EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
TB/COVID-19 GLOBAL STUDY GROUP

Tuberculosis and COVID-19 co-infection: description of the global cohort

The TB/COVID-19 Global Study Group

The complete list of contributors of the TB/COVID-19 Global Study Group is provided in the Acknowledgements section

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Shareable abstract (@ERSpublications)
High mortality (11%) was observed with COVID-19/TB co-infection associated with older age, male gender and invasive ventilation. Efforts to avoid SARS-CoV-2 infection in TB patients are recommended to prevent excess morbidity and mortality. https://bit.ly/3mSylCK

Cite this article as: The TB/COVID-19 Global Study Group. Tuberculosis and COVID-19 co-infection: description of the global cohort. *Eur Respir J* 2022; 59: 2102538 [DOI: 10.1183/13993003.02538-2021].

This article has an editorial commentary: https://doi.org/10.1183/13993003.00149-2022

Received: 21 Sept 2021
Accepted: 1 Nov 2021

Abstract

Background Information on tuberculosis (TB) and coronavirus disease 2019 (COVID-19) is still limited. The aim of this study was to describe the features of the TB/COVID-19 co-infected individuals from a prospective, anonymised, multicountry register-based cohort with special focus on the determinants of mortality and other outcomes.

Methods We enrolled all patients of any age with either active TB or previous TB and COVID-19. 172 centres from 34 countries provided individual data on 767 TB-COVID-19 co-infected patients, (>50% population-based).

Results Of 767 patients, 553 (74.0%) out of 747 had TB before COVID-19 (including 234 out of 747 with previous TB), 71 (9.5%) out of 747 had COVID-19 first and 123 (16.5%) out of 747 had both diseases diagnosed within the same week (n=35 (4.6%) on the same day). 85 (11.08%) out of 767 patients died (41 (14.2%) out of 289 in Europe and 44 (9.2%) out of 478 outside Europe; p=0.03): 42 (49.4%) from COVID-19, 31 (36.5%) from COVID-19 and TB, one (1.2%) from TB and 11 from other causes. In the univariate analysis on mortality the following variables reached statistical significance: age, male gender, having more than one comorbidity, diabetes mellitus, cardiovascular disease, chronic respiratory disease, chronic renal disease, presence of key symptoms, invasive ventilation and hospitalisation due to COVID-19. The final multivariable logistic regression model included age, male gender and invasive ventilation as independent contributors to mortality.

Conclusion The data suggest that TB and COVID-19 are a "cursed duet" and need immediate attention. TB should be considered a risk factor for severe COVID disease and patients with TB should be prioritised for COVID-19 preventative efforts, including vaccination.

Introduction

Tuberculosis (TB), with its estimated 10 million cases and 1.3 million deaths annually, continues to be a global health priority [1]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus disease 2019 (COVID-19) pandemic has required concerted public health focus and action because of its rapid global spread, clinical severity, high mortality rate with 4 million deaths, and capacity to overwhelm healthcare systems [2–5]. The impact of COVID-19 on TB services has been well described, with a reduction of the number TB cases diagnosed and managed in most countries as a combined result of reduced access, delayed diagnosis with more advanced forms and overstretched health services among other reasons [6–11]. According to the World Health Organization (WHO) report, there was a 18% decrease of TB case notifications between 2019 and 2020 (from 7.1 to 5.8 million cases) [1]. Conservative models suggest that a 20% increase in TB deaths in the next 5 years is likely as a result of the pandemic [12, 13].

The clinical and immune-pathological interaction between the two diseases and the drivers of dual COVID-19/TB disease mortality are not yet fully understood [14–17]. A first pilot study of the Global

Tuberculosis Network (GTN) on 49 TB/COVID-19 co-infected patients from eight countries was published in 2020 [18], suggesting that although signs and symptoms are largely the same, TB is frequently diagnosed concomitant with or after COVID-19 and that dual infection may be associated with an increased case-fatality rate. A second GTN study on 69 TB/COVID-19 patients [10] suggested an overall 12.6% case-fatality rate, higher than the 1–2% mortality rate reported for drug-susceptible TB [1] and for COVID-19 [4], identifying age and comorbidities as the main determinants for mortality. Subsequent studies from South Africa and the Philippines suggested that COVID-19 patients with TB have a 2.7 [19] and 2.17 [20], respectively, higher risk of mortality compared with COVID-19 patients without TB [20]. No large multicountry cohort of TB and COVID-19 patients has been reported to date.

In 2020 the GTN, in collaboration with several organisations (Groupe de Recherche et Enseignement en Pneumo-Infectiologie, a working group from the Société de Pneumologie de Langue Française; Sociedad Española de Neumología and Cirugía Torácica; Brazilian Society of Pulmonology and Tuberculosis; and the Moscow Society of Phthisiology, among others), national TB programmes (Chile, Colombia, Niger, Oman, Panama, Paraguay, Portugal, Serbia and Slovakia), partners and clinicians, developed a global repository of TB and COVID-19 patients. The repository was shared with the WHO to inform the development of global guidance [1, 21]. The aim of this study is to describe the features of the TB and COVID-19 co-infected individuals using this repository, with special focus on the determinants of mortality and other short-term outcomes.

Methods

Study design

The study is based on a prospective, anonymised, multicountry register-based cohort (annex 1). We worked with WHO and the GTN to identify respondents and send invitations to 175 centres in 37 countries [22]. The centres and countries providing data are listed in annex 2 and figure 1; we enrolled all patients (including children and adolescents) notified to these centres between March 2020 (first case reported on 12 March 2020) and June 2021. The questionnaire and process was piloted and has been

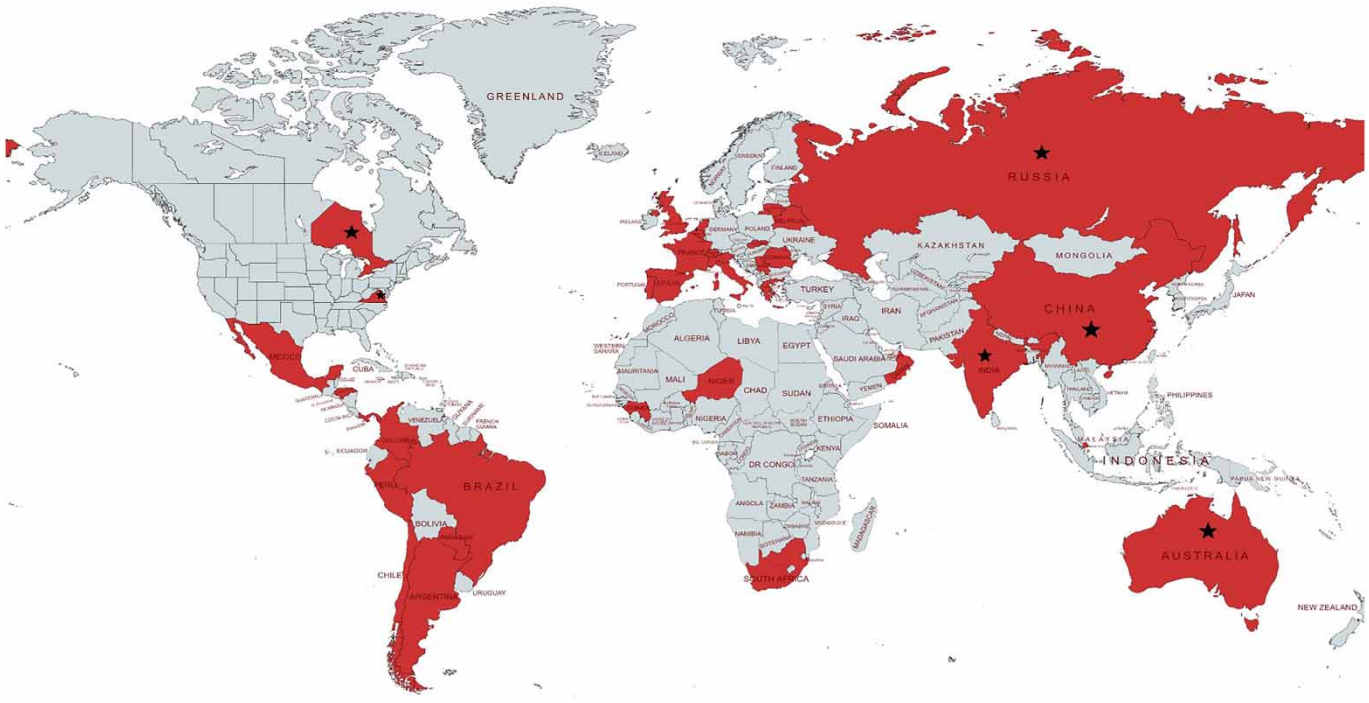

FIGURE 1 Global distribution of the countries/states/regions participating in the study. The following states/territories are covered in the study (★): Australia (New South Wales); Canada (Ontario state): China (Wenzhou and Luzhou); India (New Delhi, Mumbai and Maharashtra states); the Russian Federation (Arkhangelsk, Moscow and Volvograd Oblasts); Switzerland (Vaud county); USA (Virginia state). 21 countries (Argentina, Belarus, Belgium, Brazil, Chile, China, France, Republic of Guinea, India, Italy, Mexico, Niger, Panama, Peru, Portugal, Romania, Russia, Singapore, Spain, Switzerland and UK) reported at least one tuberculosis/coronavirus disease 2019 case in 2020. Other countries (Australia, Canada, Colombia, Greece, Honduras, Lithuania, the Netherlands, Oman, Paraguay, Serbia, Slovakia, South Africa and USA) started reporting from 2021.

described previously [10, 18, 23]. We enrolled all patients of any age from these centres with either active TB or previous TB and COVID-19 [18] simultaneously.

Variables and definitions

The data were obtained *via* an electronic collection form using variables standardised and harmonised with the WHO and piloted in our previous study [18, 21], including anonymised patients' demographic data, laboratory, radiological and clinical status at diagnosis of TB and COVID-19, and details on follow-up.

Case definitions follow WHO classification [1]. We define previous TB patients as those who had TB and completed anti-TB treatment at any time in the past before diagnosis of COVID-19. The TB/COVID-19 cases collected in our study were compared with country/regional surveillance systems to estimate coverage in agreement with investigators (annex 2). All data were cleaned and harmonised throughout the dataset and investigators were contacted in at least two rounds of data cleaning to ensure quality of the dataset before final analysis. The cause of death was analysed as reported by each investigator.

Data analysis

A descriptive analysis was performed on all patients, presenting the details of TB and COVID-19 in the cohort. Considering the relevant proportion of patients from Europe and the number of European countries (15 out of 34) reporting data were also stratified by geographical origin.

We summarised variables using frequencies and percentages and calculated mean±SD for normally distributed data and medians with interquartile ranges (IQR) for non-normally distributed data. Unpaired t-tests were used to compare continuous variables with normal distributions and categorical variables were compared using Chi-squared or Fisher exact test. We used nonparametric tests (*e.g.* Mann–Whitney U-test) for data that could not be converted into a standard distribution.

We were interested in determinants of mortality of COVID-19 and evaluated the effect of prognostic factors on these end-points by univariable and multivariable logistic regression models. Covariates that were significant prognostic factors at single variable analysis ($p<0.05$) were tested for inclusion in the multivariable model in a forward fashion using likelihood ratio tests at each step and used Akaike's information criterion to decide on the final model. For all variables, two-sided p-values $\leqslant 0.05$ were considered statistically significant. All variables, when biologically plausible, were tested for interaction. Based on the results of the final multivariable model, we developed a nomogram for risk prediction (annex 3). The nomogram displays the predicted and confounding probabilities for each variable and overall as points on a scale from 0 to 100 in a user-friendly graphical interface and the overall scale corresponds to the predicted overall probability of the outcome for a patient.

Ethics

The ethics committee of the Maugeri Care and Research Institute, Tradate, Italy (the coordinating centre) approved the study on 26 May 2020 (CE 2020/May 26). Each participating centre or country signed a confidentiality and data-sharing agreement with the coordinating centre and obtained local ethics committee clearance or had a waiver indicating no requirement for ethical approval due to the local regulations [18, 23, 24].

Results

In total, 172 centres from 34 countries provided individual data on 767 TB-COVID-19 co-infected patients (annex 2). Ascertainment of COVID-19/TB was very high and in most of countries (or regions/states or metropolitan areas) (18 out of 34, 52.9%) >80% of these patients were notified to us.

Description of the TB/COVID-19 cohort

The demographic, epidemiological and clinical characteristics of the 767 TB/COVID-19 patients are summarised in table 1.

Most patients were male (70.4%, 540 out of 767), with a median (IQR) age of 44 (31–58) years. The majority were vaccinated with bacillus Calmette–Guérin (90.7%, 349 out of 385). 11.1% (80 out of 717) had a history of migration in the past 5 years and 11.5% (83 out of 724) were HIV co-infected.

Of 767 patients, 553 (74.0%) out of 747 had TB before COVID-19 (including 234 out of 747 with previous TB), 71 (9.5%) out of 747 had COVID-19 first and 123 (16.5%) out of 747 had both diseases diagnosed within the same week (35 (4.6%) of them on the same day).

TABLE 1 Demographic, epidemiological and clinical characteristics of 767 tuberculosis (TB)/coronavirus disease 2019 (COVID-19) cases

Age, years	44 (31–58)
Males	540/767 (70.4)
Immigrated in the past 5 years	80/717 (11.2)
Occupation	
Unemployed	318/705 (45.1)
Employed	254/705 (36.0)
Retired	108/705 (15.3)
Student	25/705 (3.6)
BCG vaccinated	349/385 (90.7)
Pregnancy	2/224 (0.9)
Alcohol abuse (⩾14 drinks per week in men or ⩾7 drinks per week in women)	112/687 (16.3)
Smoking status	
Nonsmoker	382/636 (60.1)
Current smoker	184/636 (28.9)
Former smoker	70/636 (11.0)
Vaping status	
No vape	485/523 (92.7)
Current vape	36/523 (6.9)
Former vape	2/523 (0.4)
Intravenous drug user	
No drug user	631/655 (96.3)
Current/regular	9/655 (1.4)
Current/not regular	4/655 (0.6)
Former drug user	11/655 (1.7)
HIV positivity	83/724 (11.5)
CD4 count pre-COVID-19 infection, cells·μL^{-1} (n=28)	164.5 (46–344)
CD4 count during COVID-19 infection, cells·μL^{-1} (n=20)	88 (41.3–247)
HIV treatment administered	29/83 (34.9)
COPD	59/751 (7.8)
Diabetes mellitus	157/753 (20.8)
Uncontrolled diabetes mellitus (HbA1c ⩾9%)	40/136 (29.4)
Poorly controlled diabetes mellitus (HbA1c 7–9%)	28/136 (20.6)
Well-controlled diabetes mellitus (HbA1c <7%)	18/136 (13.2)
Unknown diabetes mellitus control	50/136 (36.8)
Renal failure	53/713 (7.4)
Dialysis	17/43 (39.5)
Liver disease	60/700 (8.6)
Timing of TB and COVID-19 diagnosis	
TB diagnosed before COVID-19[#]	553/747 (74.0)
Days of TB diagnosis before COVID-19 diagnosis (n=318)[¶]	78 (38–145)
Years between TB end and COVID-19 diagnosis (n=229)[+]	2.3 (1.0–6.3)
COVID-19 diagnosed before TB	71/747 (9.5)
Days of COVID-19 diagnosis before TB diagnosis (n=71)	28 (15–42)
COVID-19 and TB diagnosed within the same week (including patients diagnosed on the same day)	123/747 (16.5)
Days of TB and COVID-19 diagnosis within the same week (n=123)	1 (0–4)
COVID-19 and TB diagnosed within the same day	35/747 (4.7)

Data are presented as median (interquartile range) or n/N (%). BCG: bacille Calmette–Guérin; HbA1c: glycated haemoglobin. [#]: patients with active TB and previous TB; [¶]: patients with previous TB excluded; [+]: patients with previous TB.

Characteristics of patients with TB in the TB/COVID-19 cohort

As shown in table 2, the majority of patients had newly diagnosed TB (618 out of 723, 85.5%) and bacteriologically confirmed disease (612 out of 732, 83.6%) with pulmonary localisation (648 out of 755, 85.8%); the majority (517 out of 607, 85.2%) had pan-susceptible TB.

Overall, 248 (39.2%) out of 633 patients presented unilateral or bilateral cavities. Approximtely one-third of the patients (209 out of 625, 33.4%) performed at least one lung function test; pulse oximetry being the most utilised.

TABLE 2 Descriptive analysis of tuberculosis (TB) in the TB/coronavirus disease 2019 cohort

TB form	
Failure	17/723 (2.4)
Relapsed	59/723 (8.2)
Loss to follow- up	29/723 (4.0)
New case	618/723 (85.5)
TB laboratory confirmation	612/732 (83.6)
Site	
Pulmonary TB	648/755 (85.8)
Extrapulmonary TB	189/738 (25.6)
Pulmonary–extrapulmonary TB	80/733 (10.9)
Extrapulmonary TB	
Pleural TB	52/189 (27.5)
TB lymphadenitis	42/189 (22.2)
Multiple locations	31/189 (16.4)
Central nervous system	17/189 (9.0)
Other	15/189 (7.9)
Bone TB	11/189 (5.8)
Gastrointestinal TB	7/189 (3.7)
TB peritonitis	5/189 (2.6)
Genitourinary TB	4/189 (2.1)
TB pericarditis	2/189 (1.0)
Unknown	3/189 (1.6)
Radiology at TB diagnosis	
Bilateral pulmonary cavitary lesion	118/633 (18.6)
Bilateral pulmonary cavitary lesion+other	5/633 (0.8)
Unilateral pulmonary cavitary lesion	121/633 (19.1)
Unilateral pulmonary cavitary lesion+other	4/633 (0.6)
Bilateral pulmonary infiltrate (no cavities)	108/633 (17.1)
Bilateral pulmonary infiltrate (no cavities)+other	7/633 (1.1)
Unilateral pulmonary infiltrate (no cavities)	94/633 (1.8)
Unilateral pulmonary infiltrate (no cavities)+other	8/633 (1.3)
Other lesions	143/633 (22.6)
Not done	25/633 (3.9)
Lung function tests at TB diagnosis	
Lung function tests at TB diagnosis	209/625 (33.4)
S_{O_2}, % (n=214)	97 (94–98)
F_{iO_2}, % (n=112)	21 (21–21)
P_{O_2}, mmHg (n=40)	77.9 (65.7–93.8)
P_{CO_2}, mmHg (n=40)	35.2±7.5
pH (n=39)	7.45 (7.40–7.47)
Microbiology	
TB microbiology (one or more tests)	638/652 (97.8)
Solid culture	441/638 (69.3)
Gene Xpert	410/638 (64.5)
Liquid culture	324/638 (50.9)
First-line LPA	105/638 (16.5)
Second-line LPA	28/638 (4.4)
Drug resistance pattern at TB diagnosis	
Pan-susceptible TB	517/607 (85.2)
Drug-resistant TB	90/607 (14.8)
Hospitalisation	
Hospitalisation during anti-TB treatment	388/614 (63.2)
Duration of hospitalisation, days (n=342)	31 (14–90)

Data are presented as n/N (%), median (interquartile range) or mean±SD. S_{O_2}: oxygen saturation; F_{iO_2}: fraction of inspired oxygen; P_{O_2}: partial pressure of oxygen; P_{CO_2}: partial pressure of carbon dioxide; LPA: line probe assay.

The majority of patients with TB (388 of the 614 with information, 63.2%) were hospitalised during anti-TB treatment for a median (IQR) duration of 31 (14–90) days.

Characteristics of COVID-19 patients in the TB/COVID-19 cohort

SARS-CoV-2 laboratory confirmation was available for 723 (94.8%) out of 763 patients; the remaining patients' diagnoses of COVID-19 were based on clinical and radiological criteria (table 3). The majority of COVID-19 patients reported signs and symptoms (538 out of 669, 80.4%); fever (386 out of 538, 71.7%) and dry cough (311 out of 538, 57.8%) being the most frequently reported. Other typical COVID-19 symptoms such as taste and olfactory disorders were reported by 56 (10.4%) and 48 (8.9%) out of 538 patients, respectively. Among the 266 patients who had a computed tomography (CT) scan, 228 (85.7%) had typical or atypical "ground-glass" opacities. 401 (64.8%) out of 619 patients with detailed information had at least one functional assessment of the respiratory system, most commonly pulse oximetry (397 out of 401, 99.0%).

Overall, 452 (61.7%) out of 732 patients were hospitalised for COVID-19 for a median (IQR) duration of 14 (8–22) days.

Mechanical ventilation was necessary for 113 patients; 46 (7.4%) out of 626 requiring intubation, while 67 (10.7%) out of 626 received noninvasive ventilation.

Azithromycin, hydroxychloroquine, antiretroviral drugs, corticosteroids and anticoagulants were the drugs most frequently prescribed during the first wave of the epidemic (table 3).

The number of comorbidities in the patients who survived and died are summarised in table 3 and annex 3. Cardiovascular and endocrine comorbidities were the most commonly observed; mostly hypertension and diabetes mellitus.

Age, gender and mortality

Out of 767 patients in the cohort, 85 (11.08%) died; 41 (14.2%) out of 289 in Europe and 44 (9.2%) out of 478 outside Europe ($p=0.03$) (table 4).

Overall, the median (IQR) age of the patients in Europe was higher than outside Europe: 49 (36–63) years *versus* 39 (29–54) years ($p<0.0001$). This is also true for the patients who died (70 years, 59–80.5 years *versus* 57.5 years, 44.3–71.8 years; $p=0.004$). In Europe, more patients aged >65 years died in comparison with the rest of the world (26 out of 41, 63.4% *versus* 18 out of 44, 40.9%; $p=0.04$).

More males were present among those who died *versus* those who survived (70 out of 85, 82.4% *versus* 470 out of 682, 68.9%; $p=0.01$) (table 4).

Comorbidities and their impact on COVID-19 mortality

The comorbidities per patient and geographical location, grouped into main categories, are summarised in tables 3 and 4, and annex 3.

Patients with more than one comorbidity were more frequently observed among those who died (73 out of 85, 85.9% *versus* 343 out of 682, 50.3%; $p<0.0001$) and in Europe (183 out of 289, 63.3% *versus* 233 out of 478, 48.7%; $p<0.0001$) (table 4)

In table 5, the results of the logistic regression analysis to assess the relationship between demographic, epidemiological, clinical variables and mortality are summarised.

In the univariate analysis on mortality the following variables reached statistical significance: age, being male, having more than one comorbidity, type 2 diabetes mellitus, cardiovascular disease, chronic respiratory disease, chronic renal disease, presence of key symptoms, invasive ventilation and hospitalisation due to COVID-19 (table 5). The final multivariable logistic regression model included age (10-year increase), male gender and need for invasive ventilation as independent contributors to mortality (table 5). Adding other covariates did not significantly increase the performance of the model. A nomogram for the estimation of the risk of death was generated on the basis of the final multivariable model. As depicted in figure 2, each indicator is measured, and the corresponding points are assigned using the row "score". Thus, the sum is reported on the row "total score", and the corresponding probability of death is identified in the row "probability (%) of death".

In the overall cohort, the presence of previous TB was higher among the patients who died than in those who survived (34 out of 85, 40.0% *versus* 200 out of 682, 30.2%), the difference not being statistically significant; no difference was found between European *versus* non-European patients (table 4).

TABLE 3 Descriptive analysis of coronavirus disease 2019 (COVID-19) in the tuberculosis (TB)/COVID-19 cohort

	All patients	Alive	Deceased
Patients		682	85
SARS-CoV-2 laboratory confirmation	723/763 (94.8)		
Signs and symptoms			
COVID-19 signs and symptoms (one or more symptoms)	538/669 (80.4)		
Fever	386/538 (71.7)		
Dry cough	311/538 (57.8)		
Shortness of breath	192/538 (35.7)		
Headache	133/538 (24.7)		
Tiredness	114/538 (21.2)		
Sore throat	96/538 (17.8)		
Malaise	96/538 (17.8)		
Chest pain	88/538 (16.3)		
Myalgia	87/538 (16.2)		
Nasal congestion	73/538 (13.6)		
Taste disorders	56/538 (10.4)		
Diarrhoea	52/538 (9.7)		
Olfactory disorders	48/538 (8.9)		
Vomiting/nausea	38/538 (7.1)		
Arthralgia	36/538 (6.7)		
Abdominal pain	34/538 (6.3)		
Irritability/confusion	34/538 (6.3)		
Other symptoms (loss of appetite, rhinorrhoea, difficulty of breathing, haemoptysis, conjunctivitis, among others)	74/538 (13.7)		
Diagnosis			
COVID-19 laboratory confirmed (one or more tests)	723/763 (94.7)		
PCR diagnosis	683/758 (90.1)		
SARS-CoV-2 PCR diagnosis	41/758 (5.4)		
CT scan diagnosis	54/758 (7.1)		
Presumptive diagnosis	61/758 (8.0)		
Other diagnosis (chest radiography, rapid antigen test)	17/758 (2.2)		
Radiology at diagnosis			
CT scan	109/642 (17.0)		
Chest radiography	214/642 (33.3)		
CT scan and chest radiography	157/642 (24.5)		
Radiology not done	162/642 (25.2)		
CT scan findings			
Typical ground-glass opacity/opacities, bilateral	126/266 (47.4)		
Typical ground-glass opacity/opacities, unilateral	40/266 (15.0)		
Atypical ground-glass opacity/opacities	56/266 (21.1)		
Typical ground-glass opacity bilateral and atypical ones	6/266 (2.2)		
No COVID-19 lesion(s) (no opacity)	38/266 (14.3)		
Lung function tests at COVID-19 diagnosis			
Lung function tests at COVID-19 diagnosis	401/619 (64.8)		
S_{O_2}, % (n=397)	96 (94–98)		
F_{iO_2}, % (n=269)	21 (21–21)		
P_{O_2}, mmHg (n=99)	80 (63–95)		
P_{CO_2}, mmHg (n=100)	37 (33–41)		
pH (n=100)	7.4 (7.4–7.5)		
Ventilation and oxygen therapy			
No ventilation	513/626 (81.9)		
Noninvasive	67/626 (10.7)		
Invasive	46/626 (7.4)		
Supplemental oxygen during COVID-19	198/619 (32.0)		
Hospitalisation			
Hospitalisation due to COVID-19	452/732 (61.7)		
Duration of hospitalisation, days (n=395)	14 (8–22)		
Concomitant hospitalisation due to TB/COVID-19 co-infection	250/737 (33.9)		
Duration of concomitant hospitalisation, days (n=223)	16 (10–24)		

Continued

TABLE 3 Continued

	All patients	Alive	Deceased
PCR conversion rates			
PCR conversion	271/474 (57.2)		
From start of treatment to PCR conversion, days (n=196)	14.5 (11–22)		
Treatment			
Treatment for COVID-19 (one or more drugs)	346/639 (54.1)		
Antivirals			
Lopinavir/ritonavir	24/336 (7.1)		
Darunavir/cobicistat or darunavir/ritonavir	21/336 (6.2)		
Favipiravir	11/336 (3.3)		
Remdesivir	5/336 (1.5)		
Other antivirals	4/336 (1.2)		
Immunomodulators			
Glucocorticoids (methylprednisolone, betamethasone, ciclesonide, other glucocorticoids)	115/336 (34.2)		
Intravenous immunoglobulin	3/336 (0.9)		
IL-6 inhibitors	2/336 (0.6)		
Bevacizumab (antibody against VEGF-A)	1/336 (0.3)		
Anticoagulants			
Enoxaparin	72/336 (21.4)		
Other therapeutic anticoagulants	22/336 (6.5)		
Miscellaneous			
Azithromycin	212/336 (63.1)		
Hydroxychloroquine	191/336 (56.8)		
N-acetyl-cysteine	22/336 (6.6)		
Plasma from recovered patients	3/336 (0.9)		
Interferon	3/336 (0.9)		
Other nonsteroidal anti-inflammatory drugs	2/336 (0.6)		
Number of comorbidities			
0		339 (49.7)	12 (14.1)
1		196 (28.7)	24 (28.2)
2		97 (14.2)	18 (21.2)
3		29 (4.3)	9 (10.6)
4		15 (2.2)	8 (9.4)
5		2 (0.3)	4 (4.7)
6		2 (0.3)	5 (5.9)
7		1 (0.1)	3 (3.5)
8		1 (0.1)	2 (2.4)

Data are presented as n, n/N (%) or median (interquartile range). SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CT: computed tomography; S_{O_2}: oxygen saturation; F_{iO_2}: fraction of inspired oxygen; P_{O_2}: partial pressure of oxygen; P_{CO_2}: partial pressure of carbon dioxide; IL: interleukin; VEGF-A: vascular endothelial growth factor.

Patients with active TB had higher probability of death (OR 1.5) compared with those with previous TB (table 5).

Clinical outcomes of COVID-19 patients

Out of 767 patients (figure 3), 682 (88.9%) survived and 85 (11.1%) died. Among 682 patients surviving, 379 (55.6%) were hospitalised, of whom 315 were discharged (221 with symptoms resolved, 36 not resolved and 58 with no or unknown symptoms) and 64 were still in hospital at the time of the analysis (two with symptoms resolved, 44 not resolved and 18 with no or unknown symptoms); 265 patients were never hospitalised (119 with symptoms resolved, 32 not resolved and 114 with no or unknown symptoms). No detailed information on hospitalisation was available for 38 patients (two with symptoms resolved, four not resolved and 32 with no or unknown symptoms).

Among the patients who died, 42 (49.4%) out of 85 died from COVID-19; 31 (36.5%) out of 85 from COVID-19 and TB and one (1.2%) out of 85 died from TB only. Among the patients who died for other reasons, five (5.9%) died with COVID-19 (n=2 multiple comorbidities, n=1 presumptive cancer, n=1

TABLE 4 Characteristics of the patients alive or deceased in the coronavirus disease 2019 (COVID-19) cohort and stratification by geographical origin

	Vital status			Geographical location		
	Alive[#]	Deceased[¶]	p-value	Europe	Not Europe	p-value
Patients	682	85		289	478	
Age, years	41 (30–55)	65 (48–77)	<0.0001	49 (36–63)	39 (29–54)	<0.0001
Age ⩾65 years	83 (12.2)	44 (51.8)	<0.0001	68 (23.5)	59 (12.3)	<0.0001
Males	470 (68.9)	70 (82.4)	0.01	209 (72.3)	331 (69.3)	0.37
Non-European	434 (63.6)	44 (51.8)	0.03			
⩾1 comorbidity	343 (50.3)	73 (85.9)	<0.0001	183 (63.3)	233 (48.7)	<0.0001
⩾2 comorbidities	147 (21.6)	49 (57.7)	<0.0001			
Number of comorbidities	1 (0–1)	2 (1–4)	<0.0001			
Diabetes mellitus	125 (18.3)	32 (37.7)	<0.0001	63 (21.8)	94 (19.7)	0.48
Cardiovascular disease	105 (15.4)	41 (48.2)	<0.0001	79 (27.3)	67 (14.0)	<0.0001
Chronic respiratory disease	71 (10.4)	22 (25.9)	<0.0001	46 (15.9)	47 (9.8)	0.01
HIV	68 (10.0)	12 (14.1)	0.14	25 (8.7)	55 (11.5)	0.21
Chronic liver disease	50 (7.3)	10 (11.8)	0.15	47 (16.3)	13 (2.7)	<0.0001
Chronic renal disease	38 (5.6)	15 (17.7)	<0.0001	33 (11.4)	20 (4.2)	<0.0001
Invasive ventilation	15 (2.7)	31 (41.3)	<0.0001	14 (5.0)	32 (9.3)	0.04
Previous TB	200 (30.2)	34 (40.0)	0.07	79 (27.7)	155 (33.6)	0.09
Hospitalisation due to COVID-19	381 (59.0)	71 (83.5)	<0.0001	220 (76.4)	232 (52.3)	<0.0001
Duration of hospitalisation, days	14 (8–22)	10 (4–24)	0.007	14 (9–22)	13 (6–24)	0.11
Concomitant hospitalisation due to TB/COVID-19 co-infection	216 (31.7)	34 (40.0)	0.19	136 (31.7)	114(40.0)	0.005
Duration of concomitant hospitalisation	16 (10–24)	8 (4–20)	0.11	16 (11–22)	14 (6–26)	0.36
Death				41 (14.2)	44 (9.2)	0.03
Death at age ⩾65 years				26/41 (63.4)	18/44 (40.9)	0.04
Age of patients who died, years				70 (59–80.5)	57.5 (44.3–71.8)	0.004
Dead with ⩾1 comorbidity				38/183 (20.8)	35/233 (15.0)	0.13
Dead with diabetes mellitus				19/63 (30.2)	13/94 (13.8)	0.01
Dead with cardiovascular disease				26/79 (32.9)	15/67 (22.4)	0.16
Dead with chronic respiratory disease				13/46 (28.3)	9/47 (19.2)	0.30
Dead with HIV				3 (12.0)	9 (16.4)	0.61
Dead with chronic liver disease				7/47 (14.9)	3/13 (23.1)	0.68
Dead with chronic renal disease				11/33 (33.3)	4/20 (20.0)	0.30
Dead with active TB				20/206 (9.7)	31/307 (10.1)	0.89

Data are presented as n, median (interquartile range) or n/N (%), unless otherwise stated. TB: tuberculosis. [#]: all patients in the cohort based on the latest information available (see text and figure 3 for details); [¶]: all patients who died based on the latest information available. The detailed causes of death are reported in the text and in figure 3.

sarcoidosis, n=1 HIV); the remaining six (7.0%) died after resolution of COVID-19 (n=2 sepsis, n=2 multiple comorbidities, n=1 pneumonia, n=1 pulmonary thromboembolism).

Discussion

Our study described, for the first time, the features of the TB and COVID-19 co-infected individuals in a large cohort of 767 patients from 172 centres in 34 countries with specific focus on the risk factors for mortality and other outcomes.

The main characteristics of the cohort confirmed our previously described findings from the pilot study [18]: the patients are young (median age 44 years), and the majority are male, with drug-susceptible pulmonary TB. The commonest symptoms reported were fever, dry cough and dyspnoea, with approximately one out of 10 patients with typical symptoms for COVID-19 (olfactory and taste disorders). The majority of patients who underwent CT imaging presented typical or atypical ground-glass opacities, confirming the relevance of this radiological sign for the diagnosis of COVID-19 [25], which co-exist with the radiological features of TB (cavities and infiltrates).

Interestingly, 74% of the patients had TB diagnosed before COVID-19 (including 234 patients with previous TB, corresponding to 31.3% of the whole cohort); 16.5% were diagnosed within the same week (the presence of signs and symptoms prompted the clinicians to undertake imaging, which revealed potentially pre-existing TB on top of COVID-19) [18]; and 9.5% had COVID-19 diagnosed first.

TABLE 5 Logistic regression analysis to assess the relationship between demographic, epidemiological, clinical variables and mortality

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years (10-year increase)	1.82 (1.58–2.09)	<0.0001	1.93 (1.60–2.32)	<0.0001
Male (yes *versus* no)	2.08 (1.16–3.71)	0.014	2.92 (1.38–6.16)	0.005
⩾1 comorbidity (yes *versus* no)	6.01 (3.21–11.27)	<0.0001		
Diabetes mellitus (yes *versus* no)	2.69 (1.67–4.35)	<0.0001		
Cardiovascular disease (yes *versus* no)	5.12 (3.19–8.22)	<0.0001		
Chronic respiratory disease (yes *versus* no)	3.00 (1.74–5.18)	<0.0001		
HIV (yes *versus* no)	1.48 (0.77–2.87)	0.241		
Chronic liver disease (yes *versus* no)	1.69 (0.82–3.46)	0.155		
Chronic renal disease (yes *versus* no)	3.00 (1.74–5.18)	<0.0001		
Invasive ventilation (yes *versus* no)	25.18 (12.64–50.13)	<0.0001	28.22 (1.37–64.39)	<0.0001
Active TB (yes *versus* no)	1.5 (1.0–2.5)	0.069		
Presence of key symptoms (yes *versus* no)	49.3 (19.7–123.9)	<0.0001		
Hospitalisation due to COVID-19 (yes *versus* no)	3.54 (1.95–6.41)	<0.0001		
Duration of hospitalisation (1-day increase)	0.98 (0.96–1.01)	0.072		
Europe (yes *versus* no)	1.63 (1.04–2.57)	0.034		

Multivariable model −2 log likelihood: 301.6, p<0.0001; percentage of cases correctly classified: 91%; area under the curve: 0.89 (0.86–0.91). TB: tuberculosis; COVID-19: coronavirus disease 2019.

A key question from our preliminary study [18] was on the role of SARS-CoV-2 in the progression of TB infection to disease as observed in other viral diseases (*e.g.* HIV) [5, 18]. While our study is not specifically designed to answer this question, we found 71 patients who had COVID-19 diagnosed before TB; of these, 35 were diagnosed >30 days prior (with sufficient time to develop TB disease) and 33 had pulmonary TB. Of 25 patients with complete radiological information, 12 (48%) had cavities, a condition which is likely to develop in >30 days. Therefore, this indirect evidence from our data suggests that

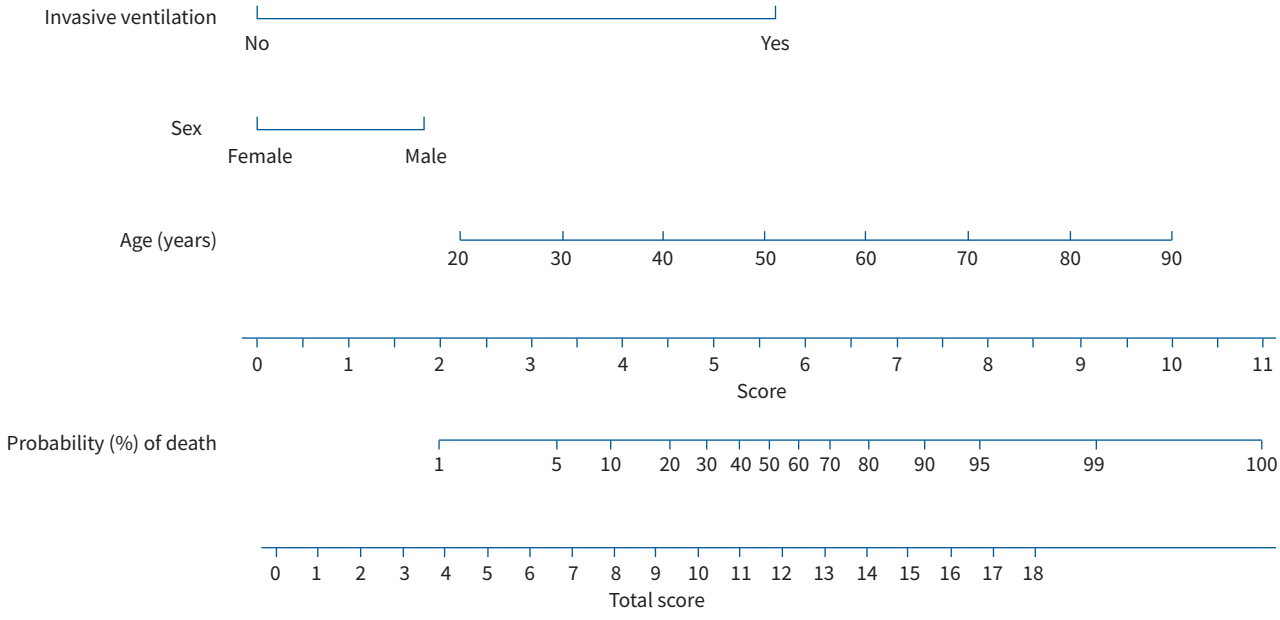

FIGURE 2 Nomogram for the estimation of the risk of death, generated on the basis of the multivariable logistic regression analysis. As depicted, each indicator is measured, and the corresponding points are assigned using the row "score". Thus, the sum is reported on the row "total score", and the corresponding probability of the outcome is identified in the row "probability (%) of death". As an example on how to use this nomogram, an 80-year-old woman not requiring invasive ventilation would have a probability of death <20%. In contrast, an 80-year-old woman requiring invasive ventilation during hospitalisation would have a probability of death >80%.

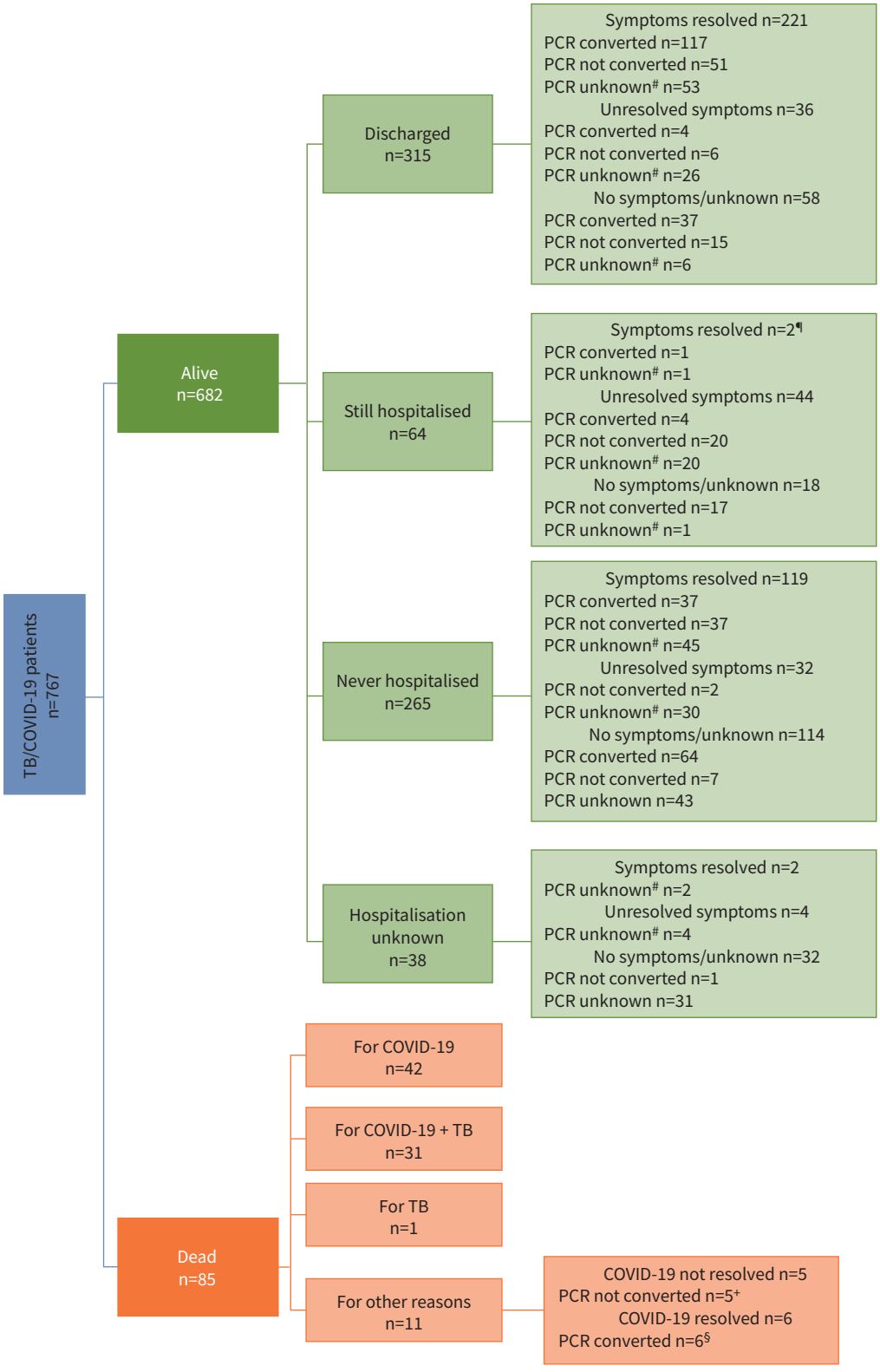

FIGURE 3 Clinical outcome of coronavirus disease 2019 (COVID-19) among tuberculosis (TB)/COVID-19 patients. #: including patients with PCR not done; ¶: n=2 with symptoms resolved remain hospitalised for TB; +: n=2 for multiple comorbidities, n=1 for suspected cancer, n=1 for sarcoidosis, n=1 for HIV; §: n=2 for sepsis, n=2 for multiple comorbidities, n=1 for bilateral Gram-negative nosocomial pneumonia, *Morganella morganii*, n=1 for pulmonary thromboembolism (with COVID-19 clinically diagnosed and PCR unknown).

COVID-19 may not have a major role in advancing TB infection to TB disease. Further longitudinal studies observing the patients with TB infection and COVID-19 over time and comparing the proportion of those who acquire TB disease with a control group without COVID-19 may offer better insight to an interaction.

The TB/COVID-19 patients with higher mortality were male, belonged to older age groups and underwent invasive ventilation, with more comorbidities than those with no need for (invasive) ventilation. These determinants of death are similar to those described for mono-disease COVID-19 or TB [4, 26].

Another important question arising from previous studies [10, 14, 18, 27] relates to the resources required for managing patients with TB and COVID-19. The study results indicate that an important proportion of patients needed ventilation (18%, of whom 7.4% required intubation) and 32% supplemental oxygen, the vast majority during hospitalisation (61.7% of the patients required a median of 14 days of admission because of COVID-19, in addition to those needed for TB). The need for competent staff to manage TB/COVID patients with respiratory failure has been a problem in several countries, where clinicians working within the TB programme were redeployed to work within the COVID-19 emergency [6–9, 14]. Evidence is continuing to emerge on the negative impact of COVID-19 on TB services [9, 28]. A recent global study indicates a significant decline in TB and TB infections diagnosed, with an increase of telemedicine use in 2020 in comparison with 2019 [9]. Reduction in the performance of global TB detection and care due to COVID-19 pandemic are expected to have devastating impact on TB mortality [29].

An issue that has recently gained increasing interest is that of post-TB lung disease (PTLD), as 13–68% of new TB cases and 75–96% of patients with multidrug-resistant TB completing anti-TB treatment suffer from TB sequelae [30, 31]. This condition [30–36] includes obstructive, restrictive or mixed-pattern lung function abnormalities, reduced exercise capacity and impaired quality of life. A summary of clinical standards to adequately manage PTLD, which includes post-treatment evaluation and identification of patients with sequelae likely to benefit from pulmonary rehabilitation, has been published recently [36].

Similarly, COVID-19 appears to commonly cause sequelae (the so-called “long-COVID” syndrome) [37–39], characterised by fatigue, sleeping difficulties, low grade fever, depression, anxiety, impacting cardiac, pulmonary and renal functions, and discussions are ongoing on the potential role of post-COVID-19 rehabilitation [14, 40–42].

A combination of post-COVID-19 and PTLD sequelae and the need for assessment and potential follow-up and rehabilitation can pose additional stress on health services in terms of human and economic resources.

Our study has several strengths, including a large sample size and the inclusion of countries from all continents. Furthermore, several variables collected in our study are not routinely collected in the surveillance systems at country level, making the study important to better understand the TB/COVID-19 interactions and to design *ad hoc* studies aimed at answering specific outstanding questions. Furthermore, approximately half of the countries/territories (18 out of 34) provided population-based data representative of their respective TB/COVID patients.

Among the main study limitations, Africa and Asia were under-represented; the number of paediatric patients was limited (six patients, two of them aged <1 year); some centres were unable to provide all the information requested on a few variables (particularly laboratory data); and ~10% of the patients had COVID-19 diagnosed based on the clinical and radiological findings, following the respective countries’ policy during the emergency phases of the pandemic. The timing of our study does not allow comment on the differential impact of emerging SARS-CoV-2 variants and TB, which will require ongoing monitoring and review.

In addition, as the cohort was composed of TB and COVID-19 patients, it was not possible undertake a comparative analysis against patients with TB or COVID-19 alone. In addition, it was not possible to draw conclusions on the effect of the different drugs prescribed, and we note that our cohort was prescribed a range of therapies by treating clinicians, including some now demonstrated to have no impact on COVID-19 outcomes. Future studies looking at the cohort will be able to examine the effect of steroids or monoclonal antibodies.

Furthermore, it was not possible to perform the analysis of TB-specific outcomes as an important proportion of patients are still undergoing anti-TB treatment.

The study will continue to evaluate early and final anti-TB treatment outcomes through periodic updates, as to make the "cohort" a "living" one.

Conclusions

This first description of a large global cohort provides important information for clinical and public health management of patients co-infected by TB and COVID-19. The similarity of signs and symptoms for the two diseases has been confirmed alongside the importance of the radiological presence of ground-glass opacities for the diagnosis of COVID-19. Preliminary information seems to suggest that COVID-19 is unlikely to represent a major determinant triggering TB infection to active TB.

The high (12%) mortality of co-infected patients may be explained by older age and male gender, with an important contribution also played by comorbidities (particularly cardiovascular disease and diabetes mellitus). The reason why males died more than females may be explained by the potential higher prevalence of comorbidities and risk factors.

Efforts to prevent SARS-CoV-2 infection in TB patients is warranted, including reinforcing of social distancing, mask wearing and other measures as appropriate to local epidemiology. Encouraging vaccination against SARS-CoV-2 for people with a current or past diagnosis of TB will also be valuable in preventing morbidity and mortality related to COVID-19 disease.

The combination of COVID-19 and TB adds to the clinical complexity in patient management (*e.g.* need for supplemental oxygen, invasive or noninvasive ventilation and specialised staff), significantly impacting health services. The impact of COVID-19 on long-term pulmonary sequelae in patients with TB and the need for pulmonary rehabilitation is yet to be determined.

As patients reported similar symptoms, it advisable for health services to screen patients for both diseases whenever possible, taking advantage of the possibility to obtain imaging rapidly, and stimulating adoption of rapid molecular testing for TB and COVID-19. Although our study does not provide specific data on this, it seems clinically advisable to treat both conditions as soon as possible following international recommendations.

Last, but not least, the experience gained during the COVID-19 pandemic will allow us to make better use of telemedicine interventions, thus reducing the burden of physical access to health services and transmission. Unnecessary hospitalisation should be actively discouraged [7, 9, 27].

Overall, the data suggest that TB and COVID-19 are a "cursed duet" and need immediate attention.

Acknowledgement: The project is supported by the Global Tuberculosis Network (GTN). This article belongs to the scientific activities of the WHO Collaborating Centre for Tuberculosis and Lung Diseases, Tradate, ITA-80, 2020–2024- GBM/RC/LDA.

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Conflict of interest: None declared.

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