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Review of clinical profile, risk factors, and outcome in patients with Tuberculosis and COVID -19

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Abstract Coronavirus disease (COVID 19) has involved millions of people all over the world. Tuberculosis (TB) continues to affect millions of people every year with high mortality. There is limited literature on the occurrence of COVID 19 in patients with TB. We reviewed the available data on various clinical details, management, and outcome among patients with COVID-19 and TB. 8 studies reported a total of 80 patients with this coinfection. These patients were reported from 9 different countries, with Italy reporting the largest number of cases. Migrant, males constituted a major proportion of cases. Most reported patients were symptomatic. Fever, dry cough, and dyspnea were the most commonly reported symptoms. Bilateral ground glass opacities were more common in COVID 19 infection and cavitory lesions were more common in patients with TB. Most reported TB patients had been found to have *mycobacterium tuberculosis* from sputum culture in the background of pulmonary TB. Most patients of TB were treated with multidrug regimen antitubercular therapy. In all 8 studies, COVID 19 was treated as per the local protocol. Mortality was reported in more than 10% of patients. Mortality was higher in elderly patients (> 70 years) and amongst patient with multiple medical comorbidities. (www.actabiomedica.it)

Key words: Tuberculosis, COVID -19, Diagnosis, Outcome, Mortality, Evidence

Introduction

Following the declaration of the novel coronavirus outbreak as a public health emergency by the World Health Organization, the Coronavirus disease 2019 (COVID-19) pandemic continues to be a significant global health crisis. (1) As of September 30th, more than 33 million people have been affected in 188 countries. Reported death has been more than a million. Among symptomatic patient's respiratory manifestations continues to be predominant.(2) Patients with older age, multiple comorbidities including advanced chronic obstructive lung disease, and associated cardiovascular illnesses are reported to be at risk of the worst outcome.(3,4) At the same time Tuberculosis

(TB) continues to a global burden with around 2.5 million new patients and .3 million deaths annually. (5) There is a paucity in clinical literature reporting interactions and the impact of TB among patients with COVID 19. (6) We did a systemic review to obtain the available literature on the clinical manifestation, diagnosis, management and outcome among patients with coinfection of COVID-19 and TB.

Methods

We searched in various electronic databases including Pub Med, Embase, Medline, and Google scholar for articles on COVID-19 and TB. We used keywords

including “COVID-19”, “Coronavirus disease 2019” “pulmonary tuberculosis,” TB”, and “tuberculosis”. Studies reporting clinical details of COVID-19 and TB patients were included in this review. Publications including clinical trials, cohort studies, case-controlled studies, case series, and case reports that were published between 1 December 2019 to 30 September 2020 were eligible to be included in this review. (7) We excluded articles that included opinions, letters, recommendations, guidelines, and failed to provide any patient related information. We included peer reviewed articles on adults with TB and COVID-19, that have been published in scientific journals. (8) We also excluded abstracts, and preprints that had not undergone peer review and published articles on children with the coinfection. In this review, we only included articles that were published in English. (9)

Results

As of September 30th, we identified 113 articles in PubMed which discussed the details of COVID -19

and tuberculosis. Among these only 8 articles had clinical details of patients with TB and COVID 19 as shown in Table 1. One of them was a case series of 3 patients, four were case reports, and 3 were retrospective cohort studies. (10-13).

Definitions

COVID - 19: Across the studies presence of COVID -19 was reported following confirmation with molecular biology. In absence of SARS CoV -2 PCR, classical bilateral ground glass pattern in HRCT, in a patient with a significant risk of exposure was also used for diagnosis. (13-16) The diagnosis and management of COVID- 19 has been changing constantly. In the beginning in view of limited availability of PCR and the delayed turnaround time of the result, patients were empirically considered COVID – 19 positives based on risk of exposure, contact history. Classical imaging findings would often be available before the availability of the PCR result. (15) All patients were ultimately found to have serological conformation of COVID – 19.

Table 1. showing the details of reported COVID 19 patients with TB

Number	Study	Patients	Age (Mean)	CT finding	Mortality
Active Pulmonary TB					
1	He et al	1	76	B/L GGO, RUL Cavity	-
2	Tadolini et al	42	45.5	B/L GGO, B/L Cavity, U/L cavity	+
3	Motta et al	20	70	B/L GGO, U/L infiltrates	+
4	Kumar et al	1	38	CXR: B/L infiltrates	+
5	Tham et al	4	32	CXR: B/L Cavitory lung lesion, B/L and U/L pleural effusion	-
6	Farqihi et al	1	60	B/L GGO	-
7	Vilbrun et al*	1	26	CXR: Non specific	-
Post TB sequelae					
1	He et al	2	46.5	B/L GGO	-
2	Tadolini et al	7	69	B/L GGO, U/L infiltrates	+
Extra Pulmonary TB					
1	Ata et al (TB meningitis)	1	28	CXR: B/L infiltrates CT: B/L GGO	-

*Multi Drug Resistant Tuberculosis; B/L: bilateral, GGO: Ground glass opacity, RUL: right upper lobe, U/L: Unilateral, CXR: Chest Xray, CT: Computed tomography, TB: Tuberculosis

TB: Patients were divided into two subgroups. Patients with the presence of positive microbiological studies were reported to have active disease. Patients with a history of TB, and completion of treatment were considered to have post TB sequel. Further clinical type of TB was classified as Pulmonary and extrapulmonary based on the presence of involvement of lung parenchyma. Treatment wise TB was reported to be pan-susceptible and drug resistant based on the available susceptibility profile of the organism. Mutli-drug resistant (MDR) TB was defined as the presence of resistance of the isolate to isoniazid and rifampin. (10,11)

COVID -19 and TB coinfection: This was defined with the presence of COVID -19 positivity in patients with TB. Patients were further sub grouped based on the disease status of TB. Patients with i) newly diagnosed TB before the diagnosis of COVID -19, ii) newly diagnosed TB after the diagnosis of COVID -19, iii) diagnosis of COVID -19 in TB patients who are in the middle of completing their treatment were grouped as COVID – 19 with active TB. Patients who had any history of TB with or without treatment, suspected to have latent TB, and had completed antitubercular therapy recently were grouped as COVID -19 with TB sequel. All studies reporting TB and COVID -19,

included patients with a diagnosis of TB any time in the past to include patients with consequences of TB. (10,11,15,17)

Epidemiology

These 8 studies cumulatively reported 80 patients with COVID -19 in the background of TB. Seventy patients were reported to have active pulmonary tuberculosis at the time of COVID – 19 diagnosis. Most of these reported cases had been recruited from nine countries and three continents, mostly by the Global Tuberculosis Network. (10,11,18) Figure 1 shows the different countries with reported TB and COVID- 19 coinfection. To date, Countries reporting TB and COVID cases have been Belgium, Brazil, France, Italy, Russia, Singapore, Spain, Switzerland, India and China. Among these Italy has reported the highest percentage of cases (51%). With the recent upsurge of cases in developing countries, we can anticipate a rise in the numbers of patients with TB and COVID -19 coinfection. TB and COVID coinfection has been reported across both genders and different age groups. COVID 19 co-infection has been reported in TB patients before diagnosis, after diagnosis, and during



Figure 1. Showing countries reporting cases of COVID 19 and TB coinfection.

the entire course of being on treatment for TB. The 2 cohort studies reported that coinfections were commoner in migrants and males.

Migrants constituted more than 50% of patients in both groups. Similarly, both groups had more than 80% of males. Interestingly one study also reported that 41% of the patients were smokers, 31% of the patients were unemployed and 20% of the patients had a history of alcohol abuse. (11,16) Both TB and COVID-19 are reported to have high infectivity.(19) A single COVID-19 patient is known to infect 2.5 people within a short span of 5 days, and a patient with pulmonary tuberculosis can infect around 15 patients an year. (20)

Clinical Features

Pulmonary TB patients present with fever, productive cough, and constitutional symptoms. In the subsets of patients with COVID -19, and TB symptoms at the time of presentation continues to be similar to patients without TB. (10,11) Unlike patients with isolated COVID- 19 illnesses most reported patients with coinfection are symptomatic. This could be because of the selection bias in recruiting only symptomatic patients presenting to the hospital. Fever, dry cough, and dyspnea have been reported as the commonest symptoms. (11,19) Other reported symptoms have been chest tightness, chest pain, and diarrhea. (10) Among symptomatic patients, hypoxia has also been documented requiring oxygen supplementation. These studies are limited regarding the physical examination findings. (10,11) The same could be because of the rapid availability of microbiological confirmatory testing, imaging modalities, and the various other factors contributing to a reduction in patient and provider interaction. Among patients with TB, COVID-19 can occur before, during or after the onset of the illness, which further hinders the clinical picture among patients.

Microbiology

Almost all reported patients had mycobacterial infections secondary to *mycobacterium tuberculosis*.

Sputum culture (45%), Nucleic Acid Amplification Test (NAAT-26.5%), and sputum smear positivity (18.4%) were used as the diagnostic tool for Tuberculosis. There is also a report of infections secondary to *mycobacterium bovis*. Both drug susceptible and drug-resistant mycobacterial strains have been reported with the former being the commoner (82%). Resistance to an isolated ATT has been reported in around 18% of patients and MDR TB isolates have been identified in 9% of co infections. (10,11,18)

Laboratory Panel

Initial case series reported the presence of leucopenia, lymphocytopenia with elevated inflammatory markers including ESR, CRP and LDH. Other reported laboratory abnormalities in this subset of patients were low serum albumin, raised ALT, an abnormal glucose level, and raised CPK.10 Studies on COVID -19 patients have persistently reported multiple laboratory abnormalities in patients with severe disease. Among patients with severe COVID -19 presenting with cytokine storm raised levels of procalcitonin, ferritin, interleukin -2 (IL-2), IL-7, and tumor necrosis factor have been reported. (21) Similarly, severe COVID-19 patients with cardiac injury have been reported to have raised levels of troponin, CK – MB, myoglobin, D – dimer, high sensitive troponin, and NT pro BNP. (22) The impact of COVID -19 and TB coinfection on inflammatory markers and markers of cardiac injury remains unknown.

Imaging

High resolution computed tomography (HRCT) and chest radiograph (CXR) has been used to identify the patterns of pulmonary involvement. (3) Imaging details are available in all (98%) of patients in the above studies. (6) HRCT has been the initial modality of imaging in more than 40% of patients. Imaging findings that have been reported in the TB patients developing COVID 19 are the development of multiple, bilateral ground glass opacity, and consolidations with air bronchogram. (6,11,18) Among patients with

TB and COVID 19 unilateral pulmonary infiltrates were seen in 33% of patients and bilateral infiltrates were reported in 19% of patients. Chest CT findings suggesting the diagnosis of pulmonary TB have been cavitating lung lesions. (11,18) Among patients with TB bilateral cavitory lesions have been reported more often (27%) as compared to the unilateral cavitory lesion (21%). Other patterns that have been reported in imaging are miliary pattern, crazy paving, and tree in bud pattern. The pattern of pulmonary involvement secondary to COVID 19 in TB patients continues to be the same as that of non-TB patients. (3,6) In this subset of patients, GGO is still the commonest pattern of pulmonary involvement. Interestingly alike non TB patient GGO has been reported to resolve following improvement of COVID 19 illness in TB patients as well. (14-16)

Risk Factors:

Reported predisposing factors in TB patients with COVID 19 have been similar to that of TB patients without COVID 19. Medical comorbidities like COPD, diabetes, HIV, renal failure, liver disease, alcohol abuse, and smoking have been reported in the study by Tadolini et al. (18) This study also reported demographic factors including male gender and migrant population in higher proportions of patients. As both COVID-19 and TB tend to spread in overcrowded areas, among poor and malnourished population these comorbidities and circumstances can have synergistic impact. (15,23)

Types of TB

Both pulmonary (73%) and extra-pulmonary TB have been reported among patients with COVID -19, with the former being the commoner. Disseminated TB as defined by the presence of evidence of TB in multiple (>1) organs have also been reported to have COVID-19. Sites of isolated extrapulmonary TB that have been reported in COVID -19 patients are lymph node, bone, larynx, CNS, gastrointestinal, peritoneal, genitourinary, pleural and spinal in location. (18,24)

Treatment

All the patients with active TB were reported to be treated with the multidrug regimen antitubercular therapy. Among patients with pan-susceptible organism treatment regimen constituted isoniazid, rifampin, pyrazinamide, and ethambutol. (3,11) In one patient with multidrug resistant TB as detected by resistance to rifampicin in Xpert PCR, bedaquiline, levofloxacin, linezolid, and clofazimine was used in combination with pyrazinamide. Various therapeutic agents that were used to treat COVID-19 in patients with TB co-infection were hydroxychloroquine, azithromycin, lopinavir/ritonavir, darunavir/cobicistat combination. (11,18) Glucocorticoids including methylprednisolone and dexamethasone have also been administered to these subsets of patients. There have been reports of administration of anticoagulation (enoxaparin, parnaparine) as well. (18) While the antitubercular regimens used were similar, therapies used for COVID-19 were varied across all patients. Most treatment details including the reason for the choice of therapy, the doses of medications, the duration of medications, the details of medication interactions, dosage modifications and adverse drug events were not reported for either form of therapy consistently. (24,25)

Complications

Complications that have been reported in this subset of patients are hypoxemia, respiratory failure, acute respiratory distress syndrome (ARDS), the requirement of noninvasive ventilation, glucose abnormalities, a prolonged hospital stay (maximum 130 days in hospital), and superimposed bacterial infection. (3,11,18) Details of other organ involvement were mostly not available even in the patients with complications and mortality. (26,27)

Mortality

Motta et al described 2 cohorts of patients with TB and COVID 19. The first cohort had 49 patients from 8 countries and the second cohort had 20 hospitalized patients with TB and COVID-19. 53% and 85% of

patients from these cohorts were migrants. They reported a mortality rate of 11.3% and 14.3% in the patients respectively. (11) They reported that mortality was more likely among elderly patients with COVID 19 and TB. The 2 reported contributors to mortality were an age of > 70 years and the presence of > 2 medical comorbidities. Motta et al found that migrants had lesser mortality, and they attributed the same to the younger age and the absence of medical comorbidities in these patients. (11,18) In all three studies, TB was not a major contributor to mortality. Among the TB patients with reported mortality, COVID 19 was contributory to worst outcome and mortality. (3,11,18) Interestingly patients with mortality had acquired COVID-19 via nosocomial transmission.

BCG and COVID 19:

Innate immunity is thought to be instrumental in the course and severity of COVID 19. This had been postulated based on higher prevalence and mortality of COVID -19 patients in countries with a lower rate of Bacillus Calmette –Guerin (BCG) administration. A recent review showed a strong correlation between the BCG and cross protection from COVID -19, with every 10% increase in BCG administration resulting in 10.4% reduction in COVID – 19 mortality. (28-30)

However, this epidemiological study was not designed to show causality and direct association. Another study reported that COVID -19 mortality was remarkably higher in countries without mandatory BCG vaccination. This study reported that seven countries with mandatory BCG vaccination for their population had lesser mortality as compared to countries that had stopped BCG administration for twenty years. This protection was reported across different strains of BCG excluding Denmark strain. (29,30) In the present scenario, with a further increase in the number of cases and mortalities in countries with good BCG administration status this concept continues to be clarified further. Interestingly one of the above studies reported that 3 of the 8 patients with mortality had been vaccinated with BCG.30

Limitations:

All the eight articles including the 3 studies have been retrospective. These studies lacked a strict inclusion

and exclusion criteria and have been liberal in defining TB. Given a small sample size, these studies have not been able to establish the statistical significance of the co-infection. (31) these studies were limited in defining the severity and patterns of organ involvements in patients with COVID-19. Similarly, they were limited in terms of laboratory investigations including biochemical profile, inflammatory markers, and coagulation profile. (32,33) They were limited in identifying the impact of COVID – 19 on TB and vice versa. These studies did not look at the interactions of various drugs that are used for treating this subset of patients. (34) We also excluded non-English articles and children in this review.

Future Strategies:

In future clinical studies should incorporate the appropriate classifications of patients with TB and COVID 19. Studies should differentiate the various factors pertinent to TB, and COVID- 19. (35,36) They should incorporate in detail the various parameters including clinical presentation, physical findings, and detailed laboratory parameters. Consistent reporting of clinical outcomes including morbidity, major organ involvement, the requirement of intensive care, and invasive, noninvasive ventilation, the requirement of vasopressors would facilitate further understanding of these diseases. (35,37) Future studies should incorporate a standardized treatment algorithm for both infections. Interactions amongst multiple medications and adverse drug events need to be reported. The standardized multidrug antitubercular regimen can be safely continued following physician's recommendations based on the susceptibility pattern. Regimens used for COVID-19 should be used as per available evidence and guidelines in the symptomatic patients. (38) Implementing strict infection control interventions for all hospitalized patients (particularly for those at higher risk, e.g. elderly and patients with co-morbidities including TB) is the need of the hour. (39) Among non-hospitalized TB patients social distancing, patient education, availability of rapid testing, the continuation of antitubercular therapy, establishment of a robust triaging, specialized care unit, international scientific collaboration, and governmental support would be crucial in controlling the cumulative impact of both these infections. (39-41)

Conclusion:

Studies on the impact of COVID-19 in patients with TB are limited. Most cases reported have been from Italy. This co-infection has been reported in patients across all age groups. Co-infection rates are higher in males and migrants. Most reported patients with co-infection have been symptomatic. In these symptomatic patients with COVID 19 and TB, the clinical presentation, and the imaging findings tend to be similar to the patients without TB. Elderly patients and patients with more than two comorbidities are reported to be at higher risk of mortality.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethical statement: The article doesn't contain the participation of any human being and animal.

Verification: All authors have seen the manuscript and agree to the content and data. All the authors played a significant role in the paper.

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