

# **COVID-19 and Pulmonary Tuberculosis, Between Coinfection and Reactivation from Latent Tuberculosis Patient: A Systematic Review**

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## **Abstract**

**Introduction:** Globally, cases of pulmonary tuberculosis (PTB) are rising by 4%, while new cases have declined in many nations, most notably by 14% in Indonesia. During the COVID-19 pandemic, the number of undiagnosed and untreated PTB patients could rise and infect more people. In particular, CD8<sup>+</sup> lymphocytes were decreased in COVID-19. Perhaps this is the cause of the rise in cases, but there is no data to show it. Aim: Determine current data about the PTB with COVID-19 coinfection and possible reactivation of PTB after COVID-19 infection in LTB patient.

**Methods:** This systematic review is based on PRISMA statements using Pubmed, EBSCOHost, Science Direct and Cochrane from December 2019 to July 2022. Inclusion and exclusion criteria were set to select studies that included. We analyze risk of bias of all included studies with JBI critical appraisal tools.

**Results:** This study had 107,425 patients in total from 20 studies. All studies were deemed to have low overall author bias risks. A critical component of PTB defense is CD8<sup>+</sup>. By reducing lymphocytes, COVID-19 can encourage the growth of PTB, which might therefore result in coinfection or the reactivation of existing PTB.

**Conclusion:** COVID-19 possibly increase case of PTB in form of co-infection or reactivation of PTB in LTB patients. This needs special attention for patients that have infected by COVID-19 to followed up for risk developing PTB.

**Keywords:** Coinfection, COVID-19, Reactivation, Tuberculosis

**COVID-19 dan Tuberkulosis Paru,  
Antara Koinfeksi dan Reaktivasi dari Laten Tuberkulosis:  
Sebuah Kajian Sistematis**

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**Abstrak**

**Pendahuluan:** Secara global, kasus tuberkulosis paru (TB Paru) meningkat sebesar 4%, sementara kasus baru telah menurun di banyak negara, terutama di Indonesia sebesar 14%. Selama pandemi COVID-19, jumlah pasien PTB yang tidak terdiagnosis dan tidak diobati dapat meningkat dan menginfeksi lebih banyak orang. Secara khusus, limfosit CD8+ mengalami penurunan pada COVID-19. Mungkin ini adalah penyebab peningkatan kasus, tetapi tidak ada data yang menunjukkannya. Tujuan: Menentukan data terkini mengenai koinfeksi PTB dengan COVID-19 dan kemungkinan reaktivasi PTB setelah infeksi COVID-19 pada pasien TB paru.

**Metode:** Tinjauan sistematis ini didasarkan pada pernyataan PRISMA dengan menggunakan Pubmed, EBSCOHost, Science Direct dan Cochrane dari Desember 2019 hingga Juli 2022. Kriteria inklusi dan eksklusi ditetapkan untuk memilih studi yang disertakan. Penulis menganalisis risiko bias dari semua studi yang disertakan dengan alat penilaian kritis JBI.

**Hasil:** Penelitian ini memiliki total 107.425 pasien dari 20 studi. Semua studi dianggap memiliki risiko bias penulis yang rendah secara keseluruhan. Komponen penting dari pertahanan PTB adalah CD8+. Dengan mengurangi limfosit, COVID-19 dapat mendorong pertumbuhan PTB, yang kemudian dapat menyebabkan koinfeksi atau reaktivasi PTB yang sudah ada.

**Kesimpulan:** COVID-19 dapat meningkatkan kasus PTB dalam bentuk koinfeksi atau reaktivasi PTB pada pasien TB paru. Hal ini perlu mendapat perhatian khusus bagi pasien yang telah terinfeksi COVID-19 untuk ditindaklanjuti karena berisiko terkena PTB.

**Kata Kunci:** COVID-19, Koinfeksi, Reaktivasi, Tuberkulosis

**Introduction**

Pulmonary Tuberculosis (PTB) cases in Indonesia are increasing by 18% from 819.000 to 969.000.<sup>1,2</sup> There has been a new notification drop from Indonesia by 14% in TB Global Report 2021.<sup>1</sup> This shows the possibility patients were undiagnosed and untreated but the case of PTB in Indonesia are still huge. Worst case scenario that could be happen shown in TB Global report in 2022 by increased cases of PTB. This is because of the “time lag” that undiagnosed and untreated patients could infect others.<sup>2</sup> There is the impact of the pandemic COVID-19 that caused this time lag such as (1) patients that afraid to check their symptoms to healthcare facilities,

(2) community mobility regulations from the government during the pandemic COVID-19 by level (I – IV), and (3) unequal accessibility to online health services. During pandemic COVID-19, we learn that COVID-19 infection regarding of severity could have impact to immune system. COVID-19 could decrease of lymphocyte such as memory T cells and cytotoxic CD8+ cells.<sup>3</sup> In the other hand, immune system are important especially in latent tuberculosis (LTB) patients so the Mycobacterium tuberculosis (M.tb) would not develop in to active state. It estimates that 25% earth population already infected with M.tb but only 5% in active condition and 95% in latent phase.<sup>4</sup> Reactivation of latent tuberculosis could be happen in the patient in immu-

nocompromised condition. We hypothesized there are reactivation of latent tuberculosis after COVID-19 infection but because lack of awareness it's underreported. Therefore, we conduct this systematic review to determine current data about the PTB with COVID-19 coinfection and possible reactivation of PTB after COVID-19 infection in LTB patient.

**Method**

**Literature Search Strategy**

This systematic review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Literature searches were performed on the PubMed, Cochrane, Science Direct and EBSCOhost databases. To find related literature, we used the following keywords: “Latent Tuberculosis” OR “Latent Tuberculosis Infection” AND “COVID-19” OR “SARS-CoV-2” OR “2019-nCoV” AND “Tuberculosis”. The literature to be reviewed is a study published between December 2019 and July 2022. Further details on the search strategy can be seen in Figure 1.

Literature in the form of observational studies (cross-sectional and cohort), case reports, case series, systematic reviews and meta-analysis, (4) Study using English. Several exclusion criteria have been set as follows: (1) Patients diagnosed with TB during a pandemic without a history of COVID-19 infection before/ during/after TB diagnosis, (2) Diagnosis of TB without using radiological or microbiological evidence, (3) Patients with suspected COVID-19 with a history of TB.

**Data Extraction and Study Quality Assessment**

From all the literature that met the inclusion criteria set, we extracted the relevant data. The extracted data included author, year of publication, study design, sample size, and study results (Table 1). We critical appraise all included studies to determine risk of bias with Joanna Briggs Institute (JBI) critical appraisal tools. All authors analyze and discuss to score all risk of bias. Any mismatch/disagreement were solved in discussion with all authors.

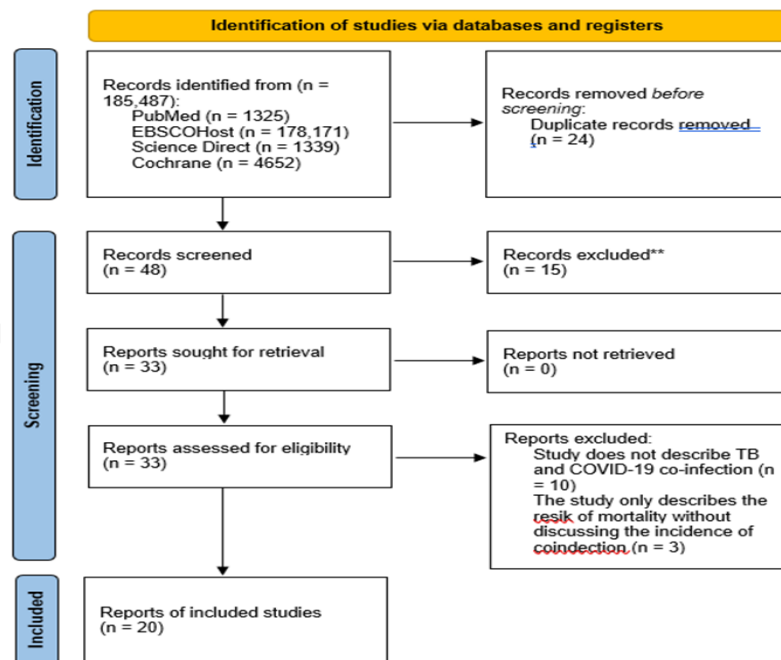


Figure 1. Literature Search Strategy According to PRISMA Flowchart.

**Inclusion and Exclusion Criteria**

The inclusion criteria were set as follows: (1) The study took place from December 2019 – June 2022, (2) Open Access, (3)

**Result**

All authors analyze risk of bias to all included studies using JBI critical appraisal tools (Figure 2). All studies considered low

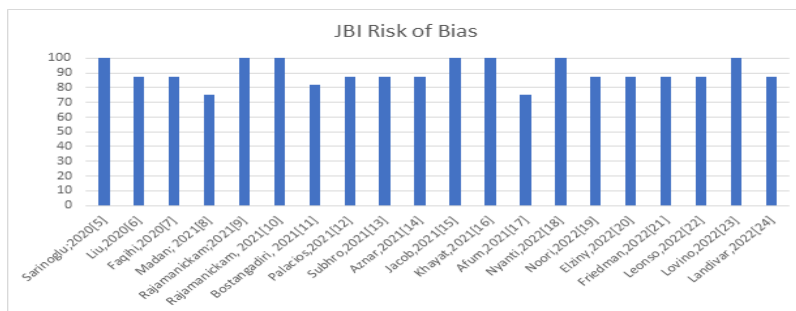


Figure 2. JBI Risk of Bias Score of All Included Studies

risk of bias from all authors.

In total, 20 studies included with 107,425 total patients (Table 1). Several stud-

ies reported case of coinfection of PTB with COVID-19 and several report PTB after COVID-19 suspected from LTB patients.

Table 1. Data Extraction Table

Author, year of study	Study Design	Study Location	Study title	n	Study Results
Sarinoglu; 2020 <sup>11</sup>	Cross-sectional	Turkey	Tuberculosis and COVID-19: An overlapping situation during the pandemic	30	Two patients had both COVID-19 and TB diagnoses. One patient had a COVID-19 diagnosis first, followed by a TB diagnosis, whereas another received a COVID-19 diagnosis first.
Liu,2020 <sup>12</sup>	Case Report	China	Severe COVID-19 cases with a history of active or latent tuberculosis	3	One patient had concurrent MDR-TB and COVID-19 infections, and there were two patients with positive IGRA results followed by COVID-19 infections. As TB coinfection can result in immunosuppression in the first place, it is not advised to administer corticosteroids to COVID-19 patients who also have TB.
Faqihi, 2020 <sup>13</sup>	Case Report	Saudi Arabia	COVID-19 in a patient with active tuberculosis: A rare case-report	1	A 60-year-old man comes in with a chest ache, myalgia, a persistent productive cough, and other symptoms. The patient underwent RT-PCR testing, and COVID-19 was detected. The patient has a history of tuberculosis and has had treatment outside of Saudi Arabia
Madan; 2021 <sup>14</sup>	Cross-Sectional	India	Impact of Latent Tuberculosis on Severity and Outcomes in Admitted COVID-19 Patients	60	There are 15 people with latent TB who have COVID-19 infection. Patients with latent TB showed higher levels of lymphocytes and monocytes than other patients but less radiological damage (p 0.05).
Rajamanickam; 2021 <sup>15</sup>	Cross-Sectional	India	Latent tuberculosis co-infection is associated with heightened levels of humoral, cytokine and acute phase responses in seropositive SARS-CoV-2 infection	133	72 LTBI – and 61 LTBI+. Comparatively to LTBI persons, LTBI+ people who were seropositive for SARS-CoV_2 infection had higher levels of humoral, cytokine, and acute-phase responses. Hence, in those who are seropositive for SARS-CoV-2 infection, LTBI is linked to regulation of cytokine and antibody responses as well as systematic inflammation.
Rajamanickam; 2021 <sup>16</sup>	Cross-Sectional	India	Effect of SARS-CoV-2 seropositivity on antigen – specific cytokine and chemokine responses in latent tuberculosis	118	There were 24 LTBI patients without COVID and 35 LTBI patients who tested positive for COVID-19. 39 COVID patients without LTBI, and 20 COVID patients without LTBI and COVID-19. Compared to healthy controls, LTBI patients were not less able to increase chemokine and cytokine responses. LTBI patients’ cytokine and chemokine responses were unaffected by SARS-CoV-2 infection.

Table 1. Data Extraction Table

Author, year of study	Study Design	Study Location	Study title	n	Study Results
Bostangadiri, 2021 <sup>17</sup>	Systematic Review	Italy	Mycobacterium tuberculosis and SARS-CoV-2 Coinfections: A Review	106.033	891 of them had both TB and COVID-19 infections. According to some accounts, COVID-19 may cause latent TB to active or aggravate respiratory symptoms. Independent of any other underlying disease or patient state, it appears that both active TB and TB that has already been treated are risk factors for COVID-19 in terms of severity and fatality
Palacios, 2021 <sup>18</sup>	Cohort	Spanish	Clinical and epidemiological correlates of low IFN-gamma responses in mitogen tube of QuantiFERON assay in tuberculosis infection screening during the COVID-19 pandemic: A population-based marker of COVID-19 mortality?	90	90 LTBI patients, 33 COVID negatives, and 57 COVID-19 positives. IGn-g levels dropped as a result of a drop in CD8+ concentrations. Uncover the possibilities of TB reactivation.
Subhro, 2021 <sup>19</sup>	Case Report	India	COVID-19 and Pulmonary Tuberculosis – A diagnostic dilemma	3	3 patients diagnosed with COVID-19 with TB co-infection
Aznar, 2021 <sup>20</sup>	Cohort	Spanish	Impact of the COVID-19 pandemic on tuberculosis management in Spain	169	Extra pulmonary TB is the most common kind of TB found in COVID-19 patients (75/169). IR 10.25 per 100.000 people in 2019 and IR 9.31 per 100.000 people for cases of co-TB-COVID-19 infection.
Jacob, 2021 <sup>21</sup>	Case Report	India	Coinfection of SARS-CoV-2 and MTB: How not to miss the wood for the trees	1	Immunosuppressive treatment is being given to a 20-year-old lady with multiple sclerosis. COVID-19 has been identified in the patient by PCR. X-rays revealed lung opacity, but the patient had a history of weight loss. Further tests revealed that the patient had TB. Infected people with TB may also have COVID-19 infection.
Khayat, 2021 <sup>22</sup>	Case Report	Saudi Arabia	COVID-19 promoting the development of active tuberculosis in a patient with latent tuberculosis infection: A case report	1	A PCR-confirmed COVID-19 diagnosis in a 40-year-old female. She displayed consolidation in the right superior lung lobe 7 weeks later, at which point microbiological TB was identified. The patient interacted with a girl who had used anti tuberculosis drug in the two years prior.
Afum, 2021 <sup>23</sup>	Cross-Sectional	Ghana	Diagnosis of tuberculosis among COVID-19 suspected cases in Ghana	774	there are 6 (0.8%) co-infected TB and COVID-19 patients in Ghana

Table 1. Data Extraction Table

Author, year of study	Study Design	Study Location	Study title	n	Study Results
Nyanti, 2022 <sup>24</sup>	Case-Report	Malaysia	Pulmonary tuberculosis and COVID-19 coinfection: Hickam's Dictum revisited	3	Patient 1 had endobronchial tuberculosis that tested positive on smears; she was unintentionally detected as a result of abnormalities to her CT-Scan and finally achieved a full recovery. Patient 2 is a COVID-19 patient who passed away but was later identified as having tuberculosis as a result of a positive sputum culture. Patient 3 had empirical TB treatment because they had radiographic signs of tuberculosis.
Noori, 2022 <sup>25</sup>	Case-Report	United States of America	Reactivation of Tuberculosis in the Setting of COVID-19 Infection	1	One month prior, a 76-year-old man had a minor COVID-19 infection. In the left apical of the chest radiograph, there are two opaque, reticulonodular patches. Patients used PCR to confirm TB. Since the patients are from TB endemic areas, they can have TB reactivation. When a patient has a prior history of COVID-19, TB infection should be suspected
Elziny, 2022 <sup>26</sup>	Case-Report	Qatar	Case Report: development of miliary pulmonary tuberculosis in a patient with peritoneal tuberculosis	1	A 29-year-old guy was identified as having miliary pulmonary TB after recovering from COVID-19 for two weeks. It's possible that COVID-19 infection speeds up the development of TB infection.
Friedman, 2022 <sup>27</sup>	Case-Report	United States of America	Reactivation of latent tuberculosis in a COVID-19 patient on corticosteroid treatment	1	A 70-year-old female with a COVID-19 diagnosis who has never been exposed to the disease or had TB before. Patients with confirmed reactivation of TB were cared for six days. The patient's origin as a TB endemic location are known.
Leonso, 2022 <sup>28</sup>	Case-Report	United States of America	A Rare Case of Latent Tuberculosis Reactivation Secondary to a COVID-19 infection	1	Tb reactivation from latent TB was discovered in a 74-year-old Filipino woman 3 months after she had recovered from COVID-19. The therapy can aid in the transformation of latent TB into active TB when it is known that the patient is taking high dosages of steroids.
Lovino, 2022 <sup>29</sup>	Case-Report	Italy	Latent tuberculosis reactivation in the setting of SARS-Cov-2 infection: The analysis of the radiological features that help the diagnosis.	1	A 45-year-old guy arrives with fever and dyspnea. COVID-19 beta version is present. 15 days of COVID-19 therapy and twice-negative swabs. Hemoptysis, myalgia, and a productive cough followed three months later. Both the patient's culture and smear results were favorable. Both no prior to TB history and no interaction with TB patients
Landivar, 2022 <sup>30</sup>	Case-Report	Spanish	Tuberculosis Reactivation After Severe SARS-CoV-2 Pneumonia	1	A serious COVID-19 diagnosis in a 69-year-old lady necessitated artificial ventilation. After receiving critical care for 22 days, the patient was discharged. Before being identified with COVID-19, the patient's latent TB infection was known to exist. A biopsy of the nodule found by the CT-Scan 3 months after COVID-19 revealed active TB.

## Discussion

### Potential Mechanism Relation of COVID-19 and PTB

Immune response in patients with COVID-19 can go through various pathways to the occurrence of reduced lymphocyte.<sup>3</sup> This condition occurs due to reduce of memory T cells and cytotoxic CD8<sup>+</sup> cells. Flow cytometric analysis in COVID-19 patients showed a reduced number of helper T Cells in peripheral blood and reduced number of cytotoxic CD8<sup>+</sup> T cells in severe cases.<sup>3,5</sup> Reduced lymphocyte could result in cell apoptosis in the lung, thereby causing susceptibility to other pathogenic infections. This happens because the cells are increasingly damaged due to apoptosis, facilitating the development of pathogens in these tissues. Other mechanism as spinal cord suppression during cytokine storms and pulmonary sequestration during COVID-19 pneumonia also possible causing reduced lymphocyte.<sup>3</sup> Study from China also showed significantly decreased number of CD8<sup>+</sup> cells in COVID-19.<sup>6</sup> Several studies showed T Cells, especially CD8<sup>+</sup> plays important role in the protection against PTB.<sup>8-10</sup> Decreased of immune response due to reduced T-Cell could increase risk of getting active TB. This could relate of COVID-19 patients may be at increased risk of PTB even if their COVID-19 symptoms are cured.<sup>7</sup>

By those mechanism, it's possible that patient infected by COVID-19 and decrease of the lymphocyte support the development of PTB in the form of co-infection or reactivation. COVID-19 treatment especially using steroid possibly promote immunosuppressive condition that support development of PTB. Special attention is necessary to early detection PTB before it develop into complicated that would be worst prognostic to the patient.

### Current Knowledge between COVID-19 and PTB

An infection with COVID-19 can raise the likelihood of having active PTB by seven times, according to a nationwide population-based cohort study from Thailand.<sup>7</sup> This may explain why the prevalence of TB increased by 4% globally, from 10.1 million to 10.6 million, however the authors could only locate one study that indicated a link between PTB and COVID-19. To determine the risk of COVID-19 to PTB, especially in countries with a high TB burden, more research is

required.

Tight community mobilization regulations, including mask regulation, may have decreased PTB transmission. These regulations could prevent droplet transfer, but the evidence indicating an increase in PTB raises a serious concern about how this could have happened. This may occur if there were restrictions on working from home, and internal transmission cannot be avoided. Particularly for undiagnosed and untreated patients living with other family members, in-house transmission may occur. This may lead to an increased in PTB cases in a family clusters, which may be the cause of an increase in PTB cases during and maybe after the COVID-19 pandemic.

## Conclusion

COVID-19 infection possibly increased case of PTB in form of co-infection or reactivation of PTB in LTB Patients. This needs special attention for patients that have infected COVID-19 to followed up for risk developing PTB.

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