

Brief Summary of Findings on the Association Between Tuberculosis and Severe COVID-19 Outcomes

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Five cohort studies and one ecological study were retrieved that reported data on underlying tuberculosis and severe COVID-19 outcomes, including mortality and hospitalization.

- The evidence indicates tuberculosis was associated with an increased risk of mortality,¹ and limited evidence from one study⁶ suggested an increase in the risk of hospitalization was associated with underlying tuberculosis in COVID-19 patients. However, one study is insufficient to definitively conclude an increase in risk and new evidence may change these conclusions on hospitalization.

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A. Methods

The aim of this review was to identify and synthesize the best available evidence on the association between tuberculosis and severe COVID-19 outcomes in order to update the Centers for Disease Control and Prevention (CDC) website on underlying conditions for a consumer and a provider-specific website with more rigorous information.

A.1. Literature Search

A list of search terms was developed to identify the literature most relevant to the population, exposure, comparator, and outcomes (PECO) question. Clinical experts and library scientists were consulted to develop a robust list of search terms. These terms were then incorporated into search strategies, and these searches were performed in OVID using the COVID-19 filter from the end of the previous literature search (December 2020). The detailed search strategies for identifying primary literature and the search results are provided in Part B. Subject matter experts supplemented the literature search results by recommending relevant references published before December 2020. References were included if retrieved by the chronic lung disease literature search and reported exposures and outcomes relevant to this review.

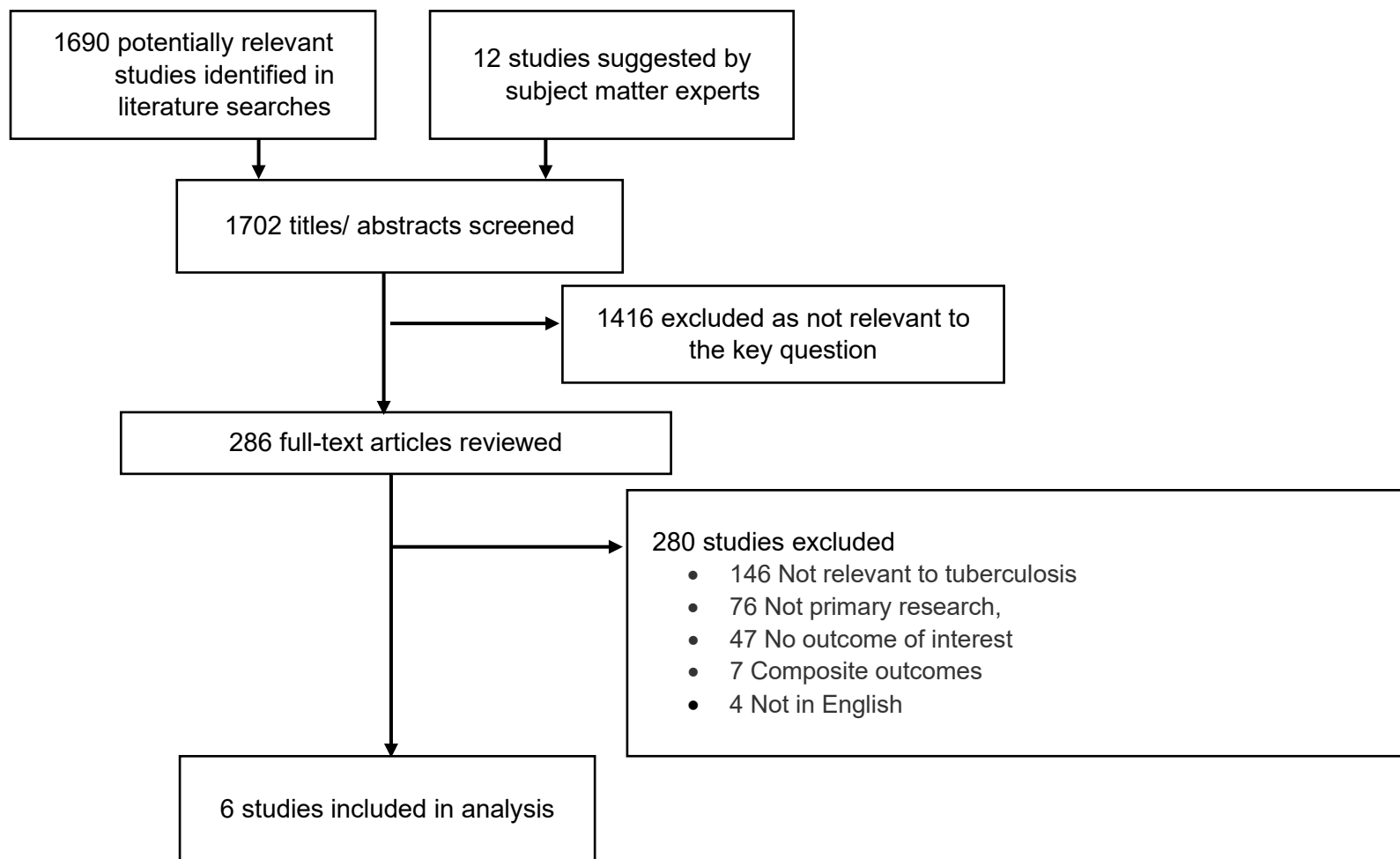
A.2. Study Selection

Titles and abstracts from references were screened by dual review (initials: M.C., J.K.K., D.O.S., T.R., C.S., E.C.S., or M.W.). Full-text articles were retrieved if they were:

1. relevant to the PECO question;
2. primary research, and
3. written in English.

Part B presents the full list of exclusion criteria. The full texts of selected articles were then screened by two independent reviewers, and disagreements were resolved by discussion (Initials J.K.K., C.O., D.O.S., K.T.R., C.S., E.C.S., or M.W.). After the full-text screening was complete, a bibliography of the articles selected for inclusion was vetted with subject matter experts. Additional studies suggested by the subject matter experts were screened for inclusion as described above. The results of the study selection process are depicted in Figure 1.

Figure 1. Results of the Study Selection Process



A.3. Data Extraction and Synthesis

Methodologic data and results of relevant outcomes from the studies meeting inclusion criteria were extracted into standardized evidence tables. Data and analyses were extracted as presented in the studies. For the purposes of this review, statistical significance was defined as $p \leq 0.05$.

A.4. Aggregation of the Evidence

The internal validity associated with each study was assessed using scales developed by the Division of Healthcare Quality Promotion and scores were recorded in the evidence tables. Part B includes the questions used to assess the quality of each study design. The strength, magnitude, precision, consistency, and applicability of results were assessed for all comparators. The overall confidence in the evidence base is reported in the aggregation tables in Part B.

A.5. Reviewing and Finalizing the Systematic Review

Draft findings, aggregation tables, and evidence tables, are presented to CDC subject matter experts for review and input. Following further revisions, the summary will be published on the CDC website.

Systematic Literature Review Results

B.1. Search Strategies and Results

Table 1 Chronic Lung Disease Search Conducted March 17, 2021

#	Search History
1	chronic lung disease
2	respiratory system disease*
3	reactive airway disease*
4	emphysema
5	chronic bronchitis
6	COPD
7	Chronic obstructive pulmonary disease
8	Asthma *
9	allergic asthma
10	irritant asthma
11	Interstitial lung disease
12	Pulmonary fibrosis
13	idiopathic pulmonary fibrosis
14	nonspecific interstitial pneumonitis
15	hypersensitivity pneumonitis
16	sarcoidosis

17	pneumoconiosis
18	asbestosis
19	coal workers pneumoconiosis
20	silicosis
21	bronchiectasis
22	cystic fibrosis
23	pulmonary vascular disease
24	pulmonary hypertension
25	bronchopulmonary dysplasia
26	bronchiolitis obliterans
27	asthma*
28	reactive airway disease*
29	CF
30	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	Limit 30 to covid-19
32	(202012* or 2021*).dt
33	(202012* or 2021*).dc
34	32 or 33
35	31 and 34
36	Deduplicate

B.2. Study Inclusion and Exclusion Criteria

Inclusion Criteria: Studies were included at the title and abstract screen if they:

- were relevant to the key question “what is the association between tuberculosis and severe COVID-19 outcomes?”;
- were primary research;
- were written in English (can be seen as [language] in title); and
- Examined humans only.

Exclusion Criteria: Studies were excluded at full text review if they:

- were not available as full text;
- were a conference abstract, poster, letter to the editor, or reply letter;
- examined lung transplant, cancer, or immunocompromised populations;
- reported autopsy results; and
- reported only composite outcome measures for “severe COVID-19 outcomes”.

B.3. Evidence Review: Tuberculosis and Severe COVID-19

B.3.a. Strength & Direction of Evidence

Table 2. The Association Between Tuberculosis and Severe COVID-19 Outcomes

Severe COVID-19 Outcome	Results
Mortality	<p>Overall, the evidence suggests the presence of underlying tuberculosis is associated with an increased risk, hazard, or odds of mortality.</p> <ul style="list-style-type: none"> • Strength of Association: Two studies reported unadjusted measure of association of 0.88 to 1.28. Two studies reported adjusted measures of effect ranging from 1.65 to 2.17. • Precision of Association: Of the four studies reporting confidence intervals, all were wide, and three studies reported confidence intervals that crossed the null. • Consistency of Association: Overall, the evidence is consistent, pointing in the direction of increased risk of mortality with confidence intervals that cross the null. • Applicability of Association: The population and settings were directly applicable to the question. <p>Six studies reported data on mortality and underlying tuberculosis in COVID-19 patients, and all were found to have a low or moderate threat to internal validity.</p> <ul style="list-style-type: none"> • Four cohort studies^{2, 3, 5, 6} (N = 10,575) reported effect measures or proportions suggesting an increase in mortality among patients with underlying or preexisting tuberculosis ([1.28 (95% CI: 0.71 - 2.29), p = NR]² to [2.17 (95% CI: 1.40 - 3.37), p = NR]⁶). Two cohort studies reported multivariable analyses suggesting an increase in the adjusted odds of mortality among people with COVID-19 and tuberculosis compared with people with COVID-19 alone. One of these studies⁶ (N = 530) used propensity score matching to adjust for underlying conditions, age, sex, and location, and reported a significant increase in the odds of mortality for patients with underlying tuberculosis. The other⁵ (N = 7,780) reported a non-significant increase in the adjusted odds of in-hospital mortality for patients with tuberculosis, adjusting for all other chronic respiratory diseases. One cohort study² (N = 1,075) reported univariable analyses suggesting an increase in the odds of mortality for those with COVID-19 and underlying tuberculosis compared to those without and another³ (N = 1,190) reported a significantly higher prevalence of underlying tuberculosis in patients who died compared to patients who survived. <ul style="list-style-type: none"> ○ One study² reported a confidence interval that crossed the null and one³ reported a low number of patients with tuberculosis, reducing our confidence in the findings. • Two studies^{1, 4} suggested a decrease in the odds of mortality with the presence of tuberculosis. <ul style="list-style-type: none"> ▪ One cohort study¹ (N = 21,922) reported univariable analyses suggesting a decrease in the odds of mortality for those with COVID-19 and underlying tuberculosis compared to those without, however, the confidence interval was wide and crossed the null reducing our confidence in this association [OR: 0.88 (95% CI: 0.21 – 3.70), p<0.001]. ▪ One ecological study⁴ (N = 1,544 US counties) reported on the association between county-level of COVID-19 case fatality ratios and tuberculosis. The study conducted a mixed-effects multinomial logistic regression model with an odds ratio for association between COVID-19 CFR classification (HH or LL) and age-adjusted mortality rates of other

	diseases. There was a protective association between county-level COVID-19 case fatality rates and county-level, age-adjusted mortality due to tuberculosis among counties with high COVID-19 mortality that were surrounded by counties with high COVID-19 mortalities [HH: aOR: 0.094 (95%CI: 0.012-0.761), p=0.027], [LL: aOR: 0.142 (95% CI: 0.026-0.784), p=0.025].
Hospitalization	Overall, the limited evidence from only one study suggested an increase in the risk of hospitalization. The study was found to have a moderate threat to internal validity. Aggregation indices are not measured for outcomes with only one study. <ul style="list-style-type: none"> One propensity-matched cohort study⁶ (N = 530) matched on underlying conditions, age, sex, and location, and reported a significant increase in the risk of hospitalization for patients with underlying tuberculosis [RR: 1.20 (95% CI: 1.04-1.38), p=0.012]

B.3.b. Extracted Evidence

Table 3 Extracted Studies Reporting the Association Between Tuberculosis and Severe COVID-19 Outcomes

Study	Population and Setting	Exposure	Definitions	Results
<p>Author: Fisman¹</p> <p>Year: 2020</p> <p>Data Extractor: CS</p> <p>Reviewer: DOS</p> <p>Study design: Predictive modeling</p> <p>Study Objective: To develop and validate parsimonious, sensitive, and specific prediction rules for infection-related death in individuals with COVID-19 in Ontario.</p> <p>IVA Score: 25 (moderate)</p>	<p>Population: N=1,734 (derivation cohort) N=1,796 (validation cohort) N=21,922</p> <p>Setting: 34 public health units using provincial public health case management data system</p> <p>Location: Canada</p> <p>Study dates: January 23-May 15, 2020</p> <p>Inclusion criteria: Patients within the public health case management system with laboratory-confirmed SARS-CoV-2 infection via validated nucleic acid amplification test, including RT-PCR and nucleic acid sequencing.</p> <p>Exclusion criteria: NR</p>	<p>Medical Condition, n/N (%): Anemia or hemoglobinopathy: Tuberculosis: 52/21,922 (0.2%)</p> <p>Control/Comparison group, n/N (%): <i>Calculated by ERT:</i> No tuberculosis: 21,870//21,922 (99.8%)</p>	<p>Medical Condition(s): <i>Tuberculosis:</i> ND</p> <p>Severity Measure(s): NR</p> <p>Clinical marker: NR</p> <p>Treatment/ Associated Therapy: NR</p> <p>Outcome Definitions: <i>Mortality:</i> ND <i>ICU admission:</i> NR <i>Intubation:</i> NR <i>Ventilation:</i> NR <i>Hospitalization:</i> NR <i>Non-elective readmissions:</i> NR</p> <p>Comments: none</p>	<p>Severe COVID-19: <i>OR: Univariable (Univariate) Logistic Regression</i></p> <p>Mortality, n/N (%), or Median (IQR): <i>Tuberculosis:</i></p> <ul style="list-style-type: none"> OR: 0.88 (95%CI: 0.21–3.70); p<0.001 <p>Severity of Condition: NR</p> <p>Duration of Condition: NR</p> <p>Treatment/ Associated Therapy: NR</p> <p>Comorbid Conditions: NR</p> <p>Risk Markers: NA</p> <p>Long-term Sequelae: NR</p>
Author: Li G ²	Population: N=1,075	Health Condition Category:	Medical Condition(s):	Severe COVID-19:

Study	Population and Setting	Exposure	Definitions	Results
<p>Year: 2020</p> <p>Data Extractor: CO</p> <p>Reviewer: ECS/MW/DOS</p> <p>Study Design: Cohort study</p> <p>Study Objective: To explore risk factors that drive mortality in patients (who received neither dexamethasone nor remdesivir).</p> <p>IVA Score: 21 (moderate)</p>	<p>Setting: Hospitals</p> <p>Location: China, European regions, and North America</p> <p>Study dates: January - April 2020</p> <p>Inclusion criteria: COVID-19 patients recorded during study dates.</p> <p>Exclusion criteria: Patients who received either remdesivir or dexamethasone, were hospitalized after May 1 and had missing data of therapy, or were from countries with limited online data.</p>	<p>Cerebrovascular disease; Chronic heart disease; Chronic liver disease; Diabetes; Chronic respiratory disease; Risk factors; Cancer</p> <p>Medical Condition, n/N (%): Tuberculosis: 6/399(2%)</p> <p>Control/Comparison group, n/N (%): No Tuberculosis: 393/399 (98%)</p>	<p>Tuberculosis: ND</p> <p>Severity Measure(s): NR</p> <p>Clinical marker: NR</p> <p>Treatment/ Associated Therapy: NR</p> <p>Outcome Definitions: <i>Mortality:</i> ND <i>ICU admission:</i> NR <i>Intubation:</i> NR <i>Ventilation:</i> NR <i>Hospitalization:</i> NR <i>Non-elective readmissions:</i> NR</p> <p>Comments: none</p>	<p><i>HR: Hazard Ratio</i> <i>*Odds ratio [OR] (95% CI) calculated by ERT; n/N (%)</i></p> <p><i>Mortality, n/N (%), or Median (IQR):</i> Tuberculosis: <ul style="list-style-type: none"> • HR: 1.28 (95%CI: 0.71-2.29); p=0.68 • *OR: 1.55 (95%CI: 0.31-7.78) • Non-survivor: 3/157 (2%) • Survivor: 3/242 (1%) </p> <p>Severity of Condition: NR</p> <p>Duration of Condition:</p> <p>Treatment/ Associated Therapy: NR</p> <p>Comorbid Conditions: NA</p> <p>Risk Markers: NA</p> <p>Long-term Sequelae: NR</p>
<p>Author: Liu J³</p> <p>Year: 2020</p> <p>Data Extractor: JKK</p> <p>Reviewer: DOS</p> <p>Study Design: Cohort</p> <p>Study Objective: To analyze the clinical features and potential predictors for deterioration and/or death in COVID-19 patients.</p> <p>IVA Score: 23 (moderate)</p>	<p>Population: N=1,190</p> <p>Setting: Hospital</p> <p>Data Source: electronic medical records</p> <p>Location: China</p> <p>Study Dates: December 29, 2019 – March 2, 2020</p> <p>Inclusion Criteria: All adult patients hospitalized with confirmed COVID-19 from Wuhan Infectious Disease Hospital with available laboratory results. COVID-19 diagnosis was according to WHO interim guidance.</p> <p>Exclusion Criteria: NR</p>	<p>Health Condition Category: Chronic Lung Disease</p> <p>Medical Condition, n/N (%): Tuberculosis: 15/1190 (1.3%)</p> <p>Control/Comparison Group, n/N (%): No Tuberculosis: 1175/1190 (98.7%)</p>	<p>Medical Condition(s): Tuberculosis: ND</p> <p>Severity Measure(s): NR</p> <p>Clinical Marker: NA</p> <p>Outcome Definitions: <i>Mortality:</i> ND <i>ICU admission:</i> NR <i>Intubation:</i> NR <i>Ventilation:</i> NR <i>Hospitalization:</i> NR <i>Non-elective readmissions:</i> NR</p> <p>Comments: None</p>	<p>Severe COVID-19: <i>Mortality, n/N (%):</i> Tuberculosis: <ul style="list-style-type: none"> • Deceased: 5/157 (3.3%) • Alive: 10/1,033 (1.4%) • p=0.0475 </p> <p>Severity of Condition: NR</p> <p>Duration of Condition: NR</p> <p>Comorbid Conditions: NR</p> <p>Risk Markers: NA</p> <p>Long-term Sequelae: NR</p>

Study	Population and Setting	Exposure	Definitions	Results
<p>Author: Mollalo⁴</p> <p>Year: 2021</p> <p>Data Extractor: DOS/JKK</p> <p>Reviewer: CS</p> <p>Study Design: Modelling</p> <p>Study Objective: To apply spatial and statistical analysis to better understand the geospatial distributions of the COVID-19 mortality rate (MR) and case fatality rate (CFR) in US.</p> <p>IVA Score: 22 (moderate)</p>	<p>Population: N=1,544 counties</p> <p>Setting: Nationwide</p> <p>Data Source: USAFacts data base and University of Washington Global Health Data Exchange</p> <p>Location: US</p> <p>Study Dates: January 22 – November 22, 2020</p> <p>Inclusion Criteria: Cumulative COVID-19 cases and deaths collected from <i>USAFacts</i>; age-adjusted mortality rates of 20 covariates collected from <i>University of Washington Global Health Data Exchange</i>.</p> <p>Exclusion Criteria: Counties with less than 16 reported deaths were excluded from subsequent analyses.</p>	<p>Medical Condition, n/N (%): Tuberculosis: NR</p> <p>High-High (HH): counties with high COVID-19 mortality surrounded by counties with high COVID-19 mortalities; hotspot</p> <p>Low-Low (LL): counties with low COVID-19 mortality surrounded by counties with low COVID-19 mortalities; coldspot</p> <p>Control/Comparison Group, n/N (%): Non-significant (NN): counties with non-significant COVID-19 mortalities</p>	<p>Medical Condition(s): Tuberculosis: ND</p> <p>Severity Measure(s): NR</p> <p>Clinical Marker: NR</p> <p>Outcome Definitions: <i>Mortality:</i> COVID-19 case fatality ratio (CFR): proportion of recorded death over the confirmed cases COVID-19 mortality rate (MR): mean COVID-19 mortality rate per 100,000 individuals <i>ICU admission:</i> NR <i>Intubation:</i> NR <i>Ventilation:</i> NR <i>Hospitalization:</i> NR <i>Non-elective readmissions:</i> NR</p> <p>Comments: None</p>	<p>Severe COVID-19: <i>aOR: Mixed-effects multinomial logistic regression model; Odds Ratio for association between COVID-19 CFR classification (HH or LL) and age-adjusted mortality rates of other diseases:</i></p> <p>Mortality, n/N (%): Tuberculosis</p> <ul style="list-style-type: none"> • HH: aOR: 0.094 (95%CI: 0.012-0.761); p=0.027 • LL: aOR: 0.142 (95%CI: 0.026-0.784); p=0.025 <p>Severity of Condition: NR</p> <p>Duration of Condition: NR</p> <p>Comorbid Conditions: NR</p> <p>Risk Markers: NR</p> <p>Long-term Sequelae: NR</p>
<p>Author: Oh⁵</p> <p>Year: 2021</p> <p>Data Extractor: MW</p> <p>Reviewer: CS</p> <p>Study Design: Retrospective cohort</p> <p>Study Objective: To investigate various chronic respiratory diseases (CRDs) that</p>	<p>Population: N=122,040 N=7,780 COVID-19+</p> <p>Setting: National Health Insurance Service database</p> <p>Location: South Korea</p> <p>Study dates: January 1- June 26, 2020</p> <p>Inclusion criteria: Individuals ≥20 years old, had a respiratory disease diagnosis by the</p>	<p>Health Condition Category: Cerebrovascular Disease, Chronic Heart Disease, Chronic Liver Disease, Neurocognitive Disorders, Diabetes, Chronic Kidney Disease, Chronic Lung Disease, Risk Factors, Immunocompromised Status, Blood Disorders, Cancer, Disabilities</p> <p>Medical Condition, n/N (%): Tuberculosis of lung: 608/122,040 (0.5)</p> <p>Control/Comparison group, n/N (%): No tuberculosis of lung: 121,432/122,040 (99.5)</p>	<p>Medical Condition(s): <i>Tuberculosis of lung:</i> A15</p> <p>Severity Measure(s): NA</p> <p>Clinical marker: NR</p> <p>Treatment/ Associated Therapy: NR</p> <p>Outcome Definitions: <i>Mortality:</i> ND <i>ICU admission:</i> NR <i>Intubation:</i> NR <i>Ventilation:</i> NR <i>Hospitalization:</i> NR <i>Non-elective readmissions:</i> NR</p>	<p>Severe COVID-19: <i>aOR: Adjusted odds ratio; multivariable logistic regression</i></p> <p>Mortality, n/N (%), or Median (IQR): <i>Tuberculosis of lung:</i></p> <ul style="list-style-type: none"> • aOR: 1.65 (95%CI: 0.48-5.64); p=0.423 <p>Severity of Condition: NA</p> <p>Duration of Condition: NR</p> <p>Treatment/ Associated Therapy: NR</p> <p>Comorbid Conditions: NR</p>

Study	Population and Setting	Exposure	Definitions	Results
<p>affect the risk of COVID-19 among the general population in South Korea, and to examine the effect of different CRDs on hospital mortality among patients with COVID-19 in South Korea.</p> <p>IVA Score: 25 (moderate)</p>	<p>International Classification of Diseases codes, and prescription information concerning drugs and/or procedures from 2015-2020 were included. COVID-19 negative individuals were extracted from the national database using stratification methods with regard to age, sex, and residence in February 2020.</p> <p>Exclusion criteria: NR</p>		<p>Comments: None</p>	<p>Risk Markers: NA</p> <p>Long-term Sequelae: NR</p>
<p>Author: Sy⁶</p> <p>Year: 2020</p> <p>Data Extractor: ECS</p> <p>Reviewer: JKK</p> <p>Study Design: Retrospective propensity score matched cohort</p> <p>Study Objective: To compare the risk of and time-to-death and recovery in COVID-19 patients with and without TB coinfection in the Philippines.</p> <p>IVA Score: 26 (moderate)</p>	<p>Population: N = 530</p> <p>Setting: Philippine national COVID-19 surveillance</p> <p>Location: Philippines</p> <p>Study dates: May 17 – June 15, 2020</p> <p>Inclusion criteria: All reported COVID-19 cases in the Philippines during study dates confirmed with RT-PCR from laboratories accredited by the DOH and Research Institute for Tropical Medicine.</p> <p>Exclusion criteria: Patients with missing covariates on variables from the propensity score matching.</p>	<p>Health Condition Category: Chronic Lung Disease</p> <p>Medical Condition, n/N (%): Tuberculosis: 106/530 (20%)</p> <p>Control/Comparison group, n/N (%): No Tuberculosis: 424/530 (80%)</p>	<p>Medical Condition(s): Tuberculosis: confirmed TB = a history of or a current diagnosis of TB Comorbidity data: encoded in case identification form</p> <p>Severity Measure(s): NR</p> <p>Clinical marker: NR</p> <p>Treatment/ Associated Therapy: NR</p> <p>Outcome Definitions: <i>Mortality:</i> deaths during active COVID-19, and declared as a death by the DOH-EB <i>ICU admission:</i> NR <i>Intubation:</i> NR <i>Ventilation:</i> NR <i>Hospitalization:</i> NR <i>Non-elective readmissions:</i> NR</p> <p>Comments: None</p>	<p>Severe COVID-19: <i>Propensity score matched using nearest neighbor matching of propensity scores, a caliper of 0.05, and with no replacement</i> <i>RR: Relative Risk</i></p> <p>Mortality, full cohort, n/N (%):</p> <ul style="list-style-type: none"> • HR: time to death was shorter in propensity score matched patients with TB than those without in both the full cohort (p=0.0031) and the subsample of admitted patients (p=0.0052) • RR: 2.17 (95%CI: 1.40 - 3.37); p = 0.001 • Tuberculosis: 25/106 (23.6) • No Tuberculosis: 46/424 (10.8) • p = 0.001 <p>Mortality, sub-analysis of admitted persons n/N (%):</p> <ul style="list-style-type: none"> • RR: 2.25 (95%CI: 1.35-3.75); p=0.002 • Tuberculosis: 18/66 (27.3%) • No Tuberculosis: 32/264 (12.1%) • p = 0.004 <p>Hospitalization, full cohort n/N (%):</p> <ul style="list-style-type: none"> • RR: 1.20 (95%CI: 1.04-1.38); p=0.012 • Tuberculosis: 67/106 (63.2%) • No Tuberculosis: 236/424 (55.7%) • p = 0.038

Study	Population and Setting	Exposure	Definitions	Results
				<p>Severity of Condition: NR</p> <p>Duration of Condition: NR</p> <p>Treatment/ Associated Therapy: NR</p> <p>Comorbid Conditions: No statistically significant difference in proportion of underlying comorbidities between COVID-19(+) persons with or without TB. Comorbidities included Hypertension, diabetes, cancer, renal cancer, cardiac disease, asthma, COPD, and autoimmune disease.</p> <p>Risk Markers: NR</p> <p>Long-term Sequelae: NR</p>

B.3.c. Internal Validity Assessments of Extracted Studies

Table 4. Internal Validity Assessments of Extracted Studies Reporting the Association Between Tuberculosis and Severe COVID-19 Outcomes

	Author Year	Fisman 2020 ¹	Li G 2020 ²	Liu J 2020 ³	Mollalo 2021 ⁴	Oh 2021 ⁵	Sy 2020 ⁶
	Outcome(s)	Mortality	Mortality	Mortality	Association between COVID-19 mortality and mortalities for other diseases	Mortality	Mortality, Hospitalization
Domain	Signaling question	Data retrieved from electronic medical records	Data retrieved from medical records	Data extracted from electronic medical records	Data retrieved from USAFacts and multiple databases	Data extracted from National Health Insurance Service database	Data provided to the National Department of Health
Study Elements	Design appropriate to research question	1	1	1	1	1	1
	Well described population	1	0	1	1	1	1
	Well described setting	1	0	1	1	1	1
	Well described intervention/ exposure	1	1	1	1	1	1
	Well described control/ comparator	1	1	1	1	1	1
	Well described outcome	1	1	1	1	1	1
Selection Bias: Sampling	Clear timeline of exposures/ interventions and outcomes	1	1	1	0	1	1
	Randomization appropriately performed	0	0	0	0	0	0
	Allocation adequately concealed	0	0	0	0	0	0
Selection Bias: Attrition	Population sampling appropriate to study design	1	1	1	1	1	1
	Attrition not significantly different between groups	1	1	1	1	1	1
	Attrition <10-15% of population	1	1	1	1	1	1
Information Bias: Measurement and Misclassification	Attrition appropriately analyzed	1	0	1	1	1	1
	Measure of intervention/ exposure is valid	1	1	1	1	1	1
	Measure of outcome is valid	1	1	1	0	1	1
	Fidelity to intervention is measured	0	0	0	0	0	0
	Fidelity to intervention is valid	0	0	0	0	0	0
	Prospective study	1	1	1	0	1	1
Information Bias:	Adequately powered to detect result	1	0	0	0	1	1
	Outcome assessor blinded	0	0	0	0	0	0
	Study participant blinded	0	0	0	0	0	0
	Investigator/ data analyst blinded	0	0	0	0	0	0

	Author Year	Fisman 2020 ¹	Li G 2020 ²	Liu J 2020 ³	Mollalo 2021 ⁴	Oh 2021 ⁵	Sy 2020 ⁶
	Outcome(s)	Mortality	Mortality	Mortality	Association between COVID-19 mortality and mortalities for other diseases	Mortality	Mortality, Hospitalization
Domain	Signaling question	Data retrieved from electronic medical records	Data retrieved from medical records	Data extracted from electronic medical records	Data retrieved from USAFacts and multiple databases	Data extracted from National Health Insurance Service database	Data provided to the National Department of Health
Performance & Detection	Data collection methods described in sufficient detail	1	1	1	1	1	1
	Data collection methods appropriate	1	1	1	1	1	1
	Sufficient follow up to detect outcome	1	1	1	1	1	1
Information Bias: Analytic	Appropriate statistical analyses for collected data	1	1	1	1	1	1
	Appropriate statistical analyses are conducted correctly	1	1	1	1	1	1
	Confidence interval is narrow	0	0	0	1	0	1
Confounding	Potential confounders identified	1	1	1	1	1	1
	Adjustment for confounders in study design phase	0	0	0	0	0	1
	Adjustment for confounders in data analysis phase	1	1	0	1	1	0
Reporting Bias	All pre-specified outcomes are adequately reported	1	1	1	1	1	1
Other Bias	No other sources of bias	1	1	1	1	1	1
COI	Funding sources disclosed and no obvious conflict of interest	1	1	1	1	1	1
SCORE	Threat to internal validity	25	21	23	22	25	26
	Low, Moderate, High	Moderate	Moderate	Moderate	Moderate	Moderate	Low

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Abbreviations

Acronym	Full
95% CI	95% confidence interval
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
BMI	body mass index
BPD	bronchopulmonary dysplasia
CF	cystic fibrosis
CFR	case fatality ratio
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
CRD	chronic respiratory disease
ECMO	extracorporeal membrane oxygenation
EHR	electronic health record
EMR	electronic medical record
ERT	evidence review team
IQR	Interquartile range
GLM	generalized linear model
HH	high-high counties
HR	hazard ratio
ICD10	International Classification of Diseases 10
ICNARC	Intensive Care National Audit and Research Centre
ICS	inhaled corticosteroids
ICU	intensive care unit
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IVA	Internal validity assessments
LL	low-low counties
MR	mortality Rate

ND	not defined
NR	not reviewed
OR	odds ratio
PCR	polymerase chain reaction
PECO	population, exposure, comparator, and outcomes
PMSI	Programme de Medicalisation des Systemes d'Information
RR	rate ratio
RT-PCR	real time polymerase chain reaction