Original Article

COVID-19 and tuberculosis coinfection: A case–control study from a tertiary care center in South India

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Abstract

Context: Coronavirus disease 2019 (COVID-19) and tuberculosis (TB), are presently the major infectious diseases imposing a consequential public health threat and their coinfection has a significant impact on the outcome. **Aims:** To evaluate the clinical features and outcomes of COVID-19-TB coinfected cases compared to solely COVID-19-infected cases. **Settings and Design:** A retrospective observational study was conducted between August 1, 2020, to February 28, 2022, at a tertiary care hospital. **Materials and Methods:** In this case-control study, an equal number of gender-age-matched COVID-19 and TB coinfected patients and COVID-19 cases without TB were included using simple random sampling. **Statistical Analysis Used:** The data was analyzed using SPSS v 26. Categorical variables were compared using the Chi-square test, and an independent *t*-test or Mann-Whitney U test was applied for the quantitative variables in the univariate analysis. A *P*-value of less than 0.05 was considered significant. **Results:** A total of 27 patients were included in each group. Upper lobe involvement (44%) and pleural effusion (22%) were significantly more common in TB-COVID-19 cases when compared to the control group (7% and 4%, respectively; $P < 0.05$). Moreover, median levels of C-reactive protein and ferritin were significantly higher in TB-COVID-19 coinfection. **Conclusions:** Chest radiology and a higher level of certain biomarkers like C-reactive protein and ferritin can help to suspect TB in COVID-19 patients and vice-versa.

Keywords: Case-control, clinical features, coinfection, COVID-19, TB

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Introduction

Mycobacterium tuberculosis (MTB), the causative agent of tuberculosis (TB), is an ancient predator of mankind, infecting millions of people globally every year. TB was considered the leading cause of death from a single infectious agent until the highly contagious coronavirus disease 2019 (COVID-19) emerged.[1] In December 2019, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported from Wuhan, China, and rapidly turned into a pandemic.[2] As of June 28, 2023, more than 767 million confirmed COVID-19 cases and more than six million

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deaths have been recorded worldwide.[3] One of the collateral damages of COVID-19 has been the derailment of public health priorities and the impairment of essential healthcare services like TB control programs.[4] The World Health Organization (WHO) Global Tuberculosis Report 2021 documented an 18% decline in newly diagnosed TB along with an alarming increase in death due to TB.[1] TB and COVID-19 are known to primarily infect the lungs and exhibit similar symptoms of cough, fever, and breathlessness, which make it challenging for primary care physicians to differentiate between the two at presentation. This becomes all the more difficult in cases of coinfection.[5,6] This present study, therefore, aimed to describe the demographic characteristics, clinical symptoms, comorbidities, coinfections, clinical biomarkers, radiographic features, management, and prognosis of patients with TB-COVID-19 compared to COVID-19 cases without TB.

Materials and Methods

This was a retrospective observational study where hospital records between August 1, 2020, to February 28, 2022, were screened for concurrent COVID-19 and active TB (newly diagnosed or on treatment) infection at our tertiary care hospital. An equal number of gender-age-matched patients with COVID-19 infection but without TB from the same time period were included in the study using simple random sampling. This study was approved by the Institutional Ethical Committee.

A patient was diagnosed with COVID-19 if they were positive by reverse transcriptase-polymerase chain reaction assay or antigen testing. All COVID patients were classified as mild, moderate, and severe/critical infections according to WHO staging.[7] The tuberculosis patients were either clinically or microbiologically diagnosed as per the National TB Elimination Programme (NTEP), and based on the site of involvement, they were categorized as pulmonary TB (in case of any pulmonary involvement) or extrapulmonary TB (if sites other than lungs were involved).[8]

A standardized proforma was prepared to collect relevant demographic, clinical, radiological, and laboratory reports, along with therapeutic management and prognosis of the enrolled cases. The clinical symptoms, comorbidities, COVID-19 severity, radiology investigation, clinical biomarkers, and mortality of cases with TB and COVID-19 coinfection were compared with COVID-19 cases (age and gender-matched) without TB.

The data was analyzed using SPSS v 26. Qualitative variables were reported as frequency and percentage, whereas quantitative variables were presented as mean (±standard deviation) or median (interquartile range). Categorical variables were compared using the Chi-square test, and an independent *t*-test or Mann–Whitney U test was applied for the quantitative variables in the univariate analysis. A *P*-value of less than 0.05 was considered significant.

Results

A total of 27 cases of TB-COVID-19 coinfection and an equal number of controls were recruited during the study period. The mean age of both groups was 47.3 ± 21.6, with a 74% (20/27) male population. Of the 27 patients, a confirmatory microbiological TB diagnosis was available in 16 (59.2%) patients. The rest 40.7% of the patients were diagnosed based on a combination of clinical, radiological, and pathological findings. Pulmonary TB (PTB) was detected in 59.2% (16/27) of patients while the rest had extrapulmonary TB (EPTB). The anatomical sites of infection for 11 EPTB cases were: Central nervous system (3/11, 27.3%), lymph node (3/11, 27.3%), spine (2/11,18.1%), pleural (1/11, 9.1%), abdominal (1/11, 9.1%) and genitourinary (1/11, 9.1%). The majority of the TB patients (19/27, 70.4%) were diagnosed with TB when they were admitted with the diagnosis of COVID-19. The rest of the patients were already on anti-tubercular treatment (ATT) at the time of admission for COVID-19. An univariate analysis was performed to compare the patients with TB-COVID-19 co-infection and those with only COVID-19 infection, which is presented in Table 1.

Upper lobe involvement on Chest X-rays and pleural effusion was significantly more common in those patients with TB-COVID-19 coinfection. Also, median levels of C-reactive protein and ferritin were significantly higher in TB-COVID-19 coinfection.

Discussion

TB and COVID-19 are respiratory infections with similar presenting features of cough, fever, and breathlessness. In the era of the COVID-19 pandemic, the overlapping symptoms may mask active TB case detection. This might lead to further spread of TB and poorer treatment outcomes, especially in TB-endemic countries.[9] Although the presentation of TB is more insidious, whereas COVID-19 is more acute, it often becomes difficult to differentiate between the two. It becomes all the more challenging when both diseases present concurrently.

There is a lack of understanding of the immunopathological interplay of COVID-19 and TB syndemic, which leaves several unanswered questions on disease prognosis, clinical management, and determinants of mortality in TB-COVID-19 coinfection.[10] Studies have shown that TB might increase susceptibility to COVID-19 infection.[11,12] On the other hand, COVID-19 infection leads to significant reduction and functional exhaustion in total T cell counts, thereby increasing susceptibility to TB.[13] Also, the use of steroids during COVID-19 infection increases immunosuppression and thereby increases the chances of reactivation of TB.[14] In this study, however, there was no difference between the steroid use in the TB-COVID-19 group when compared to the control COVID-19 group.

Similar to previously published works, fever, cough, and dyspnea were the main presenting features in patients with TB-COVID-19 coinfection.[15,16] Since the radiological manifestations in both diseases may be varied, it may be difficult to differentiate the two diseases based on X-ray alone. Computed tomography scans may be helpful in such situations, but they are not available in many resource-limited settings. In our study, we found that upper

Table 1: Univariate analysis comparing patients with Tuberculosis-COVID-19 coinfection and those with only COVID-19 infection

Parameters	TB-COVID-19 (*n*=27)	COVID-19 (*n*=27)	*P*
Comorbidities			
Diabetes	10 (37%)	9 (33%)	0.776
Hypertension	6 (22%)	9 (33%)	0.362
Chronic Kidney Disease	2 (7%)	5 (18%)	0.224
Hypotension	6 (22%)	3 (11%)	0.273
Acute Kidney Injury	3 (11%)	5 (18%)	0.444
Coinfection			
Human immunodeficiency virus (HIV)	2 (7%)	0	0.15
Symptoms at admission			
Fever	13 (48%)	17 (63%)	0.273
Cough	12 (44%)	11 (41%)	0.78
Dyspnea	6 (22%)	6 (22%)	1
Haemoptysis	2 (7%)	0	0.15
Chest pain	2 (7%)	0	0.15
COVID-19 severity			
Mild	11 (41%)	9 (33%)	0.491
Moderate	10 (37%)	8 (30%)	
Severe	6 (22%)	10 (37%)	
Involvement of lungs			
Unilateral	8 (30%)	2 (7%)	0.097
Bilateral	15 (56%)	15 (56%)	
Upper lobe involvement	12 (44%)	2 (7%)	0.002
Cavitation	3 (11%)	0	0.075
Pleural Effusion	6 (22%)	1 (4%)	0.043
Oxygen requirement	14 (52%)	16 (59%)	0.584
Noninvasive ventilation	7 (26%)	10 (37%)	0.379
Mechanical Ventilation	7 (26%)	8 (30%)	0.761
Hemodialysis	3 (11%)	7 (26%)	0.161
Steroids	15 (56%)	14 (52%)	0.785
Clinical biomarkers			
Erythrocyte Sedimentation Rate (ESR)	46 (23.5-90.5)	48 (33-62.5)	0.122
Total Leucocyte Count	8800 (6950-13600)	6200 (5200-11250)	0.126
Platelet count	224,000 (167,000-279,500)	191,000 (171,000-191,500)	0.246
Neutrophil-Lymphocyte ratio	14.15 (5.5-21.6)	5.5 (2.76-25)	0.094
C-Reactive Protein (CRP)	92.2 (28.6-160.7)	54 (33.8-190.68)	0.031
Aspartate transaminase	46.5 (31.5-70.5)	29 (27.5-39)	0.351
Alanine transaminase	16.5 (13-34)	18 (16.5-19.5)	0.149
Ferritin (FER)	1440 (482-2000)	650 (585-716)	0.011
Days of stay in the intensive care unit	7.5 (3-11)	8 (5-11)	0.510
Death	9 (33%)	8 (30%)	0.770

lobe involvement and pleural effusion were significantly more common in cases when compared to control. Since both these findings are more specific to TB, their presence may be used to suspect TB in patients with COVID-19. Pleural effusion was noted in 22% of cases in our study. Another systematic review of 89 COVID-TB cases reported that 11.24% has pleural effusion.[17]

We observed significantly higher levels of C-reactive protein and ferritin in TB-COVID-19 cases. Song WM *et al.* reported markedly elevated levels of inflammatory markers, like CRP, ESR, Procalcitonin (PCT), FER, and Lactate dehydrogenase (LDH) in COVID-TB patients.[17] Larger studies from different countries are required to set a standard cutoff value to differentiate between the two entities.

Although some studies have suggested that the presence of TB may lead to increased severity of COVID, such a finding was not observed in our study. Similarly, no significant difference was observed with respect to mortality outcomes in both study groups. This could be due to the smaller sample size and retrospective nature of the present study, which were the main limitations.

In conclusion, concurrent TB and COVID-19 may be present in TB-endemic areas. Upper lobe involvement, pleural effusion, and higher levels of biomarkers like C-reactive protein and ferritin can help in suspecting TB in COVID-19 patients and vice-versa.

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Conflicts of interest

There are no conflicts of interest.

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