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Systematic Review

COVID-19 and tuberculosis reactivation: a systematic review assessing most common risk factors

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ABSTRACT

COVID-19 as a pandemic not only shifted the focus of the healthcare system from other diseases but also affected the disease progression of infections like tuberculosis which remained a leading killer in the past worldwide. COVID-19 itself is said to reactivate latent tuberculosis as shown in animal experiments. Immunomodulators such as corticosteroids and tocilizumab which are being used for covid treatment even further predisposes patients to tuberculosis reactivation and increased progression of the disease. Diabetes is already known to be a risk factor for tuberculosis reactivation and impact tuberculosis progression and worsen the situation. The exact mechanism of interaction of covid-19 and tuberculosis and their effect on each other remains unknown. Considering high prevalence of tuberculosis and the current scenario of covid-19 in world, there is need to study the impact of covid-19 infection on tuberculosis progression or reactivation and commonly associated risk factors. We conducted a systematic search of the online databases to collect data of patients who had tuberculosis reactivation or increased progression of disease after covid-19 infection. Data of a total of 18 patients was retrieved and used for the syntheses of the study. Diabetes was present in 50% of the patients. 55.5% patients were administered corticosteroids for covid-19 treatment later presenting with tuberculosis. Tocilizumab however was administered to 22.2% patients who also received corticosteroids. 27.7% patients suffered tuberculosis reactivation after covid-19 infection without history of diabetes and corticosteroid or tocilizumab administration. None of the patients were reported to have HIV infection. Major risk factors present in patients included corticosteroid administration and diabetes. However, tuberculosis reactivation was seen even in absence of these factors indicating that covid-19 infection may itself be responsible for tuberculosis reactivation. The exact mechanism however remains unknown and further clinical studies are needed to know the same.

Keywords: COVID-19, Tuberculosis reactivation, Diabetes, Corticosteroids, Tocilizumab

INTRODUCTION

Tuberculosis (TB) remained the leading infectious killer in the world however COVID-19 which was first identified in Wuhan was declared a pandemic by WHO and soon the whole world was largely impacted by COVID-19. The focus of the whole world shifted from diseases like tuberculosis to COVID-19. For the treatment of COVID-19 infection corticosteroids are being used which have risk of reactivation of tuberculosis.[1,2] Apart from corticosteroids other immunomodulators such as tocilizumab which are also commonly used in severe COVID-19 patients are also suspected to cause reactivation of a number of infections including tuberculosis.[3] Not only administration of immunomodulators but chronic conditions like diabetes is a risk factor for tuberculosis reactivation which shouldn't be overlooked.[4] Animal studies suggested that COVID-19 is itself a risk factor and responsible for the reactivation of dormant tuberculosis that further needs to be clinically correlated specially in the era when every third person is said to have tuberculosis infection in the world as per WHO.[5]

The aim of the study was to conduct a systematic search of the online databases for records including data of patients with tuberculosis reactivation after COVID-19 infection and evaluate the common risk factors associated with it.

METHODS

This was a retrospective study conducted using online databases as per PRISMA 2020 checklist. The study and protocol were not registered and protocol was not prepared. A systematic search of Pubmed database, Pubmed Central database and Cochrane Library (full text search) was performed using the Boolean expression [(COVID-19 or coronavirus or SARS-CoV-2) and (tuberculosis or TB) and reactivation] from point of inception to 10 May 2022.

No filters or limits were used for the search. Both the authors conducted the search independently and final selection was done by discussion.

The references of records assessed for eligibility were also screened for potentially eligible articles. Records including the data of patients with increased progression or reactivation of tuberculosis after the COVID-19 infection were included in the study and this was used as the inclusion criteria. Data from 15 records was retrieved and used for the syntheses of the study. The data was manually entered in Microsoft excel and a table of cases arranged in ascending order of publication date was created. HIV status of patient, if not reported, was assumed to be negative. Meta-analysis of the data was not performed.

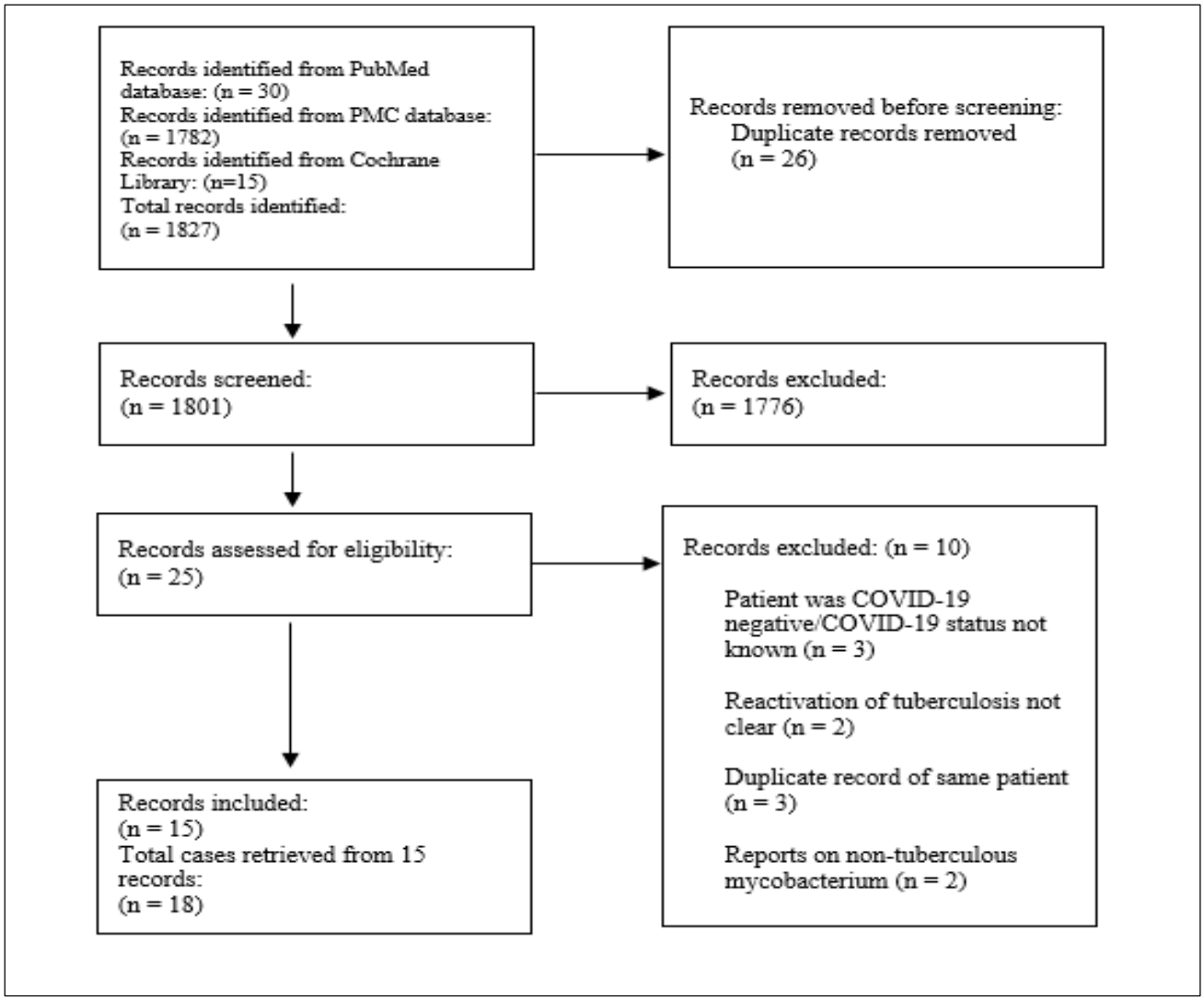

Table 1: Flow chart of literature search.

RESULTS

15 records were included in the study i.e.; 13 case reports and 2 case series which included data of 18 patients. The mean age of patients was 54.77±15.31 years and a total of 72.2% patients were male. 50% of the patients had diabetes. 27.7% of patients developed tuberculosis reactivation without administration of corticosteroids or tocilizumab or history of diabetes. Corticosteroids were administered in a total of 55.5% patients. Tocilizumab was

found of be administered in 22.2% patients out of which all were also administered corticosteroids. None of the patient was reported to have HIV infection. Assessment of risk of bias of records was not performed (Table 1).

Table 1: Cases of Tuberculosis reactivation after COVID-19 infection.

S. no.	Reported by	Year	Age (years)/ gender	TB reactivation	Diabetes	CST used	TCZ used
1	Sasson et al[6]	2020	44/M	Pulmonary	No	Yes	Yes
2	Garg et al[7]	2020	44/M	Pulmonary	Yes	Yes	Yes
3	Khayat et al[8]	2021	40/F	Pulmonary	No	No	No
4	Elziny et al[9]	2021	29/M	Peritoneal TB progressing to pulmonary TB	No	No	No
5	G. Lee et al[10]	2021	49/M	Pulmonary	No	Yes	No
6	Liu et al[11]	2021	46/M	Pulmonary	No	Yes	No
7	Younes et al[12]	2021	71/M	Pulmonary	Yes	Yes	No
8	Younes et al[12]	2021	76/M	Pulmonary	No	No	No
9	Noh et al[13]	2021	80/F	Pulmonary	No	Yes	Yes
10	Pozdnyakov et al[14]	2021	64/M	Pulmonary	Yes	Yes	No
11	Gandotra et al[15]	2021	47/M	Pulmonary	Yes	Yes	No
12	Aguillón-Durán et al[16]	2021	43/M	Pulmonary	Yes	No	No
13		2021	44/M	Pulmonary	Yes	No	No
14		2021	49/F	Pulmonary	Yes	No	No
15	Iovino et al[17]	2022	45/M	Pulmonary	No	No	No
16	Noori at al[18]	2022	76/M	Pulmonary	No	No	No
17	Landivar et al[19]	2022	69/F	Pulmonary	Yes	Yes	Yes
18	Friedman et al[20]	2022	70/F	Pulmonary	Yes	Yes	No

Note: TB- Tuberculosis, CST- Corticosteroids, TCZ- Tocilizumab.

DISCUSSION

We found 18 cases of tuberculosis reactivation in COVID-19 patients and diabetes was found to be present in 9 out of 18 patients. However out of these 9 patients only 3 didn't had any history of corticosteroid or tocilizumab administration. 10 out of 18 patients were administered corticosteroids out of which 4 were also administered tocilizumab. 2 out of 18 patients who had diabetes were administered corticosteroid and tocilizumab who later developed tuberculosis reactivation. We found 5 cases with no history of diabetes and corticosteroid or tocilizumab administration who still developed tuberculosis after COVID-19 infection. No patient was reported to have HIV infection.

Arielle Sasson and colleagues reported a case of 44-year-old male who developed pulmonary tuberculosis few days after severe COVID-19 infection. Corticosteroids and tocilizumab were administered to patient for COVID-19 infection. No co-morbidity was reported. Patient's Chest CT scan showed consolidation in right lower lobe of lung and the cavity size increased later confirmed by further scan. Patient's sputum smear tested positive for acid-fast bacilli after which he was started on anti-tubercular treatment. The patient had positive PPD test and was treated 10 years back.[6]

A case reported by Garg and et al colleague of 44-year-old male showed tuberculosis reactivation few days after the COVID-19 treatment which included dexamethasone (20 mg IV daily) and tocilizumab (800 mg IV once). The patient was a known case of hypertension, diabetes and atrial fibrillation.[7] Khayat et al reported a case of 40-year-old female who developed tuberculosis 7 weeks after the COVID-19 treatment. Her chest CT showed consolidation in right upper lobe of lung. No significant co-morbidity or treatment history was reported. The patient had been in contact with tuberculosis patient 2 years back but screening for latent tuberculosis was not performed.[8]

Elziny et al reported a case of 29-year-old male presenting with COVID-19 infection and peritoneal tuberculosis which progressed to pulmonary tuberculosis in 2 weeks. No significant co-morbidity or treatment history was reported.[9]

Lee et al reported a case of latent tuberculosis reactivation in 49-year-old male after being treated for COVID-19 infection with dexamethasone. The patient was a known case of hypertension and gray zone lymphoma and was diagnosed with cytomegalovirus infection for which he was administered ganiciclovir. The patient was started on anti-tubercular therapy but after few weeks of hospitalization the patient died.[10]

Wang-Da et al reported a case of 46-year-old male who developed pulmonary tuberculosis after COVID-19 infection and administration of betamethasone. The patient tested negative for HIV. No other significant co-morbidity or treatment was reported.[11] Younes et al reported two cases of tuberculosis activation. A 76-year-old male with

COPD developed tuberculosis after COVID-19 infection and bamlanivimab administration. Another case of 71-year-old male with diabetes mellitus developed tuberculosis after being treated with dexamethasone for COVID-19 infection.[12]

Noh et al reported a case of 80-year-old female who was a known case of hypertension and coronary artery disease presenting with pulmonary tuberculosis 3 months after being treated with tocilizumab and corticosteroids for COVID-19 infection.[13]

Pozdnyakov et al reported a case of 64-year-old male who developed pulmonary tuberculosis after treatment of COVID-19 infection with methylprednisolone. The patient was a known case of diabetes, hypertension and dyslipidaemia.[14]

Gandotra et al reported a case of 47-year-old male who developed pulmonary tuberculosis following prednisolone administration for COVID-19 infection. The patient also developed pulmonary aspergillosis and was also diagnosed with hemophagocytic lymphohistiocytosis. The patient was a liver transplant recipient who was on Sirolimus for immunosuppression. The patient had also developed diabetes after the transplant and was on metformin therapy.[15] Aguillon-Duran et al reported 3 cases of pulmonary tuberculosis reactivation in patients previously treated for COVID-19 infection. All the 3 patients (43/M, 44/M, 49/F) were reported to have diabetes and had COVID-19 infection 3 to 6 months before the reactivation of tuberculosis. All 3 patients were reported to be negative for HIV. The 43-year-old male had history of peripheral neuropathy while 49-year-old female had history of hypertension and had been exposed to TB patient 2 years back.[16]

Iovino et al reported a case of latent tuberculosis reactivation in 45-year-old male 3 months after the patient was treated for COVID-19 infection. No significant treatment or co-morbidities were reported.[17]

Noori et al reported a case of 76-year-old male who presented with tuberculosis who had mild COVID-19 infection a month before the presentation. The patient was a known case of chronic obstructive pulmonary disease, coronary artery disease, seizure disorder and heart failure with reduced ejection fraction.[18]

Landivar et al reported a case of 69-year-old female who developed pulmonary tuberculosis few months after severe COVID-19 infection for which she received dexamethasone and tocilizumab. The patient was a known case of hypertension, diabetes, pancreatitis (autoimmune type 1). The patient was on regular metformin and prednisolone (5 mg daily) for the stated co-morbidities.[19] Friedman et al reported a case of 70-year-old female who developed tuberculosis reactivation after administration of dexamethasone for COVID-19 infection. The patient was a known case of diabetes, chronic kidney disease and hypertension.[20]

Limitation

Only case reports and case series were found to be available on online databases and no clinical study had yet been performed. Hence statistical analysis of the data can't be performed. The sample size for the study was low (i.e.; 18 patients) and hence can't be commented upon the generalizability of study.

CONCLUSION

Tuberculosis reactivation after COVID-19 infection under the influence of risk factors like diabetes and immunomodulator administration occurred most commonly in middle aged patients. Corticosteroids administration and history of diabetes is found to be the most commonly present risk factor. However, tuberculosis reactivation even occurred in patients without presence of above-mentioned risk factors indicating that covid infection may itself be a risk factor for affecting the progression of tuberculosis. High prevalence of tuberculosis and widespread use of corticosteroids for severe COVID-19 cases treatment may increase the risk of tuberculosis reactivation especially in diabetics.

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