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Tuberculosis reactivation in Covid-19 patients

A reativação da tuberculose em pacientes com Covid

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ABSTRACT

The present study aims to analyze the scientific evidence about the effects of COVID-19 in patients with pulmonary tuberculosis. This is an integrative review, in which the databases of Google Scholar, Scielo, Virtual Health Library (VHL) and PubMed were used for the selection of articles that was carried out between April 26 and May 20, 2021. The descriptors used were: "tuberculosis", "coronavirus infection", "Mycobacterium tuberculosis" combined with the Boolean operator "AND and OR". The results obtained in the analyzed literature pointed out some important issues, since it was observed that patients with MTB contaminated by SARS-CoV-2, have an accelerated symptomatic evolution, but that so far has limited evidence to establish a concrete link with the evolution to SARS-CoV-2.

Keywords: Tuberculosis, Coronavirus Infections, Patients, Pulmonary tuberculosis.

1 INTRODUCTION

In December 2019, the city of Wuhan in China became the center of an outbreak of severe acute respiratory syndrome, hitherto of unknown etiology (BRAZIL, 2020). On January 7, 2020, Chinese scientists isolated the cause of the Wuhan pneumonia case series: the novel conoravirus (*SevereAcuteRespiratorySyndromeCoronavirus* - SARS-CoV-2) that produces the disease that has been classified as COVID-19 (CoronavirusDisease *2019) (WANG* et al. , 2020).

The new coronavirus, which has had repercussions in the COVID-19 pandemic, causes various symptoms, affecting, mainly, the respiratory scope, with manifestations that can range from a mild self-limited disease to severe pneumonia, acute respiratory failure and septic shock, resulting in an exponential increase in hospitalizations and deaths (LAI *et al.*, 2020).

Tuberculosis is caused by *Mycobacterium Tuberculosis*, an intracellular microorganism that causes infections that can last a lifetime. Its spread to any site of the body occurs most commonly in immunocompromised patients (MURRAY, 2019). Several vulnerability factors are correlated with its incidence, among them: immunological, sociodemographic, housing factors, lifestyle habits and HIV co-infection, thus characterizing a neglected disease (OLIVEIRA et al., 2019).

With the outbreak of COVID-19, the increase in tuberculosis co-infection has been reported constantly, thus increasing the already high potential for morbidity and mortality of each disease (TADOLINIet al., 2020; VISCA *et al.* 2021). Despite the decrease in tuberculosis cases from 2006 to 2015, Brazil did not reach the goal of the United Nations Millennium Development Goals to reduce mortality from this disease (SILVA *et al.,* 2021).

The large effect of COVID-19 as an additional risk factor for tuberculosis mortality (and vice versa) has not yet been clearly clarified in various contexts (MOTTA *et al., 2020)* Moreover, the area of discussion is in the simple rapidity of the SARS-CoV-2 vaccine, while in tuberculosis we have an old vaccine with failed efficacy (MIGLIORI et al., 2020*).*

Considering the severity of the health crisis installed by the COVID-19 pandemic, observing the pandemic context of hospitalizations, sequelae and deaths experienced, the interest emerges to deepen the knowledge about the coronavirus, seeking scientific evidence of the relationship of COVID-19 with pulmonary tuberculosis. The study in question started from the assumption of achieving the objective of understanding the diseases involved, structuring a line of reasoning for the context that will be exposed. In addition, conducting a survey of the scientific literature is appropriate to obtain the main evidence on the subject.

The present study aims to analyze the scientific evidence about the effects of COVID-19 in patients with pulmonary tuberculosis. To this end, there was a survey of the scientific production already published on the proposed theme; characterization of the selected studies regarding the country of origin, year of publication, database of origin, methodology and sample used; and analysis of the results of the selected primary studies.

2 METHODOLOGY

It is an integrative review, which reviews and combines studies with various methodologies and thus integrates their results, expanding the possibilities of analysis of the literature, being this a fundamental method for analysis and comparison of articles in relation to the theme (SOUZA *et al.*,2010).

The database of Google Scholar, Scielo, Virtual Health Library (VHL) and PubMed was used for the selection of articles that was carried out between April 26 and May 20, 2021. The descriptors used were: "tuberculosis", "coronavirus infection", "Mycobacterium tuberculosis" combined with the Boolean operator "AND and OR". The criteria used for selection were:

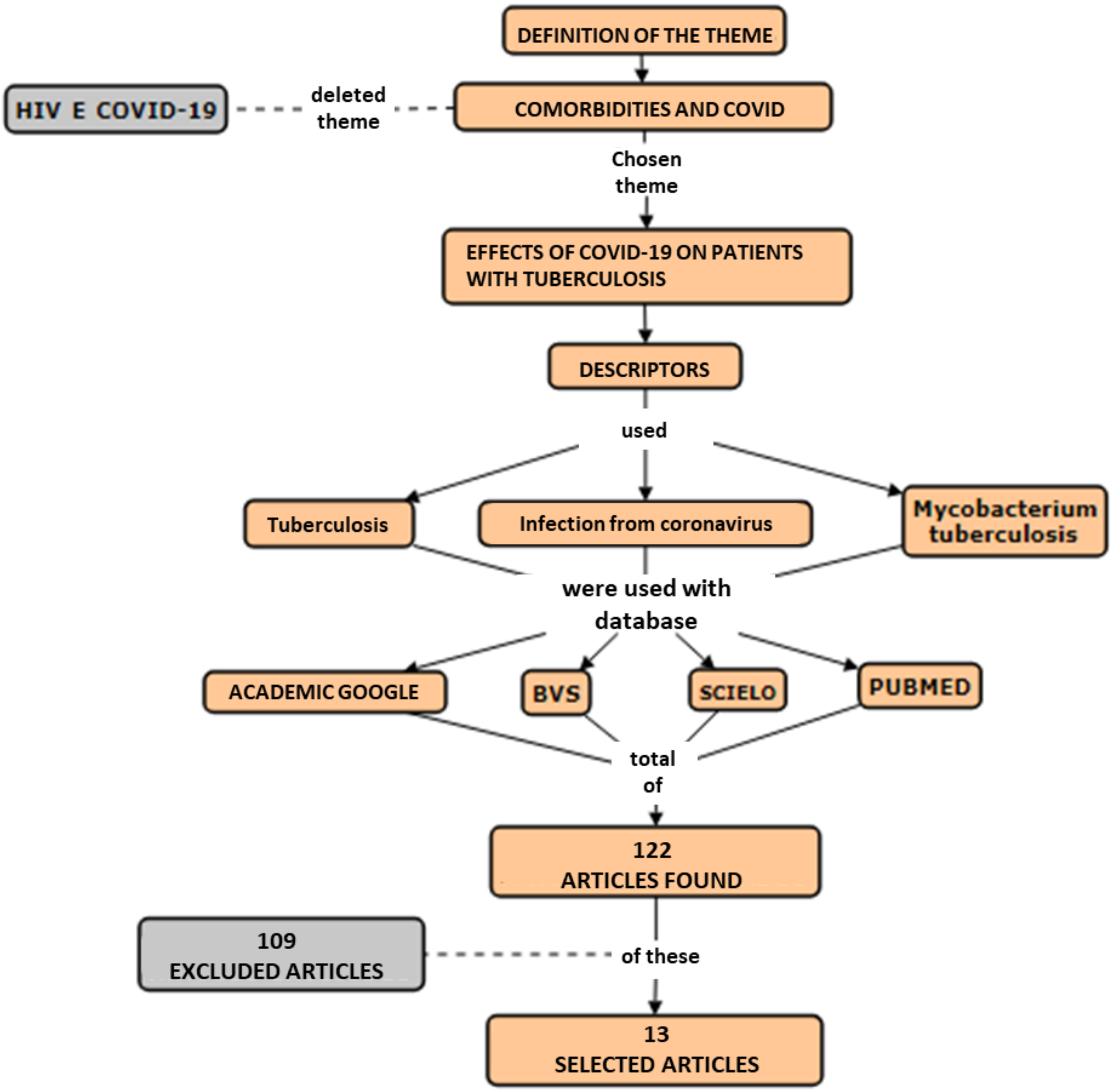
- have been published in the last 5 years;
- be accessible in full;
- be published in the languages Portuguese, English or Spanish;
- and to provide information on the subject.

Thus, the exclusion criteria were:

- date of publication greater than 5 years;
- foreign language other than those specified; and
- subjects that were not related to the objective of the theme of this research.

Thus, 122 articles were found, but only 13 met the selection criteria to present a conclusion about the material analyzed.

Figure 1: Study design flowchart



Source: elaboration of the authors

3 RESULTS AND DISCUSSION

For a better understanding of the impacts of a novel coronavirus pandemic, it is necessary to understand the experience. Since the first discovery of coronavirus occurred in 1960, since then three types of human coronaviruses capable of causing death from respiratory diseases have been reported: (CRISAN-DABIJA *et. al.*, 2020)

1. The severe coronavirus that causes severe acute respiratory syndrome (SARS-CoV, now known as SARS-CoV-1) that led to a global epidemic in 2002.

2. The Middle East respiratory syndrome coronavirus (MERS-CoV) that was discovered in 2012 and still affects people in 27 countries.

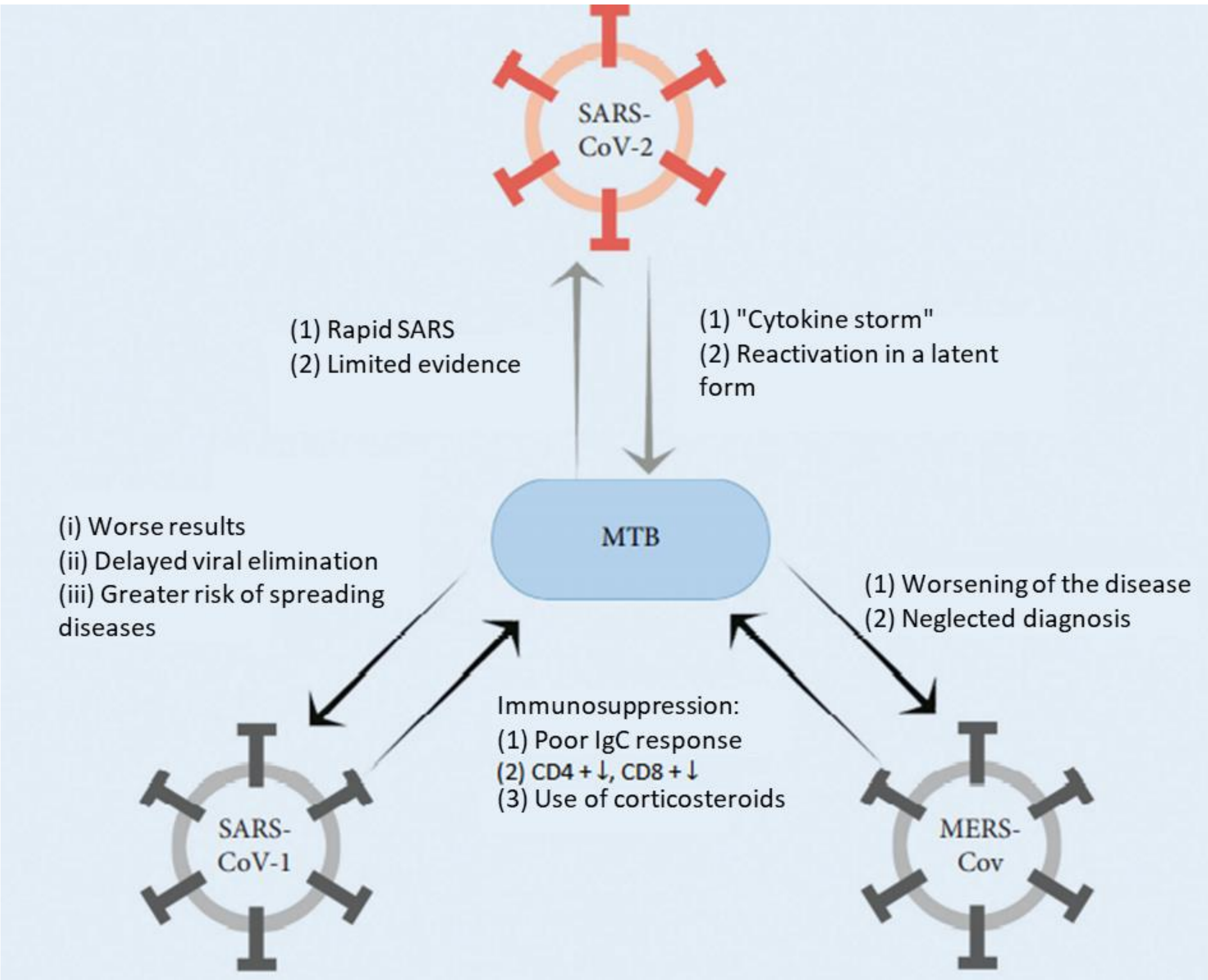
3. And the novel coronavirus (SARS-CoV-2), whose outbreak has led to a pandemic, continues with thousands of new confirmed cases every day and a growing number of deaths reported worldwide.

The risk factors associated with Covid-19 still require clarification. However, it is plausible that infection with M. tuberculosis (MTB), the pathogen that causes tuberculosis (TB) and latently infects about 25% of the global population, may be a risk factor for SARS-CoV-2 infection and severe Covid-19 pneumonia, as a study conducted in China suggested. (MACIEL; JUNIOR; DALCOLMO, 2020)

During an epidemic many measures are taken, especially in hospitals, to limit the transmission of the disease to patients not infected by COVID-19. However, overcrowded hospitals are prone to errors. Thus, patients diagnosed with TB in China reportedly acquired Severe Acute Respiratory Syndrome (SARS) due to exposure to SARS patients from the same hospital wards. Although most patients recovered without complications, SARS co-infection in TB cases led CD4+ and CD8+ T cells to significantly lower dosages and undetectable or abnormally low levels of antibodies after recovery from SARS. In addition, viral excretion was twice as high in sputum and was five times more present in the feces of patients with TB + SARS compared to SARS patients without TB, which translates into a greater potential for spread of the virus.

When dealing with a possible SARS patient from a TB-endemic region, one should never forget TB as a coexisting pathology. In addition, during the Singapore SARS-CoV-1 epidemic, cases of active TB were reported shortly after recovery from SARS, data consistent with studies in mice on the suppression of cellular immunity after a viral infection. There are also data on MERS-CoV increasing TB by added immunosuppression and reinforcing the need to evaluate a possible form of prevention. (CRISAN-DABIJA, *et. al.* 2020)

Figure 2: Known and possible interactions between MTB and coronavirus1. Source: CRISAN-DABIJA et. al., 2020, p.2.



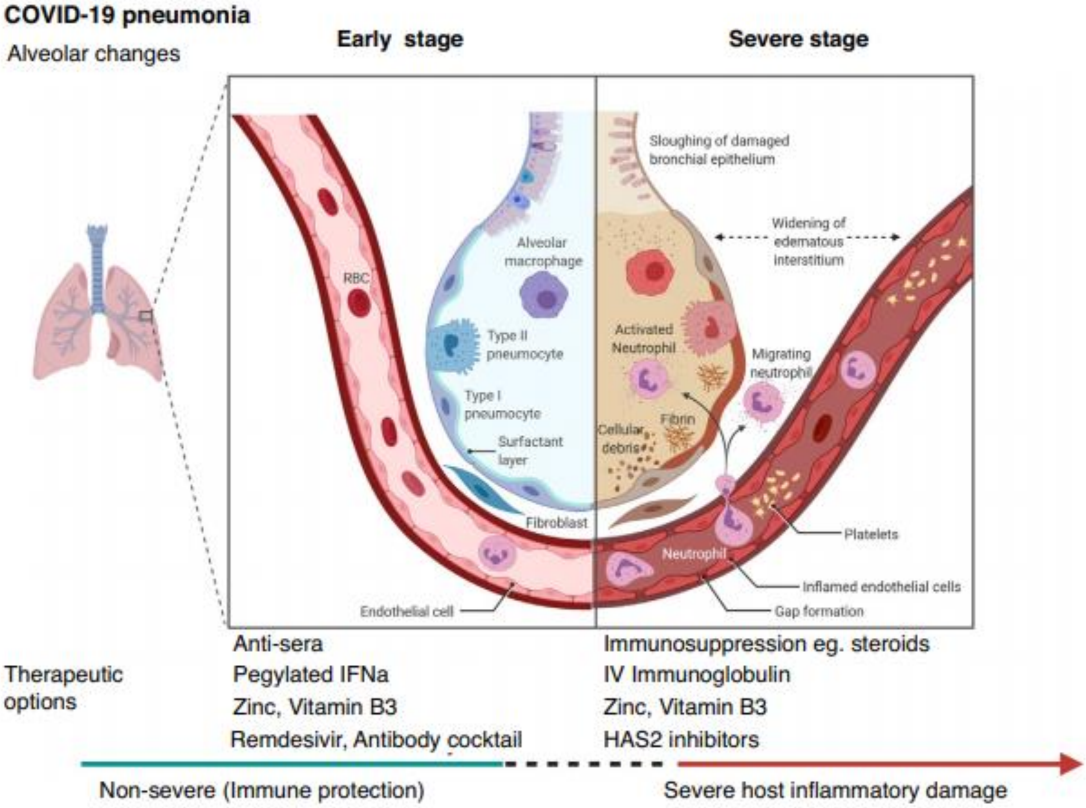
In the Figure above, the direct relationship of *Mycobacterium tuberculosis* (MTB) with SARS-CoV-1 , SARS-CoV-2 and MERS-CoV was demonstrated. As noted by Crisan-Dabija *et. al.* (2020), the relationship between patients with MTB contaminated with MERS-CoV is due to the worsening of the disease (1) and, often, to the neglected diagnosis (2) due to the similarity of the symptoms. Meanwhile, patients infected with MTB and related to SARS-CoV-1 have worse outcomes (i), with delayed viral elimination (ii) and presence of a higher risk in the spread of the disease (iii) due to the increased sputum observed. In the case of patients with MTB contaminated by SARS-CoV-2, a rapid evolution was observed (1), but so far the evidence is limited (2) to concretely correlate the favoring of the evolution of SARS-CoV-2. However, it was noted that people who already had MTB and become infected by SARS-CoV-2 suffered a "Cytokine Storm" (1) generated by the body itself and, in several reports, a latent reactivation (2) of the bacillus that causes Tuberculosis was reported.

Tuberculosis (TB) in patients with Severe Acute Respiratory Syndrome (SARS) has been reported in several studies of countries with endemic tuberculosis, such as Singapore, China or

Taiwan, in which all with patients diagnosed with TB who acquired SARS and individuals who developed TB after recovery from SARS. (CRISAN-DABIJA *et. al.*, 2020)

In addition, patients infected by SARS-CoV-1 or MERS-CoV have a considerable immunosuppression that reflects in a poor IgG response (1), in the low amount of TCD4+ and TCD8+ lymphocytes (2) and in a prolonged use of corticosteroids (3). The damage of this use can be noticed in the image below.

Figure 2: Schematic representation of COVID-19 infection progression and potential adjuvant interventions. IFNa: Interferon alfa; IV: intravenous; HAS2: Hyaluronan Synthase 2.



Source: VISCA et. al., 2021, p.159

Transient immunosuppression characterized both conditions, a reason for a poorer IgG antibody response and a delayed viral clearance in co-infected patients. In addition, patients with SARS who use corticosteroid therapy had higher immunosuppression. (CRISAN-DABIJA *et. al.*, 2020)

The use of immunosuppressive drugs for the treatment of critical cases of COVID-19, despite being done in a limited period of time, may result in a higher likelihood of TB activation caused by reactivation or new infection of *M. tuberculosis* (VISCA *et. al.*, 2021). The consequences of the use of these immunosuppressive drugs are evidenced in Figure 2, which shows an alveolus in two stages of COVID-19 progression. The left alveoli, affected by the mild form of COVID-19 and with mild drug therapy, is normofunctional. While the right alveoli, under immunosuppressive therapy, shows signs of desquamation of the epithelium, in which such impairment enables the reactivation of the MTB pathogen.

4 CONCLUSION

The present study aimed to analyze the scientific evidence about the effects of COVID-19 in patients with pulmonary tuberculosis, since both pathologies have their main site of involvement in the respiratory system. The results obtained in the analyzed literature pointed out some important issues, since it was observed that patients with MTB contaminated by SARS-CoV-2, have an accelerated symptomatic evolution, but that so far has limited evidence to establish a concrete link with the evolution to SARS-CoV-2.

In addition, it has been found that infection with M. tuberculosis (MTB), the pathogen that causes TB and latently infects about 25% of the global population, may be a risk factor for SARS-CoV-2 infection and severe Covid-19 pneumonia.

It is also noteworthy that people who have already had MTB and become infected by SARS-CoV-2 have suffered a "Cytokine Storm" generated by the body itself and, in several reports, a latent reactivation of the bacillus that causes Tuberculosis has been reported.

Finally, it is worth mentioning that this study did not intend to exhaust the theme, since the data were obtained through literature already published in the databases and that are subject to updates as new findings are presented. For now, the study in question started from the assumption of achieving the objective of understanding the diseases involved, structuring a line of reasoning for the context that was exposed.

In addition, conducting a survey of the scientific literature was indispensable to obtain the main evidence on the subject in question. In this context, it is suggested the continuation of research that deepens and that can answer with accuracy questions that were open in this study. It is hoped to have contributed to broadening the discussion and knowledge about Covid-19, especially with regard to patients with pulmonary tuberculosis.

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