Infection and Drug Resistance

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REVIEW

Clinical Features and Treatment Outcome of Coronavirus and Tuberculosis Co-Infected Patients: A Systematic Review of Case Reports

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Background: Coronavirus disease 19 (COVID-19) and *Mycobacterium tuberculosis* (MTB) are among the top ongoing health crises globally. Both cause respiratory diseases, and the clinical presentations are similar. There is no summarized information about cases of COVID-19 patients with concomitant TB infection from different settings. Therefore this review aimed to summerize the clinical features and treatment outcomes of coronavirus and tuberculosis co-infected patients.

Methods: An electronic search of case reports published between 2020 and 2021 was conducted using Google Scholar, PubMed, Scopus, and ScienceDirect. From eligible reports, data were collected for the selected variables. We analyzed the collected information using SPSS version 27 software. Descriptive statistics were computed for the selected variables.

Results: A total of 83 patient histories were collected from 47 case reports. The majority (80%) of the cases were reported for male patients. The mean age was 42.6 years (3 months to 84 years, SD=17.3). Fever was reported in 80% of cases, followed by cough (73.3%) and hypotension (37.1%). Blood cell parameters revealed lymphopenia (52%), lower hemoglobin (30%), elevated CRP (70%), elevated ferritin (28%), and increased D-dimer (23.4%). Treatment outcome is significantly associated with blood cell count results (p-0.044) and a rise in blood inflammatory cytokines(p-0.041). The mean days for viral clearance or negative PCR was 23 days (Range 5–82 days) and the overall mean duration of hospitalization was 27 days. The total death rate was 22.4%. Recovery was reported for 76.6% of cases. Survival status (p-0.613) and disease severity (p-0.68) are not significantly associated with the gender of the participants.

Conclusion: An alteration in blood cell parameters is associated with an unfavorable treatment outcome. There is a higher death rate in COVID-19/TB co-infection. The death is associated with older age, smoking or smoking history, drug abuse, and co-morbidity of non-communicable diseases. Conversely, there is a lower death rate in HIV patients.

Keywords: coronavirus, SARSCOV-2, COVID-19, *Mycobacterium tuberculosis*, tuberculosis, TB, co-infection

Background

Viral and bacterial diseases continued, causing epidemics and pandemics throughout human history. A pandemic of coronavirus disease 19 (COVID-19) and the epidemic of disease caused by *Mycobacterium tuberculosis* (MTB) are the top ongoing health crises worldwide. Coronavirus is a virus in the kingdom of Riboviria and the family of coronaviridae.[1] The viruses in this family are positive-sense RNA viruses known to cause acute respiratory syndrome (SARS).[2] COVID-19 is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2). The disease is an ongoing pandemic, claiming the lives of millions throughout the world. Until early June 2022, an estimated 529 million confirmed cases and more than 6 million deaths had been reported globally.[3] Tuberculosis (TB), on the other hand, is a chronic infectious bacterial disease affecting the lungs and other organs. Annually, there are an estimated 10 million infections and 1.4 million deaths due to TB.[4]

COVID-19 and TB patients share plenty of common clinical and radiological features.[5] Both are primarily respiratory pathogens and are highly contagious. Although the risk of COVID-19 in activating latent TB(LTBI) infection has not

Received: 14 April 2022
Accepted: 15 July 2022
Published: 27 July 2022

been studied, different case reports indicate the occurrence of TB cases either before the incidence of COVID-19,[6,7] simultaneous incidence,[8,9] or after infection with COVID-19.[10,11] The co-occurrence of these deadly pathogens causes difficulty in identifying each other. Clinical management is also challenging.[12]

Clinical features such as fever, fatigue, chest pain, cough, weight loss, night sweats, and loss of appetite have been known as identifying signs and symptoms for TB screening.[13] These signs were also common among COVID-19 patients.[14] Thus, there is an overlapping set of clinical characteristics that are common among TB/COVID-19 co-infected patients. In a study analyzing the interface of COVID-19 and TB, patients were identified to have all these signs, including fatigue without change in test or smell.[15]

It has been anticipated that the COVID-19 pandemic might affect the clinical course of TB or vice versa. A study has reported TB as an independent risk factor for severe COVID-19.[17] However, there is no consensus idea on the impact of the two diseases on each other's clinical course and patient treatment outcomes. For instance, in a study describing the clinical characteristics of COVID-19 in TB patients and factors for the disease severity, a lower risk of COVID-19 and a lower mortality risk have been noted in TB patients co-infected with COVID-19.[16]

The various published studies have been conducted at the facility level. Reviewing experiences from various settings for individual case management provides unbiased information about what happened to patients co-infected with COVID-19 and TB. In this study, we have examined case reports of COVID-19 and TB co-infection to investigate the distinguishing clinical characteristics and treatment outcomes for individual case management.

Methods

Search Strategy

We conducted a systematic review of published case reports and summarized the common reported clinical characteristics and treatment outcomes of COVID-19 and TB co-infected patients from different settings. We systematically searched electronic databases: Google Scholar, Scopus, ScienceDirect, and PubMed for case reports published in English. We followed a sensitive searching method to capture all available articles in the databases. We have restricted our search to papers published between 2020 and 2021. The electronic database search was conducted from June 1, 2021, to July 2, 2021. We used a search strategy by combining key-terms: "Coronavirus", "SARSCOV-2", "COVID-19", "Mycobacterium tuberculosis", "tuberculosis", "TB", "co-infection."

Inclusion and Exclusion Criteria

We included case reports and case series reports that described the clinical characteristics and treatment outcomes of patients with TB and COVID-19 co-infection. Eligible reports include reports containing all diagnostic and treatment parameters, from case presentation to treatment outcome, in different countries across the world. We excluded reports published in other languages than English. Studies with different study designs were also excluded. Our justification for choosing only case reports is that first, we are interested in individual clinical data from different settings. Second, we wanted to see what experiences were there from different settings while diagnosing and treating the new pandemic.

Case Report Selection Process

From database searches, we identified a total of 174 records. Due to a lack of either of the variables of interest for this review, a total of 41 records were excluded upon title screening. After abstract screening and removing the duplicates, a total of 48 reports were excluded based on the exclusion criteria. Full-text reading excluded 38 additional reports, and 47 reports remained to be included in the final review. Thus, a total of 47 case reports were included in this review (Figure 1). Eligibility assessment was performed independently by the three authors and disagreements were resolved by discussion.

Data Extraction and Quality Check

Data collection was done on an excel sheet. The data is double-checked for missing information and data entry errors. One of the review authors (HM) extracted the data from included studies, and the second author (DC) checked the

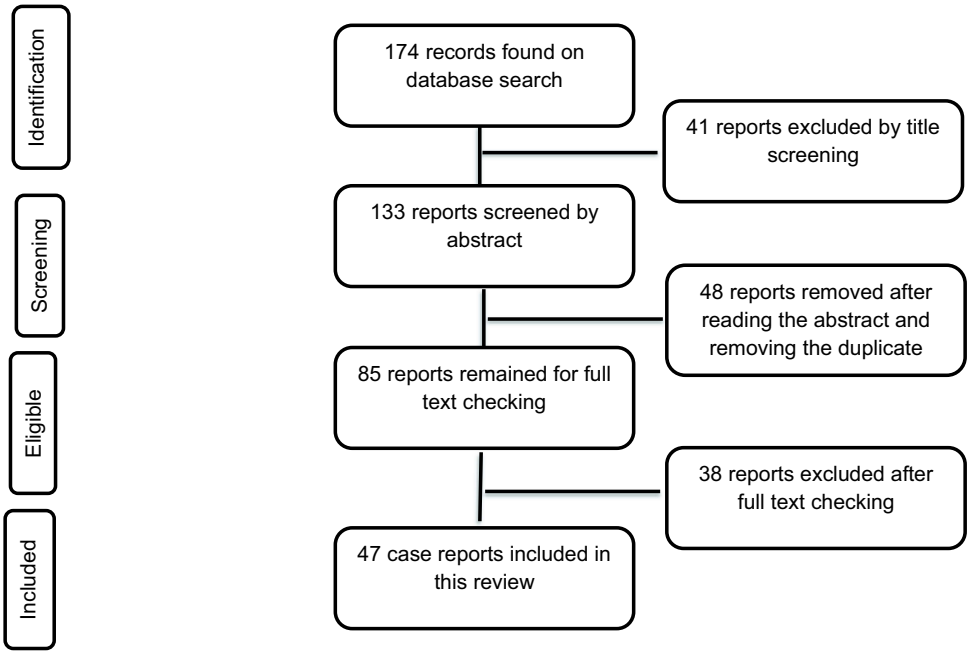

Figure 1 Flow chart diagram describing the selection of case reports included in the systematic review of clinical features and treatment outcomes of coronavirus and tuberculosis co-infected patients.

retrieved information. Any disagreements were resolved by discussion and confirmation by the third author (DB). We extracted information on the clinical characteristics of participants and the final treatment outcome. Furthermore, treatment status, days of hospitalization, travel, and previous history of TB were collected. After quality assurance measures, the data is exported into SPSS version 27 software for statistical analysis.

Statistical Analysis

Coding and recoding of qualitative variables were performed. Stratification of cases according to their outcome was performed to create an association with the predictor of the outcome. Descriptive statistics were computed for categorical variables. An odds ratio was calculated for the analysis of risk factors.

Results and Discussion

Clinical and Demographic Characteristics of Participants

A total of 83 histories of cases (patient information) from 47 reports were collected. All the cases have reported diagnosis and treatment of COVID-19 and TB co-infections. The reports consisted of as many as eight case series or a single case per report. The proportion of male patients was 80%. The mean age was 42.6 years (3 months–84 years, SD=17.3). The highest case reported was from India (9.8%), followed by Italy (8.2%) and Qatar (7.1%). The country in which the case report was published is indicated in Figure 2. Only 10.5% of patients have reported contact with active COVID-19 cases or travel history, and 4.7% had TB contact history. Among the cases, 2.45% had been treated for COVID-19 before, 8.2% had a history of TB treatment, and 2.45% had chronic hepatitis. Upon admission, 10.6% had a negative initial COVID-19 PCR test and 2.4% had an indeterminate test result.

Common Clinical Features of Coronavirus-TB Co-Infection

Only 43% of cases reported a severe illness, while others had a mild or non-apparent clinical illness. Cough was reported in 80% of cases, fever in 73%, but only 37.1% had hypotension. Half of the participants (50%) had an oxygen saturation level (SpO2) report. Most cases (30.3%) in the reviewed report had a SpO2 level of 90–97% in room air. The minimum

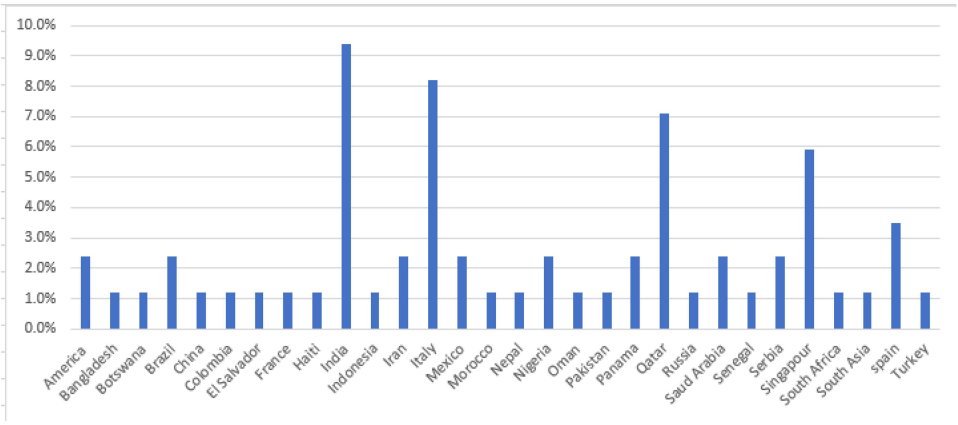

Figure 2 Number of case report distribution by country.

measurement was 68% and the highest was 99%. A lower SpO2 level is an early indicator that the patient needs medical attention.[18]

The complete blood cell analysis revealed an altered count of blood cells and lower hemoglobin in 45.3% of cases. Most of these abnormal blood cell counts are lymphopenia (52%). Lymphopenia is consistently reported as a common clinical feature of COVID-19 cases.[19–21] Therefore, given the short turnaround time for profiling blood cell parameters, such markers in addition to the clinical sign and symptom assessment might help to suspect and isolate cases for better management.[19] Lower hemoglobin levels were found in 30% of the cases. The lower hemoglobin level is associated with COVID-19 pneumonia and the worsening of the disease.[22] Blood chemistry also revealed half of the participants (50%) had a significant rise in liver enzymes. Among them, 70% had elevated C-reactive protein (CRP), 28% had elevated ferritin, and 23.4% had an increased D-dimer. Adenosine deaminase (ADA) and lactate dehydrogenase (LDH) were also common. Such an increase in liver enzyme activity is because of activation of both innate and adaptive immune responses and is an indication of systemic inflammation.[23]

There were typical COVID-19 signs and symptoms in 40.7% of cases; 22% had TB signs, and 31% had atypical or non-specific symptoms. Moreover, 7% had concurrent COVID-19 symptoms with abdominal pain. Of these, 1.2% of them had both TB and COVID-19 symptoms. Non-specific symptoms reported include muscle pain, voice changes, anxiety, and dehydration. Such nonspecific clinical manifestations may appear before the occurrence of common symptoms like fever and cough, which should be investigated closely as an initial measure for suspecting.[24]

The mean time for viral clearance or negative PCR was 23 days (range 5–82 days). However, the overall mean duration of hospitalization is higher (27 days). All the treatment of TB was done under a directly observed treatment short-course (DOTS). The common form of TB (86%) during COVID-19 coinfection appears in pulmonary TB (PTB), and the proportion of extrapulmonary TB (EPTB) is 14%. More TB (36%) has occurred after the onset of COVID-19. In 33.7% of cases, TB and COVID-19 occurred concurrently, and 30.2% were admitted for TB before developing COVID-19. A modeling study by WHO has reported that the pandemic might fuel the future TB epidemic mainly because of utilizing manpower and diagnostic utilities in response to the pandemic.[4] In addition, studies are also reporting the effect of the pandemic in promoting the activation of latent TB cases.[25]

The Risk Factors for Favorable and Unfavorable Treatment Outcomes

The total death rate was 22.4%. Among the cases with unfavorable treatment outcomes, 86.7% were primarily diagnosed with TB, and COVID-19 infection was recorded as a secondary superinfection (Table 1). Recovery was reported for 76.6% of cases. Among these, 43.9% were simultaneously diagnosed with the two diseases (Table 2). The common medications recorded in the history of survivors are ceftriaxone, azithromycin, hydroxychloroquine, clarithromycin, lopinavir/ritonavir, oseltamivir, Sovodak, remdesivir, heparin, enoxaparin, oxygen supplementation, and Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PZA), and Ethambutol (EMB) anti-TB drugs.

Table 1 Clinical Characteristics of TB Patients with COVID-19 Secondary Superinfection

First Author and Year of Publication	Country of the Study/Citizenship	Addiction	TB Site of Infection	TB History	Comorbidity	Treatment Outcomes
Ata F et al 2020[29]	India	None	PTB	Unknown	Kidney disease	Recovered
Gadelha et al 2020[6]	Brazil	Alcohol consumption	PTB	Relapse	Cardiac disease	Recovered
Motta I et al 2020[7]	Italy/Spain	Drug/Alcohol/ Smoking	PTB	Contact/ Unknown	Cardiac disease/ Hypertensio, kidney disease, HIV	Died
Sarinoglu RC et al 2020[37]	Turk	None	PTB	Unknown	DM, Kidney disease/ Hypertension	Recovered
Vilbrun SC et al 2020[38]	Haiti	None	PTB	Unknown	Hypertension	Recovered
Baskara MA, et al 2021[41]	Indonesia	None	PTB	Unknown	Diabetic	Recovered
Fard NG et al 2021[43]	Indonesia	None	EPTB	Unknown	Kidney disease	Recovered
Farias L et al 2020[44]	Italy	Drug abuse	PTB	Unknown	Hypertension	Recovered
Gbenga TA et al 2020[45]	Nigeria	None	PTB	Unknown	None	Died
Gerstein S et al 2021[46]	El Salvador	Alcohol consumption	EPTB	Unknown	None	Recovered
Sarma U et al 2020[5]	India	None	PTB	Unknown	Diabetic	Recovered

Survival or death is not associated with the gender of the participants (p-0.613, Cramer's V-0.01). The odds ratio of the unfavorable treatment outcome (death) in both sexes is 0.9 (95% CI, 0.23–3.75). Gender was reported as a risk factor for death in COVID-19 patients, in which the male gender is indicated as a risk.[20] The lower association of gender as a predictor of unfavorable treatment outcomes in this review might be due to the lower female-to-male ratio. On the other hand, being older is significantly associated with death (p 0.001). Age, together with other variables, was also reported as an independent risk factor for death among such patients.[26]

Treatment outcome is significantly associated with blood cell count results (p 0.044). The odds ratio of an unfavorable treatment outcome is 0.236 (95% CI: 0.61–0.9) in individuals with altered blood cell counts. A study conducted in the USA, using blood samples of confirmed COVID-19 cases, also showed a significant association between lower mean lymphocyte count and death.[19] Similarly, a rise in blood inflammatory cytokines such as CRP, D-dimer, ferritin, and IL-6 has a significant association with the treatment outcome (p-0.041). The odds of unfavorable treatment outcomes are 0.289 times higher in individuals having raised inflammatory cytokines (95% CI:0.084–0.99). Such a cytokine storm potentially predicts mortality and can be used as a preliminary indicator for intensive care and treatment.[27]

After adjusting for patients with no addiction, 66% of smokers and 37.5% of drug abusers have died. Smoking or smoking history is a risk for death (AOR=7, 95% CI;0.86–56.9). Similarly, drug abusers are more likely to die than non-drug users (AOR=1.8;95% CI;0.2–15).

A higher percentage of deaths was recorded among patients with co-morbidities such as anemia (40%), hypertensive patients (41.7%), patients with chronic renal failure (42.9%), and patients with hepatitis B virus and/or liver disease (60%). This finding was consistent with a meta-analysis that identified comorbidity as a facilitator of increased case fatality in any infectious disease.[28]

The death rate is comparatively lower among HIV patients (28.6%). Another case series report also showed no extensive morbidity or mortality associated with COVID-19 cases in people living with HIV (PLWH).[20] Antiretroviral therapy might play a protective role in patients with HIV. However, validation of this hypothesis in a larger longitudinal cohort is important.

Table 2 Treatment Outcome of Patients Simultaneously Diagnosed for COVID-19 and TB

First Author and Year of Publication	Country of the Study	Covid-19 Treatment	TB Treatment	Treatment Outcomes
Chen ZY et al 2020[30]	China	Lopinavir/ritonavir, Umifenovir hydrochloride, Interferon alpha, Corticosteroids	Standard first line (RHZE)	1 patient died, 2 recovered
Essajee F et al 2020[31]	South Africa	dexamethasone	Standard first line (RHZE)	recovered
Freij BJ et al 2020[32]	America	Dexamethasone, hydroxychloroquine, azithromycin	Not treated	Died
Martínez Orozco JA et al 2020[33]	Mexico	Not reported	Standard first line (RHZE)	Recovered
Motta I et al 2020[7]	Spain	Hydroxy-chloroquine, ritonavir/lopinavir, azithromycin, piperacillin, tazobactam	Standard first line (RHZE)	Died
Mulale UK et al 2021[34]	Botswana	Not reported	Standard first line (RHZE)	Died
Rivas N et al 2020[35]	Panama	Levofloxacin, azithromycin	Standard first line (RHZE)	Recovered
Shabrawishi M et al 2021[36]	Saudi Arabia	ceftriaxone and azithromycin.	Standard first line (RHZE)	Recovered
Yadav S et al 2020[10]	India	Not reported	Standard first line (RHZE)	Recovered
Yousaf Z et al 2020[11]	Qatar	Ceftriaxone, Azithromycin, and Hydroxychloroquine	Standard first line (RHZE)	Recovered
Al Lawati R et al 2021[39]	Oman	ceftriaxone, clarithromycin and oseltamivir, Hydroxychloroquine and lopinavir/ritonavir	Standard first line (RHZE)	Recovered
AlKhateeb MH et al 2020[40]	South Asia	Not reported	Standard first line (RHZE)	Recovered
Chowdhury D et al 2020[42]	Bangladesh	Favipiravir, ceftriaxone, clarithromycin	first line (RHZE)	Recovered
Luciani M et al 2020[47]	Italy	lopinavir/ritonavir, hydroxychloroquine	first line (RHZE)	Recovered
Maaroufi A et al 2021[48]	Morocco	(lopinavir/ritonavir), azithromycin, dexamethasone	first line (RHZE)	Recovered
Ortiz-Martínez Y et al 2021[49]	Columbia	ampicillin/sulbactam, doxycycline, dexamethasone	first line (RHZE)	Died
Patil S et al 2021[50]	India	remdesivir, methyl prednisolone, heparin	first line (RHZE)	Recovered
Pujari S et al 2020[51]	India	methylprednisolone	first line (RHZE)	Recovered
Rajput D et al 2021[52]	India	Not reported	first line (RHZE)	Recovered
Rodriguez JA et al 2021[53]	America	convalescent plasma, remdesivir, hydroxychloroquine, azithromycin	Not treated	Died
Sanyaolu A et al 2020[54]	Nigeria	Clarithromycin, Hydroxychloroquine, and lopinavir/ritonavir	first line (RHZE)	Recovered
Stjepanović M et al 2021[55]	Serbia	azithromycin, chloroquine, fluoroquinolone, cephalosporine	first line (RHZE)	Recovered
Valdivieso-Jiménez JA et al 2020[56]	Mexico	cephalosporins, amikacin, macrolide, carbapenems	first line (RHZE)	Recovered
Wong SW et al 2021[57]	Singapore	Remdesivir	first line (RHZE)	Recovered

Only a single case (1.17%) of multi-drug-resistant TB (MDR TB) was reported, which might be an indicator of the reactivation of latent tuberculosis during the COVID-19 era. Moreover, non-tuberculosis mycobacteria (NTM) were also isolated from two cases in which untreated cases had died. The role of NTM in this regard needs further study.

The Implication of Patient Characteristics for Disease Severity

About 60% of severe cases end in death. Disease severity is higher at older ages (> 30 years), which accounts for 73.3%. Other reports were also in line with this finding.[20] Disease severity is mainly dependent on the immune status of the individual, and the deterioration of the immune system at advanced age might play a crucial role in disease severity. In addition, 20% of severe cases were also reported among children 5 years of age. Many (86.7%) severe cases have reported fever. Fever is also reported as the major clinical sign of the disease.[24] However, only 46.7% of severe cases had a coughing symptom. Disease severity has no significant association with gender (p-0.68, OR =0.9, 95% CI; 0.12–4.9). However, more severe cases were noted among females (27.7%) as compared to males (22.4%) in this review. Disease severity was also high among patients with another comorbidity (65%).

Conclusion

Fever, cough, hypotension, altered blood cell count and liver enzymes, and lower hemoglobin are common in COVID-19/TB co-infection. An alteration in blood cell parameters is associated with an unfavorable treatment outcome. There is a higher death rate in COVID-19/TB co-infection, and it is associated with older age, smoking or smoking history, drug abuse, and co-morbidity of non-communicable diseases. Conversely, there is a lower death rate in HIV patients. This might be the role of antiviral drugs. Further studies associating immune cell function in HIV patients need to be investigated.

Recommendation

A large-scale longitudinal study is needed to see the more precise co-appearance of the two respiratory pathogens, mainly in TB diagnostic and treatment initiating centers.

Limitation of the Review

This review is not without limitations. First, the articles collected in this review are only cases in which we are unable to calculate the prevalence of the co-occurrence of the two diseases. Next, the quality assurance measures in all reported parameters of cases are not indicated and thus are not measurable.

Abbreviations

ADA, Adenosine Di Aminase; AOR, Adjusted Odds Ratio; BCG, Bacillus Calmette Guerin Vaccine; COVID 19, Corona Virus Disease −2019; CRP, Inflammatory Reactive C- Protein; DOT, Directly Observed Therapy; HIV, Human Immuno-Deficiency Virus; LDH, Lactate De Hydrogenase; MTB, Mycobacterium Tuberculosis; OR, Odds Ratio; PCR, Polymerase Chain Reaction; PLWH, Peoples Living with Human Immuno-Deficiency Virus; RHZE, Rifampicin, Isoniazid, Pyrazinamide, Ethambutol; SARS COV 2, Severe Acute Respiratory Syndrome Corona Virus; TB, Tuberculosis; WHO, World Health Organization.

Data Sharing Statement

The data related to this document can be obtained by contacting the principal investigator.

Acknowledgment

We acknowledge clinicians for reporting and publishing the cases used for reviewing this article.

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Author Contributions

All authors have made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no conflicts of interest in relation to this work.

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