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GLOBAL TUBERCULOSIS NETWORK AND TB/COVID-19 GLOBAL STUDY GROUP

Long-term outcomes of the global tuberculosis and COVID-19 co-infection cohort

Global Tuberculosis Network and TB/COVID-19 Global Study Group

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Shareable abstract (@ERSpublications)
In 778 TB/COVID-19 co-infected patients, 77% TB treatment success and 11% TB mortality was observed, with 71% recovering from COVID-19 and 13% COVID-19-associated mortality. Mortality was higher in those diagnosed with COVID-19 before/during TB treatment. https://bit.ly/3PQSw17

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Abstract

Background Longitudinal cohort data of patients with tuberculosis (TB) and coronavirus disease 2019 (COVID-19) are lacking. In our global study, we describe long-term outcomes of patients affected by TB and COVID-19.

Methods We collected data from 174 centres in 31 countries on all patients affected by COVID-19 and TB between 1 March 2020 and 30 September 2022. Patients were followed-up until cure, death or end of cohort time. All patients had TB and COVID-19; for analysis purposes, deaths were attributed to TB, COVID-19 or both. Survival analysis was performed using Cox proportional risk-regression models, and the log-rank test was used to compare survival and mortality attributed to TB, COVID-19 or both.

Results Overall, 788 patients with COVID-19 and TB (active or sequelae) were recruited from 31 countries, and 10.8% (n=85) died during the observation period. Survival was significantly lower among patients whose death was attributed to TB and COVID-19 *versus* those dying because of either TB or COVID-19 alone ($p<0.001$). Significant adjusted risk factors for TB mortality were higher age (hazard ratio (HR) 1.05, 95% CI 1.03–1.07), HIV infection (HR 2.29, 95% CI 1.02–5.16) and invasive ventilation (HR 4.28, 95% CI 2.34–7.83). For COVID-19 mortality, the adjusted risks were higher age (HR 1.03, 95% CI 1.02–1.04), male sex (HR 2.21, 95% CI 1.24–3.91), oxygen requirement (HR 7.93, 95% CI 3.44–18.26) and invasive ventilation (HR 2.19, 95% CI 1.36–3.53).

Conclusions In our global cohort, death was the outcome in >10% of patients with TB and COVID-19. A range of demographic and clinical predictors are associated with adverse outcomes.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has significantly affected tuberculosis (TB) services worldwide [1]. Globally, national TB programmes struggled to provide care, resulting in an unprecedented interruption of essential services. Studies have demonstrated that access to TB care has worsened during the pandemic [2–6]. The World Health Organization (WHO) reported an overall decrease in TB notifications, from 7.1 million in 2019 to 5.8 million in 2020, with a partial recovery in 2021, and an additional 100 000 TB deaths between 2019 and 2020 [1].

Since the beginning of the pandemic, TB and COVID-19 co-infected cases have been described: they can occur concomitantly, or COVID-19 can precede TB or occur in patients with TB sequelae. Both diseases primarily affect the lungs and share similar symptoms, such as fever and cough, posing diagnostic challenges and delayed diagnosis [7]. COVID-19 and TB co-infection may lead to severe acute illness [8–11]. Studies have demonstrated that concomitant TB and COVID-19 increase mortality and chronic lung sequelae [12, 13].

Despite studies suggesting synergistic amplification of mortality related to co-infection, no cohort studies have evaluated the effects of COVID-19 on long-term TB outcomes or *vice versa*, particularly since TB

treatment outcomes were generally not reported in previous publications [9, 10, 14]. The first published report from the Global TB–COVID-19 cohort did not provide final TB outcomes, because many patients were still undergoing anti-TB treatment [10]. The objectives of this study were to evaluate the long-term outcomes and risk factors for the mortality of TB–COVID-19 patients in a global cohort.

Methods

We conducted a prospective, multicountry study. In collaboration with the WHO, invitations were sent to 174 centres in 31 countries from all continents [10]. The centres and countries providing data are listed in figure 1 and the supplementary material. Patients of any age, with either active or previous TB disease and COVID-19 were enrolled from 1 March 2020 and followed up until 30 September 2022. Both hospitalised and community-treated patients were included. All TB patients were included at the time of COVID-19 diagnosis and COVID-19 patients were included when TB diagnosis was made. TB and COVID-19 case definitions follow WHO classification [1, 15]. We define previous TB patients as those who had TB and completed anti-TB treatment at any time in the past before the diagnosis of COVID-19. The coordinating centre (Istituti Clinici Scientifici Maugeri, Tradate, Italy) and the participating clinics had ethics clearance in accordance with their institutional regulations.

Clinical data were collected *via* a standardised electronic form. Previously validated WHO TB outcomes were used [1]. The causes of death were attributed to TB; to TB+COVID-19; to TB+COVID-19+other cause; to COVID-19; or any other cause. COVID-19 outcomes were categorised as recovery; non-recovery (*e.g.* patients still in the acute phase or still with a positive test and/or symptoms); or death [16]. Recovered cases were stratified as discharged; never hospitalised for COVID-19; hospitalised for reasons other than TB and/or COVID-19; or unknown hospitalisation (*e.g.* when it is not known whether the patient was hospitalised or not). Non-recovered cases were subcategorised as discharged; never hospitalised for COVID-19; diagnosis during hospitalisation for other reasons; still hospitalised for COVID-19 non-recovered; or unknown hospitalisation.

The proportions of death from TB, from COVID-19 and for any reason were calculated by geographical regions as follows: Latin America (Argentina, Brazil, Chile, Colombia, Honduras, Mexico, Paraguay and

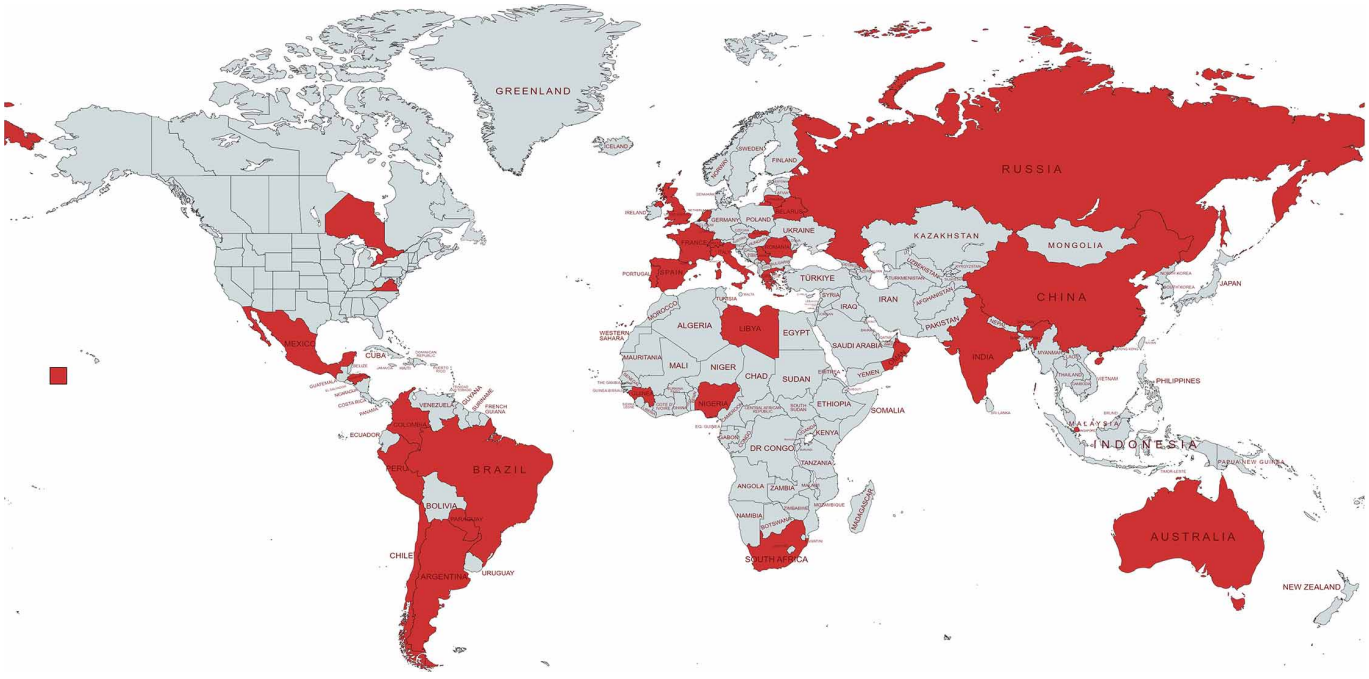


FIGURE 1 Global distribution of the countries/states/regions participating in the study. The following states/territories are covered in the study update: Australia (New South Wales); Canada (Ontario state); China (Wenzhou and Luzhou regions); India (New Delhi, Mumbai and Maharashtra states); Russian Federation (Arkhangelsk, Moscow and Volvograd oblasts); Switzerland (Vaud county); USA (Virginia state). 29 out of 34 countries participating in the first global study [10] provided treatment outcome updates and two countries (Nigeria and Libya) were enrolled in the study at a later stage, providing data with treatment outcomes.

Peru); North America, Western and Central Europe plus Oman in the Eastern Mediterranean Region (Canada, France, Italy, Lithuania, the Netherlands, Oman, Portugal, Romania, Serbia, Slovakia, Spain, Switzerland, UK and USA); Eastern Europe (Belarus and Russian Federation); Africa (Guinea, Libya, Nigeria and South Africa); and Asia (China, India and Singapore).

Geographic groupings were chosen with consideration for epidemiological similarities, as validated in the previous study of the Global TB–COVID-19 cohort [1, 10].

Data analysis was performed using IBM SPSS Statistics (version 22.0; IBM Corporation, Armonk, NY, USA). Data were presented as number of cases, mean±SD or median and interquartile range (IQR) for non-normally distributed data. Categorical comparisons were performed by Chi-squared test using Yates's correction, or Fisher's exact test. Continuous variables were compared using the t-test or Wilcoxon test. Kaplan–Meier curves were used for cumulative survival analyses, and the log-rank test was used to compare the survival of TB, COVID-19 and TB+COVID-19. Survival analysis was performed using Cox proportional risk-regression models: 1) events were defined as death from TB or COVID-19; 2) we censored data if no events occurred at the end of the follow-up period (30 September 2022). All statistically significant variables in the univariate analysis were selected to be included in the Cox regression. We did a stepwise variable selection procedure in order to find the best model. Hazard ratios and 95% confidence intervals are presented. A two-sided p-value <0.05 was considered significant for all analyses.

Results

Overall, 788 patients with TB and COVID-19 were enrolled from 31 countries; 29 of the 34 countries which participated in the first global treatment outcome study provided updates and two additional countries were included (Libya and Nigeria; suplementary material). The mean±SD age was 45.5±18.3 years; 533 (67.8%) patients were male; 83 (10.7%) were HIV co-infected; and 80 (11.9%) had drug-resistant TB. 303 (38.5%) patients needed hospitalisation due to TB and 349 (44.3%) due to COVID-19; 16 (2.0%) patients needed mechanical ventilation due to TB and 35 (4.4%) due to COVID-19; 87 (11.0%) patients needed supplemental oxygen due to TB and 151 (19.2%) due to COVID-19.

Out of 788 patients, information on the time of TB and COVID-19 diagnosis was available in 777 (98.6%) (table 1). For 282 (36.3%) out of 777 patients, the diagnosis of COVID-19 followed the end of TB treatment. Of them, 204 (72.3%) had completed TB treatment >1 year earlier (range 1–79 years), while for the remaining 78 (27.7%) patients the median (IQR) time from the end of TB treatment to COVID-19 diagnosis was 5 (3–8) months.

Among the 495 patients who had COVID-19 diagnosed before or during TB treatment, 125 (25.3%) had both diseases diagnosed within the same week; 296 (59.8%) had COVID-19 diagnosed before the start of

TABLE 1 Summary of anti-tuberculosis (TB) treatment outcomes in 788 patients, stratified by time of coronavirus disease 2019 (COVID-19) diagnosis after the end of TB treatment *versus* before or during TB treatment

	TB patients	COVID-19 diagnosis[#]		p-value
		After the end of TB treatment	Before or during TB treatment	
Cured	284 (36)	109 (38.7)	172 (34.7)	0.311
Treatment completed	324 (41.1)	147 (52.1)	173 (34.9)	<0.0001
Treatment successful	608 (77.2)	256 (90.8)	345 (69.7)	<0.0001[¶]
Died	85 (10.8)		83 (16.8)	
Cause of death				
TB	17/85 (20)		15/83 (18.1)	
TB+COVID-19	46/85 (54.1)		46/83 (55.4)	
TB+COVID-19+other	4/85 (4.7)		4/83 (4.87)	
COVID-19	9/85 (10.6)		9/83 (10.8)	
Other	9/85 (10.6)		9/83 (10.8)	
Failure	3 (0.4)	1 (0.4)	2 (0.4)	0.620
Lost to follow-up	92 (11.7)	25 (8.9)	65 (13.1)	0.094
Total	788	282/777	495/777	

Data are presented as n (%), n/N (%) or n, unless otherwise stated. [#]: for 11 out of 788 patients, data were unavailable on timing of COVID-19 diagnosis in relation to TB treatment; [¶]: baseline TB treatment success was significantly higher when the diagnosis of COVID-19 occurred after the end of TB treatment (90.8%), in comparison with cases where the diagnosis was made before or during TB treatment (69.7%) (p<0.0001).

TB treatment (median 3 months, IQR 1.4–4.9 months) and 74 (14.9%) had COVID-19 diagnosed during TB treatment (median time from TB treatment start 1.1 months, IQR 0.5–1.6 months).

TB and COVID-19 outcomes are shown in relation to COVID-19 diagnosis (if COVID-19 diagnosis was after the end of anti-TB treatment, or before or during anti-TB treatment) in tables 1 and 2. TB outcomes were available for all patients (table 1) and COVID-19 outcomes were available for 778 patients (table 2).

Recovery from COVID-19 was more frequent when COVID-19 diagnosis was before or during TB treatment than when it was after the end of TB treatment (76.3% *versus* 60.1%; p<0.0001). Non-recovery of COVID-19 cases was higher among patients with COVID-19 diagnosis after the end of TB treatment (26.8%) than in those with COVID-19 diagnosis before or during TB treatment (10.3%) (p<0.0001).

The factors associated with TB mortality (table 3) in univariate analysis were older age (HR 1.04, 95% CI 1.03–1.04; p<0.0001), HIV infection (HR 2.92, 95% CI 1.65–5.18; p<0.0001), COPD (HR 2.66, 95% CI 1.39–5.06; p=0.004), diabetes mellitus (HR 2.25, 95% CI 1.37–3.67; p=0.002), renal failure (HR 3.26, 95% CI 1.64–6.45; p=0.001), liver disease (HR 2.31, 95% CI 1.17–4.58; p=0.025), supplemental oxygen needed during COVID-19 (HR 7.31, 95% CI 3.86–13.83; p<0.0001) and invasive ventilation (HR 7.02, 95% CI 3.52–13.99; p<0.0001). In Cox regression analysis, the variables independently associated with TB mortality were age (HR 1.05, 95% CI 1.03–1.07; p<0.0001), HIV infection (HR 2.29, 95% CI 1.02–5.16; p=0.044) and invasive ventilation (HR 4.28, 95% CI 2.34–7.83; p<0.0001).

Risk factors associated with COVID-19 mortality (table 3) in univariate analysis were older age (HR 1.03, 95% CI 1.02–1.04; p<0.0001), male sex (HR 1.66, 95% CI 1.02–2.69; p=0.050), COPD (HR 2.51, 95% CI 1.36–4.63; p=0.004), diabetes mellitus (HR 2.68, 95% CI 1.71–4.22; p<0.0001), renal failure (HR 5.26, 95% CI 2.83–9.78; p<0.0001), having COVID-19 signs and symptoms (HR 4.18, 95% CI 1.79–9.77; p=0.001), supplemental oxygen needed during COVID-19 (HR 25.33, 95% CI 12.28–52.26; p<0.0001) and invasive ventilation (HR 28.28, 95% CI 13.68–58.47; p<0.0001). In Cox regression analysis, the factors independently associated with COVID-19 mortality were age (HR 1.03, 95% CI 1.02–1.04; p<0.0001), male sex (HR 2.21, 95% CI 1.24–3.91; p=0.007), supplemental oxygen needed during COVID-19 (HR 7.93, 95% CI 3.44–18.26; p<0.0001) and invasive ventilation (HR 2.19, 95% CI 1.36–3.53; p=0.001).

TABLE 2 Coronavirus disease 2019 (COVID-19) outcomes (known in 778 patients) stratified by time of COVID-19 diagnosis (after the end of anti-tuberculosis (TB) treatment *versus* before or during anti-TB treatment)

	COVID-19 patients	COVID-19 diagnosis[#]		p-value
		After the end of TB treatment	Before or during TB treatment	
Recovered	551 (70.8)	166 (60.1)	377 (76.3)	<0.0001
Discharged	261 (47.4)	77 (46.4)	183 (48.5)	
Never hospitalised for COVID-19	164 (29.8)	49 (29.5)	108 (28.6)	
Diagnosis during hospitalisation for other reasons	74 (13.4)	3 (1.8)	71 (18.8)	
Unknown hospitalisation	52 (9.4)	37 (22.3)	15 (4.0)	
Non-recovered	125 (16.1)	74 (26.8)	51 (10.3)	<0.0001
Discharged[¶]	24 (19.2)	20 (27.0)	4 (7.8)	
Never hospitalised for COVID-19	10 (8.0)	3 (4.1)	7 (13.7)	
Diagnosis during hospitalisation for other reasons	2 (1.6)		2 (3.9)	
Still hospitalised for COVID-19	4 (3.2)	1 (1.4)	3 (5.9)	
Unknown hospitalisation	85 (68.0)	50 (67.6)	35 (68.6)	
Cause of death	102 (13.1)	36 (13.0)	66 (13.4)	0.980
TB	1 (1.0)		1 (1.5)	
TB+COVID-19	46 (45.1)		46 (69.7)	
TB+COVID-19+other	4 (3.9)		4 (6.1)	
COVID-19	38 (37.3)	29 (80.6)	9 (13.6)	
COVID-19+other	6 (5.9)	6 (16.7)		
Other	7 (6.9)	1 (2.8)	6 (9.1)	
Total[+]	778/788	276/770	494/770	

Data are presented as n (%) or n/N, unless otherwise stated. [#]: for eight out of 778 patients, data were unavailable on timing of COVID-19 diagnosis in relation to TB treatment; [¶]: one patient with voluntary discharge; [+]: 10 patients had unknown COVID-19 outcomes.

TABLE 3 Univariate analysis of factors associated with tuberculosis (TB) and coronavirus disease 2019 (COVID-19) mortality

	TB deaths			COVID-19 deaths			Overall deaths		
	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Age years	57.0±18.9	44.1±17.8	<0.0001	61.6±18.4	42.9±17.0	<0.0001	60.2±18.3	42.8±17.0	<0.0001
Male	63 (74.1)	470 (67.0)	0.232	78 (76.5)	446 (66.2)	0.050	91 (75.2)	442 (66.5)	0.074
BCG vaccinated	31 (93.9)	290 (89.8)	0.757	36 (92.3)	285 (89.9)	0.782	43 (93.5)	278 (89.7)	0.597
Alcohol abuse	14 (20.3)	95 (14.9)	0.315	13 (14.8)	95 (15.5)	0.976	15 (15.2)	94 (15.5)	0.999
Active smoker	18 (28.1)	168 (28.1)	0.999	21 (25.9)	164 (28.4)	0.744	23 (24.7)	163 (28.6)	0.513
Intravenous drug user	1 (1.5)	6 (1.0)	0.516	1 (1.1)	6 (1.0)	0.999	1 (1.0)	6 (1.0)	0.999
HIV	19 (22.9)	64 (9.2)	<0.0001	16 (15.8)	67 (10.1)	0.116	21 (17.9)	62 (9.4)	0.010
COPD	14 (16.7)	49 (7.0)	0.004	16 (15.8)	47 (7.0)	0.004	20 (16.9)	43 (6.4)	<0.0001
Diabetes mellitus	28 (32.9)	126 (17.9)	0.002	36 (35.3)	114 (16.9)	<0.0001	43 (35.5)	111 (16.7)	<0.0001
Renal failure	13 (16.5)	36 (5.7)	0.001	20 (20.4)	28 (4.7)	<0.0001	23 (20.5)	26 (4.3)	<0.0001
Liver disease	12 (15.4)	46 (7.3)	0.025	11 (11.3)	47 (7.8)	0.331	14 (12.6)	44 (7.4)	0.096
Pulmonary TB	76 (89.4)	579 (83.3)	0.197	87 (87.0)	558 (83.3)	0.427	104 (87.4)	551 (83.4)	0.332
Extrapulmonary TB	20 (25.0)	188 (27.4)	0.751	23 (24.5)	184 (27.8)	0.586	27 (24.5)	181 (27.5)	0.589
Drug-resistant TB[#]	11 (17.5)	69 (11.3)	0.216						
COVID-19 signs and symptoms				89 (93.7)	465 (78.0)	0.001	104 (94.5)	452 (77.5)	<0.0001
Supplemental oxygen during COVID-19	40 (74.1)	147 (28.1)	<0.0001	70 (88.6)	117 (23.5)	<0.0001	72 (81.8)	115 (23.5)	<0.0001
Invasive ventilation	16 (27.6)	28 (5.1)	<0.0001	32 (40.0)	12 (2.3)	<0.0001	32 (34.8)	12 (2.4)	<0.0001
Antivirals				8 (14.0)	54 (21.3)	0.288			
Immunomodulators				2 (3.5)	3 (1.2)	0.229			

Data are presented as mean±SD or n (%), unless otherwise stated. BCG: bacille Calmette–Guérin. [#]: even analysing only patients with active TB, there was no difference between groups (11 (16.2%) died *versus* 59 (14.6%) who did not die; p=0.885).

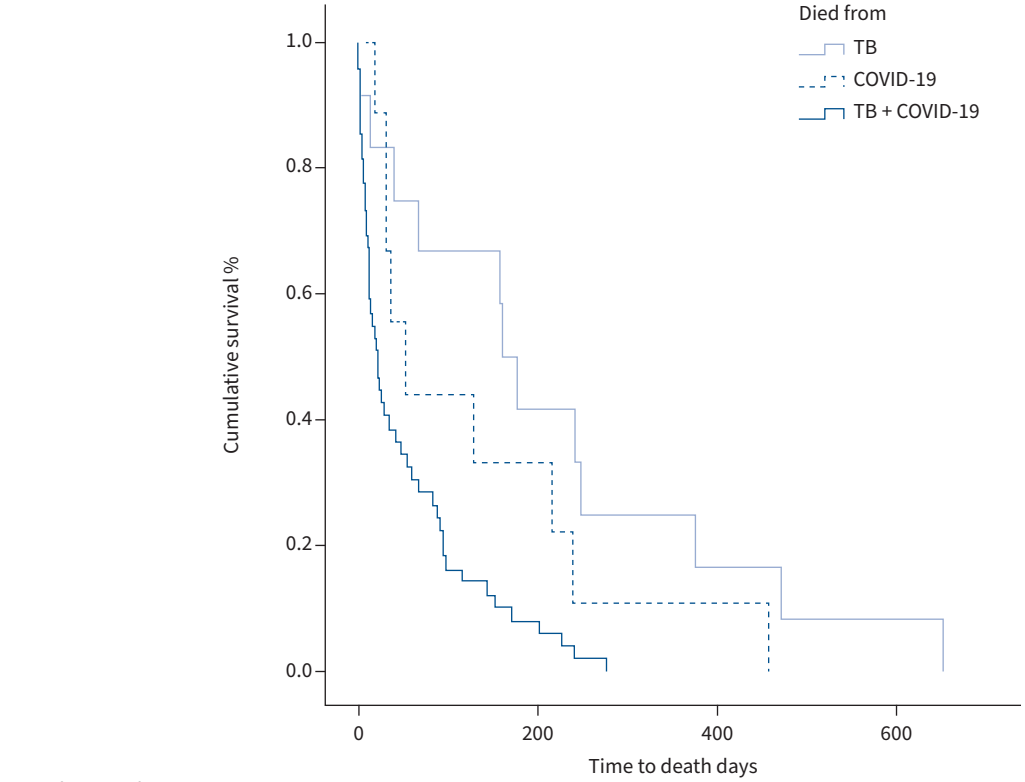
The factors associated with overall mortality (table 3) in the univariate analysis were older age (HR 1.03, 95% CI 1.02–1.03; p<0.0001), HIV infection (HR 2.06, 95% CI 1.20–3.53; p=0.010), COPD (HR 2.89, 95% CI 1.64–5.12; p<0.0001), diabetes mellitus (HR 2.76, 95% CI 1.80–4.21; p<0.0001), renal failure (HR 5.54, 95% CI 3.03–10.13; p<0.0001), having COVID-19 signs and symptoms (HR 5.02, 95% CI 2.16–11.70; p<0.0001), supplemental oxygen needed during COVID-19 (HR 14.64, 95% CI 8.19–26.16; p<0.0001) and invasive ventilation (HR 22.13, 95% CI 10.82–45.27; p<0.0001). In the Cox regression analysis, the factors independently associated with overall mortality were age (HR 1.03, 95% CI 1.02–1.05; p<0.0001), supplemental oxygen needed during COVID-19 (HR 3.77, 95% CI 1.98–7.17; p<0.0001) and invasive ventilation (HR 2.28, 95% CI 1.39–3.72; p=0.001).

Figure 2 shows the comparison of Kaplan–Meier survival curves of patients whose death was attributed to TB alone (median time to death 168.0 days, IQR 45.3–342.8 days), COVID-19 alone (median time to death 52.0 days, IQR 30.5–227.5 days) or a combination of TB and COVID-19 (median time to death 21.0 days, IQR 8.0–90.0 days). The log-rank test for the comparison of the three groups was statistically significant (p=0.001).

In total, 341 patients from Latin America, 289 from North America, Western Europe and the Middle East, 59 from Eastern Europe, 35 from Africa and 64 from Asia were included. Table 4 shows patient characteristics according to the geographical region. Patients from North America, Western Europe and the Middle East were older, had a lower percentage of HIV and invasive ventilation and a higher rate of hospitalisation. Latin America had a higher percentage of HIV, and lower percentages of drug-resistant TB and hospitalised patients. Asia had higher percentage of males, drug-resistant TB and hospitalised patients, and lower percentages of HIV and use of supplemental oxygen during COVID-19. Africa had a lower percentage of hospitalised patients.

Discussion

In our global cohort, we evaluated death and other long-term outcomes of patients with TB and COVID-19. Among all included patients, we found a TB treatment success rate of 77.2%, and a 10.8% mortality. Conversely, most COVID-19 cases (70.8%) recovered, with 13.1% deaths. TB treatment success and completion of treatment was greater when the diagnosis of COVID-19 occurred after the end of TB treatment; that is, when the diagnosis of the two diseases was not concomitant. Conversely, most patients who died were in the group in which the COVID-19 diagnosis was before/during TB treatment, underscoring that concomitant TB and COVID-19 is associated with greater severity and worse outcomes



Number at risk				
Died from TB	12	5	2	1
Died from COVID-19	9	3	1	0
Died from TB + COVID-19	49	4	0	0

FIGURE 2 Kaplan–Meier survival curves of tuberculosis (TB) deaths, coronavirus disease 2019 (COVID-19) deaths and TB+COVID-19 deaths. Log-rank test: p=0.001.

and faster median time to death (figure 2). We have already shown that TB and COVID-19 co-infection may be associated with more severe clinical conditions than either disease alone [9, 10, 12] and with a T-cell impairment to *in vitro* response to severe acute respiratory syndrome coronavirus 2 [17, 18]. Boulle *et al*. [12] demonstrated that patients with TB and COVID-19 have a mortality risk up to 2.7 times higher compared to patients with COVID-19 without TB. Our mortality rate is similar to those found in our previous cohorts of patients co-infected with TB and COVID-19, of 11% [10] and 12.3% [9]. In addition,

TABLE 4 Deaths from tuberculosis (TB), coronavirus disease 2019 (COVID-19) and deaths for any reason (overall deaths) according to the geographical region

	Latin America	North America, Western Europe and the Middle East	Eastern Europe	Africa	Asia	p-value
Age years	41.7±17.7	51.7±18.8	44.6±16.1	42.5±16.1	39.8±14.4	<0.0001
Male	224 (66.1)	193 (66.8)	43 (72.9)	20 (57.1)	53 (82.8)	0.045
HIV	55 (16.6)	15 (5.2)	9 (15.3)	4 (12.1)	0	<0.0001
Drug-resistant TB	17 (5.3)	22 (9.8)	27 (45.8)	2 (8.7)	12 (26.7)	<0.0001
Hospitalised patients	127 (37.2)	226 (78.2)	59 (100)	11 (31.4)	49 (76.6)	<0.0001
Supplemental oxygen during COVID-19	67 (37.4)	95 (35.7)	9 (15.3)	5 (55.6)	11 (17.2)	<0.0001
Invasive ventilation	21 (11.7)	13 (4.8)	3 (5.2)	0	7 (10.9)	0.020
Deaths from TB	38 (11.1)	38 (11.1)	5 (8.5)	7 (20.0)	4 (6.3)	0.112
Deaths from COVID-19	43 (12.6)	45 (15.9)	4 (6.8)	2 (6.3)	8 (12.5)	0.247
Overall deaths	51 (15.0)	48 (16.6)	7 (11.9)	7 (20.0)	8 (12.5)	0.749

Data are presented as mean±SD or n (%), unless otherwise stated.

older age, male gender and invasive ventilation were also associated with COVID-19 mortality in other studies [9, 10, 19].

The risk factors for TB mortality found in the present report (*i.e.* older age, HIV infection and invasive ventilation) are similar to other studies [20–24]; however, our cohort provides more detailed description and quantification of risk. Müller *et al*. [20] reported that the mortality among TB patients was higher in older subjects, and in those with a high comorbidity index. In addition, HIV infection remains a major risk factor for TB mortality in our COVID-19 co-infected cohort [21, 22]. As expected, the likelihood that a person with TB would die was significantly higher if they needed invasive ventilation [24]. This illustrates the importance of early recognition and treatment of COVID-19 and TB, respectively, to avoid worsening of the condition of the patient, requiring the need for ventilation. Clinical risk scores, as developed and validated by several groups, may be usefully employed to identify those at higher risk of more severe disease and support early intervention to improve outcomes in future [19, 25].

A higher number of recovered cases of COVID-19 was recorded when COVID-19 diagnosis occurred before/during TB treatment; however, in almost 20% of patients the diagnosis emerged during hospitalisation for other reasons. These may have been mild or asymptomatic COVID-19 cases detected by increased systematic screening in this patient cohort, or possibly the result of hospital transmission [26]. It is likely that the outcomes seen in our cohort are at least in part explained by early oligosymptomatic COVID-19 cases, with a better prognosis in this group. Conversely, those who were diagnosed with COVID-19 after the end of TB treatment appeared to have a poorer prognosis with a higher number and proportion of "non-recovery" COVID-19 cases. This observation suggests that people with pre-existing lung disease due to TB have worse outcomes and might recover more slowly than those affected during acute illness. At the height of the COVID-19 pandemic, hospitals faced a shortage of beds, with priority given to hospitalisation of critically ill patients [5, 6, 27]. Furthermore, we did not find statistically significant difference between patients who used and those who did not use antivirals and immunomodulators for COVID-19. In addition to the relatively small sample size, rifampicin, affecting most antivirals and Janus kinase inhibitors in a negative way, might potentially reduce the therapeutic effect of these drugs [7, 28].

Our longitudinal study reports on the early and medium-term TB- and COVID-19-related mortality observed in the cohort. There is recent evidence suggesting added mortality as an attributable consequence of post-TB lung disease. Even after treatment, the long-term mortality rate of TB patients is almost three times higher than in the general population, with deaths occurring mostly during the first year after the end of treatment [29]. Additionally, there are emerging reports [30, 31] suggesting that the increased COVID-19 mortality risk is not limited to the acute episode of COVID-19, but rather to post-COVID-19/long COVID processes [32–34] and that risk is closely linked to clinical risk and progression, including hospitalisation and intensive care. Mainous *et al*. [30] demonstrated that the 12-month adjusted all-cause mortality risk was significantly higher for patients with a COVID-19 hospitalisation, compared to mild COVID-19 and those without COVID-19. There is good evidence [33] that COVID-19 carries a substantially increased risk of death, which remains high over the year following the initial episode.

Considering that post-TB lung disease is identified in >50% of patients [32–36], and post-COVID-19 sequelae are thought to affect between 10% and 35% of COVID-19 survivors and up to 85% of those COVID-19 patients who required hospitalisation [37], it is extremely important to follow-up these patients in the long term, to establish strategies to avoid excess mortality associated with each of these two diseases and particularly with co-infection, and to define the need and plan for pulmonary rehabilitation, which appears to have emerging evidence in its support. TB should be considered prior to start or continuation of immunosuppressive medication, including high-dose corticosteroids or other immunosuppressive agents used in intensive care for severe COVID-19. When prioritising COVID-19 vaccination access, TB survivors should be included in at-risk populations, regardless of their age group.

Our study has some limitations. First, there were some missing data, as some centres were unable to provide all the requested information (*e.g.* on COVID-19 outcomes, date of COVID-19 diagnosis or causes of death other than TB and/or COVID-19). Approximately half of the countries (18 out of 34) provided representative data from their TB/COVID-19 cohorts; although large in sample size and having a global perspective, we cannot exclude that selection and/or survival bias exists, as the patients' inclusion was not randomised. Second, the number of paediatric participants was limited, probably as a combined effect of the low prevalence of co-infection in children and of the predominance of adult-oriented TB services among participating centres (*i.e.* although they are open to patients of any age, children tend to report to paediatric services, not much represented in the cohort). Furthermore, in the analysis of mortality by

region, we have low numbers from Asia and Africa, which might explain why no statistically significant difference have been found. We have not used the classification of countries as per WHO regions in order to support epidemiological similarities among groups, which may limit comparison with other published data.

Despite these concerns, we included a large dataset from all continents, which contains population-based data from more than half (although not from all) the countries/states/territories included in the study. The present report benefits from observation of longitudinal outcomes, and, to our knowledge, this is the largest study describing long-term outcomes of TB and COVID-19 co-infected patients.

In conclusion, death was reported as an outcome in >10% of patients co-infected with TB and COVID-19. A range of demographic and clinical predictors are associated with adverse outcomes, including age, clinical course including hospitalisation or invasive ventilation and immunosuppression. Some of these risk factors have been described previously, and our study quantifies this risk in a longitudinal study, to enable clinicians and policy-makers to improve care planning. Conversely, in our cohort, >70% of surviving patients had favourable outcomes (*i.e.* recovered COVID-19 and successful TB treatment). Future studies should evaluate the long-term pulmonary sequelae of these patients and elicit the effectiveness of and establish the need for pulmonary rehabilitation, as well as the protective role of anti-COVID-19 vaccination, and potentially of other available vaccines [38].

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