RESEARCH ARTICLE

Outbreaks of COVID-19 in a tuberculosis treatment sanatorium on the Thailand-Myanmar border: a retrospective cohort analysis

[version 1; peer review: 1 approved with reservations]

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Abstract

Background: Tuberculosis (TB) is a chronic condition, with overlapping symptoms to those of coronavirus disease 2019 (COVID-19). There has been inconsistent evidence on whether TB is a predisposing factor for developing severe COVID-19. The aim of this report is to explore whether TB influences the severity of COVID-19.
Methods: COVID-19 cases at two TB sanatoria on the Thailand-Myanmar border were reviewed. Demographic, clinical and laboratory data including TB treatment and co-morbidities, were analyzed. Characteristics and COVID-19 clinical outcomes were compared between two groups of patients: TB and those without TB (the caretakers and the medical personnel). Multivariable ordered logistic regression was conducted to compare the risk of severe COVID-19 between the two groups.
Results: Between September 2021 and March 2022, 161 COVID-19 cases were diagnosed. Over half of the COVID-19 patients were infected with TB (n= 104, 64.6%), and the rest were not (n=57, 35.4%). The median (interquartile range) age was 48 (33.5-57.0) and 27 (23-33) years in the TB and in the non-TB COVID-19 patients, respectively. Before COVID-19 infection, 78.7% (122/155) of patients had received at least one dose of COVID-19 vaccine. The median cycle threshold value at diagnosis was not different between TB (18.5, IQR 16.1-32.3) and non-TB patients (18.8, 15.1-30.0). Fever, gastrointestinal symptoms

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Any reports and responses or comments on the

and ageusia were more common in non-TB patients. Six patients (3.8%, 6/156) all from the TB group became severe of which five (3.2%, 5/156) required oxygen therapy. One TB patient died (1/104, 0.96%) of lung cancer. After adjustment for potential confounders, the final clinical severity was not different between the two groups (adjusted odds ratio 1.21, 95% confidence interval 0.45–3.28).
Conclusions: TB was not associated with severe outcomes in the two TB sanatoria. The high uptake of COVID-19 vaccination and active screening could have impacted on disease progression and prevented unfavorable outcomes.

Keywords
Coinfection, COVID-19, Tuberculosis, Active screening, sanatoria

article can be found at the end of the article.

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Introduction

Tuberculosis (TB) is an important communicable disease in Myanmar and Thailand as both have been enlisted as high TB burden countries by the World Health Organization (WHO)[1]. The efforts to control the disease along the Thailand-Myanmar border have been compromised by the coronavirus 2019 (COVID-19) pandemic[2,3]. This pandemic has reversed years of gains in global TB control activities, especially access to TB diagnosis and treatment[1]. To control COVID-19 infection, many countries closed their borders since early 2020, restricting migration of people as well as trans-border TB control activities across the Thailand-Myanmar border.

It is well established that the severity of COVID-19 infection is often affected by certain comorbidities such as cardio-respiratory diseases, diabetes and conditions that decrease immune defenses[4,5]. Therefore, it can be expected that TB would represent a considerable comorbidity and a risk factor for severe COVID-19 disease[6,7] due to the pre-existing lung damage and reduced antibody and T-cell responses to COVID-19 infection[5,8,9]. A systematic review which included 146 patients coinfected with TB and COVID-19 from 18 countries found that the mortality from COVID-19 was 13% in the coinfected patients, compared with the global average of 6.6%[10].

The deleterious or aggravating effect of COVID-19 and TB disease co-infection was also explored in a meta-analysis[6] focusing on the clinical characteristics and disease course among survivors and deceased. The main finding was the similar pooled odds ratios in the COVID-TB group as compared to the non-TB "control" group COVID-19 infected patients: 2.21 (95% CI: 1.80, 2.70) for death and 2.77 (95% CI: 1.33, 5.74) for severe COVID-19 disease. However another systematic review found that COVID-TB patients had higher risk of severity[4,11] as well as higher mortality; 13% compared to 6.6% in people with COVID-19 alone (global mortality)[4]. One study stated that coinfected patients had similar risk of mortality as well as prolong recovery times from COVID-19[12] compared to non-TB COVID patients. Though, most of the studies in these two reviews were cases reports or case series including only COVID-TB coinfected patients without comparator or a few studies with non-TB control group either COVID-19 outpatients or those hospitalized for other morbidities. On the contrary, there are multiple studies[13–15] concluding that coinfection did not cause statistically significant changes in mortality and disease severity of COVID-19 infection. A cross-sectional study stated that there may be an increased risk of contracting COVID-19 in patients who had a pre-existing TB diagnosis, but there were no statistically increased incidence of Intensive Care Unit admission, intubation or mortality rate when compared with those in the non-TB infected patients[14]. However patients in the non-TB comparator group were older-aged with co-morbidities which could be the main reason for being hospitalized and being more sick than younger COVID-TB co-infected patients.

Shoklo Malaria Research Unit (SMRU) is one of the health-service providing organizations on the Thailand-Myanmar border providing TB diagnosis, care and treatment and control activities (Figure 1). Two TB treatment centers (one in Thailand and the other in Myanmar) adopting a sanitarium

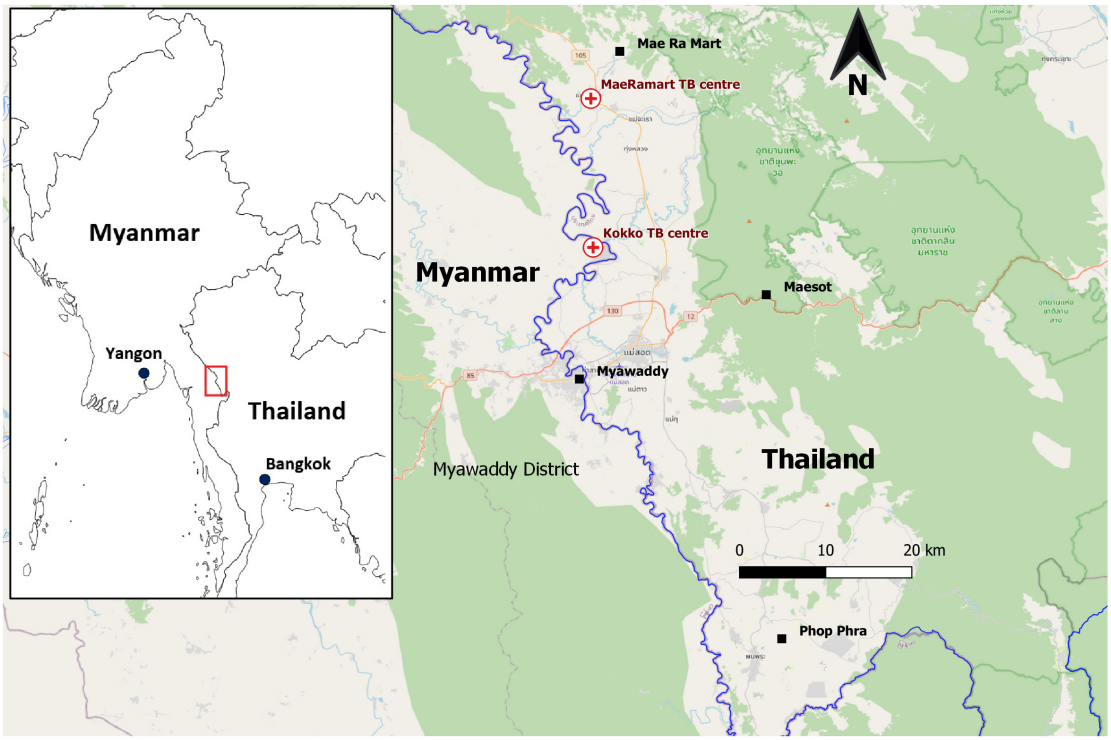

Figure 1. Geographical locations of SMRU two TB treatment sanatoria.

model were established in 2010. During the COVID-19 pandemic, two outbreaks of COVID-19 occurred in these two TB sanatoria involving both TB patients and people without TB (i.e., their caregivers in the compounds and medical staff). The aim of this report is to describe the two COVID-19 epidemics between September 2021 and April 2022 (Figure 2). We compared the characteristics and outcomes of COVID-19 between TB and non-TB patient groups, as well as the association between TB infection and COVID-19 severity.

Methods

Study setting

Both TB sanatoria provide a residential care to all TB patients who are registered in the SMRU TB program. The program is specifically designed for underserved migrants, ethnic minorities and displaced populations along the border who have difficulties to access proper health care and in whom adherence to treatment is poor. Once patients are diagnosed with TB, they are treated free of charge with the WHO-recommended regimens along with the accommodation, nutrition and psychosocial supports throughout the course of treatment.

TB patients are accommodated in a single separated room, each having 10sqft in dimension and well designed for adequate airflow and lighting. The rooms are organized in a way to facilitate infection control and by types of TB, stages of anti-TB treatment and bacteriological clearance status (smear positive, smear negative and multi-drug resistant [MDR]-TB treatment areas). Strictly Directly Observed Treatment (DOT) is applied for anti-TB medications by the medical staff. The comorbidities are also treated by experienced medical teams in each center during the course of treatment. Family members of the patients are allowed to stay in the sanatoria and take care for their relatives.

Study design and study population

This is a retrospective cohort analysis carried out on patients who were residing in two TB sanatoria during the pandemic period from September 2021 to April 2022, and who contracted COVID-19 infection. The study involved extracting and merging demographic, clinical, and diagnostic results from routinely collected patients charts, forms and laboratory database. The cohort comprised active TB patients, their caregivers, and medical staff, with the exclusion of one patient who was lost to follow-up and had unknown outcomes.

Diagnosis of TB and COVID-19

Tuberculosis was microbiologically diagnosed by using conventional microscopic examination (Ziehl-Neelsen stain), molecular technique (GeneXpert system) and radiologically by

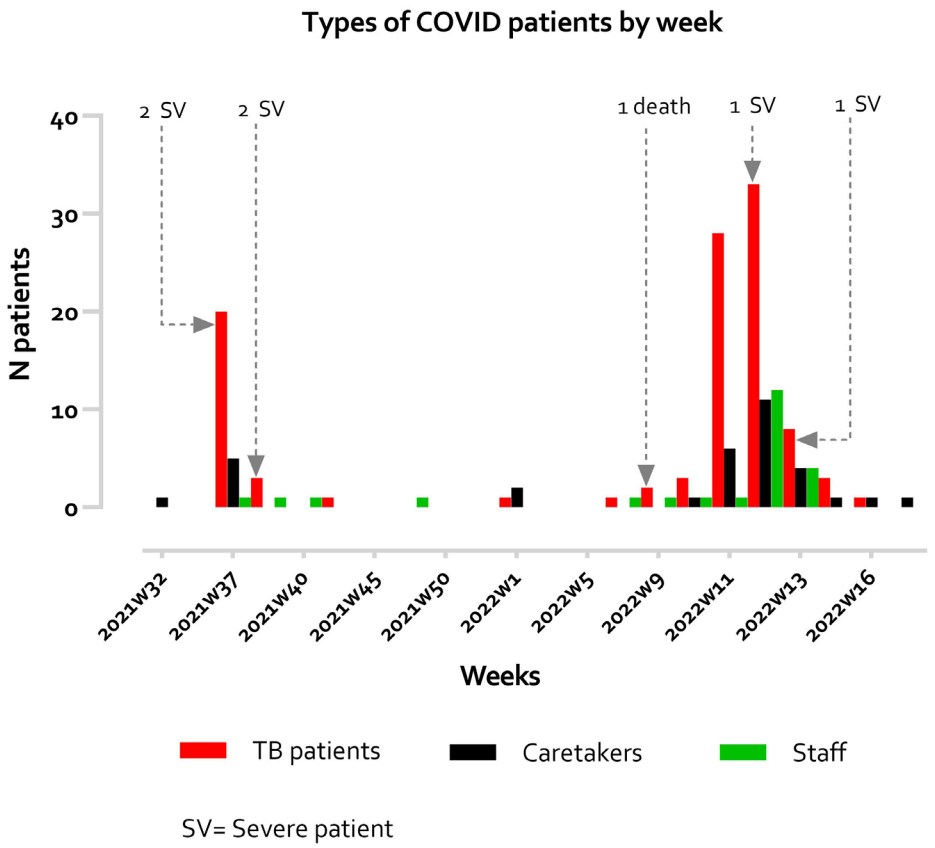

Figure 2. Types of COVID-19 patients by week.

chest X-ray along with clinical examination. In case of rifampicin resistance detected by GeneXpert, anti-TB drug susceptibility testing was performed.

COVID-19 infection was diagnosed by taking nasopharyngeal swab and tested by either real-time reverse transcription polymerase chain reaction (RT-PCR), including Sansure® Novel Coronavirus (2019-nCoV) Nucleic Acid Diagnostic kit (detects N and ORF1ab genes) and/or Xpert Xpress SARS-CoV-2[16] (detects E and N2 genes); or immunochromatographic antigen based rapid test (RDT), Standard Q COVID-19 Ag. All the diagnostics were performed according to the manufacturers' instructions and guidelines from Ministry of Public Health, Thailand[17].

Containment and control measure

Strict infection control measures against COVID-19 were applied in both TB treatment centers in accordance with the instructions released by the local and countries health authorities. Moreover, active screening of COVID-19 infection was applied to all the new coming TB patients and caretakers at the entry as well as to all contact cases of COVID-19 confirmed cases within the treatment centers. All residences including medical staff were tested for COVID-19 infection if they were clinically suspected or in contact with confirmed patient of COVID-19. Movement restrictions amongst the patient buildings were also deployed by defining the infectious zones within the treatment centers. COVID-19 vaccines were provided in January 2021 in the treatment center in Thailand and then expanded to the treatment center in Myanmar in April 2021.

Case definition and case management

The case definition and COVID-19 case management guidelines were based on the updated recommendations from by the Disease Control Department of the Ministry of Public Health, Thailand[17], WHO[18–20] and the Centers for Disease Control and Prevention, United States[21].

At the time of diagnosis, COVID-19 cases were classified as:

- Asymptomatic COVID-19 confirmed case
- Confirmed case with mild symptoms and no risk factors
- Confirmed case with mild symptoms and risk factors
- Confirmed case with pneumonia and hypoxia

Risk factors included: age over 60 years old; chronic obstructive pulmonary disease (COPD) and other chronic lung diseases (excluding pulmonary TB); chronic kidney disease; chronic cardiovascular disease and congenital heart disease; cerebrovascular disease; diabetes; obesity (body mass index ≥ 35 kg/m^2); cirrhosis; immune deficiency conditions, and lymphocyte count < 1000 cells/mm[3,17].

Data collection

The demographic and clinical data of the patients were obtained from their case report forms. The data extraction process was performed by the investigators, who are also the clinicians responsible for the patients' care. The extraction involved collecting information from the patients' routine clinical records and registry books, which was then entered into an Excel spreadsheet. To ensure accuracy, the data was cross-checked by another clinician. Some information relating to vaccination and clinical details were missing as they were not recorded. The laboratory information such as diagnosis and investigation results of individual patients were extracted from the laboratory database.

Outcomes

The clinical severity of COVID-19 infection was categorized as follow:

- asymptomatic
- mild/moderate (symptomatic patients without evidence of pneumonia or hypoxia (or) clinical signs of pneumonia (RR>18/min) with $S_pO_2 > 91\%$ on air)
- severe ($S_pO_2 < 90\%$ on air (or) RR> 30/min) and critical (Respiratory failure required mechanical ventilation, Septic shock, other organs failure requiring ICU care).

COVID-19 outcomes were categorized as fully recovered, recovered with sequels, death and loss to contact.

Data analysis

A descriptive analysis was performed for all COVID-19 infected patients who resided in the TB sanatoria. The variables were summarized by percentage for categorical variables and mean and standard deviation or median with interquartile range for continuous variables. Outcomes of COVID-19 were compared between TB patients and people without TB. For normally distributed continuous variable, unpaired t-test or ANOVA were used. For those data which could not be converted into a standard distribution, Mann-Whitney U test was used. For categorical variables, Chi-squared or Fisher's exact test were used. For those with more than two categories, Bonferroni's correction was used for assessing the statistical significance of the pairwise comparisons for each category. C-Reactive Protein (CRP) was grouped into four to reflect a level of severity of inflammation[22,23]. The clinical severity was compared between TB and non-TB COVID-19 patients using ordered logistic regression. The potential confounders (age, sex, vaccination status, and presence of comorbidity, cycle threshold [Ct] value at diagnosis, active case finding, and calendar year) were adjusted in the multivariable analyses. Multiple imputation using chained equations was conducted for Ct value and vaccination status using *mi impute* command in Stata/SE 17.0 (StataCorp, TX, USA) for 20 times and combined by Rubin's rule using *mi estimate* command. All confounders, the outcome and study site were included in the imputation model.

Ethics approval

The analysis plan was presented to the local ethic advisory board of the Tak Province Border Community Ethics Advisory Board (T-CAB)[24], which provided for the use of routinely

recorded patient records with anonymization of personal data.

The study synopsis was also presented to the Oxford Tropical Research Ethics Committee (OxTREC) and waiver was granted.

Results

A total of 161 COVID-19 infected patients were diagnosed at two SMRU TB sanatoria during a period from 1 September 2021 to 30 April 2022. There were two outbreaks in September 2021 and March 2022 (Figure 2), during which the Delta and Omicron variants circulated in this area, respectively. Some information relating to vaccination (in 2 TB and 4 non-TB patients) and clinical details (in 5 non-TB patients) were missing.

A summarized description on demographic, epidemiology and clinical information of all COVID-19 infected patients was described in Table 1.

Table 1. Demographic, epidemiological and clinical characteristics of 161 COVID-19 infected patients in two TB sanatoria on the Thailand-Myanmar border in 2021–2022.

	TB patients (n=104)	Non-TB patients* (n=57)	p-value
Clinic			
TB sanatorium in Thailand	37/104 (35.6)	40/57 (70.2)	<0.001
TB sanatorium in Myanmar	67/104 (64.4)	17/57 (29.8)	
Period			
First outbreak (September 2021)	24/104 (23.1%)	10/57 (17.5%)	0.55
Second outbreak (March 2022)	80/104(76.9%)	47/57 (82.5%)	
Age (years)	48 (33.5-57.0)	27 (23-33)	<0.001
Male	62/104 (59.6)	28/57 (49.1)	0.20
COVID-19 vaccination completion status at the time of COVID-19 infection			
No vaccination	23/102 (22.6)	10/53 (18.9)	<0.001
1st dose received	36/102 (35.3)	5/53 (9.4)	
2nd dose received	43/102 (42.2)	22/53 (41.5)	
Booster dose received	0/102 (0)	16/53 (30.2)	
Type of COVID-19 vaccination (first dose)			
Astrazeneca	24/79 (30.4)	2/43 (4.7)	NA
Covishield	10/79 (12.7)	6/43 (14.0)	
Sinopharm	34/79 (43.0)	12/43 (27.9)	
Sinovac	11/79 (13.9)	23/43 (53.5)	
Pfizer	0/79 (0)	2**	
Comorbidity			
HIV	13/104(12.5)	3/57(5.3)	0.18
Diabetes	9/104 (8.7)	1/57(1.8)	0.10
Renal disease	3/104 (2.9)	1/57(1.8)	1.00
Asthma or obstructive lung diseases	6/104 (5.8)	1/57(1.8)	0.42
Hypertension or heart disease	11/104 (10.6)	0/57(0)	0.01

	TB patients (n=104)	Non-TB patients* (n=57)	p-value
Diagnosis tools of COVID-19 infection			
Reverse Transcription PCR	87/104 (83.7)	53/57 (93.0)	0.14
Rapid Diagnostic Test	17/104 (16.4)	4/57 (7.0)	
Type of TB diagnosed			
Sputum-positive pulmonary TB	65/104 (62.5)	NA	NA
Sputum-negative pulmonary TB	35/104 (33.7)	NA	
Extra-pulmonary TB	4/104 (3.9)	NA	
Type of TB treatment			
Initial treatment regimen (IR)	68/104 (65.4)	NA	NA
Retreatment regimen (RR)	21/104 (20.2)	NA	
Multi-Drug Resistant regimen (MDR-TB)	15/104 (14.4)	NA	
Timing of TB and COVID-19 diagnosis			
TB diagnosed before COVID-19 infection	102/104 (98.1)	NA	NA
TB diagnosed after COVID-19 infection	2/104 (1.9)	NA	
Days to COVID-19 diagnosed following TB treatment	110 (53-167)	NA	
Days to TB treatment following COVID-19 infection	28 (7-50)	NA	

*Non-TB patients include caretakers (33) and health care workers from two TB sanatoria (24).

**Pfizer vaccine was received as a booster dose (3rd dose) to two health care workers

NA: not applicable

Proportion or median (Inter-quartile range) is shown. P-values were derived by either Fisher's exact test or Mann-Whitney's U test.

Over half of the cohort were TB patients (n= 104, 64.6%). The second group was non-TB infected patients (n=57, 35.4%), with caretakers to TB patients (33/57, 57.9%) and health care workers of two TB sanatoria (24/57, 42.1%).

TB patients were more likely to have at least one comorbidity (39/104, 38.0%) than non-TB patients (5/57, 8.8%). Amongst comorbidities, HIV-coinfection was the most common (n=16/161, 9.9%) followed by diabetes (10/161, 6.2%), hypertension (8/161, 5.0%), chronic respiratory diseases (6/161, 3.7%), and renal disease (1/161, 0.6%). A total of six TB patients and one non-TB patient had multiple comorbidities. Overall, 78.7% (122/155) received at least one dose of a COVID-19 vaccine: 75.5% (79/102) in TB group and 81.1% (43/53) in non-TB group before they were tested positive for COVID-19. However, while there was no patient who had completed three doses in TB group (0/102), 30.2% (16/53) of no-TB group had a complete vaccination series. There was no difference between the two groups in duration from the first dose of vaccine to the day of COVID test positive, median (min-max): 77 (2-421) vs 78 (2-427) days.

Amongst the COVID-19-infected TB patients, 98.1% (102/104) had already started treatment for TB at the time of diagnosis of COVID-19. The median (IQR) time of COVID-19 diagnosis from the start of TB treatment among them (n=102) was 110 days (53-167). Only 2 out of 104 TB patients (1.9%) were diagnosed as TB after COVID-19.

Description of COVID-19 infection

The details of clinical presentation, outcomes and laboratory results were summarized in Table 2.

Over 87% of cases were diagnosed with RT-PCR test (140/161). Among the diagnosed cases of COVID-19 by RT-PCR, the median (IQR) of Ct value of SARS2 N gene was 18.5 (16.1-32.3) in TB patients (n=104), which was not different from 18.8 (15.1-30.0) in non-TB infected COVID-19 patients (n=57).

At the time of diagnosis, the most common clinical presentations were cough with sneezing (78.9%, 123/156), body ache and pain (51.3%, 80/156), fever (48.1%, 75/156) and impaired

Table 2. Descriptive analysis of COVID-19 infected patients who resided in two TB sanatoria. N (%).

	TB patients (n=104)	Non-TB patients (n=57)	p-value
Active screening	72/104 (69.2)	27/57 (47.4)	**0.006**
Ct value (SARS2 N gene) at diagnosis	18.5 (16.1-32.3)	18.8 (15.1-30.0)	0.47
Signs and symptoms of COVID-19 infection			
Fever	38/101 (37.6)	37/55 (67.3)	<0.0001
Respiratory system	80/101 (79.2)	43/55 (78.2)	0.88
Gastrointestinal system	2/101 (2.0)	6/55 (11.1)	0.02
Musculoskeletal system	50/101 (49.5)	30/55 (54.6)	0.55
Loss of smell	10/101 (9.9)	7/55 (12.7)	0.60
Loss of taste	24/101 (23.8)	24/55 (43.6)	0.01
Case classification at time of COVID-19 diagnosis			
Asymptomatic	11/102 (10.8)	9/55 (16.4)	0.33†
Mild symptoms with no risk factors	49/102 (48.0)	41/55 (74.6)	0.001†
Mild symptoms with risk factors	39/102 (38.2)	5/55 (9.1)	<0.001†
Symptomatic with severe pneumonia	3/102 (2.9)	0/55 (0)	0.55†
Laboratory investigation at baseline			
Conducted	58/101 (57.4)	6/55 (10.9)	
Abnormal Complete Blood Count	33/58 (56.9)	1/6 (16.7)	<0.001
C-Reactive Protein grading			1.00
Normal (<8 mg/L)	30/55 (54.6)	3/5 (60.0)	
Grade I (8-20mg/L)	11/55 (20.0)	1/5 (20.0)	
Grade II (21-40mg/L)	7/55 (12.7)	1/5 (20.0)	
Grade III (>40mg/L)	7/55 (12.7)	0/5 (0)	
Treatment			
Antibiotics	13/101 (12.9)	3/55 (5.5)	
Anticoagulant	2/101 (2.0)	3/55 (5.5)	
Antiviral	10/101 (9.9)	1/55 (1.8)	
Systemic steroid	6/101 (5.9)	2/55 (3.5)	
Oxygen therapy	5/101 (5.0)	0/55 (0)	
Worst clinical severity during the course of COVID infection			**0.64**
Asymptomatic	17/100 (17.0)	10/55 (18.2)	
Mild/Moderate	77/100 (77.0)	44/55 (78.2)	
Severe	6/100 (6.0)	1/55 (3.6)	
Outcomes of COVID-19 infection			**0.58**
Fully recovered	103/104 (99.0)	56/57 (99.0)	
Recovered with sequels	0/104 (0)	0/57 (0)	
Death	1/104 (1.0)	0/57 (0)	
Loss to contact	0/104 (0)	1*/57 (1.0)	

† P-value for significance: 0.0125. *One COVID-19 positive case from non-TB patient group (caretaker to TB patient) has left for home inside Myanmar. She was well on last contact with the clinic a week after abscondment.

taste function (30.8%, 48/156). Some clinical symptoms were significantly more common in non-TB patient group, particularly fever (p<0.0001), gastrointestinal symptoms (p 0.02) and impaired taste function (p 0.01). Clinical information for four patients were missing or incomplete and were dropped for analysis.

In terms of clinical severity, most of the COVID-19 cases (121/155, 78.1%) were defined as "mild to moderate", a few cases (7/155, 3.9 %) were "severe" because of S_pO_2<90% on ambient air or respiratory rate (RR) > 30/min and the rest (27/155, 17.4%) were "asymptomatic". Systemic steroid was used in 8 out of 156 (5%) patients, and oxygen therapy with nasal cannula was needed during the course of infection for 5 out of 156 (3%) cases. All the cases that required oxygen were in the TB-infected group. Among them, one TB patient had to take low dose oxygen therapy for the underlying COPD before he was diagnosed with COVID-19 infection. Among patients with severe symptoms six were TB patients and one was clinic staff. Of the six TB cases two were on initial TB treatment, three on retreatment, one was on MDR regimen. Three patients with TB had oxygen drop (S_pO_2<94%), three had moderate anaemia and one had mild anaemia[25]. Two TB patients had co-morbidity; one with HIV infection and the other with mental disorder.

After adjusting for age, sex, vaccination status (none; one; two or more doses), presence of comorbidity, Ct value at the diagnosis, diagnosis by active case finding, and calendar year, the risk of developing severer disease of COVID-19 was not different in TB-patients compared with non-TB patients (adjusted odds ratio 1.21, 95% CI 0.45-3.29, p=0.71). Diagnosis by active case finding, and infections in 2022 (assumed Omicron variant) compared with those in 2021 (assumed Delta variant) was associated with lower risk of developing severe disease (Table 3).

A total of 159 out of 161 patients (98.8%) fully recovered from COVID-19 infection but one patient (1/104, 0.96%) in TB-infected group died. The overall mortality in this cohort was 0.62% (1/161). This was a 73-year old man with underlying sputum smear negative pulmonary TB who received a retreatment regimen due to presumptive TB clinical symptoms and radiological findings on chest X-ray. Sputum microscopy smear examination and molecular testing for sputum specimens were negative. The radiological finding showed a malignant mass in upper and middle zone of the right lung with adjacent structural invasion and ribs destruction. He received Astra-Zeneca vaccine two weeks after TB treatment started. He had significant weight loss with no clinical progress during two-month initial phase of TB treatment and got infected with COVID-19. He was treated with parenteral antibiotics, anticoagulant, systemic steroids and other palliative care but the deterioration was progressed to death. This patient probably died of underlying pulmonary malignancy compounded by COVID-19 infection.

Discussion

Reflecting worldwide epidemic waves of the Delta and Omicron variants of COVID-19 infection, two outbreaks of

Table 3. Ordered logistic regression analysis for the odds of higher clinical severity of COVID-19 in TB and non-TB patients.

	N	Univariable	Multivariable (CC)	Multivariable (MI)
Characteristic		OR (95% CI)	OR (95% CI)	OR (95% CI)
TB patients	155	1.30 (0.59-2.83)	1.08 (0.38-3.06)	1.21 (0.45-3.29)
Age (year)	155	1.02 (0.99-1.04)	1.01 (0.98-1.04)	1.01 (0.98-1.04)
Female	155	0.64 (0.30-1.38)	0.58 (0.24-1.39)	0.58 (0.25-1.34)
Vaccination status	150			
None		Reference	Reference	Reference
1		4.30 (1.25-14.80)	3.05 (0.72-13.00)	2.60 (0.66-10.28)
≥ 2		1.33 (0.52-3.42)	1.60 (0.54-4.74)	1.38 (0.49-3.88)
Comorbidity	155	1.40 (0.60-3.28)	1.13 (0.40-3.18)	0.97 (0.37-2.59)
CT value at diagnosis	136	0.95 (0.91-1.00)	0.97 (0.92-1.02)	0.96 (0.91-1.01)
Omicron (Year 2022)	155	0.39 (0.13-1.15)	0.33 (0.10-1.04)	0.32 (0.10-0.99)
Active case finding	155	0.28 (0.11-0.70)	0.28 (0.10-0.83)	0.28 (0.11-0.76)

CC: Complete case analysis (n=133), CI: confidence interval, MI: multiple imputation analysis,

N: number assessed, OR: Odds ratio

COVID-19 infection occurred at the SMRU TB sanatoria on Thailand-Myanmar borders between September 2021 and March 2022.

Respiratory (sneezing, cough, and sore throat) and musculoskeletal (joint pain and muscle ache) symptoms were the most common presentation of COVID-19 infection in the cohort. However, fever ($p<0.0001$), gastrointestinal related symptoms ($p=0.02$) and impaired sensation on taste (hyposmia to ageusia) ($p=0.01$) were more common in non-TB patient group. In TB patient's cohort, having complex symptoms of TB disease and side effects of anti-TB medicines could mask the typical presentation of COVID-19 infection compared to relatively healthy group of non-TB patients.

There were no major differences in disease severity and outcomes of COVID-19 infection between the TB and non-TB groups after adjustment for potential confounders. In terms of case management, there was no case requiring the transfer to intensive care during the course of COVID-19 infection. There was one fatality in a COVID-19/TB co-infected elderly man, probably due to lung cancer. The overall situation was comparably less severe than the morbidity and mortality reported in local and regional COVID-19 statistics. The findings from this report are similar to other studies showing that COVID-19/TB co-infection does not cause statistically significant increase in the mortality or disease severity[13,15]. Moreover, COVID-19/TB coinfection may result in a less severe presentation and course of infection[14], particularly when active case finding (i.e. earlier detection) for COVID-19 was taken place in TB patients.

This is contrary with the findings from some other studies showing that tuberculosis represents a considerable comorbidity and risk factor for severe COVID-19 disease[5,11]. However, one must be cautious in interpreting findings from the studies because they may not widely reflect the general population, and the studied group were potentially hospitalized as a precautionary measure due to their pre-existing diagnosis of tuberculosis which could have introduce a bias in comparing the COVID-19 only group, who were admitted due to clinical severity of their infection. The authors acknowledged that the finding may be cofounded by multiple factors including epidemiological disparities between the groups[14]. In this cohort, although non-TB cases were younger and had less comorbidities than TB-infected cases, the clinical severity and overall outcome was not different between TB and non-TB patients, which could be probably due to the active screening of TB patients were diagnosed earlier. On the other hand, non-TB patients included in this study were not selected based on clinical severity or the risks of developing severe COVID-19 disease. Although the number of non-TB patients was small, this group can be more representative of the general population in this area, which was not the case in most other hospital-based studies. Earlier detection of COVID-19 infection because of active screening at the entry and higher uptake of COVID-19 vaccine in this cohort might have been one reason for the overall good clinical outcomes in both TB-infected and non-infected patients.

There were some limitations in the study. Although we compared the clinical severity adjusted by potential confounders with multiple imputation for missing variables to take into account of the observational nature of this cohort, there could be unobserved differences between TB and non-TB patients. Particularly, modifications in case classification, severity level and treatment guidelines from time to time has given inconsistency at individual patient management. As the resources were limited, a systemic and continuous viral load monitoring using molecular testing could not apply to detect a definite negativity of COVID-19 infection in every cases. Although the overall severity was not so high and was not very different between TB and non-TB patients, only one mortality in this cohort was a TB-infected patient and our relatively small number of patients did not allow us to assess whether there was a clear difference in mortality between TB and non-TB patients. In addition, there was the absence of a prior sample size calculation in this study, which may affect the statistical power and generalizability of the findings. Hence, the results should be interpreted with caution.

Although the published literature on TB/COVID-19 coinfection has increased in recent times, there appears to be little consensus to the extent to which TB is a risk factor for severe COVID-19 infection. The presence of confounding variables that may influence the above findings and highlight the need for careful factor analysis to ascertain which conclusions are accurate and clinically applicable. It is an important area of continued research as the elucidation of the pathophysiological mechanisms surrounding coinfection will be a vital influence on public health initiatives, infection control protocols and shielding guidance for patients who are suffering from TB in times when COVID-19 prevalence rates are still a cause for global concern.

Data availability

Raw data and related database are available on request according to the MORU Tropical Health Network data sharing policy. Data can be applied for via the MORU website.

Acknowledgements

We would like to acknowledge the contributions of all SMRU staff involved in management of patients in TB treatment sanatoria and also laboratory technicians who supported with timely laboratory results for effective clinical management.

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?

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SUMMARY OF STUDY
Htet Ko Ko Aung and colleagues present a retrospective cohort study conducted over the span of 8 months during 2 COVID-19 outbreaks in 2 tuberculosis (TB) clinics on the Thailand-Myanmar border. Participants include both TB patients at the 2 clinics as well as medical staff and caregivers (participants without TB).

The authors describe demographic and clinical characteristics as well as clinical outcomes of study participants, stratifying by participant type (TB or no TB). The main analysis focuses on comparing disease severity (one of 3 levels: asymptomatic, mild/moderate and severe) between participant types. The main study conclusion is that there was no evidence in this study of differences in clinical severity of CVODI-19 between TB patients and participants without TB.

I generally congratulate the authors on an informative and important study, employing generally sound scientific research methods. I do have some comments / queries which I give below in a structured format. Every comment is flagged by "COMMENT X:" where X is a number which hopefully makes it easier for the authors to respond to specific comments.

PRESENTATION
Generally the manuscript is clear and accurate, with good referencing to other literature in the field. There are a number of minor typos and language issues that should be revised (see list below).

STUDY DESIGN
The retrospective cohort design is generally appropriate to answer the primary research question (does COVID-19 severity differ between TB patients and people without TB). The specialised setting

within TB clinics, with the control group consisting of caregivers and medical staff (i.e. individuals probably better informed about infection control, importance of vaccine and access to COVID-19 treatments) will however limit some of the generalisability of the study findings. Nevertheless, these findings are valid and important to share with the research community.

METHODS & REPRODUCIBILITY
Neither the underlying data nor the analysis code are directly available.

Data can be requested through the researchers' institution, but the link to do so only refer to the data sharing policy and not directly to instructions how to request this particular dataset.

COMMENT R1: I would urge the authors to deposit their Stata analysis code on a code repository for easier reproducibility and removing any ambiguities about the specific analysis procedures that can be left from a text description of what was done.

COMMENT R2: I would similarly urge the authors to deposit the minimal dataset needed to reproduce the analyses from the present manuscript on a data repository. I understand that this may not be possible due to data policies and local regulations, in which case the authors could consider deriving a synthetic dataset based on the real analysis dataset. At the very least a direct link to request access for this particular dataset should be provided - the fewer hoops to jump through, the better.

STATISTICAL ANALYSIS & INTERPRETATION
Mostly the methods employed are clearly described, straightforward and appropriate. I do, however, have a few specific comments on the statistical analysis.

COMMENT S1: Please provide full details of the ordinal logistic regression model that was used. I also did not see any discussion of model fit and diagnostics, but this is important given that ordinal logistic regression makes an assumption of proportional odds which should be checked.

COMMENT S2: While participants are recruited from 2 different TB clinics, and Table 1 shows that these 2 clinics differ at least in the TB patient : non-tb participant ratio, the analyses do not seem to account for clinic. Presumably there may be all kinds of other differences, not captured through measured variables, that may impact on outcomes, so I would suggest that the authors adjust for clinic in the analysis model or at least do a sensitivity analysis to investigate the effect of clinic on the study conclusions.

COMMENT S3: The authors make use of multiple imputation for the main analysis. This is great, but they should state clearly what imputation model was used with the MICE approach (presumably the Stata default, which would be PMM - but should be stated explicitly).

COMMENT S4: The authors use a few times language that rules out an association or effect or difference (e.g. "TB was not associated with severe outcome" for the main study conclusion, "no difference between the two groups" for duration from vaccination to test positivity, "18.5 [...] which was not different from 18.8 [...]", ...). I think this language should be rephrased to make it clear that in this particular study there was not enough evidence to support such associations etc

or that differences (e.g. 18.5 is not the same as 18.8; similar but not the same, so different) were not statistically significant. You do not have enough evidence to reject the null hypothesis in these cases, but that does not necessarily mean that the null is true.

MINOR COMMENTS

COMMENT M1: The study involved 161 participants. But some variables seem to have missing data (e.g. 133 is the number of participants included in the complete case analysis, 155 is the denominator for COVID-19 vaccination status, 155 (though this is given as 156 in the abstract) for disease severity, ...), it would be helpful if Tables 1 and 2 could also list the amount of missing data for each variable.

COMMENT M2: In the third paragraph of the introduction, the sentence "The main finding was the similar pooled odds ratios in the COVID-TB group as compared to the non-TB “control” group COVID-19 infected patients: 2.21 (95% CI: 1.80, 2.70) for death and 2.77 (95% CI: 1.33, 5.74) for severe COVID-19 disease." is not fully clear. At least specify what groups the OR quoted here compares - since the confidence intervals exclude 1, one could read this to mean that TB very much increases the risk of death or severe disease, but clearly that is not what the authors meant to say here.

COMMENT M3: In the 'Containment and control measure' section, if I read it correctly then controls got tested daily for COVID-19 as they reported to the clinic but TB patients were only tested upon admittance? OR does 'active screening' mean continuous testing during the stay in the clinic. Maybe good to clarify how often TB and non-TB participants were tested for COVID-19.

COMMENT M4: In the 'Data analysis' section, specify when the Chi-squared and when the Fisher test was used and/or indicate in a footnote to Tables 1 and 2 which test was used when.

COMMENT M5: Please give a reference for Rubin's rules in the 'Data analysis' section.

COMMENT M6: For Tables 1 and 2, it would also be great to see results stratified by clinic -- maybe as supplementary material tables?

COMMENT M7: Table 1 and third paragraph of the results section: might be worth to also state the overall p-value for comparing co-morbidity between TB and non-TB participants (Table 1 only formally compares each specific co-morbidity while the text states any comorbidity but does not give a p-value). I am not too fussed about getting a p-value but given that p-values are calculated for most other things, it would be consistent to give one here too.

COMMENT M8: Table 1, unclear why no comparison (p-value given as "NA") is made between TB and non-TB participants in distribution of first dose of COVID-19 vaccine.

COMMENT M9: Last sentence of the third paragraph of the 'Results' section reads "Only 2 out of the 104 TB patients (1.9%) were diagnosed as TB after COVID-19". This is a bit puzzling as by design the TB patients would have been recruited based on their TB status (as patients of the clinics). Presumably either some patients had their TB identified as a result of showing up to a test centre for COVID-19 then got admitted or else some of the caregivers or medical staff became TB positive during the study. Might be worth clarifying what happened here.

COMMENT M10: Table 2 for case classification at COVDI-19 diagnosis: unclear why each level is compared between groups rather than comparing the entire distribution of diagnosis levels (as done for other categorical variables with mutually exclusive levels in the very same table). I would recommend just giving a single p-value for comparing all levels between the 2 groups.

COMMENT M11: p-values are variable reported to 2 or 3 decimal digits. Please give them consistently to the same number of decimal digits.

COMMENT M12: I would probably put the case classification at COVID-19 diagnosis and the worst clinical severity during the disease course right next to each other in the table rather than having other variables summarised between them.

COMMENT M13: Can you double-check the Ors for the vaccination status levels? While the CIs are large and include 1, the ORs are consistently >1, which would mean that 1 or 2+ doses of the vaccine had on average more severe COVID-19 disease than no vaccination (even if not statistically significant). This direction of effect seems puzzling. It may be true, but worth double-checking.

COMMENT M14: Second last paragraph of the manuscript, rephrase the sentence "In addition, there as the absence of a prior sample size calculation [...]". While it is clear what is meant, the sentence does not fully make sense. You could do a retrospective effect size calculation, stating which effect sizes the study would be powered to detect with the achieved sample size. (Note: The key is not to compare that to the estimated ORs; e.g. if the minimum powered effects size is 1.9 and you report an OR of 2.1, that does not necessarily mean that that finding was powered or another one where the point estimate is 1.5 is not necessarily underpowered.) Or you could simply state that the study was not formally powered for the analyses that were done. But doing or not doing a sample size calculation in itself does not impact on study power -- what does is the actual recruitment.

TYPOS & SYNTAX

This is a bit tricky as there is no line numbering with Wellcome Open Research, which would make it much easier to refer to the lines where the typos occurred. Hopefully the indications below are clear.

* About half-way down in the third paragraph of the introduction section, remove "Though," from the start of the sentence.

* About half-way down in the third paragraph of the introduction section, remove "On the contrary," from the start of the sentence.

* In the second to last sentence of the third paragraph of the introduction section: "but there were no statistically increased incidence" -- the 'were' should be 'was'.

* 'Containment and control measure' section title: that should probably be a plural ("measures")?

* 'Data analysis' section, "Rubin's rule" should be plural: "Rubin's rules".

* Third paragraph in the 'Results' section: 'three doses in TB groups' --> 'three doses in the TB groups' (missing preposition 'the')

* Fifth paragraph of section 'Description of COVID-19 infection', "severer" --> "severe"

* Table 3; I would clarify the levels for the vaccination status variables: "None", "1 dose", "2+ doses" rather than "None", "1" and "2".

* 2nd paragraph of the 'Discussion' section: "[...] more common in non-TB [...]" --> "[...] more common in the non-TB [...]" (missing preposition 'the')

* 2nd paragraph of the 'Discussion' section: "In TB patient's cohort [...]" --> "In the TB patients cohort [...]" (missing preposition 'the' and patients not patient's)

* 3rd paragraph of the 'Discussion' section: "statistically significant increase in the mortality or disease severity" --> "statistically significant increases in mortality or disease severity" (plural for increase and a superfluous 'the' preposition)

* 3rd paragraph of the 'Discussion' section: "particularly when active case finding [...] was taken place in TB patients" --> "particularly through active case finding [...] in TB patients"

* 4th paragraph of the 'Discussion' section: "some other studies" --> "other studies"

* 4th paragraph of the 'Discussion' section: "which could be probably due to the active screening of TB patients were diagnosed earlier" --> "which could be due to the active screening of TB patients who, as a result, were diagnosed earlier".

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a biostatistician working mostly in infectious, tropical disease applications, including TB and SARS-CoV-2 / COVID-19 research.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 25 Oct 2023

Aung Pyae Phyo

Thank you very much for your time and thorough suggestions. We genuinely appreciate your valuable feedback. We have carefully considered each of your comments and have made the necessary revisions to our paper accordingly. Your insights have been immensely helpful in improving the quality of our work.

COMMENT R1: I would urge the authors to deposit their Stata analysis code on a code repository for easier reproducibility and removing any ambiguities about the specific analysis procedures that can be left from a text description of what was done.
REPLY R1: Agreed. Please see the attached STATA do-file.

COMMENT R2: I would similarly urge the authors to deposit the minimal dataset needed to reproduce the analyses from the present manuscript on a data repository. I understand that this may not be possible due to data policies and local regulations, in which case the authors could consider deriving a synthetic dataset based on the real analysis dataset. At the very least a direct link to request access for this particular dataset should be provided - the fewer hoops to jump through, the better.
REPLY R2: We don't provide the full patient dataset in "online open access" e.g., as supplementary files to a journal article nor through "External repository without case-by-case assessment" where MORU has no oversight or control of secondary uses made of the data. However, the full dataset can be requested from MORU data sharing committee **datasharing@tropmedres.ac** for the purpose of secondary or meta-analysis.

STATISTICAL ANALYSIS & INTERPRETATION Mostly the methods employed are clearly described, straightforward and appropriate. I do, however, have a few specific comments on the statistical analysis.

COMMENT S1: Please provide full details of the ordinal logistic regression model that was used. I also did not see any discussion of model fit and diagnostics, but this is important given that ordinal logistic regression makes an assumption of proportional odds which should be checked.
REPLY S1: Proportional odds assumption was checked with omodel command in Stata and the p-value was 0.68. Goodness of fit was assessed by ordinal version of the Hosmer–Lemeshow test using ologitgof command and the p-value was 0.93.

COMMENT S2: While participants are recruited from 2 different TB clinics, and Table 1 shows that these 2 clinics differ at least in the TB patient: non-tb participant ratio, the analyses do

not seem to account for clinic. Presumably there may be all kinds of other differences, not captured through measured variables, that may impact on outcomes, so I would suggest that the authors adjust for clinic in the analysis model or at least do a sensitivity analysis to investigate the effect of clinic on the study conclusions.
Reply S2: We used cluster-robust standard error accounting for the clustering within the two clinics. We have updated the figures accordingly. See table 3.

COMMENT S3: The authors make use of multiple imputation for the main analysis. This is great, but they should state clearly what imputation model was used with the MICE approach (presumably the Stata default, which would be PMM - but should be stated explicitly).
REPLY S3: It is revised as following: “Multiple imputation using chained equations was conducted for Ct value and vaccination status using mi impute command for 20 times and combined by Rubin’s rules 24 using mi estimate command. All confounders, the outcome and study site were included in the imputation model. We used logistic regression for vaccination status, ordered (ordinal) logistic regression for severity grade, and truncated regression for Ct values (limiting to 0 to 45) for imputation. The observations with missing outcome (n=6) were used for imputation but were excluded from the analysis models.”

COMMENT S4: The authors use a few times language that rules out an association or effect or difference (e.g. "TB was not associated with severe outcome" for the main study conclusion, "no difference between the two groups" for duration from vaccination to test positivity, "18.5 [...] which was not different from 18.8 [...]", ...). I think this language should be rephrased to make it clear that in this particular study there was not enough evidence to support such associations etc or that differences (e.g. 18.5 is not the same as 18.8; similar but not the same, so different) were not statistically significant. You do not have enough evidence to reject the null hypothesis in these cases, but that does not necessarily mean that the null is true.
REPLY S4: Thanks for the suggestion. We have revised accordingly.

MINOR COMMENTS
COMMENT M1: The study involved 161 participants. But some variables seem to have missing data (e.g. 133 is the number of participants included in the complete case analysis, 155 is the denominator for COVID-19 vaccination status, 155 (though this is given as 156 in the abstract) for disease severity, ...), it would be helpful if Tables 1 and 2 could also list the amount of missing data for each variable.
REPLY M1: Thanks for the suggestion. We have added accordingly.

COMMENT M2: In the third paragraph of the introduction, the sentence "The main finding was the similar pooled odds ratios in the COVID-TB group as compared to the non-TB “control” group COVID-19 infected patients: 2.21 (95% CI: 1.80, 2.70) for death and 2.77 (95% CI: 1.33, 5.74) for severe COVID-19 disease." is not fully clear. At least specify what groups the OR quoted here compares - since the confidence intervals exclude 1, one could read this to mean that TB very much increases the risk of death or severe disease, but clearly that is not what the authors meant to say here.
REPLY M2: OR was 2.21 & 2.77 for death & severe disease in COVID-TB group, similarly higher than COVID patients without TB. Sorry for the confusion. We have corrected.

COMMENT M3: In the 'Containment and control measure' section, if I read it correctly then controls got tested daily for COVID-19 as they reported to the clinic but TB patients were only tested upon admittance? OR does 'active screening' mean continuous testing during the stay in the clinic. Maybe good to clarify how often TB and non-TB participants were tested for COVID-19.
REPLY M3: TB patients were tested upon admission and whenever they got symptomatic or contact with COVID confirmed patient.

COMMENT M4: In the 'Data analysis' section, specify when the Chi-squared and when the Fisher test was used and/or indicate in a footnote to Tables 1 and 2 which test was used when.
REPLY M4: We use Fisher’s exact test for table 1. Corrected accordingly. COMMENT M5: Please give a reference for Rubin's rules in the 'Data analysis' section. REPLY M5: We have added the citation.

COMMENT M6: For Tables 1 and 2, it would also be great to see results stratified by clinic -- maybe as supplementary material tables? REPLY
M6: Please see above. There was no apparent difference in clinical management between two clinics.

COMMENT M7: Table 1 and third paragraph of the results section: might be worth to also state the overall p-value for comparing co-morbidity between TB and non-TB participants (Table 1 only formally compares each specific co-morbidity while the text states any comorbidity but does not give a p-value). I am not too fussed about getting a p-value but given that p-values are calculated for most other things, it would be consistent to give one here too.
REPLY M7: Added as per suggestion.

COMMENT M8: Table 1, unclear why no comparison (p-value given as "NA") is made between TB and non-TB participants in distribution of first dose of COVID-19 vaccine.
REPLY M8: P value is added.

COMMENT M9: Last sentence of the third paragraph of the 'Results' section reads "Only 2 out of the 104 TB patients (1.9%) were diagnosed as TB after COVID-19". This is a bit puzzling as by design the TB patients would have been recruited based on their TB status (as patients of the clinics). Presumably either some patients had their TB identified as a result of showing up to a test centre for COVID-19 then got admitted or else some of the caregivers or medical staff became TB positive during the study. Might be worth clarifying what happened here.
REPLY M9: We have re-phrased for clarity.

COMMENT M10: Table 2 for case classification at COVDI-19 diagnosis: unclear why each level is compared between groups rather than comparing the entire distribution of diagnosis levels (as done for other categorical variables with mutually exclusive levels in the very same table). I would recommend just giving a single p-value for comparing all levels between the 2 groups.

COMMENT M11: p-values are variable reported to 2 or 3 decimal digits. Please give them consistently to the same number of decimal digits.
REPLY M10 & 11: Revised accordingly.

COMMENT M12: I would probably put the case classification at COVID-19 diagnosis and the worst clinical severity during the disease course right next to each other in the table rather than having other variables summarised between them.
REPLY M12: Revised accordingly.

COMMENT M13: Can you double-check the ORs for the vaccination status levels? While the CIs are large and include 1, the ORs are consistently >1, which would mean that 1 or 2+ doses of the vaccine had on average more severe COVID-19 disease than no vaccination (even if not statistically significant). This direction of effect seems puzzling. It may be true, but worth double-checking.
REPLY M13: We have checked the vaccination records again and defined the vaccination status as effective when a person received two or more doses 14 days or more prior to the infection. Updated results are presented in the revised manuscript.

COMMENT M14: Second last paragraph of the manuscript, rephrase the sentence "In addition, there as the absence of a prior sample size calculation [...]". While it is clear what is meant, the sentence does not fully make sense. You could do a retrospective effect size calculation, stating which effect sizes the study would be powered to detect with the achieved sample size. (Note: The key is not to compare that to the estimated ORs; e.g. if the minimum powered effects size is 1.9 and you report an OR of 2.1, that does not necessarily mean that that finding was powered or another one where the point estimate is 1.5 is not necessarily underpowered.) Or you could simply state that the study was not formally powered for the analyses that were done. But doing or not doing a sample size calculation in itself does not impact on study power -- what does is the actual recruitment.
REPLY M14: Thank you for your comment. Some might argues against the sample size calculation for secondary data analyses (as is discussed here https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7286546/), and in our case, analyses have been completed, so we decide not to conduct sample size calculation retrospectively at this stage. We have deleted this sentence from the Limitations, particularly because generalizability is not affected by the lack of sample size calculation.

TYPOS & SYNTAX

This is a bit tricky as there is no line numbering with Wellcome Open Research, which would make it much easier to refer to the lines where the typos occurred. Hopefully the indications below are clear.
* About half-way down in the third paragraph of the introduction section, remove "Though," from the start of the sentence. **Done**
* About half-way down in the third paragraph of the introduction section, remove "On the contrary," from the start of the sentence.
* In the second to last sentence of the third paragraph of the introduction section: "but there were no statistically increased incidence" -- the 'were' should be 'was'. **Done**.

* 'Containment and control measure' section title: that should probably be a plural ("measures")? **Done**
* 'Data analysis' section, "Rubin's rule" should be plural: "Rubin's rules". **Done**
* Third paragraph in the 'Results' section: 'three doses in TB groups' --> 'three doses in the TB groups' (missing preposition 'the') **Done**
* Fifth paragraph of section 'Description of COVID-19 infection', "severer" --> "severe" **Done**
* Table 3; I would clarify the levels for the vaccination status variables: "None", "1 dose", "2+ doses" rather than "None", "1" and "2". **Changed**.
* 2nd paragraph of the 'Discussion' section: "[...] more common in non-TB [...]" --> "[...] more common in the non-TB [...]" (missing preposition 'the') **Done**.
* 2nd paragraph of the 'Discussion' section: "In TB patient's cohort [...]" --> "In the TB patients cohort [...]" (missing preposition 'the' and patients not patient's) **Done**
* 3rd paragraph of the 'Discussion' section: "statistically significant increase in the mortality or disease severity" --> "statistically significant increases in mortality or disease severity" (plural for increase and a superfluous 'the' preposition) **Done**
* 3rd paragraph of the 'Discussion' section: "particularly when active case finding [...] was taken place in TB patients" --> "particularly through active case finding [...] in TB patients" **Done**
* 4th paragraph of the 'Discussion' section: "some other studies" --> "other studies" **Removed**
* 4th paragraph of the 'Discussion' section: "which could be probably due to the active screening of TB patients were diagnosed earlier" --> "which could be due to the active screening of TB patients who, as a result, were diagnosed earlier". **Revised**

Competing Interests: No competing interests were disclosed.