen to the immunomodulation tend to induce an unbalanced inflammatory response, which can promote the progression and worsening of both diseases. Understanding the nature of the interactions between *M. tuberculosis* and SARS-CoV-2 will be crucial for the development of therapeutic strategies against co-infection.

1. Introduction

Considered by the World Health Organization (WHO) as the "public enemy number one", coronavirus disease 2019 (COVID-19) brought chaos to the healthcare systems across the globe. Suddenly, humanity was faced with a deadly new pathogen, capable of spreading quickly and aggressively through the host's organism, as among society as well. While the COVID-19 second wave haunts nations that already seemed to have overcome the pandemic some countries, like Brazil, are still hostages to SARS-CoV-2. In Africa, South America and Southeast Asia, the crisis may become even worse, as COVID-19 may end up converging with another deadly disease: the tuberculosis (TB) [1,2].

In contrast with COVID-19, which we are just beginning to understand, TB is an ancient threat that menaces mankind since prehistoric ages, for at least 70,000 years [3]. This coevolution has shaped *M. tuberculosis* as a pathogen highly adapted to coexist and thrive among the humanity. Consequently, it is estimated that 2 billion people are latently infected with TB worldwide (LTBI) [4]. Each individual with LTBI has approximately a 10% chance of developing the disease in its active form throughout life, however, this risk may vary geographically and rise to 50% in individuals co-infected by the human

immunodeficiency virus (HIV) [4]. Although, TB persists as the leading cause of death among infectious diseases; however, since April 2020 COVID-19 has shown similar numbers of daily deaths worldwide [5]. The convergence between these two deadly diseases raises concern among health authorities, especially in TB endemic countries.

The consequences of the COVID-19 pandemic poses serious challenges to TB control programs, mainly by impairing TB diagnosis and treatment. Due to the similarities between TB and COVID-19 symptoms, countries with a precarious diagnostic structure suffer to properly identify these infections; this issue negatively influences in therapeutic decision-making and, therefore, impacts in prognosis of both diseases [6–9]. TB treatment adherence and continuity are also affected by the lack of resources, drugs and medical supplies, as well as by the reduction of the mobility of patients and healthcare professionals; which can result in treatment failure and, consequently, in an increase in incidence of multidrug-resistant TB (TB-MDR) [10,11]. Another crucial aspect is that both TB and COVID-19 share similar social determinants, including poverty, overcrowding, diabetes and air pollution [12]. Some countries are already facing these side effects of the pandemic, however, the consequences of COVID-19 for TB go far beyond logistical and administrative issues [13].

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Many individuals who develop active TB are immunocompromised and/or live in a situation of social vulnerability. In this context, the emergence of the acquired immunodeficiency syndrome (AIDS), in the middle of the 20th century, has enhanced TB dissemination, which was relatively controlled until then [14–16]. *M. tuberculosis* and HIV interact cooperatively, impairing host's defenses, as the immune system is exhausted and both pathogens spread through the organism [17,18]. The synergy between these diseases resulted in a deadly syndemic of global proportions; currently TB is the main cause of death among HIV-seropositive individuals. COVID-19 rises now as a new menace, due to its devastating impact on the immune system and, mainly, to the lung functions [19,20].

Therefore, becomes clear the urgency for further studies focused on TB/COVID-19 co-infection, in order to try to contain this new pathogen association. This article presents a brief systematic review of TB/COVID-19 co-infection on the current literature, focusing on case reports and cohorts studies, in an effort to point out the main immunological aspects involved in this pathology.

2. Methodology

2.1. Research databases

This review was performed in accordance with the guidelines of the Center for Reviews and Dissemination (CRD) of York University [21]. The search for suitable studies was focused on papers available on the PubMed database, published until August 31, 2020.

The search strategy was based on the use of the following keywords, combined or separated, always accompanied by "tuberculosis" and "COVID-19" among them: "immune response", "SARS", "mycobacterium", "coronavirus" and "co-infection". In addition, the bibliography of the reviewed studies was also evaluated to support the results discussion.

2.2. Study selection

Two authors (GM and MF) carried out the studies selection for this review independently; any divergences were resolved in discussion with the help of the third author (AP). The following selection criteria were applied:

- Study design: cohorts and case reports;
- Sample size: at least 20 cases of TB/COVID-19 co-infection per study;
- Study population and assessed outcome: individuals proven to be co-infected with LTBI or active TB and COVID-19, regardless of the outcome.

After the first searches on PubMed, combining the keywords previously mentioned, a total of 144 results were obtained. Most of these publications were duplicated or diverged from the scope of this review. After a superficial analysis of the titles and abstracts, 11 case report and cohort studies were selected. These studies were then evaluated, considering the number of TB/COVID-19 co-infected individuals, the description of the clinical data and the information regarding the treatment outcome. At the end of the selection process, only 6 studies were chosen to compose this review.

The reason for focusing on studies with larger samples and more complete data sets, is because they provide a better representation of the general population, in addition to being more a robust evidence of the relationships between pathogens.

2.3. Data extraction

From the 6 studies that met to the review selection criteria, the following information was extracted: study design, sample size, clinical features, outcomes, main findings and limitations. Two authors (GM and MF) independently assessed all data, with differences being discussed

and solved with a help of a third author (AP).

2.4. Data synthesis and analysis

All the data collected from the reviewed studies were critically assessed by the authors and summarized in Table 1. Some of the information, regarding the clinical characteristics of the TB/COVID-19 co-infection, was not described in a standardized manner in their respective articles, therefore, not all the data presented in Table 1 can be paired between the studies. In addition, some of the mentioned studies were published before the outcome information's could be evaluated, therefore, they do not present this data.

3. Results

The results of this review are described in Table 1. In summary, most of the evaluated studies point to an association between TB and COVID-19. Both active TB and a previous history of TB seem to be related to an increased risk for the development of COVID-19, as well as worsening the infection prognosis [22–27].

However, there are still few clinical data on TB/COVID-19 co-infection, and some of the first published case reports and cohort studies have significant limitations. In general, the samples sizes are quite small, most of studies have been conducted in countries with a low TB burden and clinical features are not well described on the papers. Another important aspect is the lack of information on other pre-existing diseases and comorbidities, such as obesity, hypertension or diabetes; in most of cases, it is even difficult to identify whether TB was diagnosed before or during treatment for COVID-19.

Despite these limitations, the reviewed studies offer an evidence that supports that TB contributes to the susceptibility and the worsening of COVID-19. However, it is worth mentioning that other factors such as social conditions, comorbidities, elderly and access to healthcare directly influences the prognosis of TB/COVID-19 co-infection.

4. Discussion

The first cohort evaluating the association between TB and COVID-19 consisted of international cooperation, grouping 49 cases of co-infection from 8 different countries; this study identified a higher mortality among elderly people with a previous history of TB, however, regional differences in the COVID-19 treatment protocols may have interfered in the evaluated outcomes [22]. The study published by Chen et al. reported that TB increases the susceptibility to COVID-19 and the severity of its symptoms [23]. Nevertheless, it is worth mentioning some significant limitations of this study, such as its small sample size and the lack of clinical criteria to define the presence of TB. Two Italian cohorts also investigated the interactions between TB and COVID-19, in both of them; most of the cases were composed of migrants and refugees. Both studies also suggest that the co-infection is a clinically manageable condition, although that it can be potentiated due by elderly or in the presence of comorbidities [24,25]. Another study, conducted in the Philippines, reinforced the deleterious role of TB over COVID-19, associating the co-infection with a greater risk of morbidity and mortality [26]. However, the most significant evidence of the influence of TB on the prognosis of COVID-19 came from a South African cohort conducted by Davies et al. Data of more than 3 million patients treated by the public health system, with or without COVID-19, were compared taking into account the presence of other comorbidities, including TB and HIV. The results indicate that both the previous history of TB, as well as current TB and TB associated with HIV increase the risk of death in patients infected with COVID-19 [27].

Recently, two other reviews, including a meta-analysis, were conducted with data from case reports and cohorts of co-infected TB/COVID-19 individuals [12,28]. Both studies did not identify a direct association of TB with the worsening of COVID-19, however, it should be

Table 1
Review of the main TB/COVID-19 cohorts published so far.

Reference	Country	Sample Size (co-infected/total)	Clinical features	Outcomes (% deaths)	Study main findings	Limitations
Tadolini (22)	Multinational	49/49	Majority of males, 43 were symptomatic. 36 had active TB and another 13 had a previous history of TB. Some patients also had other comorbidities, such as HIV infection, diabetes and cancer	18 recovered individuals, 25 still on treatment and 6 deaths	Larger studies are needed to understand the role played by SARS-CoV-2 in the progression from latent TB infection to the active disease, as well as the role of <i>M. tuberculosis</i> in the progression of COVID-19. In seven cases, COVID-19 occurred in patients with TB sequelae. They were older than the other patients and had higher mortality (although not statistically significant)	International cohort composed of a heterogeneous cluster of cases, with differences in therapeutic protocols and access to healthcare services, cannot be considered representative either of the European nor of the global situation.
Chen (23)	China	36/86	Co-infected individuals showed a faster development of respiratory symptoms, as well as a more severe clinical manifestation.	Not available.	TB infection likely increases susceptibility to SARS-CoV-2, and increases COVID-19 severity	The inclusion criteria applied to classify individuals with TB are not very specific, making the co-infected group composed of a miscellany of cases with heterogeneous clinical manifestations. Lack of information on social determinants and comorbidities that may be influencing the co-infection prognosis
Stochino (24)	Italy ^a	20/20	Majority of males, 13 had lymphocytopenia and one had thrombocytopenia. Severe respiratory failure was observed only in the deceased patient. Biochemical tests did not show major deviations from expected values, except for D-dimer levels	12 recovered individuals, 5 still on treatment and 1 death	The impact of TB/COVID-19 co-infection appears to be clinically manageable with proper care. Rigorous infection control practices and personal protection devices are fundamental to prevent the risk of in-hospital transmission, especially when dealing with a highly vulnerable population	Clinical symptoms may have been partly under-estimated due to cultural and linguistic barriers as the vast majority of patients were recent immigrants. The duration of follow-up was limited to a few weeks, thus not allowing for assessment of longer-term outcomes
Motta (25)	Italy ^a	69/69	Among the individuals who died, the vast majority were male, elderly and with comorbidities such as hypertension, alcoholism and diabetes	61 recovered individuals and 8 deaths	Mortality is likely to occur in elderly patients with comorbidities; TB might not be a major determinant of mortality; migrants in this study had lower mortality, probably because of their younger age and lower number of co-morbidities	International cohort composed of a heterogeneous cluster of cases, with differences in therapeutic protocols and access to healthcare services, cannot be considered representative either of the European nor of the global situation.
Sy (26)	Philippines	172/860	Majority of males, many with hypertension and/or diabetes. Most of deaths were among older individuals and with several comorbidities	95 recovered individuals and 43 deaths (34 unknown)	Co-infection with TB increased morbidity and mortality in COVID-19 patients	Lack of information on social determinants and comorbidities that may be influencing the co-infection prognosis
Davies (27)	South Africa	2128/22308	Majority of females, many with hypertension and/or diabetes. Most of deaths were among older individuals and with several comorbidities	Coinfected HIV seronegative individuals 879 Previous TB + COVID-19: 45 deaths 155 Current TB + COVID-19: 10 deaths Coinfected HIV seropositive individuals 864 Previous TB + COVID-19: 42 deaths 172 Current TB + COVID-19: 16 deaths	Both past history of TB, current TB and TB associated with HIV increase the risk of death in patients infected by COVID-19	Lack of information on social determinants and comorbidities that may be influencing the co-infection prognosis

^a Although the studies were carried out in Italy, most of the cases evaluated were in migrants.

noted that these reviews only evaluated the literature available until then, not including the results of the South African cohort, for example [27]. An assessment conducted by a task force composed of specialists in immunology and microbiology, concluded that despite the current lack of data on co-infection, it is quite likely that there is indeed a relationship between TB and the worsening prognosis of COVID-19, as well as

COVID-19 with the progression of TB. However, there has not yet been time for these analyzes to be properly conducted [29]. Over time, more studies describing TB/COVID-19 should be published, confirming these hypotheses. Even so, the lack of data from TB endemic countries and with a high incidence of COVID-19, such as Brazil and India, remains intriguing. What can already be established as a consensus is that

co-infection is particularly dangerous for people in conditions of social vulnerability, the elderly and people with other comorbidities, such as diabetes and hypertension. Considering that a significant part of the individuals who develop active TB is part of this group highlights the need for special attention to these populations during the pandemic.

There is still no experimental data of immunopathological aspects regarding TB/COVID-19 co-infection. However, based on the findings of population studies, together with what is already known about the etiology of each disease, it is possible to discuss some aspects of co-infection. Both TB and COVID-19 have airborne transmission, both affect mainly the lungs, have similar symptoms and share the same social determinants. However, *M. tuberculosis* and SARS-CoV-2, present significant differences in their pathogenesis, understanding them, as well as learning about their interactions may contribute to the development of new strategies for the prevention and treatment of TB/COVID-19 co-infection. *M. tuberculosis* and SARS-CoV-2 may act synergistically when they share the same host. *M. tuberculosis* interferes drastically in the pulmonary microenvironment; during latent TB infection, the persistence of mycobacteria induces a chronic pro-inflammatory response in the lung parenchyma, which is necessary to maintain the structural integrity of granuloma [30–32]. The main cytokines that contribute to the containment of the bacillus, TNF and IFN- γ , also play a key role in the pro-inflammatory immunomodulation of the response against SARS-CoV-2 [33]; it is likely that stimuli against TB and COVID-19 add up in co-infected individuals, leading to the accumulation of active cells in the lung, cytokine storms and, therefore, immunopathology. The death of lung cells, due to necrosis and pyroptosis, also results in the local dispersion of DAMPs, which intensifies the inflammatory feedback in the lower respiratory tract.

The pulmonary alveoli are like battlegrounds for TB and COVID-19. However, while *M. tuberculosis* silently infiltrates into the lungs, trying to avoid the over-stimulation of the immune system, SARS-CoV-2 presents a much more aggressive approach, inducing pyroptosis and promoting immunopathology and tissue damage [34,35]. In most cases, individuals with a balanced immune system respond satisfactorily to both infections, containing or eliminating pathogens [36]. However, recent evidences indicate that, even during latency, *M. tuberculosis* persists multiplying and causing cavitory lesions [37]. The maintenance of granulomas requires fine and permanent immunomodulation, where disturbances caused by other infectious agents, such as HIV, tend to induce the activation of the disease [38,39]. Nevertheless, none of the reviewed studies set out to verify a possible causal relationship between the reactivation of TB due to SARS-CoV-2 infection. In contrast, the damage produced by TB in the lungs added to its impact on local immunity, increases the body's susceptibility to airborne pathogens [22]. This is probably the main reason for the increased risk of developing COVID-19 in patients with current or past history of TB.

The Th1 immune response against TB is characterized by the predominance of specific phagocytes and CD4 + T lymphocytes; however, the defenses against SARS-CoV-2 also depends on specialized lymphocytes [40–43]. At first, the TB/COVID-19 co-infection should delay or jeopardize the response against SARS-CoV-2, while successive inflammatory stimuli over time would result in a generalized exhaustion of T cells [44,45]. Both in TB and COVID-19, lymphocytes act as immune mediators, orchestrating the release of cytokines and chemokines at the infectious site; lymphopenia resulting from coinfection directly affects this regulation of the immune response against pathogens. The main consequence observed from lymphopenia is the exacerbated expression of cytokines, mainly pro-inflammatory [31,33,42,46–48]. Some of these cytokines expressed in co-infection may also have side effects, such as an increased expression of the ACE2 receptor on cell surface, stimulated by the IFN- γ [49]. IL-4 and IL-13 are associated with immunopathological damage and with a worse prognosis for TB and COVID-19 [50,51]. The collapse in immune homeostasis due to lymphopenia is also followed by a considerable increase in the number of neutrophils infiltrated into the lungs [52]. Neutrophils, by themselves, do not contribute as much to the

control of infections by *M. tuberculosis* or SARS-CoV-2 in the chronic phase; however, their presence is associated with the intensification of inflammatory stimuli and tissue damage [52]. In fact, the relationship between the number of lymphocytes and neutrophils has already been identified as a possible risk marker for TB and for COVID-19 [53,54].

From a macroscopic perspective, the cavitory lesions caused by TB reshape the pulmonary architecture [55]. The necrotic parenchyma is replaced by a fibrotic epithelium, reducing the surfaces available for gas exchange; bronchiectasis and bronchostenosis that are formed restrain the airflow, while obstructed capillaries compromises the lung fluid drainage [56–58]. In general, the macrostructural changes resulting from TB compromise the functioning and defense of the lower respiratory tract, which could be a complication given the consequences of an exacerbated inflammatory response against SARS-CoV-2, such as a formation of an edema. Consequently, the lung becomes more susceptible to severe complications, such as pneumonia and respiratory failure; this is likely one of the reasons why individuals with previous history of TB, presenting pulmonary scars and fibrosis, seems to be more susceptible to SARS-CoV-2 and have a worse COVID-19 prognosis [22,26,27]. However, it should be noted that TB present a very heterogeneous spectrum of lesions, which vary according to the bacterial strain and the host's immune response [59]. These findings reinforces the need for special attention in cases of iterant or resistant TB [60–63].

Some of the pharmacological strategies proposed to control the damage caused by COVID-19 involve the modulation of immune response with corticosteroids, in order to try to reduce excessive inflammation [64]. However, the use of immunomodulators should be evaluated considering the clinical history of each individual and taking into account the epidemiological characteristics of the local population. Drugs with anti-inflammatory function, such as TNF- α blockers, for example, can increase the susceptibility to opportunistic pathogens, such as *M. tuberculosis*, or even compromise the structural integrity of granulomas, [65,66]. Therefore, despite the urgent need to develop of new therapies against COVID-19, we must be cautious when choosing the treatment regimen so that these drugs do not disturb immune homeostasis and result in unwanted side effects [67,68].

5. Final considerations

What we know about the TB epidemiology and pathology can contribute extremely to our efforts against COVID-19 pandemic; likewise, what we are learning while facing COVID-19 can be of great help in the development of new diagnostic and therapeutic strategies against TB [69,70]. Although the attention of the scientific community is focused on SARS-CoV-2, we cannot forget about older threats. Before the pandemic, TB was already neglected, even though it was the deadliest infectious disease in the world. However, with the arrival of COVID-19, the call for investment in TB control and research programs becomes even more urgent. The review's findings indicate that TB increases susceptibility to COVID-19, as well as contributing to the worsening of its symptoms subset. Individuals in a situation of social vulnerability or presenting comorbidities have a worse prognosis. On the other hand, there are still no data regarding the influence of SARS-CoV-2 on the TB progression. Given the evidence of a probable synergism between *M. tuberculosis* and the new coronavirus, such as the severity of symptoms and sequelae of co-infection, the need for further practical studies of the TB/COVID-19 pathogenesis is evident. It is possible that in the coming months there will be an increase in the number of cases of active TB, as a side effect of the COVID-19 pandemic. Therefore, understanding how pathogens share and proliferate in the pulmonary microenvironment, as well as elucidating the mechanisms involved in the susceptibility and prognosis of both infections, will be fundamental for the development of new strategies for the prevention and treatment of TB/COVID-19 co-infection.

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