Clinical characteristics of COVID-19 and active tuberculosis co-infection in an Italian reference hospital

To the Editor:

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China, in December 2019. In February 2020, an outbreak was detected in the Lombardy region of Italy, resulting in the first major outbreak outside Asia [1].

Tuberculosis (TB), the leading cause of death worldwide from a single infectious agent (1.5 million people per year) [2], like COVID-19, is mainly transmitted through the respiratory route and affects the lungs.

Risk factors such as advanced age and some comorbidities, such as diabetes and chronic respiratory diseases, are associated with poor outcomes in both TB and COVID-19 [3]. However, only limited information about COVID-19 and active TB co-infection has been reported so far [4–6]. Concerns remain that COVID-19 could have a negative impact on the clinical course of TB and its ultimate outcome [7, 8].

This study describes clinical, radiological and laboratory characteristics of a series of COVID-19 patients with concurrent active TB in a hospital in Sondrio province, Lombardy region, in northern Italy.

Patients with active TB admitted to the hospital were analysed to assess the impact of COVID-19 on their clinical course, as well as the radiological and laboratory consequences of the co-infection. TB diagnosis relied mainly on Xpert MTB/RIF and chest radiography (CXR) followed by culture confirmation and phenotypic and genotypic drug susceptibility testing (DST). At the time of TB diagnosis, patients were also tested for HIV. COVID-19 diagnosis was based on the results of real-time RT-PCR for SARS-CoV-2 from nasopharyngeal swabs. Radiological results at COVID-19 diagnosis were compared with the most recent radiographs available prior to the onset of COVID-19 to assess any change in pulmonary TB (PTB)-related lesions. A patient was considered COVID-19 laboratory-negative if two consecutive swabs, ⩾24 h apart, were negative. Follow-up swabs were performed after 14 days from diagnosis and then every 7 days until two consecutive swabs had a negative result [9]. Clinical data were recorded during a follow-up period of 6–41 days following the first positive swab. The study was approved by the ethics committee of Monza e Brianza (code 3377). Categorical variables are reported as absolute frequencies and percentages, while continuous variables are reported using median and interquartile range (IQR).

Among the 24 in-patients diagnosed with active TB, we identified 20 cases with COVID-19 co-infection. Of those, 14 patients were referred from other hospitals in northern Italy and were admitted between 3 and 28 March 2020. On 25 March, a patient (P01), hospitalised in a single room since 14 March, underwent nasopharyngeal swab after reporting a documented COVID-19 case in the household. Since then, five patients (P02–06) with fever were tested and were positive. Subsequently, all the remaining patients were tested (P07–24): P07–17 were diagnosed with COVID-19 on 31 March, and P18–20 who tested negatively on 31 March became positive on 13 April. Four patients (P21–24) screened for SARS-CoV-2 had negative nasal swab results repeatedly and were excluded from analysis. Among the 20 TB patients diagnosed with COVID-19 co-infection, 12 (60%) were males and the median (IQR) age was 39 (27–47) years: considering country of birth, the median ages were 37 (27–46) and 48 (47–60) years for foreign-born (85%) and Italian nationals, respectively. Overall, 50% of patients had a body mass index

@ERSpublications
The COVID-19 infection rate was high in patients with active tuberculosis. Major clinical complications were seen only in two patients, thus requiring *ex novo* oxygen supply, one of whom with advanced tuberculosis died. Nasal swab viral clearance was rapid. https://bit.ly/3cdvdZJ

Cite this article as: Stochino C, Villa S, Zucchi P, *et al*. Clinical characteristics of COVID-19 and active tuberculosis co-infection in an Italian reference hospital. *Eur Respir J* 2020; 56: 2001708 [https://doi.org/10.1183/13993003.01708-2020].

<18.5 $kg \cdot m^{-2}$ at admission and eight had comorbidities, but none had HIV co-infection (table 1). Three patients reported having been vaccinated with bacillus Calmette–Guérin.

19 patients (95%) had PTB and, among them, three (P11, P13 and P14) had also extrapulmonary involvement: two patients (P11 and P13) had renal and neurological (P11 with TB meningeal abscess and small brain granulomas; P13 with TB meningitis and encephalitis) localisation; whereas one (P14) patient had a disseminated form with pericardial, pleural, splenic and bone TB. TB was diagnosed using Xpert MTB/RIF (18/19; 95%); in 14 patients, the diagnosis was confirmed by culture. In one case, diagnosis was confirmed by bone biopsy (1/19; 5%). At admission, CXR showed a multilateral involvement in 12/19 (63%) cases. Only one patient (P19) had an exclusively extrapulmonary TB (abdominal lymph nodes) that was diagnosed through needle aspiration.

Five patients (P07, P10, P17–18, P20) were infected with a drug-resistant strain: three were isoniazid resistant (through genotypic DST in P10) and two were multidrug-resistant. The standard anti-TB treatment regimen (isoniazid, rifampicin, ethambutol and pyrazinamide) was used in 14 cases, while in six patients therapy was tailored based on clinical characteristics and DST results. Hydroxychloroquine (200 mg twice a day) was administered to all patients with COVID-19 co-infection and was well tolerated. No antiviral therapy was administered since no patient met the condition of intensive care admission for its use. Patients requiring second-line anti-TB drugs (prothionamide, linezolid, terizidone and clofazimine) for treatment of multidrug-resistant forms (P18 and P20) were monitored through ECG and no QT interval prolongation was observed.

The median time from TB diagnosis and SARS-CoV-2 detection was 30 days (range 19–69 days). The comparison of CXR after COVID-19 diagnosis with the latest available one (on average 32 days earlier, range 7–88 days) showed that in 12 patients (63%) TB lesions were reduced (on average 30 days before, range 7–88 days), whereas seven patients (35%) had worsening TB lesions (on average 32 days earliest, range 14–57) and in one with extrapulmonary TB there was no change. At CXR, three patients (15%) (P02, P06, P20) had mild-to-moderate interstitial thickening associated with COVID-19, and one (P13) had ground glass pattern compatible with COVID-19 on computed tomography (CT) scan.

A general lymphocytopenia (total lymphocyte count <1500 mm^{-3}) was detected in 13 patients (65%) and one patient (P18) had thrombocytopenia (platelet count <150×10^3 mm^{-3}). Increased serum levels of transaminase (both aspartate aminotransaminase and alanine aminotransaminase) was observed in two cases (P19 and P20) who were known to have previously suffered from anti-TB drug-induced hepatitis. 19 (95%) patients had high D-dimer levels (>250 $ng \cdot mL^{-1}$), but only five (P01, P04, P06–07, P11) >2000 $ng \cdot mL^{-1}$, and 11 of them (58%) had an increased ferritin concentration (>300 $ng \cdot mL^{-1}$). One patient, P19, affected by sickle cell anaemia, had a ferritin level of 5036 $ng \cdot mL^{-1}$ attributed to frequent blood transfusions.

Oxygen supplementation was required in four patients at admission (P02, P05, P08, P17); in three patients (P02, P08, P17) it was soon discontinued and in one reduced from 2 to 1 $L \cdot min^{-1}$ (P05). During hospitalisation, three patients required *ex novo* oxygen supply (P06, P11, P13) due haemoglobin desaturation below 95%. Among them, two had respiratory complications: one had a pneumothorax due to subpleural blebs rupture (P11) which required temporary oxygen supplementation until thoracic drainage, and one elderly patient (P06), with advanced PTB and cachexia, developed COVID-19 pneumonia and severe hypoxia (requiring 10 $L \cdot min^{-1}$ oxygen supplementation), dying 6 days after COVID-19 diagnosis.

Follow-up swabs were performed in 19 co-infected patients. In 12 patients (63%) the test converted to negative after 14 days from the first nasal swab (P01, P03, P05, P07–10, P14–15, P18–20). Four additional patients (21%) had a negative test after 28 days (P4, P11, P12, P16). In the three remaining patients, nasal swabs became negative on day 35 (P13) and day 42 (P02 and P17).

This is the first series of patients co-infected with TB and COVID-19 in one single care centre. In our series, 20 in-patients with TB (19 PTB) were diagnosed with COVID-19 through an active screening programme in the 24 in-patients in the ward implemented after the first six cases were identified (P01–06). In the immediate 3–4 weeks following COVID-19 diagnosis, the clinical course of TB and COVID-19 co-infection was generally benign and only one patient died (5% case fatality rate).

Several hypotheses can be made on the dynamics of the spread of the infection in the ward. First, prior to COVID-19 diagnosis in P01, subjects with TB could sit in common areas within the ward wearing a surgical mask. This policy probably facilitated transmission including through contamination of objects and surfaces. Second, transmission could have been caused by infected staff wearing FFP-3 masks with exhalation valve that may have contributed to spreading viral particles when the wearer exhales [10]. Finally, it is possible that transmission occurred through occasional visitors who were allowed in the ward,

TABLE 1 Characteristics of patients co-infected with active tuberculosis (TB) and coronavirus disease 2019 (COVID-19)

Patients	Age years	Sex	BMI[#]	Comorbidities	TB localisation	Signs and symptoms[¶]	PTB pattern at TB diagnosis	Time since TB days[¶]	COVID-19 radiological signs[¶]	Pulmonary pattern (days from previous CXR/CT scan)[¶]	Abnormal biochemistry	O_2 supply
P01	20s	M	L		DS-PTB	Fever, cough, headache	Unilateral cavities[§]	20	None[§]	Improvement (19)	TLC 770 mm^{-3} Hb 9.9 $g{\cdot}dL^{-1}$ CRP 180 $mg{\cdot}L^{-1}$ Fer. 623 $ng{\cdot}mL^{-1}$ DD 3206 $ng{\cdot}mL^{-1}$	
P02	60s	M	N	COPD and epilepsy	DS-PTB	Fever	Unilateral nodules[§]	84	Minimal signs of interstitial thickening[§]	Worsening (15)	No abnormalities	Yes[§§]
P03	10s	F	L		DS-PTB	Fever, chest pain, dyspnoea, vomit, conjunctivitis	Bilateral nodules and cavities[§]	20	None[§]	Worsening (14)	DD 1104 $ng{\cdot}mL^{-1}$	
P04	20s	M	L		DS-PTB	Fever, cough, vomit	Miliary and cavities[§]	14	None[§]	Improvement (17)	TLC 980$\cdot mm^{-3}$ Fer. 517 $ng{\cdot}mL^{-1}$ DD 2161 $ng{\cdot}mL^{-1}$	
P05	30s	F	L		DS-PTB	Fever, cough	Bilateral reticules, nodules and cavities[§]	302	None[§]	Improvement (7)	Fer. 511 $ng{\cdot}mL^{-1}$ K^+ 2.50 $mmol{\cdot}L^{-1}$ DD 1179 $ng{\cdot}mL^{-1}$	Yes
P06	70s	F	L	Cachexia, chronic vomit and diarrhoea, hypertension, diabetes, mental disorders	DS-PTB	Fever, severe dyspnoea, and respiratory failure	Bilateral nodules and cavities[§], tree in bud[f]	26	Interstitial-alveolar thickening[§]	Worsening (28)	TLC 920 mm^{-3} K^+ 2.8 $mmol{\cdot}L^{-1}$ DD 5244 $ng{\cdot}mL^{-1}$ Fer. unevaluated[##]	Yes[++]
P07	30s	M	L		Hr-PTB	Fever, cough	Bilateral cavitary nodules[§]	21	None[§]	Improvement (34)	TLC 8620 mm^{-3} Fer. 379 $ng{\cdot}mL^{-1}$ DD 2516 $ng{\cdot}mL^{-1}$	
P08	20s	M	N		DS-PTB	Fever, cough	Bilateral nodules and reticules[§]	19	None[§]	Improvement (31)	No abnormalities	Yes[§§]
P09	40s	M	H	Psoriasis and FLD	DS-PTB	Cough, chest pain	Unilateral nodules[§]	6	None[§]	Improvement (25)	Fer. 978 $ng{\cdot}mL^{-1}$	
P10	40s	F	H	Diabetes	Hr-PTB[+]	Fever	Bilateral reticules, cavitary nodules[§]	8	None[§]	Improvement (18)	Fer. 370 $ng{\cdot}mL^{-1}$ DD 1029 $ng{\cdot}mL^{-1}$	
P11	20s	M	L		DS-PTB plus renal, brain, and meningeal TB	Fever, cough, chest pain, headache	Miliary and cavities[§]	53	None[§]	Worsening (57)	TLC 680 mm^{-3} LDH 283 $U{\cdot}L^{-1}$ Fer. 513 $ng{\cdot}mL^{-1}$ DD 3065 $ng{\cdot}mL^{-1}$ Na^+ 125 $mmol{\cdot}L^{-1}$	Yes[++,ff]
P12	60s	F	N	Diabetes	DS-PTB	Fever	Unilateral thickenings[§]	56	None[§]	Improvement (32)	No abnormalities	
P13	40s	F	L	Anorexia nervosa	DS-PTB plus renal, brain, and meningeal TB	None	Bilateral nodules[§]	152	Ground glass[f]	Improvement (34)	TLC 720 mm^{-3} Hb 6.1 $g{\cdot}dL^{-1}$ CRP 244 $mg{\cdot}L^{-1}$ Fer. 768 $ng{\cdot}mL^{-1}$	Yes[++]

Continued

TABLE 1 Continued

Patients	Age years	Sex	BMI[#]	Comorbidities	TB localisation	Signs and symptoms[¶]	PTB pattern at TB diagnosis	Time since TB days[¶]	COVID-19 radiological signs[¶]	Pulmonary pattern (days from previous CXR/CT scan)[¶]	Abnormal biochemistry	O_2 supply
P14	60s	M	N		DS-PTB plus pericardial, pleural, splenic, and bone TB	None	Bilateral nodules and pleural effusion[§]	62	None[§]	Worsening (27)	DD 1233 ng·mL^{-1}	
P15	30s	M	L		DS-PTB	Cough	Bilateral nodules and cavities[§]	97	None[§]	Improvement (88)	Fer. 449 ng·mL^{-1} DD 1657 ng·mL^{-1} Na^+ 132 mmol·L^{-1}	
P16	40s	M	N	Diabetes	DS-PTB	Fever	Bilateral reticules and nodules[§]	43	None[§]	Worsening (44)	Fer. 775 ng·mL^{-1} DD 1492 ng·mL^{-1}	
P17	20s	F	N		Hr-PTB	Vomit	Unilateral reticules and nodules[§]	38	None[§]	Improvement (10)	No abnormalities	Yes[§§]
P18	30s	M	N		Pre-XDR-PTB	Cough	Unilateral nodules and cavities[§]	30	None[§]	Worsening (37)	TLC 1350 mm^{-3} DD 1322	
P19	20s	F	L	Sickle cell disease	DS-EPTB: abdominal LN	Chest pain, dyspnoea, vomit	Calcific lesions[§]	87	None[§]	Unchanged (47)	Hb 8.4 g·dL^{-1} PLT 9.2×10^3 mm^{-3} AST 49 U·L^{-1} ALT 46 U·L^{-1} Fer. 5036 ng·mL^{-1}[¶¶]	
P20	30s	M	N		MDR-PTB (relapse: already treated in 2015)	None	Unilateral thickening[§]	40	Interstitial-alveolar thickening[§]	Improvement (46)	TLC 1390 mm^{-3} AST 132 U·L^{-1} ALT 111 U·L^{-1}	

[#]: body mass index (BMI) was categorised as "low" (L) if <18.5 kg·m^{-2}, "normal" (N) if 18.5–25 kg·m^{-2}, "high" (H) if 25–30 kg·m^{-2}. [¶]: at COVID-19 diagnosis compared to the last available chest radiograph (CXR) result. [+]: isoniazid-resistance was detected only through genotypic drug-susceptibility test. [§]: lung pattern at CXR. [f]: lung pattern at chest computed tomography (CT) scan. [##]: ferritin (fer.) was not routinely assessed but was part of a set of exams to perform only in patients affected by COVID-19; however, due to the lag obtaining the swab results for SARS-CoV-2 it was not included. [¶¶]: frequent blood transfusions to treat severe anaemia due to sickle cell disease. [++]: O_2 supply *ex novo*. [§§]: O_2 supply at admission and then stopped. [ff]: O_2 supply was required temporarily due to pleural bleb rupture and consequent pneumothorax. PTB: pulmonary TB; M: male; F: female; FLD: fatty liver disease; DS: drug-susceptible; Hr: isoniazid resistant; XDR: extensively drug resistant; EPTB: extrapulmonary tuberculosis; LN: lymph node; MDR: multidrug-resistant; TLC: total lymphocyte count; Hb: haemoglobin; CRP: C-reactive protein; DD: D-dimer; LDH: lactate dehydrogenase; PLT: platelets; AST: aspartame transaminase; ALT: alanine transaminase.

although in limited numbers, until 29 March, wearing surgical masks. In any case, this outbreak is the result of insufficient infection control practices compounded by a higher vulnerability of TB patients.

The impact of COVID-19 co-infection on the clinical course of active TB seems to be modest in this series. Apart from fever present in most patients, no major clinical deterioration was observed with the notable exception of the one who died. In most cases, TB lesions at CXR did not worsen and only four patients had signs of newly developed pneumonia. No patient was admitted to intensive care unit or mechanically ventilated. Severe respiratory insufficiency was only seen in the patient who died.

Biochemical tests did not show major deviations from the expected values, except for D-dimer levels and lymphocytopenia; more advanced testing of immune biomarkers is in progress. Clearance of the virus from nasal swabs was rapid in 63% of patients at day 14 from COVID-19 diagnosis. Finally, there were no drug–drug interactions between anti-TB drugs and hydroxychloroquine.

Our study requires some final comments. First, the low rate of clinical and radiological deterioration in our series may be associated with the young age of most patients, low frequency of other comorbidities, including HIV infection, low prevalence of multidrug-resistant TB, and the quality of healthcare services. Second, clinical symptoms may have been partly under-estimated due to cultural and linguistic barriers as the vast majority of patients were recent immigrants. Third, lung lesions caused by COVID-19 might have been over-looked due to the use of portable CXR at patient's bed instead of CT scan given the decision to prevent further nosocomial transmission [11]. Finally, the duration of follow-up was limited to a few weeks, thus not allowing for assessment of longer-term outcomes which will be, however, assessed at a later time.

In conclusion, the impact of COVID-19 on active TB appears to be clinically manageable with proper care. Rigorous infection control practices and personal protection devices are fundamental to prevent the risk of in-hospital transmission, especially when dealing with a highly vulnerable population.

Claudia Stochino[1], Simone Villa[2], Patrizia Zucchi[3], Pierpaolo Parravicini[3], Andrea Gori[2,4] and Mario Carlo Raviglione[2]

[1]Phthisiology Unit, Sondalo Hospital, ASST Valtellina e Alto Lario, Sondrio, Italy. [2]Centre for Multidisciplinary Research in Health Science, University of Milan, Milan, Italy. [3]Dept of Internal Medicine, ASST Valtellina e Alto Lario, Sondrio, Italy. [4]Infectious Diseases Unit, Dept of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

Correspondence: Simone Villa, Centre for Multidisciplinary Research in Health Science, University of Milan, Via Francesco Sforza 35, 20122, Milan, Italy. E-mail: simone.villa@unimi.it

Received: 10 May 2020 | Accepted after revision: 25 May 2020

Author contributions: Study concept and design: A. Gori and M.C. Raviglione; acquisition of data: C. Stochino and P. Zucchi; analysis or interpretation of data: S. Villa; drafting of the manuscript: S. Villa; critical revision of the manuscript for important intellectual content: C. Stochino, P. Zucchi, P. Parravicini, A. Gori and M.C. Raviglione; statistical analysis: S. Villa; administrative, technical or material support: S. Villa, P. Zucchi and P. Parravicini; study supervision: P. Parravicini, A. Gori and M.C. Raviglione.

Conflict of interest: None declared.

References

1 Cereda D, Tirani M, Rovida F, *et al.* The early phase of the COVID-19 outbreak in Lombardy, Italy. *arXiv* 2020; preprint [https://arxiv.org/abs/2003.09320].
2 World Health Organization. Global TB Report 2019. Geneva, World Health Organization, 2019.
3 Onder G, Rezza G, Brusaferri S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA* 2020; in press [https://doi.org/10.1001/jama.2020.4683].
4 Du RH, Liang LR, Yang CQ, *et al.* Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J* 2020; 55: 2000524.
5 Tadolini M, Codecasa LR, García-García JM, *et al.* Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J* 2020; 56: 2001398.
6 Motta I, Centis R, D'Ambrosio L, *et al.* Tuberculosis, COVID-19 and migrants: preliminary analysis of deaths occurring in 69 patients from two cohorts. *Pulmonology* 2020; 26: 233–240.
7 World Health Organization. COVID-19: Considerations for Tuberculosis (TB) Care. www.who.int/tb/COVID_19considerations_tuberculosis_services.pdf Date last accessed: 21 April, 2020.
8 Dara M, Sotgiu G, Reichler MR, *et al.* New diseases and old threats: lessons from tuberculosis for the COVID-19 response (18th March 2020) www.theunion.org/news-centre/news/new-diseases-and-old-threats-lessons-from-tuberculosis-for-the-covid-19-response Date last accessed: 21 April, 2020.
9 Ministero della Salute, Consiglio superiore di Sanità. Quesiti scientifici relativi all'infezione da Coronavirus SARS-CoV-2. www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2020&codLeg=73458&parte=1%20&serie=null Date last accessed: 23 April, 2020.

10 European Centre for Disease Prevention and Control. Using face masks in the community. Stockholm, ECDC, 2020. www.ecdc.europa.eu/sites/default/files/documents/COVID-19-use-face-masks-community.pdf. Date last accessed: 20 May, 2020.
11 Hope MD, Raptis CA, Shah A, *et al.* A role for CT in COVID-19? What data really tell us so far. *Lancet* 2020; 395: 1189–1190.