THE ASSOCIATION OF SARS-COV-2 INFECTION AND TUBERCULOSIS DISEASE WITH UNFAVORABLE TREATMENT OUTCOMES: A SYSTEMATIC REVIEW

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BACKGROUND

- Tuberculosis (TB) was the leading cause of death globally due to a single infectious agent prior to the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.[1]
- SARS-CoV-2 pandemic have stressed the health system and led to substantial reductions in TB diagnosis and, after over a decade of consistent declines, the WHO estimated that TB deaths increased in 2020 and 2021.[2,3]
- Whether SARS-CoV-2 infection and its management influence tuberculosis (TB) treatment outcomes is uncertain.[4]
- We synthesized evidence on the association of SARS-CoV-2 coinfection (*Coinfection Review*) and its management (*Clinical Management Review*) on treatment outcomes among people with tuberculosis (TB) disease.

OBJECTIVES

- To conduct a systematic review to synthesize evidence on SARS-CoV-2 and TB to answer two questions:

  (1) Do persons treated for TB have worse outcomes when infected with SARS-CoV-2?

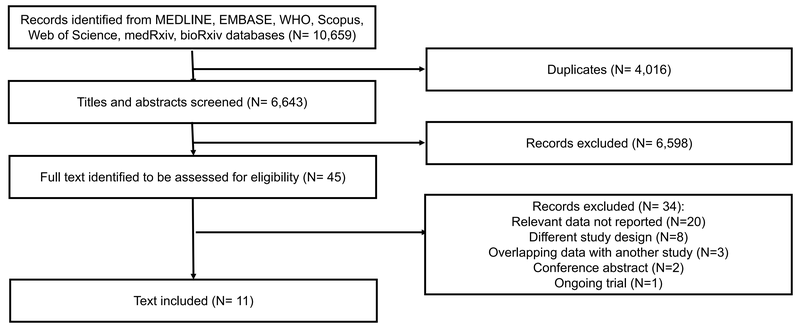
  (2) Do steroids or other immunomodulating treatments improve outcomes for persons with TB and SARS-CoV-2 coinfection?

METHODS

- This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.
- Literature search conducted from 1 January 2020 to 3 April 2023 in MEDLINE, Embase, Web of Science, Scopus, medRxiv, bioRxiv, and the WHO library databases.
- A combination of free text terms and MeSH terms containing concepts related to SARS-CoV-2, COVID-19, and tuberculosis were used.
- We included randomized controlled trials, cohort, and case-control studies published in any language with an English abstract available that (1) compared TB treatment outcomes among those who tested positive for SARS-CoV-2 compared with those who tested negative for SARS-CoV-2 and/or (2) compared TB and/or COVID-19 outcomes among those with SARS-CoV-2 and TB coinfection treated with vs. without corticosteroids or other immunomodulating treatments.
- Data collected on study population, location, design, dates of recruitment and follow-up, demographic and clinical characteristics, diagnosis methods, TB and SARS-CoV-2 treatments provided, and study outcomes.
- Study quality was assessed with an adapted Newcastle Ottawa Scale.[2]
- Data were heterogeneous and a narrative review was performed.

RESULTS

FIGURE 1: PRISMA FLOW DIAGRAM



- From 9,529 records, we included 11 studies and 7305 unique participants with a median (range) number of participants per study of 139 (20-5,409).
- No study reported data relevant to our review in their primary publication and data contributed by study authors after contact.

TABLE 1: CHARACTERISTICS OF INCLUDED STUDIES

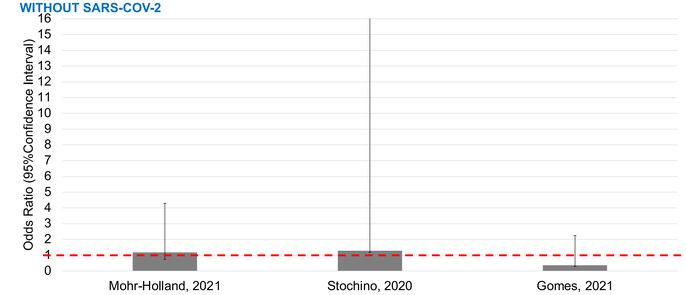
AUTHOR (YEAR)	STUDY DESIGN	COUNTRY	SETTING	STUDY PERIOD	NUMBER OF PARTICIPANTS	TB CHARACTERISTICS	HIV-COINFECTION	SEX DISTRIBUTION	AGE OF PARTICIPANTS (YEARS)
TB Patients Co-infected with SARS-CoV-2 vs. TB Patients without SARS-CoV-2									
Kilic (2022)	1	Turkey	1	Nov 2019 - Apr 2020	20 participants in total; 4 TB/SARS-CoV-2 Co-infected, 16 only TB	U	U	Co-infected: 25% F Only TB: 12% F	Median Age of: Co-infected = 45 Only TB = 53
Mohr-Holland (2021)	1	South Africa	3	Mar 2020 - Jun 2021	139 participants in total; 36 TB/SARS-CoV-2 Co-infected, 103 only TB	123 (88%) pulmonary TB; 139 (100%) RR-TB	103 (74%)	48% F	Median: 35 (IQR 30-48)
Stochino† (2020)	1	Italy	2	Mar- Apr 2020	24 participants in total; 20 TB/SARS-CoV-2 Co-infected, 4 only TB	23 (96%) pulmonary TB; 3 (13%) RR-TB	1 (4%)	Co-infected: 40% F Only TB: 50% F	Median Age of: Co-infected = 39 Only TB = 27
du Bruyn (2021)	2	South Africa	2	Jun - Aug 2020	20 participants in total; 15 TB/SARS-CoV-2 Co-infected, 5 only TB	2 (10%) RR-TB	13 (65%)	52% F	Median Age of: Co-infected = 37 Only TB = 42
Gubkina (2020)	1	Russia	2	Apr - Jul 2020	25 participants in total; 8 TB/SARS-CoV-2 Co-infected, 17 only TB*	18 (72%) pulmonary TB	U	76% F	Median: 9 (Range: 3-12)
Gomes (2021)	1	Brazil	2	Sep 2020 - Feb 2021	83 participants in total; 3 TB/SARS-CoV-2 Co-infected, 80 only TB**	73 (88%) pulmonary TB; 48 (58%) RR-TB	6 (7%)	40% F	Median: 55
Zulmansyah (2021)	1	Indonesia	2	Jun - Nov 2020	29 participants in total; 16 TB/SARS-CoV-2 Co-infected, 13 only TB	U	0 (0%)	~100% M	Range: 18-86
Kumar (2021)	1	India	3	Oct 2020 - Mar 2021	5409 participants in total; 184 TB/SARS-CoV-2 Co-infected, 5225 only TB	U	U	34% F	Median: 50
TB Patients Co-Infected With SARS-CoV-2 Receiving Steroids or Immunomodulating Treatments vs. TB Patients Co-Infected with SARS-CoV-2 Not Receiving These Treatments									
Jassat (2021)	1	South Africa	2	Oct 2020 - Apr 2022	806 participants in total; 117 receiving steroid or IM treatment, 689 no treatment	U	435 (54%)	Treatment = 47% F No Treatment = 45% F	Median Age of: Treatment = 41 No Treatment = 44
The TB/COVID-19 Global Study Group (2022)	3	Multi-country (34 total)	3	2020-2021	118 participants in total;*** 23 receiving steroid or IM treatment, 95 no treatment	99 (84%) pulmonary TB; 16 (14%) DR-TB	16 (14%)	30% F	Median: 44 (IQR 31-58)
du Bruyn (2021)	2	South Africa	2	Jun - Aug 2020	15 participants in total; 8 receiving steroids or IM treatment, 7 no treatment	2 (13%) RR-TB	8 (53%)	U	Median: 37
Davies (2022)	1	South Africa	2	Nov 2020 - Jan 2021	740 participants in total; 157 receiving steroid or IM treatment, 583 no treatment	U	439 (59.3%)	Treatment = 47% F No Treatment = 52% F	Median Age of: Treatment = 41 No Treatment = 40

Abbreviations: RR-TB, rifampicin-resistant tuberculosis; TB, tuberculosis; DR-TB, drug-resistant tuberculosis; HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; U, unknown; IM, immunomodulating. Study Design: 1: Retrospective Cohort; 2: Retrospective Case-Control; 3: Multi-study analysis with retrospective designs. Setting: 1: Outpatient; 2: Hospital; 3: Outpatient and Hospital
*16/17 (94%) participants with only TB had evidence of previous SARS-CoV-2 infection via serological test ; **21/80 (26%) participants with only TB had evidence of previous SARS-CoV-2 infection via serological test; ***Of the 118 participants, 5 (4%) had SARS-CoV-2 diagnosed >28 days prior to TB, 52 (44%) had SARS-CoV-2 diagnosed within 28 days of TB, and 61 (52%) had SARS-CoV-2 diagnosed >28 days after initiating TB treatment; †One patient in this cohort is also reported in The TB/COVID-19 Global Study Group cohort, however they are not double counted in analyses.

- Eight studies of 5749 persons treated for TB (286 [5%] with SARS-CoV-2) were included in the Coinfection Review.
- Four studies with 1572 TB patients—of whom 291 (19%) received corticosteroids or other immunomodulating treatment—were included in the Clinical Management Review

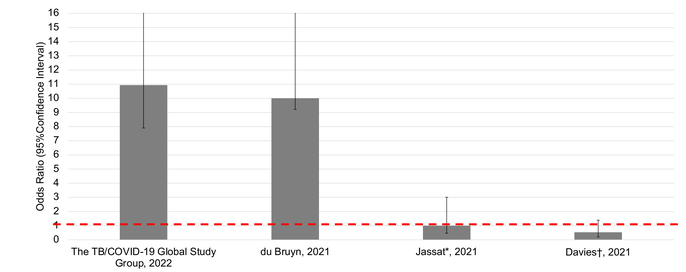
RESULTS

FIGURE 2: EVALUATING UNFAVORABLE TB OUTCOMES IN TB PATIENTS CO-INFECTED WITH SARS-COV-2 VS. TB PATIENTS WITHOUT SARS-COV-2



- Five studies reported our primary outcome (highlighted in red in Table 1)
- Two studies have no patients without SARS-COV-2 and in the other three studies, there was no significant association between SARS-CoV-2 coinfection and unfavorable TB treatment outcomes (Figure 2).

FIGURE 3: EVALUATING UNFAVORABLE TB OUTCOMES IN TB PATIENTS CO-INFECTED WITH SARS-COV-2 RECEIVING STEROIDS OR IMMUNOMODULATING TREATMENT VS. NOT RECEIVING SUCH TREATMENT



*Odds ratios for this study are adjusted based on age, sex, previous tuberculosis history, HIV/ART, and use of supplemental oxygen.
†This study estimates hazard ratios, which are adjusted based on age, sex, HIV, variant wave, full vaccination status, geographic location in Western Cape, diabetes, hypertension, chronic kidney disease, prior chronic obstructive pulmonary disease, and previous tuberculosis history.

- Four studies reported our secondary outcome (highlighted in blue in Table 1)
- There was no significant association between SARS-CoV-2/ TB coinfected receiving steroids or immunomodulating treatment on unfavorable TB treatment outcomes (Figure 2).
- Studies were likely confounded by indication and discordant findings existed among studies with vs. without statistical adjustment.

CONCLUSIONS

- It was unclear whether persons treated for TB with SARS-CoV-2 are at increased risk of unfavorable TB treatment outcomes when compared to those without SARS-CoV-2.
- It was also unclear whether the use of corticosteroids or other immunomodulating treatments were associated with improved outcomes in persons with TB/SARS-CoV-2 coinfection.
- Considering the overall low quality of the available evidence, future research is urgently needed to improve our understanding of the risk of unfavorable TB treatment outcomes by SARS-CoV-2 infection status and the optimal management of persons treated for TB with SARS-CoV-2 infection.

FINANCIAL DISCLOSURES

NKV reports receiving consulting fees from Broadstreet HEOR for unrelated projects. JRC reports receiving consulting fees from the COVID-19 Immunity Task Force (Canada) and The World Bank, for unrelated projects. Other authors do not have conflicts to declare.