



Early View

Research letter

Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases

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Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases

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Take home message:

Diagnostic, treatment and outcome details of 49 COVID-19 patients with concurrent or previous tuberculosis from 8 countries show varied clinical profiles.

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Dear Editor,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) pandemic has attracted interest because of its global rapid spread, clinical severity, high mortality rate, and capacity to overwhelm healthcare systems [1,2]. SARS-CoV-2 transmission occurs mainly through droplets, although surface contamination contributes and debate continues on aerosol transmission [3-5].

The disease is usually characterized by initial signs and symptoms [4-9] similar to those of related viral infections (e.g., influenza, SARS, Middle East Respiratory Syndrome [MERS]) and tuberculosis (TB), although prognosis and complications sometimes differ. Experience with concomitant TB and COVID-19 is extremely limited.

One case-control study of COVID-19 patients with IGRA-confirmed TB infection [10] and a single case of TB with COVID-19 were submitted but not yet published in peer-reviewed journals [11]. In a recent analysis of 1,217 consecutive respiratory specimens collected from COVID-19 patients *Mycobacterium tuberculosis* was not detected [12].

The present study describes the first-ever global cohort of current or former TB patients (post-TB treatment sequelae) with COVID-19, recruited by the Global Tuberculosis Network (GTN) in 8 countries and 3 continents. No analysis for determinants of outcome was attempted.

The study is nested within the GTN project monitoring adverse drug reactions [13,14] for which the coordinating centre has an ethics committee approval, alongside ethics clearance from participating centres according to the respective national regulation [13,14]. A specific nested database was created in collaboration with the 8 countries reporting patients with TB and COVID; the remaining countries did not observe COVID-19 yet in their patients at the moment this manuscript was written.

Continuous variables, if not otherwise specified, are presented as medians (IQR-Interquartile ranges).

Overall, 49 consecutive patients with current or former TB and COVID-19 from 26 centres in Belgium (1), Brazil (Porto Alegre, Rio Grande do Sul State; 1), France (12), Italy (17),

Russia (Moscow Region; 6), Singapore (1), Spain (10) and Switzerland (Vaud Canton; 1) were recruited (dataset updated as of April 25th, 2020, Table 1).

The first onset of COVID-19 in the cohort was observed in an Italian patient with TB sequelae on March 12th, 2020 (symptoms from March 6th).

Of 49 patients, 26 (53.0%) had TB before COVID-19, 14 (28.5%) had COVID-19 first and 9 (18.3%) had both diseases diagnosed within the same week (4 on the same day).

Forty-two (85.7%) patients had active TB [median age 45.5 (28.0-63.0) years] and 7 (14.3%) had post-TB treatment sequelae [median age: 69.0 (66.0-70.0) years; p-value= 0.01]; the patients with TB sequelae (from 5 centres in Italy, Singapore, Spain and Switzerland) were cured 8.2 (2.7-44.3) years earlier.

Overall, 26/49 (53.1%) patients were migrants, 15/48 (31.3%) unemployed, and 2/48 (4.1%) health care workers (medical doctor and radiology technician).

Forty-six (93.9%) patients had confirmed SARS-CoV-2 infection and 3 other patients (6.1%) had chest High Resolution Computerized Tomography (HRCT) highly suggestive of COVID-19 related pneumonia (bilateral ground glass opacities) [15].

Forty-eight patients had pulmonary TB (one caused by *Mycobacterium bovis*).

Thirty-seven patients had drug-susceptible (or were treated with the standard first-line regimen for new cases) and eight had drug-resistant TB (and were treated with second-line drugs).

Of the 14 non-clustered patients with COVID-19 diagnosis preceding TB, a child of Gambian origin (3 months old) had SARS-CoV-2 identified 3 days before TB diagnosis although TB was probably pre-existing (pulmonary and extra-pulmonary TB, meningitis). The child is continuing anti-TB treatment and has now recovered from COVID-19. Altogether the diagnosis of COVID-19 preceded that of TB by a median (range) time of 4 (2-10) days.

Those 14 patients, managed in 9 centres (in France, Italy, Russia, Spain) were young [median age 33 (26.0-46.0) years]; 11/14 (78.5%) were migrants.

Of the 19 patients undergoing anti-TB treatment, the diagnosis of COVID-19 was made during month 1-2 for 10 (52.6%), month 3-4 for 3 (15.7%), month 4- 6 for 3 (15.7%) and after 6 months for 3 (15.7%) patients.

Signs and symptoms attributed to COVID-19 included (in different combinations) fever (32/48, 81.2%), dry cough (27/48, 56.2%) and dyspnoea (17/48, 35.4%).

Radiological information was available for 48/49 (98.0%) patients: 23 (47.9%) presented cavities (Table 1).

Twenty-one patients manifested a typical HRCT COVID-19 pattern (bilateral ground glass opacities), whereas 23 had different patterns at HRCT or chest radiography essentially reporting TB-related lesions (e.g., infiltrates, consolidations, cavities, etc.) and 5 were not studied during the course of COVID-19 disease.

Forty-three (87.8%) patients were hospitalized and, provisionally, the overall median (IQR) number of hospital admission days was 15 (8-27). Six patients needed non-invasive ventilation and 14 oxygen supply.

Medication for COVID-19 was reported for 28 patients in all countries except Belgium and Brazil (which had a single case each): 22 (78.6%) received, in different combinations, hydroxychloroquine, 12 (42.9%) received an anti-HIV protease inhibitor (i.e. lopinavir/ritonavir, darunavir/cobicistat), 7 (25.0%) patients received azithromycin, and 1 (3.6%) patient received other drugs (i.e. enoxaparin and N-acetyl-cysteine, NAC). Seventeen (60.8%) patients received a monotherapy (i.e. 11 hydroxychloroquine, 5 lopinavir/ritonavir, and 1 azithromycin), 9 (32.1%) received a combination of two drugs (i.e. 5 hydroxychloroquine and protease inhibitor; 4 hydroxychloroquine plus azithromycin), 2 (7.1%) received ≥ 3 drugs (i.e. 1 hydroxychloroquine, lopinavir/ritonavir and azithromycin; 1 hydroxychloroquine, lopinavir/ritonavir and azithromycin, enoxaparine and NAC).

The case fatality rate was high (6/49, 12.3%); 5/6 were >60 years old and all of them had ≥ 1 co-morbidities. Given the small number of deaths, larger studies are necessary.

This preliminary analysis suggests that:

- 1) In 19/49 (38.8%) patients COVID-19 appeared during anti-TB treatment and limited or no protection against COVID-19 might have favoured SARS-CoV-2 infection (which affected two healthcare workers).
- 2) The diagnosis of TB and COVID-19 was done simultaneously or within 7 days in 9 patients, posing differential diagnosis challenges, suggesting that clinical assessments to investigate COVID-19 (e.g. clinical picture, HRCT) facilitated the identification of

(a probably pre-existing) TB. Any contribution of COVID-19 to TB pathogenesis cannot be excluded or confirmed.

- 3) Although the diagnosis of COVID-19 preceded that of TB in 14 patients, larger studies are needed to understand any role played by SARS-CoV-2 in the progression of TB infection to disease. Given that up to a quarter of the population in some regions of the work are latently infected, SARS-CoV-2 infection might boost the development of active TB in the coming months [10]. As we do not include individuals with latent TB infection followed-up over time, we cannot report on the potential contribution of COVID-19 towards development of active disease. Probably, an overlap of signs/symptoms of COVID-19 and TB occurred and COVID-19 was diagnosed earlier because of a higher index of suspicion while TB may have been there since before. Or, differently, COVID brought to clinical evaluation/diagnostic assessment TB patients at an earlier stage of disease before the occurrence of TB-related symptoms.
- 4) In 7 cases COVID-19 occurred in patients with TB sequelae. They were older than patients under anti-TB treatment and presented higher (although not statistically significant) mortality. All but one had co-morbidities (4 Chronic Obstructive Pulmonary Disease; 1 HIV co-infection plus liver and kidney diseases, hypertension and cancer present in different combinations). They presented unilateral or bilateral radiological sequelae of previous infiltrates (4 patients) or cavities (3 patients). Larger numbers are necessary to further understand the role played by TB sequelae.
- 5) The impact on the healthcare system (e.g., days of admission, intensive care unit beds, etc.) was relevant, and will deserve further evaluation.
- 6) The information on BCG (Bacillus Calmette-Guérin) vaccination is modest (30 patients with information, 19 previously vaccinated in all 8 countries) and no significant elements can be provided to the ongoing debate on its protective role.
- 7) We presently have no data on drug-drug interactions.

This is, to our knowledge, the first published cohort of patients with active TB and COVID-19. Our study represents a 'snapshot' of a cohort of patients at different stages of disease. No attempt was made to obtain representation of the larger universe of patients with both diseases and the small sample size precludes an analysis of risk factors. We cannot exclude that some findings have a casual origin.

The information available on the patients recently admitted was accurate, but some details on previous TB were incomplete, and some examinations were not performed either because the patients refused or the patients' condition was too severe. Although case reporting is comprehensive in the countries/regions covered by GTN, the study reflects the initial stages of the COVID-19 epidemic only, and representative longitudinal observations will be necessary to evaluate the interactions between COVID-19 and TB.

We believe that this descriptive research can motivate larger studies to enable analyses of interactions and determinants of outcomes in patients with both diseases. The study will continue to follow-up the patients and accrue more records. We therefore invite interested clinicians and programmes to contact the corresponding author and help improve the understanding of how to optimize care for these patients.

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Table 1. Demographic, epidemiological and clinical characteristics of a cohort of 49[^] tuberculosis patients with COVID-19 disease.

| Variable | Number/total number (%) Denominator corresponds to total number of patients for whom data are available |
|---|--|
| Age median [interquartile range] | 48 [32-69] |
| Male | 40/49 (81.6%) |
| Migrant status | 26/49 (53.1%) |
| Occupation | |
| Employed | 14/48 (29.2%) |
| Unemployed | 15/48 (31.3%) |
| Retired | 14/48 (29.2%) |
| Student | 5/48 (10.4%) |
| BCG vaccination | 19/30 (63.3%) |
| COPD/Asthma | 8/47 (17.0%) |
| Diabetes Mellitus | 8/49 (16.3%) |
| HIV infection | 6/48 (12.5%) |
| Renal failure | 5/49 (10.2%) |
| Liver disease | 7/49 (14.3%) |
| Alcohol abuse^a | 10/49 (20.4%) |
| Smoking^b | 20/49 (40.8%) |
| Drug abuse | 4/47 (8.5%) |
| TUBERCULOSIS | |

| | |
|--|--|
| Previous history of TB | 13/46 (28.3%) |
| Site | |
| Pulmonary TB only | 36/49 (73.5%) |
| Extrapulmonary TB only | 1/49 (2.0%) |
| Pulmonary TB/ Extrapulmonary TB(>1 site possible) | 12/49 (24.5%) |
| Site of extrapulmonary TB | |
| Bone | 2/13 (15.4%) |
| Lymphadenitis | 2/13 (15.4%) |
| Pleural | 2/13 (15.4%) |
| Central Nervous System | 1/13 (7.7%) |
| Laryngeal | 1/13 (7.7%) |
| Gastrointestinal | 1/13 (7.7%) |
| Peritonitis+ Lymphadenitis+ Pleural + Bone | 1/13 (7.7%) |
| Genitourinary + Lymphadenitis | 1/13 (7.7%) |
| Central Nervous System + Lymphadenitis | 1/13 (7.7%) |
| Bone + Joint + Spondylodiscitis (T5-T11) + Paravertebral abscesses | 1/13 (7.7%) |
| Radiological involvement | |
| Unilateral cavitary lesions | 10/48 (20.8%) |
| Bilateral cavitary lesions | 13/48 (27.1%) |
| Bilateral infiltrates (no cavities) | 9/48 (18.8%) |
| Unilateral infiltrates | 16/48 (33.3%) |
| Microbiology | |
| Sputum culture confirmation | 22/49 (44.9%) (+ 8 sputum culture ongoing) |
| NAAT confirmation | 13/49 (26.5%) |
| Sputum smear positive | 9/49 (18.4%) |
| Not available | 5/49 (10.2%) |
| Drug resistance | |
| Resistant | 8/45 (17.8%) (4 MDR-TB) |
| Sensitive | 37/45 (82.2%) |
| Treatment outcome | |
| Cured | 6/49 (12.2%) |
| Completed | 1/49 (2.0%) |
| On treatment | 37/49 (75.5%) |
| Died* | 5/49 (10.2%) |
| Lost to follow-up | 0 |
| Failure | 0 |
| COVID-19 | |
| Symptoms | |
| Asymptomatic | 5/48 (10.4%) |
| Symptomatic | 43/48 (89.6%) |
| Imaging | |
| Typical (bilateral ground glass opacities) HRCT picture | 21/44 (47.7%) |
| Treatment outcome | |
| Resolved | 18/49 (36.7%) |

| | |
|---------------------|---------------|
| Still on treatment | 25/49 (51.0%) |
| Died (at any date)* | 6/49 (12.3%) |

Abbreviations: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2 TB= tuberculosis; BCG=Bacillus Calmette-Guérin; COPD= chronic obstructive pulmonary disease; **a:** ≥ 14 drinks per week in men or ≥ 7 drinks per week in women; **b:** current or ex-smoker; NAAT= Nuclear Acid Amplification Test; MDR-TB= multidrug-resistant tuberculosis.

* According to the criteria for cohort analysis of treatment results the patients died during anti-TB treatment are 5 but the total number of deaths is 6 as one patient with post-TB treatment sequelae died after being cured for TB.