

## Coronavirus Pandemic

# Tuberculosis and COVID-19 coinfection: A report of two cases at a tertiary referral in Indonesia

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### Abstract

COVID-19 cases are still rising globally in the middle of the tuberculosis epidemic. Several countries have reported TB-COVID-19 coinfection that could pose a double burden in the health care facilities in developing countries. We reported two pulmonary tuberculosis patients coinfecting with COVID-19 with an overlapping clinical manifestation of tuberculosis and COVID-19 with a good prognosis at the end of COVID-19 treatment. This paper aims to discuss TB patients' susceptibility against SARS-COV-2 infection, the clinical profile of TB-COVID-19 coinfection, and the disease's prognosis. The clinician should be aware of both common disease symptoms that appear in a patient and should be confirmed and treat promptly.

**Key words:** COVID-19; tuberculosis; diagnosis; prognosis.

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### Introduction

Tuberculosis is still the main problem globally. In 2019, about 10.0 million people suffered, and 1.2 million people died from tuberculosis (TB). Indonesia has the second highest incidence of TB globally, with an incidence rate of 391 per 100,000 population. There is a 25-30% drop in cases in Indonesia. Even so, the gap between case notification and newly diagnosed TB in 2020 is still high [1].

Amid the tuberculosis epidemic, coronavirus disease 2019 (COVID-19) cases are still rising. The cases-cumulative of COVID-19 reaches about 1.3 million cases, with almost 4.9 million new cases reported. COVID-19 also shows nearly 3 million cases of death-cumulative [2]. Such a high number could create a vast new challenge such as tuberculosis coinfecting COVID-19 and a double burden in the health care facilities in developing countries.

Several countries have reported TB-COVID-19 coinfection through some studies [3-8]. Still, some aspects of TB and COVID coinfection remain unclear, including pulmonary tuberculosis as a risk factor for COVID-19, the clinical manifestation of TB-COVID-19, and the impact of the disease.

Here, we reported two cases diagnosed as active pulmonary tuberculosis coinfecting with COVID-19. This paper aims to discuss TB patients' susceptibility to SARS-COV-2 infection, overlapping clinical profile of COVID-19 and tuberculosis, and prognosis of this disease. Furthermore, we hope both cases would give insight into managing patients with TB-COVID-19 coinfection to improve the quality of care in developing countries.

### Case Report

#### Case 1

A 41-year-old female was referred to the hospital due to shortness of breath, productive cough, and high-grade fever in the past four days. The patient denied any close contact with confirmed COVID-19 cases. The patient no longer worked, was an ex-smoker, and had no diabetes or heart disease history. One month before hospital admission, the patient was diagnosed with pulmonary TB based on the acid-fast bacilli (AFB) test and was on 4FDC (Rifampicin 150 mg, Isoniazid 75 mg, Pyrazinamide 400 mg, Ethambutol HCl 275 mg in each capsule) given for intensive TB treatment based on body weight. Physical examination showed that the

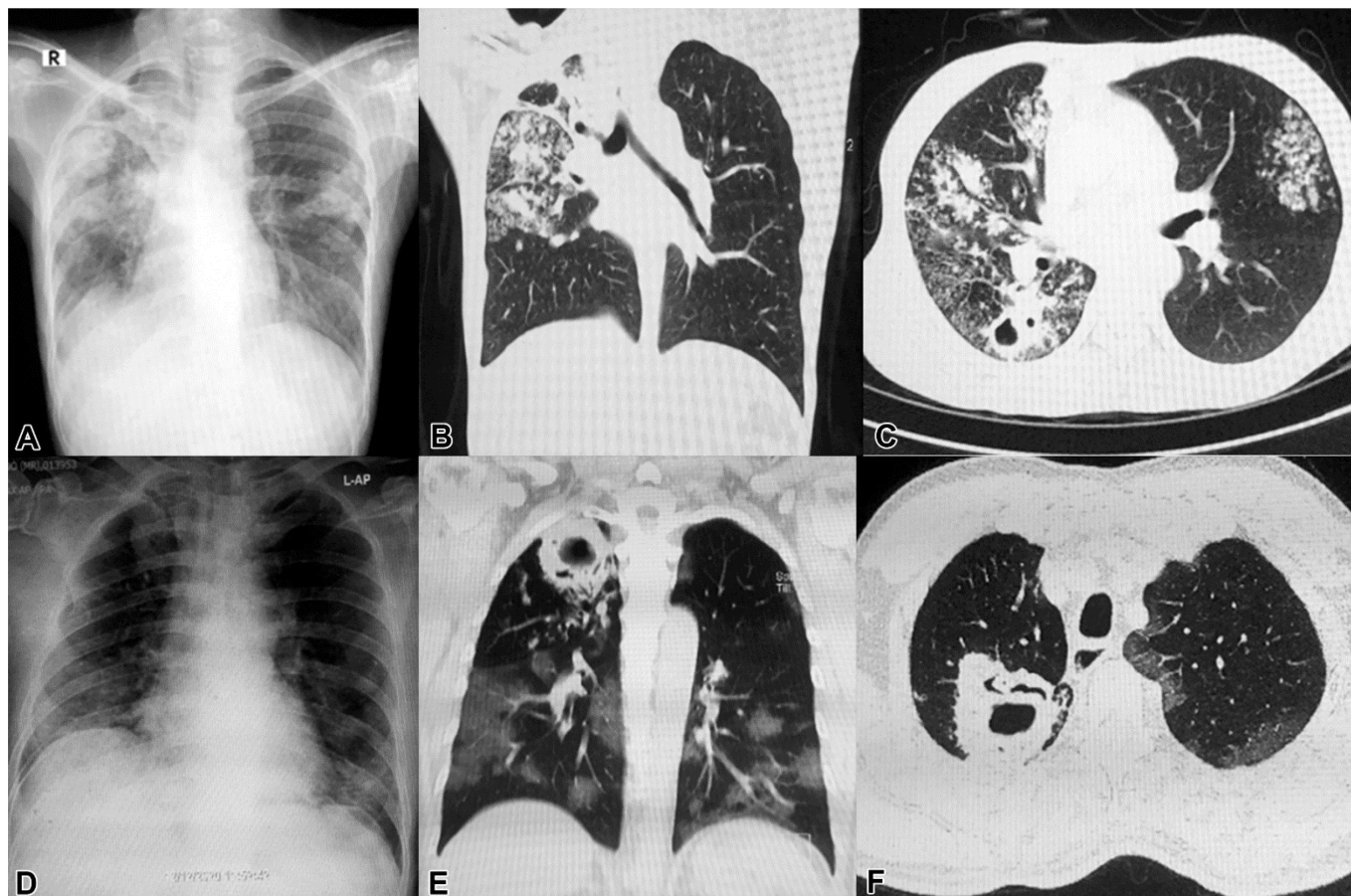
patient was compos mentis, looked pale, had a respiratory rate of 24×/minute, heart rate of 110×/minute, blood pressure 110/80 mmHg, a temperature of 39.5 °C with oxygen saturation of 95% with 2-3 liters nasal cannula, and body mass index (BMI) of 19. On lung auscultation, rales were primarily found on the upper right hemithorax.

Laboratory findings showed anemia (Hb 9.2 g/dL) with leukocytosis (15.500 cells/mL) and a high neutrophil-to-lymphocyte ratio (NLR) of 7.42. Marker of inflammation were high (CRP 130 mg/mL and ferritin 763 ng/mL), except for low procalcitonin levels (0.11 ng/mL). The patient showed coagulopathy signs with a high D-dimer (1650 ug/mL) and a low albumin level (2.2 g/dL). The patient's AFB was still positive at the time of COVID-19 diagnosis. Chest X-ray (CXR) displayed infiltrates and consolidation in the right upper lobe and medial lobe, patchy infiltrates on the left lobe. Chest CT scan showed fibroinfiltrate, consolidation, cavity, and ground-glass opacity mainly on the right upper lobe and middle lobe with retracted right hilus and trachea (Figure 1 A-C). This patient was later

confirmed as COVID-19 through RT-PCR using a nasopharyngeal swab test.

Using Indonesian National COVID-19 care, the patient received O<sub>2</sub> with a non-rebreathing mask 10-12 liter per minute and multivitamin with an additional 1 gram of vitamin C, enoxaparin sodium, and oseltamivir for the treatment per oral. Antituberculosis drugs were continued. The patient recovered slowly, with improvements in laboratory tests and CXR. This patient was discharged after 20 days of hospitalization despite minimal residual symptoms such as fatigue, cough, and persistent low-grade fever. The patient continued self-isolation, and the SARS-CoV-2 was finally negative after 35 days based on the nasopharyngeal PCR swab test. Based on the World Health Organization (WHO) TB Guideline, the patient continued the TB treatment at the Primary Health Care (Puskesmas) and responded well with antituberculosis drug confirmed by clinical improvement (increase body weight, decreasing cough, and shortness of breath) 2 months after being discharged from hospital.

**Figure 1.** Imaging of Tuberculosis cases coinfecting with COVID-19. Chest X-Ray (CXR) showed fibroinfiltrate and retracted right hilus in Case 1 (A) and infiltrate and consolidation on the right upper lobe in Case 2 (D). Chest CT scans of Case 1 (B-C) and Case 2 (E-F) showing fibroinfiltrate, cavitory lesion, and ground-glass opacities.





Case 2

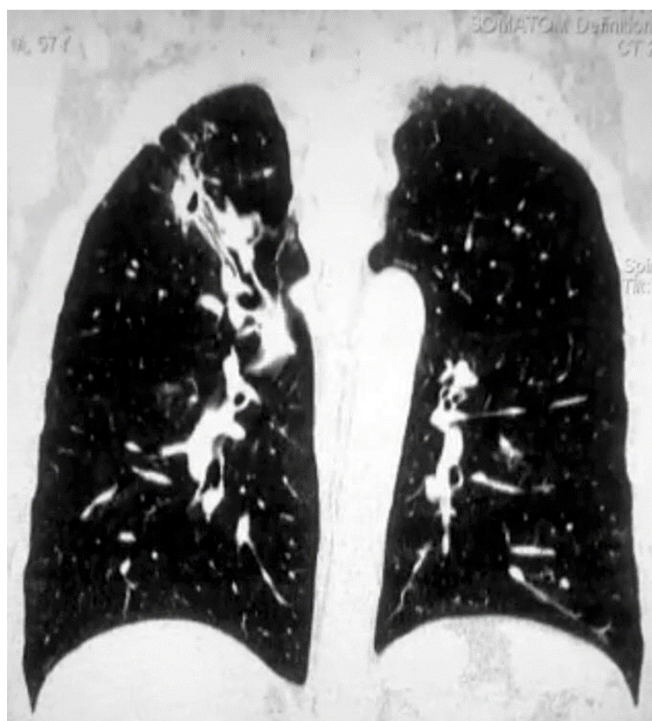
A 54-year-old male was admitted to the hospital with the primary complaint of high-grade fever and cough, with phlegm showing a streak of blood for the past four days. The patient was under routine insulin injection for Type 2 diabetes mellitus. Physical examination showed compos mentis, with a respiratory rate of 26×/minute, heart rate of 100×/minute, blood pressure 130/80 mmHg, temperature of 40 °C, and oxygen saturation of 97% with 3-4 liters nasal cannula, and BMI of 19. Lung examination showed rales, mainly on the upper right hemithorax.

Laboratory findings revealed a normal hemoglobin level (Hb 11.2 g/dL) with mild leukocytosis (11.500 cells/mL) and a high neutrophil-to-lymphocyte ratio (NLR) of 5.42. Marker of inflammation was high (CRP 135 mg/mL and ferritin 630 ng/mL) with low procalcitonin (0.06 ng/mL) and signs of coagulopathy with slightly high D-dimer (900 µg/mL) and normal albumin level (3 g/dL). The latest HbA1C level was 7.7%, and the AFB test was positive after taking samples twice in the morning. CXR depicts infiltrates and consolidation in the right upper lobe. Further, chest CT scan showed fibroinfiltrate, consolidation, and cavity on the apex and ground-glass opacity on both lungs (Figure 1 D-F). The patient was then diagnosed as COVID-19 through RT-PCR nasopharyngeal swab test.

After confirmation, the patient obtained Indonesian National COVID-19 care, including oxygen therapy with nasal cannula 3-4 litres per minute; enoxaparin sodium as an anticoagulant; multivitamin, favipiravir peroral, and standard treatment for diabetes mellitus using insulin. The patient was prescribed antituberculosis drugs 4FDC (Rifampicin 150 mg, Isoniazid 75 mg, Pyrazinamide 400 mg, Ethambutol

HCl 275 mg in each capsule) given for the first two months of intensive body weight-based TB treatment using WHO TB Guideline. The patient recovered and was discharged after ten days of hospitalization. On the follow-up, RT-PCR for SARS-CoV-2 was negative based on a nasopharyngeal swab test after 22 days. The treatment evaluation was done according to standard WHO TB guidelines by clinical parameters regarding symptoms. Side effects were also evaluated every 2-4 weeks. At the end of the second-month intensive treatment and six months of total treatment, CXR and

**Figure 2.** Follow-up Chest CT-Scan imaging of the patient. The cavitory lesion and ground-glass opacities were improved during the two months of treatment.



**Table 1.** Clinical aspects of pulmonary TB, COVID-19, and TB-COVID-19 coinfection [17,18].

Clinical Aspects	Pulmonary Tuberculosis	COVID-19
Incubation Period	Variable. Symptoms develop week to years after exposure	2-14 days
Mode of spread	Respiratory droplets from sneeze, cough, or talks	Respiratory droplets from sneeze, cough, or talks. Virus could spread through touching inanimate objects, possible spread when touching mouth, nose, or eyes.
Clinical features	Productive cough with blood, weight loss, fever and night sweats, chest pain, or weakness	Fever or chills, cough, shortness of breath, fatigue, myalgia, anosmia, rhinofaringitis manifestation, nausea or vomiting, or diarrhea.
Laboratory feature	High erythrocyte sedimentation rate, leukopenia, lymphopenia, high lactate dehydrogenase, thrombocytopenia, anemia	High erythrocyte sedimentation rate, leukopenia, lymphopenia, high lactate dehydrogenase, decreased albumin, high C-Reactive Protein, high aspartate amino transferase, high alanine aminotransferase, high creatinine kinase, leukocytosis, high bilirubin, high creatinine.
Radiological feature	Fibroinfiltrate, thick-walled cavity, cavities with air-fluid levels, clustered and military nodules and pleural effusion	Bilateral lower lobe consolidations, peripheral air. space opacities, ground glass opacities, diffuse lung opacities and pleural effusion

AFB sputum were evaluated. We did not use Quantiferon nor PCR-based test for TB treatment evaluation. The patient had an excellent clinical response, negative AFB, and CXR, and Chest CT scan improvement (Figure 2).

## Discussion

### *Nature of TB-COVID-19 coinfection*

Pulmonary tuberculosis and COVID-19 are lung infections that could co-occur and have been reported in many countries worldwide. There is little evidence that supports why tuberculosis patients are vulnerable to COVID-19 infection. It is estimated that there is a complex and bidirectional relationship between these two. As a result of tuberculosis infection, cavitary lesion compromises the functioning and defense of the lower respiratory tract by restraining airflow and fluid drainage, possibly increasing vulnerability to COVID-19 [9]. A study in Wuhan showed that 76% of 522 COVID-19 patients had CD4 and CD8 cell depletion, and the rest of the cells were exhausted [10]. Since tuberculosis and COVID-19 activate adaptive immunity [11], it is possible that this exhaustion and depletion as a source of coinfection and induced more severe presentation.

Besides these theories, a recent meta-analysis concluded that SARS-CoV-2 is more likely to infect TB patients, even though the result was insignificant (OR 2.10 CI 95% (0.61-7.18)) [12]. Basically, tuberculosis patients might be susceptible to COVID-19 infection. Thus, further factual data are needed to confirm that TB-infected patients are more susceptible to COVID-19.

Along with the above facts, it is intriguing to see TB diagnosis preceded one month of COVID-19 that might be a superinfection rather than coinfection. However, there was no existing agreement about the exact timeframe of coinfection and superinfection in TB and COVID-19. Latent tuberculosis infection is indeed a significant risk factor, especially in immunocompromised patients, as reported by Chen *et al.* [4]. However, to our knowledge, no study discusses COVID-19 induced TB latent infection exacerbation. Immunosuppressant treatment in COVID such as corticosteroid might impair immune response and activate Latent TB into active TB. This possibility should be considered in the future study of COVID and TB connection. Thus, further high-quality studies are needed to discover the true nature of the TB-COVID-19 coinfection.

### *Clinical characteristics of TB-COVID-19 coinfection*

Many studies have discussed the difference in clinical manifestation between COVID-19 and pulmonary tuberculosis. Of these studies, fever, cough, and dyspnea are the most typical manifestation to be found [3-6,13-15]. Our cases' chief complaint was acute productive cough with high-grade fever. *Dyspnea* is the main symptom found in case 2. *Dyspnea* is frequently found in COVID-19 but rarely in tuberculosis, except when the disease progresses or sequelae appear.

Interestingly, we found that case 2 had a blood streak on his phlegm. Hemoptysis is a common symptom of tuberculosis. Current reports have concluded that hemoptysis is rarely found in COVID-19. If present, there should be secondary underlying diseases, for instance, tuberculosis or pulmonary embolism, or lung malignancy. [16] In both cases, hemoptysis and rales in the upper lobe suggested pulmonary tuberculosis.

Coinfection of TB and COVID-19 should be suspected in patients with chronic signs and symptoms exacerbated when admitted to the hospital. COVID-19 is an acute disease with a 2-14 days incubation period, whereas pulmonary tuberculosis is a chronic disease with a long incubation period [17]. Clinical presentation of TB-COVID19 might vary widely depending on the immune system, the lung parenchymal involvement, and virus virulence. It might present with mild symptoms or very severe Acute Respiratory Distress Syndrome (ARDS).

Both cases present chronic underlying disease, especially case 2. Case 2 patient suffers from diabetes mellitus type 2 that is a common comorbidity in COVID-19. Both cases encountered some laboratory abnormalities, except for anemia in case 1. Previous studies also faced similar results, as showed in Table 1 [17,18]. To the best of our knowledge, there is no report regarding the impact of TB-COVID-19 coinfection in laboratory findings [18].

CXR and High-resolution Computed Tomography (HRCT) were commonly used to identify disease patterns in COVID-19. Typical pattern imaging found in pulmonary TB or COVID-19 is presented in Table 1. [17,18] To date, imaging findings of TB patients who develop COVID-19 infection are multiple bilateral or unilateral ground-glass opacity with air-bronchogram and consolidation. Our cases present a consistent CXR and CT scan presentation that suggests coinfection of TB (cavitary and fibroinfiltrate lesion) and COVID-19 (GGO and air-bronchogram) [18].

As supported by the current study, our case report portrays a vast spectrum and overlapping clinical manifestation of TB-COVID-19 coinfection. Therefore, despite the lack of recent evidence, it is recommended to undergo specific diagnostic procedures to rule out the possibility in patients who had both characters of pulmonary TB and COVID-19. Standard TB diagnostic tools include clinical signs and symptoms, imaging (CXR/CT scan), sputum smear AFB, Xpert test, culture-drug sensitivity test, and molecular typing if possible.

### *Prognosis and Disease Progression*

Prognosis and disease progression of TB-COVID-19 coinfection show vast results in current studies. Tadolini *et al.* [3] reported a 12.3% case fatality rate is mostly older patients and had one comorbidity. Motta *et al.* [6] also reported a high case fatality rate (10.6%), and most of these study subjects' were elder and had at least two comorbidities. In Italy, [5] younger and fewer comorbidities TB-COVID-19 coinfection are less likely to make patients deteriorate. A cohort study in the Philippines concluded TB-COVID-19 coinfection is 2.17 higher risk of death (95% CI: 1.40-3.37) and had longer time-to-recover ( $p < 0.05$ ) [7]. Another study in China [4] reveals that coinfection is common in severe or critical patients than in milder illnesses. In conjunction with available studies, a meta-analysis also concluded that TB-COVID-19 patients have higher severity and mortality rate with increasing recovery time irrespective of their HIV status [19]. In other words, disease severity in TB-infected patients with COVID-19 are more likely to be severe to critically ill and varied depending on host immunity and SARS-CoV-2 virulence.

Diabetes mellitus is a strong predictor of disease severity and progression in TB-COVID-19 coinfection, as depicted in case 2. Better diabetes control could improve TB therapy outcomes by augmenting host immunity. Well-controlled blood glucose in diabetes mellitus significantly lower mortality rates in TB patients compared with poorly one. Further high-quality research is needed to determine how best to manage blood glucose levels with associated comorbidities with TB-COVID-19 coinfection to reduce mortality, especially in critically ill patients [20].

Despite the above results, those studies had common limitations, including the operational definition in inclusion criteria, control in confounding factors (social determinants), treatment guidelines, and comorbidities profile which could modify the results.

Both cases had moderate symptoms and showed good recovery at the end of hospitalization with an excellent TB therapy response. Good prognosis in both cases is probably due to earlier treatment administration, younger age, and fewer comorbidities. However, this paper did not discuss any drug-drug interactions (COVID-19, TB, and comorbid regimen) affecting the treatment decision.

### **Conclusions**

COVID-19 potentially coexists with TB patients and poses a diagnostic challenge, especially in developing countries where health resources might not be limitless. Worse presentation and a higher risk of death in these diseases should increase our awareness of giving the best possible of patient care. We further recommended the importance of earlier identification and treatment initiation or disposition for the patient clinically suspected with both diseases.

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