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

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The TB/COVID-19 Global Study Group

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

The TB/COVID-19 Global Study Group*

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Take home message: 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, including vaccination are recommended to prevent excess morbidity and mortality.

Abstract

Information on tuberculosis (TB) and COVID-19 is still limited.

The aim of this study is to describe the features of the TB/COVID-19 co-infected individuals from a prospective, anonymised, multi-country register-based cohort with special focus on the determinants of mortality and other outcomes.

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).

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

85/767 patients died (11.08%) (41/289 (14.2%) in Europe and 44/478 (9.2%) outside Europe; (P=0.03)): 42 (49.4%) from COVID-19, 31 (36.5%) from COVID-19 and TB, 1/85 (1.2%) from TB and 11 from other causes.

In the univariate analysis on mortality the following variables reached statistical significance: age, being male, having >1 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.

The data suggests 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) disease (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 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 concomitantly or after COVID-19 and that dual infection may be associated with 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 co-morbidities as the main determinants for mortality. Subsequent studies from South Africa and the Philippines suggested that COVID-19 patients with TB have, respectively, a 2.7 [19] and 2.17 [20] higher risk of mortality compared with COVID-19 patients without TB [20]. No large multi-country cohort of TB and COVID-19 patients has been reported to date.

In 2020 the GTN, in collaboration with several organizations (GREPI, Groupe de Recherche et Enseignement en Pneumo-Infectiologie, a working group from SPLF, Société de Pneumologie de Langue Française; SEPAR, Sociedad Española de Neumología and Cirugía Torácica; SBPT, Brazilian Society of Pulmonology and Tuberculosis; Moscow Society of Phtisiology, 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, multi-country register-based cohort (Annex 1). We worked with WHO and the Global TB Network 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 March 12th, 2020) and June 2021. The questionnaire and process was piloted and 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 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, as patients 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 reporting (15/34) data were also stratified by geographical origin.

We summarised variables using frequencies and percentages and calculated mean and standard deviations (SD) for normally distributed 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 non-parametric tests (e.g., Mann–Whitney U test) for data which 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 endpoints by univariable and multivariable logistic regression models. Covariates which 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 ≤ 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, 18/34, 52.9%) more than 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%, 540/767), with a median (IQR) age of 44 (31-58) years. The majority were vaccinated with BCG (Bacillus Calmette-Guerin; 90.7%, 349/385). 11.1% (80/717) had a history of migration in the last 5 years and 11.5% (83/724) were HIV co-infected.

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

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

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

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

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

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

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

Mechanical ventilation was necessary for 113 patients, 46/626 (7.4%) requiring intubation while 67/626 (10.7%) received non-invasive 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 co-morbidities in the patients who survived and died are summarised in Table 3 and Annex 3. Cardiovascular and endocrine co-morbidities were the most commonly observed, mostly hypertension and diabetes mellitus.

Age, gender and mortality

Out of 767 patients in the cohort 85 died (11.08%), 41/289 (14.2%) in Europe and 44/478 (9.2%) outside Europe (P=0.03) (Table 4).

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

More males were present among those who died vs those who survived (70/85, 82.4% vs 470/682, 68.9%, P=0.01) (Table 4).

Comorbidities and their impact on COVID-19 mortality

The comorbidities per patients 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 (73/85, 85.9% vs 343/682, 50.3%; P<0.0001) and in Europe (183/289, 63.3% vs. 233/478, 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 the 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 (34/85, 40.0% vs 200/682, 30.2%), the difference not being statistically significant; no difference was found between European vs non-European patients (Table 4).

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

Clinical outcome 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 (2 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 (2 with symptoms resolved, 4 not resolved and 32 with no or unknown symptoms).

Among the patients who died, 42/85 (49.4%) died from COVID-19, 31/85 (36.5%) from COVID-19 and TB and 1/85 (1.2%) for TB only. Among the patients who died for other reasons, 5/85 (5.9%) died with COVID-19 (2 for multiple comorbidities, 1 for presumptive cancer, 1 for sarcoidosis and 1 for HIV); the remaining 6/85 (7.0%) died after resolution of COVID-19 (2 for sepsis; 2 for multiple comorbidities and one each for pneumonia and pulmonary thrombo-embolism).

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), the majority male, with drug-susceptible pulmonary TB. The commonest symptoms reported were fever, dry cough, dyspnoea, with about 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 suggested the clinicians to perform imaging, which revealed a potentially pre-existing TB on top of COVID-19) [18] and 9.5% had COVID-19 diagnosed first.

A key question from our preliminary study [18] was on the role of SARS-CoV-2 on the progression of TB infection to disease as observed in other viral diseases (e.g. HIV) [5,18]. Whilst 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 more than 30 days prior (with a 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 more than 30 days. Therefore, this indirect evidence from our data suggests that 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 are males, belong 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 re-deployed 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 tele-medicine 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 which 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 MDR-TB completing anti-TB treatment suffer from TB sequelae [30-31]. This condition [30,31,33-36] includes obstructive, restrictive or mixed-pattern lung function abnormalities, reduced exercise capacity and impaired Quality of Life (QoL). 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 recently been published [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 discussion is 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, about half of the countries/ territories (18/34) 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 (6 patients, two of them below 1 year of age), some centres were unable to provide all the information requested on a few variables (particularly laboratory data) and about 10% of the patients had COVID-19 diagnosed based on the clinical and radiology findings, following the respective countries' policy during the emergency phases of the pandemic. The timing of our study also 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. It was also 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 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, male gender, with an important contribution also played by co-morbidities (particularly cardiovascular disease and diabetes mellitus). The reason why males died more than females may be explained by the potential higher prevalence of co-morbidities 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 patients' management (e.g. need for supplemental oxygen, invasive or non-invasive ventilation and specialized 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 rapidly obtain imaging, 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 suggests TB and COVID-19 are a 'cursed duet' and need immediate attention.

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Table 1. Demographic, epidemiological and clinical characteristics of 767 TB/COVID- 19 cases

Variables		n(%)*
Median (IQR) age, years		44 (31-58)
Males, n (%)		540/767 (70.4)
Immigrated in the last 5 years, n (%)		80/717 (11.2)
Occupation, n (%)	Unemployed	318/705 (45.1)
	Employed	254/705 (36.0)
	Retired	108/705 (15.3)
	Student	25/705 (3.6)
BCG vaccinated, n (%)		349/385 (90.7)
Pregnancy, n (%)		2/224 (0.9)
Alcohol abuse (≥14 drinks per week in men or ≥7 drinks per week in women), n (%)		112/687 (16.3)
Smoking status, n (%)	No smoker	382/636 (60.1)
	Current smoker	184/636 (28.9)
	Former smoker	70/636 (11.0)
Vaping Status, n (%)	No vape	485/523 (92.7)
	Current vape	36/523 (6.9)
	Former vape	2/523 (0.4)
Intravenous Drug User (IVDU), n (%)	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, n (%)		83/724 (11.5)
Median (IQR) CD4 Count pre-COVID-19 infection, cells/μL (n=28)		164.5 (46-344)
Median (IQR) CD4 Count during COVID-19 infection, cells/μL (n=20)		88 (41.3-247)
HIV treatment administered, n (%)		29/83 (34.9)
COPD, n (%)		59/751 (7.8)
Diabetes Mellitus (DM), n (%)		157/753 (20.8)
Uncontrolled DM (HbA1c ≥9%), n (%)		40/136 (29.4)
Poorly controlled DM (HbA1c 7 - 9%), n (%)		28/136 (20.6)
Well controlled DM (HbA1c <7%), n (%)		18/136 (13.2)
Unknown DM control, n (%)		50/136 (36.8)
Renal Failure, n (%)		53/713 (7.4)
Dialysis, n (%)		17/43 (39.5)
Liver disease, n (%)		60/700 (8.6)
Timing of TB and COVID-19 diagnosis	TB diagnosed before COVID-19, n (%)**	553/747 (74.0)
	Median (IQR) days of TB diagnosis before COVID-19 diagnosis, (n=318)^	78 (38-145)
	Median (IQR) years between TB end and COVID diagnosis (n=229)^^	2.3 (1.0-6.3)
	COVID-19 diagnosed before TB, n (%)	71/747 (9.5)
	Median (IQR) 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)
	Median (IQR) days of TB and COVID-19 diagnosis within the same week, days (n=123)	1 (0-4)
	COVID-19 and TB diagnosed within the same day, n (%)	35/747 (4.7)

Legend: * Data reported as number/total number of patients for whom data are available (%);** patients with active TB and previous TB; ^patients with previous TB excluded; ^^patients with previous TB; TB: tuberculosis; COVID-19: acute respiratory syndrome coronavirus 2 (SARS-CoV-2); IQR: interquartile range; BCG: Bacille Calmette-Guerin; COPD: chronic obstructive pulmonary disease; HbA1c: Hemoglobin A1c Test.

Table 2: Descriptive analysis of TB in the TB/COVID-19 cohort

TUBERCULOSIS		**n(%)***
TB Form, n (%)	Failure	17/723 (2.4)
	Relapsed	59/723 (8.2)
	Lost to Follow up	29/723 (4.0)
	New case	618/723 (85.5)
TB laboratory confirmation, n (%)		612/732 (83.6)
Site		
Pulmonary TB, n (%)		648/755 (85.8)
Extra-Pulmonary TB, n (%)		189/738 (25.6)
Pulmonary - Extra-Pulmonary TB, n (%)		80/733 (10.9)
Extra-Pulmonary TB, n (%)	Pleural TB, n (%)	52/189 (27.5)
	TB Lymphadenitis, n (%)	42/189 (22.2)
	Multiple locations	31/189 (16.4)
	Central Nervous System, n (%)	17/189 (9.0)
	Other, n (%)	15/189 (7.9)
	Bone TB, n (%)	11/189 (5.8)
	Gastrointestinal TB, n (%)	7/189 (3.7)
	TB Peritonitis, n (%)	5/189 (2.6)
	Genitourinary TB, n (%)	4/189 (2.1)
	TB Pericarditis, n (%)	2/189 (1.0)
	Unknown, n (%)	3/189 (1.6)
Radiology at TB diagnosis		
Bilateral pulmonary cavitary lesion, n (%)		118/633 (18.6)
Bilateral pulmonary cavitary lesion + other, n (%)		5/633 (0.8)
Unilateral pulmonary cavitary lesion, n (%)		121/633 (19.1)
Unilateral pulmonary cavitary lesion + other, n (%)		4/633 (0.6)
Bilateral pulmonary infiltrate (no cavities), n (%)		108/633 (17.1)
Bilateral pulmonary infiltrate (no cavities)+ other, n (%)		7/633 (1.1)
Unilateral pulmonary infiltrate (no cavities), n (%)		94/633 (1.8)
Unilateral pulmonary infiltrate (no cavities)+ other, n (%)		8/633 (1.3)
Other lesions, n (%)		143/633 (22.6)
Not done, n (%)		25/633 (3.9)
Lung function tests at TB diagnosis		
Lung function tests done at TB diagnosis, n (%)		209/625 (33.4)
Median (IQR) sO2, % (n=214)		97 (94-98)
Median (IQR) FiO2, % (n=112)		21 (21-21)
Median (IQR) pO2, mmHg (n=40)		77.9 (65.7-93.8)
Mean (SD) pCO2, mmHg (n=40)		35.2 (7.5)
Median (IQR) pH (n=39)		7.45 (7.40-7.47)
Microbiology		
TB microbiology done (one or more tests), n (%)		638/652 (97.8)
Solid culture, n (%)		441/638 (69.3)
Gene Xpert, n (%)		410/638 (64.5)
Liquid culture, n (%)		324/638 (50.9)
First line LPA, n (%)		105/638 (16.5)
Second line LPA, n (%)		28/638 (4.4)
Drug resistance pattern at TB diagnosis		
Pan susceptible-TB, n (%)		517/607 (85.2)
Drug resistant-TB, n (%)		90/607 (14.8)
Hospitalization		
Hospitalization during anti-TB treatment, n (%)		388/614 (63.2)
Median (IQR) duration of hospitalization, days (n=342)		31 (14-90)

Legend: * Data reported as number/total number of patients for whom data are available (%); TB: tuberculosis; COVID-19: acute respiratory syndrome coronavirus 2 (SARS-CoV-2); IQR: interquartile range; sO2: Oxygen Saturation; FiO2: fraction of inspired oxygen; pO2: partial pressure of oxygen; pCO2: partial pressure of carbon dioxide; pH: potential of hydrogen; SD: standard deviation; LPA: line probe assay

Table 3. Descriptive analysis of COVID-19 in the TB/COVID-19 cohort

COVID-19		**n (%)***
SARS-CoV-2 laboratory confirmation, n (%)		723/763 (94.8)
Signs and symptoms		
COVID-19 signs and symptoms (one or more symptoms), n (%)		538/669 (80.4)
Fever, n (%)		386/538 (71.7)
Dry cough, n (%)		311/538 (57.8)
Shortness of breath, n (%)		192/538 (35.7)
Headache, n (%)		133/538 (24.7)
Tiredness, n (%)		114/538 (21.2)
Sore throat, n (%)		96/538 (17.8)
Malaise, n (%)		96/538 (17.8)
Chest pain, n (%)		88/538 (16.3)
Myalgia, n (%)		87/538 (16.2)
Nasal congestion, n (%)		73/538 (13.6)
Taste disorders, n (%)		56/538 (10.4)
Diarrhoea, n (%)		52/538 (9.7)
Olfactory disorders, n (%)		48/538 (8.9)
Vomiting/nausea, n (%)		38/538 (7.1)
Arthralgia, n (%)		36/538 (6.7)
Abdominal pain, n (%)		34/538 (6.3)
Irritability/confusion, n (%)		34/538 (6.3)
Other symptoms (loss of appetite rhinorrea, difficulty of breathing, hemoptisys, conjunctivitis among others), n (%)		74/538 (13.7)
Diagnosis		
COVID-19 laboratory confirmed (one or more tests), n(%)		723/763 (94.7)
PCR diagnosis, n (%)		683/758 (90.1)
SARS-CoV-2 PCR diagnosis, n (%)		41/758 (5.4)
CT scan diagnosis, n (%)		54/758 (7.1)
Presumptive diagnosis, n (%)		61/758 (8.0)
Other diagnosis, **(**CXR, rapid antigen test), n (%)		17/758 (2.2)
Radiology at diagnosis		
CT SCAN, n (%)		109/642 (17.0)
Chest X ray, n (%)		214/642 (33.3)
CT SCAN and Chest X ray, n (%)		157/642 (24.5)
Radiology not done, n (%)		162/642 (25.2)
CT scan findings, n (%)	Typical Ground opacity/opacities, bilateral	126/266 (47.4)
	Typical Ground opacity/opacities, unilateral	40/266 (15.0)
	Atypical Ground opacity/opacities	56/266 (21.1)
	Typical Ground 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, n (%)		401/619 (64.8)
Median (IQR) sO2, % (n=397)		96 (94-98)
Median (IQR) FiO2, %(n=269)		21 (21-21)
Median (IQR) pO2, mmHg (n=99)		80 (63-95)
Median (IQR) pCO2, mmHg (n=100)		37 (33-41)
Median (IQR) pH (n=100)		7.4 (7.4-7.5)
Ventilation and oxygen therapy		
No ventilation, n (%)		513/626 (81.9)
Non-invasive, n (%)		67/626 (10.7)
Invasive, n (%)		46/626 (7.4)
Supplemental oxygen during Covid-19		198/619 (32.0)
Hospitalization		
Hospitalization due to COVID-19, n (%)		452/732 (61.7)

Median (IQR) duration of hospitalization, days (n=395)		14 (8-22)
Concomitant hospitalization due to TB-COVID-19 co-infection, n (%)		250/737 (33.9)
Median (IQR) duration of concomitant hospitalization, days (n=223)		16 (10-24)
PCR conversion rates		
PCR conversion, n (%)		271/474 (57.2)
Median (IQR) from start treatment to PCR conversion, days (n=196)		14.5 (11-22)
Treatment		
Treatment for COVID-19 **(**one or more drugs), n (%)		346/639 (54.1)
Antivirals		
Lopinavir/Ritonavir, n (%)		24/336 (7.1)
Darunavir/Cobicistat or Darunavir/Ritonavir, n (%)		21/336 (6.2)
Favipiravir, n (%)		11/336 (3.3)
Remdesivir, n (%)		5/336 (1.5)
Other antivirals, n (%)		4/336 (1.2)
Immunomodulators		
Glucocorticoids (methylprednisolone, betamethasone, ciclesonide , other glucocorticoids), n (%)		115/336 (34.2)
Intravenous immunoglobulin (IVIG), n (%)		3/336 (0.9)
Interleukin (IL)-6 inhibitors, n (%)		2/336 (0.6)
Bevacizumab (antibody against VEGF-A), n (%)		1/336 (0.3)
Anticoagulants		
Enoxaparin, n (%)		72/336 (21.4)
Other therapeutic anticoagulants, n (%)		22/336 (6.5)
Miscellaneous		
Azithromycin, n (%)		212/336 (63.1)
Hydroxychloroquine, n (%)		191/336 (56.8)
N-acetyl-cysteine, n (%)		22/336 (6.6)
Plasma from recovered patients, n (%)		3/336 (0.9)
Interferon, n (%)		3/336 (0.9)
Other non-steroid anti-inflammatory drugs , n (%)		2/336 (0.6)
Number of comorbidities	**Alive (N=682) n(%)**	**Deceased (N=85) n(%)**
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)

Legend: * Data reported as number/total number of patients for whom data are available (%); TB: tuberculosis; SARS-CoV-2:severe acute respiratory syndrome coronavirus 2; PCR: polymerase chain reaction; CT scan: computed tomography scan; IQR: interquartile range; sO2: Oxygen Saturation;FiO2: fraction of inspired oxygen; pO2: partial pressure of oxygen; pCO2: partial pressure of carbon dioxide; pH: potential of hydrogen; VEGF-A: Vascular endothelial growth factor; SARS-CoV-2: acute respiratory syndrome coronavirus 2.

Table 4. Characteristics of the patients alive or deceased in the TB/COVID-19 cohort and stratification by geographical origin.

VITAL STATUS			
	Alive (N= 682)*	**Deceased (N= 85)****	**P-value**
Median (IQR) age, years	41 (30-55)	65 (48-77)	<0.0001
Age ≥65 years, n (%)	83 (12.2)	44 (51.8)	<0.0001
Males, n (%)	470 (68.9)	70 (82.4)	0.01
Non-European, n (%)	434 (63.6)	44 (51.8)	0.03
≥1 comorbidity, n (%)	343 (50.3)	73 (85.9)	<0.0001
≥2 comorbidities, n (%)	147 (21.6)	49 (57.7)	<0.0001
Median (IQR) no. of comorbidities	1 (0-1)	2 (1-4)	<0.0001
Diabetes Mellitus, n (%)	125 (18.3)	32 (37.7)	<0.0001
Cardiovascular Disease, n (%)	105 (15.4)	41 (48.2)	<0.0001
Chronic Resp. Disease, n (%)	71 (10.4)	22 (25.9)	<0.0001
HIV, n (%)	68 (10.0)	12 (14.1)	0.14
Chronic Liver Disease, n (%)	50 (7.3)	10 (11.8)	0.15
Chronic Renal Disease, n (%)	38 (5.6)	15 (17.7)	<0.0001
Invasive ventilation, n (%)	15 (2.7)	31 (41.3)	<0.0001
Previous TB, n (%)	200 (30.2)	34 (40.0)	0.07
Hospitalization due to COVID-19, n (%)	381 (59.0)	71 (83.5)	<0.0001
Median (IQR) duration of hospitalization, days	14 (8-22)	10 (4-24)	0.007
Concomitant hospitalization due to TB-COVID-19 co-infection, n (%)	216 (31.7)	34 (40.0)	0.19
Median (IQR) duration of concomitant hospitalization	16 (10-24)	8 (4-20)	0.11
GEOGRAPHICAL ORIGIN			
	Europe (N= 289)	**No-Europe (N= 478)**	**P-value**
Median (IQR) age, years	49 (36-63)	39 (29-54)	<0.0001
Age ≥65 years, n (%)	68 (23.5)	59 (12.3)	<0.0001
Death, n (%)	41 (14.2)	44 (9.2)	0.03
Dead ≥65 years, n (%)	26/41 (63.4)	18/44 (40.9)	0.04
Median (IQR) age of patients who died, years	70 (59-80.5)	57.5 (44.3-71.8)	0.004
Males, n (%)	209 (72.3)	331 (69.3)	0.37
≥1 comorbidity, n (%)	183 (63.3)	233 (48.7)	<0.0001
Dead with ≥1 comorbidity	38/183 (20.8)	35/233 (15.0)	0.13
Diabetes Mellitus, n (%)	63 (21.8)	94 (19.7)	0.48
Dead with Diabetes Mellitus, n (%)	19/63 (30.2)	13/94 (13.8)	0.01
Cardiovascular Disease, n (%)	79 (27.3)	67 (14.0)	<0.0001
Dead with Cardiovascular Disease, n (%)	26/79 (32.9)	15/67 (22.4)	0.16
Chronic Resp. Disease, n (%)	46 (15.9)	47 (9.8)	0.01
Dead with Chronic Resp. Disease, n (%)	13/46 (28.3)	9/47 (19.2)	0.30
HIV, n (%)	25 (8.7)	55 (11.5)	0.21
Dead with HIV, n (%)	3 (12.0)	9 (16.4)	0.61
Chronic Liver Disease, n (%)	47 (16.3)	13 (2.7)	<0.0001
Dead with Chronic Liver Disease, n (%)	7/47 (14.9)	3/13 (23.1)	0.68
Chronic Renal Disease, n (%)	33 (11.4)	20 (4.2)	<0.0001
Dead with Chronic Renal Disease, n (%)	11/33 (33.3)	4/20 (20.0)	0.30
Invasive ventilation, n (%)	14 (5.0)	32 (9.3)	0.04
Previous TB, n (%)	79 (27.7)	155 (33.6)	0.09
Dead with active TB, n (%)	20/206 (9.7)	31/307 (10.1)	0.89
Hospitalization due to COVID-19, n (%)	220 (76.4)	232 (52.3)	<0.0001
Median (IQR) duration of hospitalization, days	14 (9-22)	13 (6-24)	0.11
Concomitant hospitalization due to TB-COVID-19 co-infection, n (%)	136 (31.7)	114(40.0)	0.005

Median (IQR) duration of concomitant hospitalization	16 (11-22)	14 (6-26)	0.36

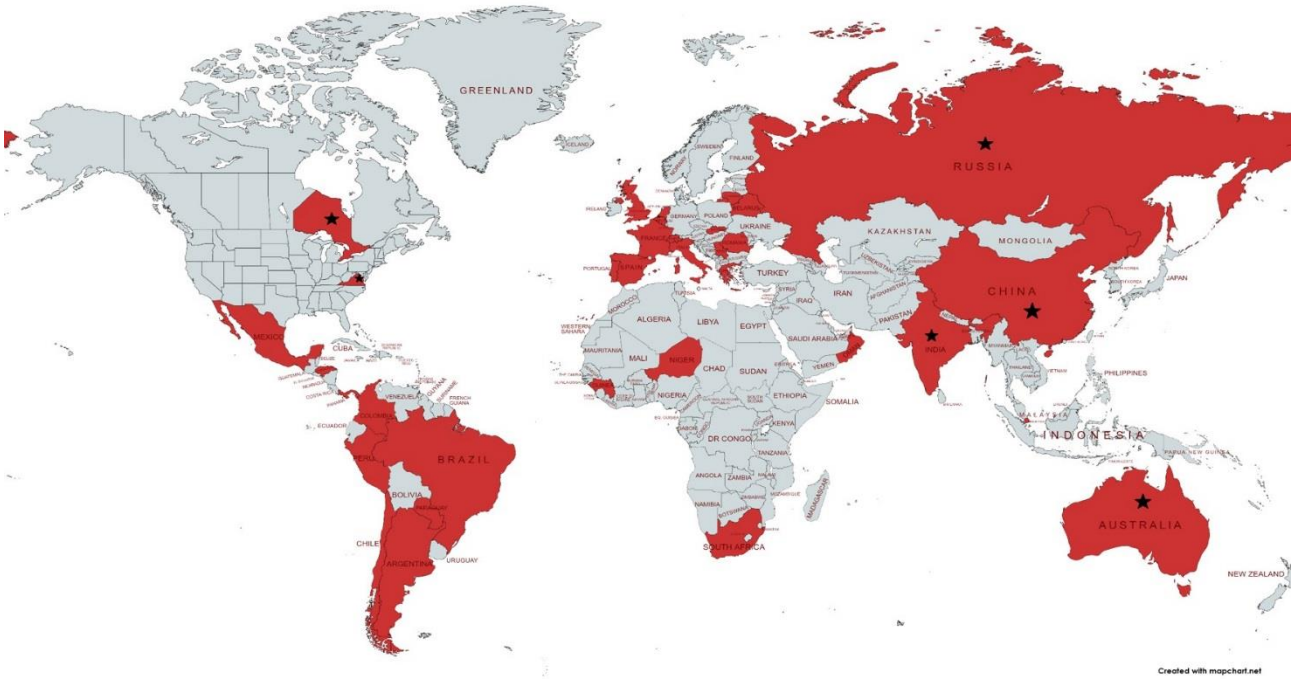
Legend: *Alive: all patients in the cohort based on the latest information available (see text and Figure 3 for details); **all patients who died based on the latest information available. The detailed causes of death are reported in the text and in Figure 3; TB: tuberculosis; COVID-19: acute respiratory syndrome coronavirus 2 (SARS-CoV-2); IQR: interquartile range.

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

Variable (comparison)	Univariable analysis		Multivariable analysis	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Age, years (10 years increase)	1.82 (1.58-2.09)	<0.0001	1.93 (1.60-2.32)	<0.0001
Males (yes vs no)	2.08 (1.16-3.71)	0.014	2.92 (1.38-6.16)	0.005
≥1 comorbidity (yes vs no)	6.01 (3.21-11.27)	<0.0001	-	-
Diabetes Mellitus (yes vs no)	2.69 (1.67-4.35)	<0.0001	-	-
Cardiovascular Disease (yes vs no)	5.12 (3.19-8.22)	<0.0001	-	-
Chronic Respiratory Disease (yes vs no)	3.00 (1.74-5.18)	<0.0001	-	-
HIV (yes vs no)	1.48 (0.77-2.87)	0.241	-	-
Chronic Liver Disease (yes vs no)	1.69 (0.82-3.46)	0.155	-	-
Chronic Renal Disease (yes vs no)	3.00 (1.74-5.18)	<0.0001	-	-
Invasive ventilation (yes vs no)	25.18 (12.64-50.13)	<0.0001	28.22 (1.37-64.39)	<0.0001
Active TB (yes vs no)	1.5 (1.0-2.5)	0.069	-	-
Presence of key symptoms (yes vs no)	49.3 (19.7-123.9)	<0.0001	-	-
Hospitalization due to COVID-19 (yes vs no)	3.54 (1.95-6.41)	<0.0001	-	-
Duration of hospitalization (1 day increase)	0.98 (0.96-1.01)	0.072	-	-
Europe (yes vs no)	1.63 (1.04-2.57)	0.034		
			Multivariable model	
			-2 Log Likelihood: 301.6	
			p<0.0001	
			% of cases correctly classified: 91%	
			AUC: 0.89 (0.86-0.91)	

Legend: OR: odds ratio; CI: confidence interval; TB: tuberculosis; COVID-19: acute respiratory syndrome coronavirus 2 (SARS-CoV-2);

Figure 1: Global distribution of the Countries/States/Regions participating in the study.



Footnote Figure 1:

★: the following States/Territories are covered in the study: Australia (New South Wales); Canada (Ontario State): China (Wenzhou and Luzhou); India (New Delhi , Mumbai & Maharashtra States); 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 United Kingdom) reported at least one TB/COVID-19 case in 2020. Other countries (Australia, Canada, Colombia, Greece, Honduras, Lithuania, Netherlands, Oman, Paraguay, Serbia, Slovakia, South Africa and USA) started reporting from 2021.

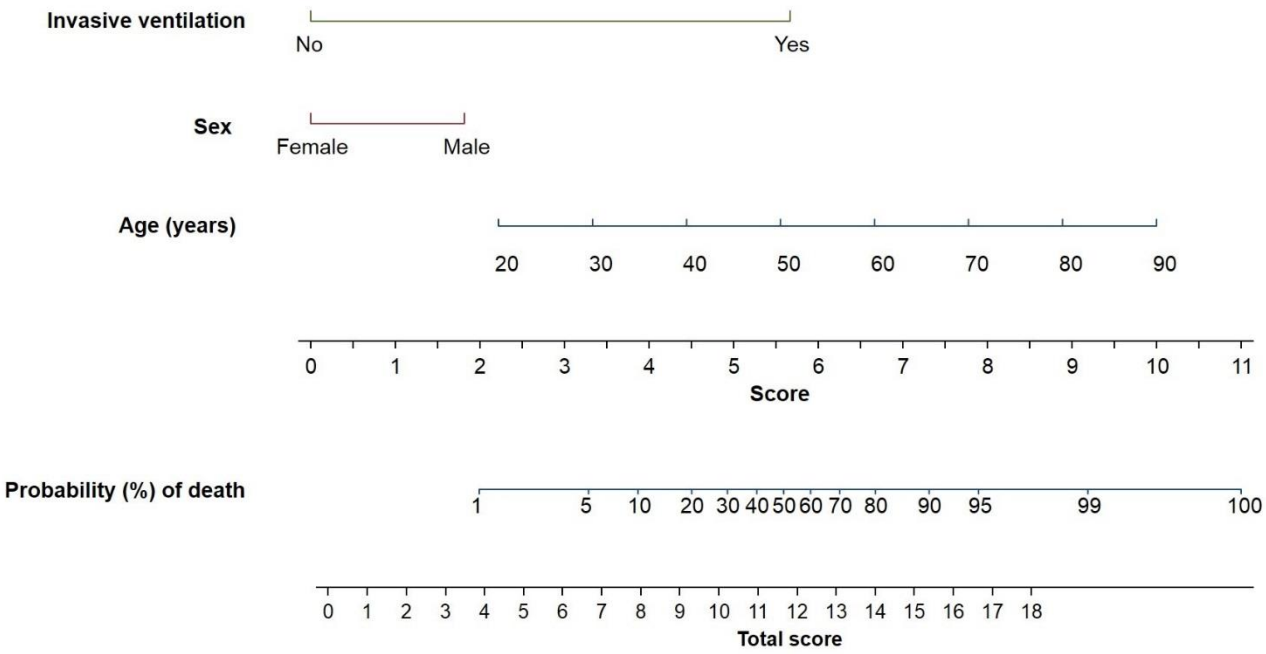


Figure 2. Nomogram for the estimation of the risk of death

The nomogram for the estimation of the risk of death was generated on the basis of the multivariable logistic regression analysis. As depicted in the figure, 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, 80-year-old woman requiring invasive ventilation during hospitalization would have a probability >80%.

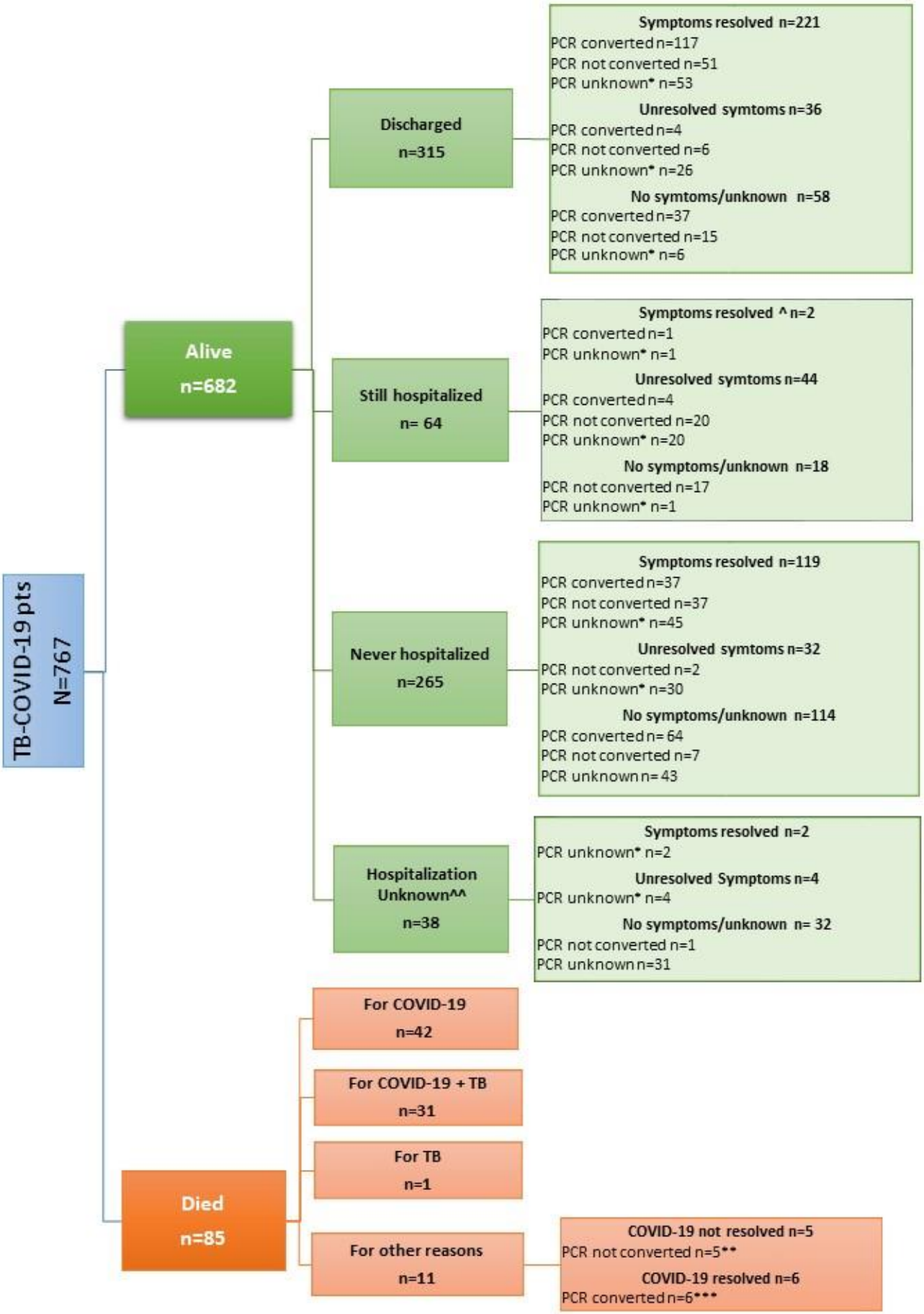
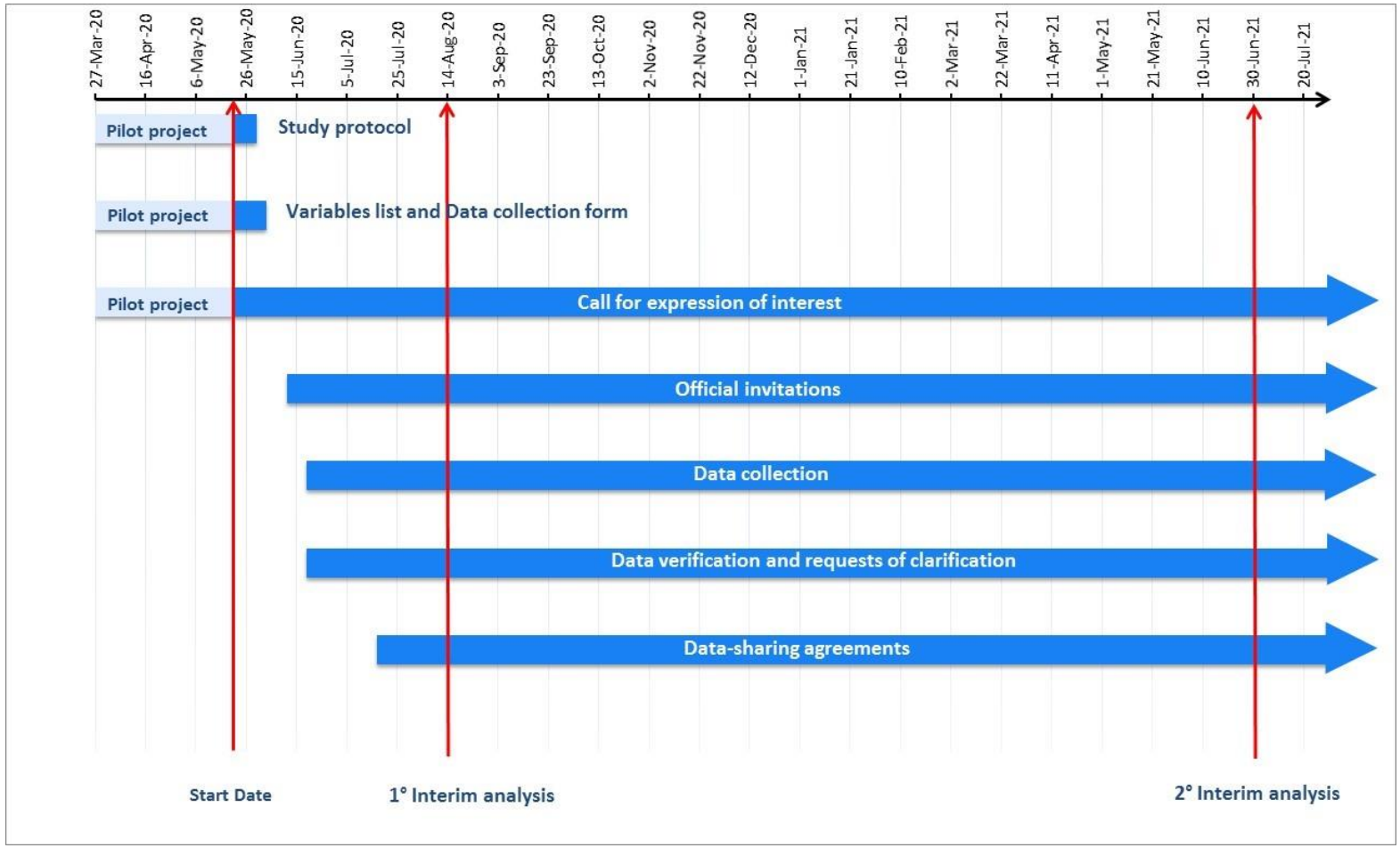

TB-COVID-19 pts
N=767
Alive
n=682
Died
n=85
Discharged
n=315
Still hospitalized
n= 64
Never hospitalized
n=265
Hospitalization Unknown^^
n=38
For COVID-19
n=42
For COVID-19 + TB
n=31
For TB
n=1
For other reasons
n=11
Symptoms resolved n=221
PCR converted n=117
PCR not converted n=51
PCR unknown* n=53
Unresolved symtoms n=36
PCR converted n=4
PCR not converted n=6
PCR unknown* n=26
No symtoms/unknown n=58
PCR converted n=37
PCR not converted n=15
PCR unknown* n=6
Symptoms resolved ^ n=2
PCR converted n=1
PCR unknown* n=1
Unresolved symtoms n=44
PCR converted n=4
PCR not converted n=20
PCR unknown* n=20
No symptoms/unknown n=18
PCR not converted n=17
PCR unknown* n=1
Symptoms resolved n=119
PCR converted n=37
PCR not converted n=37
PCR unknown* n=45
Unresolved symtoms n=32
PCR not converted n=2
PCR unknown* n=30
No symptoms/unknown n=114
PCR converted n= 64
PCR not converted n=7
PCR unknown n= 43
Symptoms resolved n=2
PCR unknown* n=2
Unresolved Symptoms n=4
PCR unknown* n=4
No symptoms/unknown n= 32
PCR not converted n=1
PCR unknown n=31
COVID-19 not resolved n=5
PCR not converted n=5**
COVID-19 resolved n=6
PCR converted n=6***

Figure 3: Clinical outcome of COVID-19 among TB/COVID-19 patients

Footnote Figure 3:
*: including pts with PCR not done; ^: 2 patients with symptoms resolution remain hospitalized for TB
**2 for multiple comorbidities, 1 for suspected cancer, 1 for sarcoidosis, 1 x HIV
***2 for sepsis, 2 for multiple comorbidities, 1 for bilateral gram negative nosocomial pneumonia, *M. morgany*, 1 for pulmonary thrombo-embolism [with COVID-19 clinically diagnosed and PCR unknown])
PCR: polymerase chain reaction

Electronic Annex 1. Study plan (Gantt chart)



Electronic Annex 2. Cases reported by participating countries and countries' estimated coverage at the time of data reporting

Countries	Cases enrolled N	Centres N	Estimated coverage Ω
Argentina	30	1	12.5%* (Buenos Aires)
Australia	2	2	20%§ (New South Wales)
Belarus	3	1	10%* (Minsk)
Belgium	1	1	100%* (Namur)
Brazil	66	6	80%§ (Rio Grande do Sul & Goías) 40%§ (Bahia & São Paulo)
Canada	1	1	5%§ (Ontario)
Chile	70	47	100%^ (Whole country)
China	4	2	100%* (Wenzhou and Luzhou)
Colombia	2	1	10%^ (Whole country)
France	10	6	50%^ (Whole country)
Greece	1	1	80%# (Northern Region) 20%^ (Whole country)
Guinea Republic	2	1	100%* (Conakry) 20%^ (Whole country)
Honduras	23	7	100%^ (Whole country)
India	37	3	80%* (New Delhi) 20%* (Nagpur) 10%* (Mumbai)
Italy	58	10	80%^ (Whole country)
Lithuania	27	2	100%* (Vilnius and Klaipedia)
Mexico	17	9	30%^ (Whole country)
Netherlands	1	1	100%^ (Whole country)
Niger	1	1	100%^ (Whole country)
Oman	13	4	100%^ (Whole country)
Panama	8	1	100%^ (Whole country)
Paraguay	80	17	100%^ (Whole country)
Peru	32	2	80%^ (Whole country)
Portugal	2	2	100%* (Vila Nova de Gaia and Espinho)
Romania	23	2	100%* (Craiova) 10%# (South Western Region) 100%* (Timisoara) 10.5%# (Western Region)
Russian Federation	65	3	100%** (Moscow, Arkhangelsk & Volvograd)
Serbia	6	1	100%^ (Whole country)
Singapore	24	2	75%^ (Whole country)
Slovakia	3	1	100%^ (Whole country)
South Africa	15	7	25%# (Western Cape Province)
Spain	24	8	70%^ (Whole country)
Switzerland	1	1	100%# (Vaud Canton)
United Kingdom	64	2	25%* (London)
USA	51	16	375§ (Virginia State)
TOTAL= 34	**TOTAL= 767**	**TOTAL= 172**	**RANGE (5%-100%)**

Legend: Ω Countries' estimate of the national/subnational coverage of the TB/COVID-19 (TB: tuberculosis; COVID-19: acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) cases at the time of data reporting; *estimated coverage in the metropolitan area(s) reporting; § estimated coverage in the state(s) reporting; # estimated coverage in the region/province/canton reporting; **estimated coverage in the 3 Oblasts reporting; ^ estimated coverage compared to cases reported in the whole country

Electronic Annex 3: Comorbidities prior to COVID-19 diagnosis in 767 patients of the TB/COVID-19 cohort

PATIENTS WITH >=1 COMORBIDITIES	ALIVE (N=343) n(%)	DEAD (N=73) n(%)
CARDIOVASCULAR DISEASE		
Hypertension	81 (23.6)	27 (37.0)
Congestive Heart Failure	16 (4.7)	12 (16.4)
Ischemic heart disease	14 (4.1)	14 (19.2)
Stroke	6 (1.7)	9 (12.3)
Atrial fibrillation	4 (1.2)	4 (5.5)
Other Cardiovascular disease	10 (2.9)	4 (5.5)
ENDOCRINE DISEASE		
Diabetes Mellitus	125 (36.4)	32 (43.8)
Hypothyroidism	6 (1.7)	3 (4.1)
IMMUNOCOMPROMISING CONDITIONS		
HIV	68 (19.8)	12 (16.4)
Autoimmune Disease	18 (5.2)	3 (4.1)
Organ Transplant	4 (1.2)	2 (2.7)
RESPIRATORY DISEASE		
Other Lung Disease	56 (16.3)	21 (28.8)
Asthma	18 (5.2)	6 (8.2)
LIVER DISEASE	50 (14.6)	10 (13.7)
RENAL DISEASE	38 (11.1)	15 (20.5)
CANCER	23 (6.7)	11 (15.1)
PSYCHIATRIC DISORDERS	18 (5.2)	8 (11.0)
NUTRITION DISORDERS	5 (1.5)	3 (4.1)
OTHER DISEASES	8 (2.3)	3 (4.1)

Legend: TB: tuberculosis; COVID-19: acute respiratory syndrome coronavirus 2 (SARS-CoV-2)