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Global prevalence, treatment and outcome of tuberculosis and COVID-19 coinfection: a systematic review and meta-analysis (from November 2019 to March 2021)

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ABSTRACT

Introduction The COVID-19 outbreak poses a significant threat to the patients with tuberculosis (TB). TB and COVID-19 (TB–COVID) coinfection means the disease caused by both *Mycobacterium tuberculosis* and SARS-CoV-2 infection. Currently, the prevalence status, treatment and outcomes of the coinfection are poorly characterised. We aimed to systematically review the evidence on this topic and provide comprehensive information to guide the control and treatment of TB–COVID coinfection.

Methods An extensive screening was conducted using six electronic databases to search eligible studies from 1 November 2019 to 19 March 2021. Prevalence rate, treatment and outcomes of TB–COVID coinfection were extracted. Random-effects models were used to calculate mean fatality rates of coinfection with 95% CIs. The risks of bias were assessed with the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Study Reporting Prevalence Data and JBI Critical Appraisal Checklist for Case Report. A meta-analysis was conducted for subgroups on in-hospital fatality rate.

Results Forty-two studies were included into the analysis (35 case reports and 7 retrospective cohort studies). Nineteen countries reported coinfected patients, including high and low TB prevalence countries. The only study revealing prevalence rate came from West Cape Province, South Africa (people aged above 20 years, 0.04% until 1 June 2020 and 0.06% until 9 June 2020). The treatment regimens for coinfected patients were highly heterogeneous. The mean overall and in-hospital fatality rates of coinfection were 13.9% (95% CI: 1.6% to 26.2%) and 17.5% (95% CI: 8.9% to 26.0%). The mean in-hospital fatality rates for high-income countries (Italy and Argentina) and low/middle-income countries (LMICs) (India, Philippines, South Africa) were 6.5% (95% CI: −0.8% to ~13.9%) and 22.5% (95% CI: 19.0% to ~26.0%).

Conclusion TB–COVID coinfection is common globally, and the coinfected patients suffer from higher fatality risk than patients with normal COVID-19. Outcomes shared significant differences between high-income countries and LMICs.

PROSPERO registration number CRD42021253660.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analysis provided comprehensive information on prevalence status, treatment plans and possible outcomes of tuberculosis and COVID-19 coinfection.
⇒ We collected evidence from case reports regarding information about patients' basic information, treatment regimens and outcomes.
⇒ Subgroup analysis was conducted to explore the possible reason for different fatality rates in different areas.
⇒ We did not include comorbidity as a keyword and Medical Subject Heading term in the searching process, which might keep us from some relevant studies.

INTRODUCTION

Individuals with chronic respiratory infections, including tuberculosis (TB), had been disproportionally hit by the COVID-19 pandemic.[1] The burden and impact of TB control and treatment are widely acknowledged with the ongoing pandemic. The number of people who fell ill with TB in 2019 is estimated to be 10 million.[2] The top seven countries account for two-thirds of the total global cases in 2018, while most high prevalence rate countries locate in South-East Asia and Africa.[3] Patients with TB have an increased risk of mortality during coinfection with COVID-19.[4] Recently, some researchers identified TB as a risk factor to severe COVID-19,[5] and some studies suspected that the COVID-19 could reactivate or worsen TB.[6 7] From the perspective of pathology, the disorders induced by SARS-CoV-2 and *Mycobacterium tuberculosis* to the immunomodulation tend to induce an unbalanced inflammatory response, promoting the progression and worsening of both diseases.[8] Besides,

the use of immunosuppressive drugs on patients with severe COVID-19 may increase the likelihood of active TB caused by reactivation or new infection.[9] On the other side, the COVID-19 outbreak has put the patients with TB and the entire healthcare system in an unprecedented crisis. Many experts have recognised the effects of the COVID-19 pandemic on TB treatment and control. As warned by Global Tuberculosis Network Group, COVID-19 has fuelled TB infections and mortality.[6] In low/middle-income countries (LMICs), the situation is even worse. As estimated by Kissler *et al*, the transmission of SARS-CoV-2 is likely to enter into regular circulation,[10] which would be a deadly threat to people in LMICs, especially when most of them cannot stand the chance of getting COVID-19 vaccine.[11] Regrettably, people in these countries are also the main victims of TB.[2]

Although cases of coinfection and studies about prevalence status have been reported from several countries,[12] we did not find a standard definition of the TB and COVID-19 (TB–COVID) coinfection. Therefore, in this systematic analysis, we preliminarily described the TB–COVID coinfection as the disease caused by both *M. tuberculosis* and SARS-CoV-2 infection. However, much of the research up to now has been descriptive in nature and focused on the observation of several coinfected patients, which can only provide weak evidence to guide the treatment for TB–COVID coinfection. Furthermore, few scholars have conducted a systematic review in this field, and there is no general agreement about the prevalence, treatment and outcome of the coinfection worldwide.

Although a few health alerts and guidelines for people with increased risk of adverse outcomes in COVID-19 have been issued by WHO and the Center for Disease Control and Prevention,[13] there is a dearth of information regarding the impact of COVID-19 in patients with TB, and the actual impact of TB on occurrence and clinical outcomes of COVID-19 is not clear. This study aims to systematically analyse the current evidence on global prevalence status, treatment protocols, and possible outcomes of TB–COVID coinfection.

METHODS

This systematic review protocol followed the International Prospective Register of Systematic Reviews (PROSPERO) guideline and has been registered in PROSPERO's database (registration number: CRD42021253660). The study followed the Preferred Reporting Items in Systematic Reviews and Meta-Analyses guideline[14] (online supplemental table 1).

Eligibility criteria of included studies

Studies on patients who had been confirmed with both TB and COVID-19 were included. We excluded studies that only mentioned the fatality and the number of coinfected patients less than 10 to avoid a large deviation in fatality rate, which would affect the results of the meta-analysis (MA).

This systematic review included any kind of treatment for TB or COVID-19, including supportive therapy, directed therapy, antiretroviral treatment, intensive care unit (ICU) care, etc.

We sought prevalence rate data of any region and figured out all countries that reported coinfected patients. The primary outcome of interest was in-hospital survival or mortality, and secondary outcomes were disease progression, time to discharge from the ICU and hospital (for survivors), and time to death (for the dead).

Case reports, cross-sectional studies and cohort studies were included to explore the global prevalence status. In addition, case reports, cross-sectional studies, cohort studies, and quasi-experimental studies that revealed the treatment and outcome of TB–COVID coinfection were targeted. We excluded all reviews, editorials or commentaries, and clinical guidelines.

Search strategy

An extensive literature search was conducted using PubMed, Web of Science, Scopus, ProQuest, Embase and Cochrane library databases. Manual reference screens from included studies were performed to ensure the inclusion of all relevant studies. The study's publication date was between 1 November 2019 and 19 March 2021. With the librarian's (JZ) help, we used building blocks searching strategy to ensure all the relevant studies were screened. The searching process used Medical Subject Heading (MeSH) terms and title/abstract words around two areas: (1) COVID-19, including COVID-19, SARS-COV-2, (2) tuberculosis, including tuberculosis, TB, Mycobacterium tuberculosis, M.tuberculosis (online supplemental table 2). The citation manager EndNote V.20 (Thomson Corporation, Canada) removed duplicate studies, and we spent special efforts on the same patients or cohorts among different papers.

Data extraction

Two reviewers (QW and SG) independently conducted the study selection (review of titles and abstracts, review of full texts and final decision), data abstraction and quality assessment. Covidence (Covidence Company, Australia) was used to help us finish all the above processes. All non-English and non-Chinese articles were translated to English by Baidu Translation (Baidu Co, China). We recorded exclusion reasons for all excluded studies in the full-text screen step during the review process. The conflicts between two reviewers were discussed and eventually resolved with another author's help (NX).

Since this systematic review got two research objectives, two categories of information were extracted: (1) data about the prevalence, (2) data about treatment and outcome. For the first category, we stressed locations (nation or province, especially for case reports) of studies and the following information: age, gender, sample size, time, prevalence rate and fatality rate. As for the second category, treatments for TB and COVID-19 were recorded separately, as well as the primary and secondary outcomes

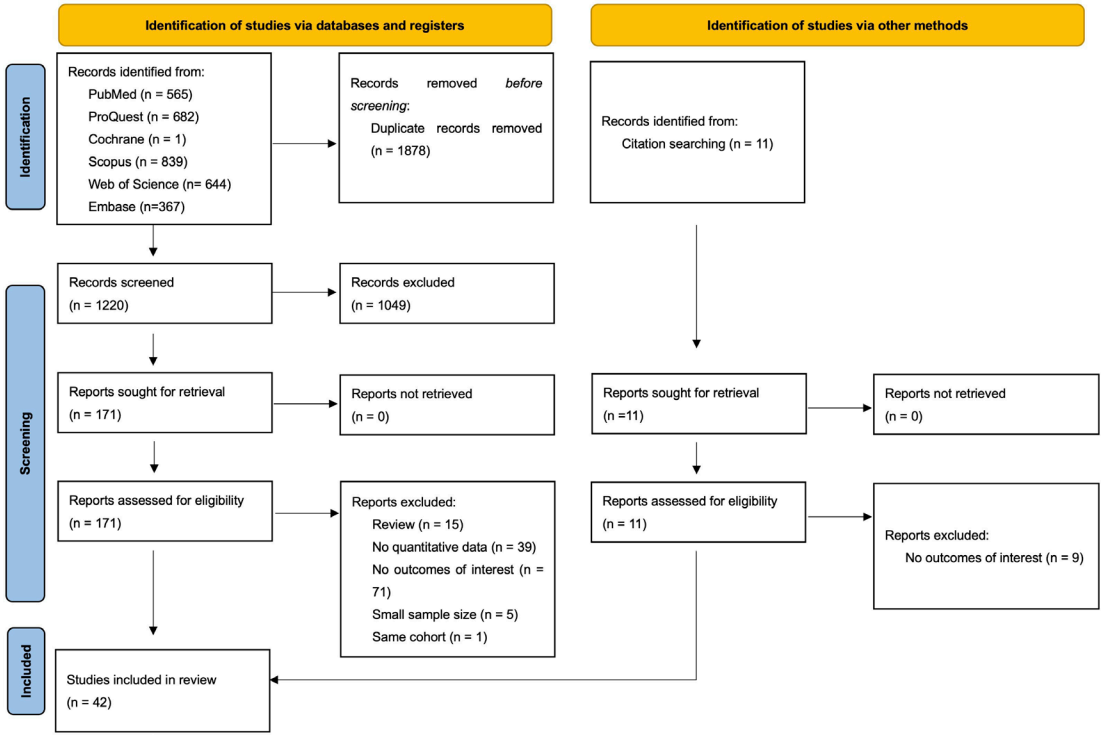

Figure 1 Flow diagram that outlines the study selection process.

(eg, disease progression, time to discharge from the ICU and hospital, and time to death). Besides, we also stressed patients' basic information in both parts, like TB site, TB type, drug resistant status, comorbidity, BCG vaccination, etc.

Quality assessment

We used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Study Reporting Prevalence Data for the prevalence part as the tool.[15] Nine questions in this checklist were set to assess the quality of studies, including sample frame, sample size, study setting, data analysis, validation, measurement and response rate. All included studies were case reports for the treatment and outcome review, so we applied the JBI Critical Appraisal Checklist for Case Report[16] as the tool which consists of eight questions about sample, patients' condition, test and assessment, intervention, data analysis, validation, measurement and response rate.

Data synthesis

A narrative synthesis method was introduced to list the prevalence status of coinfection. Key findings such as the countries and regions of the case reports were extracted to probe the potential prevalence of TB–COVID coinfection. We condensed the information about treatment into three categories: treatment before hospitalisation, treatment in hospital and treatment after discharge. We also sorted out the treatment in the hospital into four kinds: supportive treatment, antibiotics, antiviral drugs and other treatment. The narrative synthesis in this systematic review followed Cochrane's Consumers and Communication Review Group review protocol.[17] We conducted MA about the fatality rate of coinfected patients using the inverse variance statistical method to pool the data and estimate its 95% CI. Due to the highly heterogeneous treatment method for patients as well as patients themselves, we chose the random-effects model in MA, and the heterogeneity was evaluated with I^2 statistic. The funnel plot was created to test the bias.

Subgroup set

Studies were grouped into the following subgroups for further analysis: high-income country and LMIC groups. We would like to explore the possible difference in fatality rates among different types of country.

Patient and public involvement

Patients were not involved in this systematic review.

RESULTS

We searched 565 studies from PubMed, 682 from ProQuest, 839 from Scopus, 644 from Web of Science, 367 from Embase and 1 from the Cochrane database. After removing 1878 duplicate studies, we got 1220 studies and imported them into Covidence. With the help of Covidence, we excluded 1049 studies in the title and abstract screen step. Next, we carefully reviewed the full text of the remaining 171 studies, and then we excluded 131 studies from them. We also found 11 possibly relevant studies during the full-text reviewing process, 9 of which were excluded. The most common reasons for exclusion were no outcomes of interest (n=80) and no quantitative data (n=39). The entire process is shown in figure 1. Among the 42 included studies, 35 were case reports and 7 were

Table 1 Study characteristics of case reports (n=35)

Study characteristic	Studies (%)	Cases (%)
Publication year		
2020	29 (82.9)	49 (89.1)
2021	6 (17.1)	6 (10.9)
Country		
India	5 (14.3)	5 (9.1)
Indonesia	1 (2.9)	1 (1.8)
China	5 (14.3)	11 (20.0)
Saudi Arabia	2 (5.7)	2 (3.6)
Qatar	2 (5.7)	7 (12.7)
Singapore	1 (2.9)	4 (7.3)
Turkey	2 (5.7)	3 (5.5)
Haiti	1 (2.9)	1 (1.8)
Argentina	1 (2.9)	3 (5.5)
The USA	4 (11.4)	4 (7.3)
Brazil	2 (5.7)	3 (5.5)
Panama	1 (2.9)	2 (3.6)
Nigeria	2 (5.7)	3 (5.5)
South Africa	2 (5.7)	2 (3.6)
Morocco	1 (2.9)	1 (1.8)
Italy	2 (5.7)	2 (3.6)
France	1 (2.9)	1 (1.8)

retrospective cohort studies. No experimental study was identified.

Global prevalence status

Until 19 March 2021, there were 35 case reports from 17 countries, including India,[18–22] Indonesia,[23] China,[24–28] Saudi Arabia,[29 30] Qatar,[31 32] Singapore,[33] Turkey,[34 35] Haiti,[36] Argentina,[37] USA,[38–41] Brazil,[42 43] Panama,[44] Nigeria,[45 46] South Africa,[47 48] Morocco,[49] Italy[50 51] and France.[52] Totally, 55 cases were described in these 35 reports. China, India and the USA were the top three countries with the most studies, and 29 (82.9%) studies were published in 2020. Table 1 shows the study characteristics of these case reports. Besides, we also identified coinfected patients from Belgium and Switzerland in Motta *et al*'s paper.[53]

The only large-scale study about the prevalence rate came from West Cape Province, South Africa.[54] The author used the Western Cape Provincial Health Data Centre data, which included 3 460 932 individuals aged 20 years or above, about half of the population in West Cape Province. Until 1 June 2020, when testing criteria changed with public sector tests being limited to patients >55 years of age or with comorbidity, 1489 coinfected patients (including previous TB and current TB) were recorded, and the prevalence rate of coinfection was about 0.04%. Until 9 June 2020, 2128 coinfected patients (including previous TB and current TB) were recorded, and the prevalence rate was about 0.06%.

Treatment and outcome

Until the end of search, no cohort study, cross-sectional study or experimental study was identified to provide detailed information on TB–COVID coinfection treatment. Presented were the results of the included 35 studies which reported 55 coinfected patients in total. As for the basic information, 12 patients were female, and 47 patients were aged 20–60 years. Up to 50 cases were reported as patients with active TB, 12 of which got TB before COVID-19, and we could not identify infection orders about the rest of the 38 cases. Besides, four cases were reported as post-TB,[24] and one was reported as latent TB.[27] Although most cases were diagnosed with pulmonary TB, there were still some more complex conditions, like central nervous system involvement,[21 38] tuberculous meningitis,[28] tuberculous pleuritis[26 27 31] and peritoneal TB.[41] With regard to drug resistance, 37 patients' information was missing; 15, 2 and 1 of the remaining 18 cases were reported as negative,[22 23 29 30 37 39 42–44 46 48 51] positive[27 36] and likely positive.[18] All the cases were symptomatic patients with COVID-19. Check online supplemental table 3 for detailed information.

Only five patients received treatment before hospitalisation. Among them, three received anti-TB treatment (ATT),[22 34 44] one received antibiotic (amoxicillin)[38] and one took haemodialysis due to chronic kidney failure.[35] During the hospitalisation, seven patients were transferred to the ICU.[18 30 34 35 39 44 52] Up to 50 cases' detailed treatment information was reported. Various kinds of oxygen support were the most common supportive treatment (21 cases), and one patient in China received extracorporeal membrane oxygenation.[27] Except for several cases that did not provide any detailed ATT regimen (12 cases) or patients who did not receive ATT (11 cases), one or several kinds of first-line anti-TB drugs, including rifampicin, isoniazid, ethambutol and pyrazinamide, were used in most remaining cases (27 cases). For the patients with drug-resistant TB, the doctors would adjust the regimen for them.[27 36] Other kinds of antibiotics were also used, including azithromycin (21 cases), ceftriaxone (13 cases), moxifloxacin (7 cases) and linezolid (4 cases). However, we could not identify the purpose of these extra antibiotics due to the lack of information. We guessed it could be one or more of the following situations: (1) supplement to ATT regimen, (2) prevention against possible bacterial infections and (3) treatment for the existing bacterial infection. Among these 50 cases, 13 cases did not mention any kind of antiviral drug and 2 cases did not provide antiviral drugs' names. Within the remaining cases, hydroxychloroquine (HCQ) was the most used antiviral drug (21 cases), as well as lopinavir (8 cases), ritonavir (8 cases) and arbidol (7 cases). We also found that all the 20 Chinese coinfected patients did not take HCQ completely but took arbidol most. Besides, drugs like steroids (methylprednisolone, dexamethasone, prednisone, etc), anticoagulant drugs and vitamins (vitamin C, vitamin B_6, etc) were also prescribed for some patients. We identified information concerning treatment after

discharge for 10 patients; 8 of them received ATT and 2 received treatment for existing comorbidity. Although there was no doubt that the regimens for TB and COVID-19 coinfected patients were highly heterogeneous, we still could identify four main paradigms about treatment during hospitalisation: (1) simultaneous antiviral treatment and ATT,[19–21 23–26 28 30 31 34 35 39–41 43–45 49 51] (2) only ATT,[22263233353646–48] (3) only antiviral treatment,[18242627384450] (4) no antiviral treatment and ATT.[37] Check online supplemental tables 4 and 5 for detailed information about the treatment.

A minimal number of studies discussed about the pros and cons of the treatment and the possible effects of the regimens. Faqihi *et al* reported that the first-line anti-TB drug with antiviral treatment for COVID-19 might theoretically increase the risk of side effects,[30] and Yousaf *et al* stressed the importance of adjustment to the management of coinfected patients.[31] The antagonism from lopinavir/ritonavir against rifampicin had been noticed,[20 25] and Cao *et al* suggested umifenovir could be the substitute for lopinavir/ritonavir.[25] Kumar *et al* warned of additive hepatotoxicity from remdisivir due to simultaneous use of anti-tubercular drugs.[20] Faqihi *et al* gave isoniazid along with pyridoxal phosphate to avoid peripheral neuropathy,[30] and Gadelha Farias *et al* did not start antiretroviral therapy at first for the two HIV, TB and COVID-19 coinfected patients to avoid complications with ATT.[43] Confronted with liver function impairment during the treatment, Musso *et al* replaced isoniazid and pyrazinamide with amikacin and moxifloxacin to modify the ATT regimen.[51] Liu *et al*, He *et al*, Cao *et al* and Singh *et al* discussed the impact of corticosteroids on treating lung inflammation.[19 24 25 27] Liu *et al*'s recommendation was not to administer corticosteroids for COVID-19 and TB coinfected patients. Besides, since COVID-19 and TB disease might both cause immunosuppression, Liu recommended using immunomodulatory therapies such as thymosin in patients with progressively lower lymphocyte counts.[27]

About the outcome of 55 reported cases, 35 were resolved, 6 were deceased, 3 were still in treatment in hospital, 1 returned to hospital due to positive recurrence of SARS-CoV-2 RNA and 10 were missing. For patients discharged from the hospital, the length of stay ranged from 7 days to 2 months. Besides, in Vanzetti *et al*'s study, three patients described they had a longer hospital stay than average.[37] For deceased patients, the length of stay ranged from 6 to 26 days. Unfortunately, we could only find minimal information about coinfected patients' physical condition when they got discharged. Most studies only indicated that the test results for SARS-CoV-2 were negative or patients got recovered. Although Agada *et al* described the patient with poor prognostic indices, detailed physical conditions were also missing.[46] They believed the treated or untreated *M. tuberculosis* was a risk factor for a worse prognosis of patients with COVID-19.[24] In addition, long-term outcome or follow-up outcome for the TB and COVID-19 coinfected patient was absent.

Fatality rate of TB–COVID coinfection

We identified seven retrospective cohort studies that revealed the fatality rate of TB–COVID coinfection (online supplemental table 6 for detailed information). These studies came from India,[55] the Philippines,[56] Italy,[57] South Africa,[54] Argentina[58] and Russia,[59] and one was based on data from multiple countries.[53] Motta *et al*'s study provided two cohorts,[53] one of which was the same as Stochino *et al*'s study.[57] Thus, we removed the overlapped cohort. Except for Gubkina *et al*'s study whose targeted population was children and no one deceased,[59] the overall and in-hospital fatality rates fell within 5.3%~23.6% and 5.0%~27.3%. Table 2 presents the results of the included seven studies.

Quality of included studies

We used the JBI Critical Appraisal Checklist for Study Reporting Prevalence Data as the tool to assess seven included studies that revealed prevalence rate or fatality rate. The grade (yes, no, unclear or not applicable (N/A)) was shown in online supplemental figure 1 and online supplemental table 7. The results suggested that insufficient sample size and inappropriate sample frame were the main risks of bias of these studies.

We used the JBI Critical Appraisal Checklist for Case Report[16] as the tool to assess 35 included case reports, as shown in online supplemental figure 2 and online supplemental table 8. All the studies described patients' demographic characteristics clearly, and we could identify basic information about patients' history (28 studies), clinical condition (31 studies), diagnostic tests or assessment methods and the results (34 studies) for most studies. However, only 23, 20, and 22 studies provided clear messages about treatment procedures, post-intervention clinical conditions, and takeaway lessons, respectively. The most poorly reported part was adverse or unanticipated events, and only 11 studies gave a clear description, which could be a high risk of bias.

MA of fatality rate

We included six qualified studies (eight cohorts) to estimate the fatality rate of TB–COVID coinfection, three studies for overall fatality rate[53 54 56] and five studies for in-hospital fatality rate.[54–58] Gubkina *et al*'s study was excluded because its targeted population was children, which might lead to high heterogeneity in the MA. Although Davies's[54] study sample was people aged 20 years or above, we still included it into the MA.

As shown in figure 2A, the estimated overall fatality was 13.9% (95% CI: 1.6% to ~26.2%). Significant heterogeneity was observed between the studies (I^2=91.07%, p value for Q statistics <0.001). The estimated in-hospital fatality rate was 17.5% (95% CI: 8.9% to 26.0%), and heterogeneity was detected among these studies too (I^2=75.47%, p value for Q statistics <0.01) (figure 2B). We

Table 2 Fatality rate of included studies (n=7)

First author (year)	Country	Time span	Sample size	In-hospital	Age	Gender	Comorbidity	Died	Fatality rate (overall or in-hospital)
Gupta 2020[55]	India	1 February 2020–14 June 2020	22	Yes	19–67	20 male (90.9%)	Hypertension 4 (18.2%)	6	27.3 (in-hospital)
						2 female (9.1%)	Diabetes 3 (13.6%)		
							Seizure disorder 2 (9.1%)		
							Hypothyroidism 1 (4.5%)		
Motta 2020[53]	Belgium, Brazil, France, Italy, Russia, Singapore, Spain and Switzerland	12 March 2020–5 May 2020	49	No	27–70	/	/	7	14.3% (overall)
Sy 2020[56]	Philippines	17 May 2020–15 June 2020	106	No	/	73 male (68.9%)	Hypertension 22 (20.8%)	25	23.6% (overall)
						33 female (31.1%)	Diabetes 14 (13.2%)		
							Cancer 1 (0.9%)		
							Renal cancer 4 (3.8%)		
							Cardiac disease 8 (7.5%)		
							Asthma 4 (3.8%)		
							COPD 3 (2.8%)		
			66	Yes	/		Hypertension 16 (24.2%)	18	27.3% (in hospital)
							Diabetes 10 (15.2%)		
							Cancer 1 (1.5%)		
							Renal cancer 4 (6.1%)		
							Cardiac disease 7 (10.6%)		
							Asthma 1 (1.5%)		
							COPD 1 (1.5%)		
Stochino 2020[57]	Italy	/	20	Yes	27–47	12 male (60%)	/	1	5% (in-hospital)
						8 female (40%)			
Davies 2020	South Africa	Until 9 June 2020	2128	No	20 or above	/	/	113	5.3% (overall)
			469	Yes	20 or above	/	/	102	21.7% (in-hospital)

Continued

Table 2 Continued

First author (year)	Country	Time span	Sample size	In-hospital	Age	Gender	Comorbidity	Died	Fatality rate (overall or in-hospital)
Domingo 2020[58]	Argentina	1 March–30 June 2020	23	Yes	5–82	18 male (78.3%)	Smoking and other addictions 16 (69.6%)	2	8.7% (in-hospital)
						5 female (21.7%)	HIV 4 (17.4%)		
							Psychosis 1 (4.3%)		
							Pulmonary thromboembolism 1 (4.3%)		
							Arterial hypertension 1 (4.3%)		
Gubkina 2020[59]	Russia	March–June 2020	24	Yes	/	/	/	0	0% (in-hospital)

/: no information provided.
COPD, chronic obstructive pulmonary disease.

used funnel plots to explore the existence of publication bias, and the results were both positive (figure 3A,B).

To further explore the source of heterogeneity, we grouped these studies into the high-income country and LMIC subgroups. However, due to the lack of enough data, we could only conduct subgroup MA on in-hospital fatality rate. The mean in-hospital fatality rates for high-income country (Italy and Argentina) and LMICs (India, Philippines, South Africa) were 6.5% (95% CI: −0.8% to ~13.9%) and 22.5% (95% CI: 19.0% to ~26.0%). No heterogeneity was observed between studies for both subgroups (figure 2C,D). Similarly, two funnel plots were created to explore the existence of publication bias, and the results were both negative (figure 3C,D).

DISCUSSION

This systematic review identified the evidence on the prevalence status, treatment and possible outcome of TB–COVID coinfection. Although studies about coinfection were limited and quantitative data were even rarer, we still identified 42 studies, of which 35 were case reports and 7 were retrospective cohort studies.

Regarding the quality of included studies, we found that the sample sizes were insufficient, and the sampling frames were not specified, which had been the leading risk of bias for prevalence studies. In addition, the lack of reporting of adverse and unanticipated events, intervention and treatment procedures, and post-intervention conditions was a noticeable defect of the case reports. Publication bias was found in the overall and the in-hospital fatality rate of the TB–COVID coinfection, which suggested the current results stood on selected studies. As of the searching date, the number of relevant studies was limited, and cohort studies were even rarer. Besides, we did not find any experimental study about TB–COVID coinfection. Considering the quality of current evidence, we think more studies are urgently needed to evaluate the prevalence, treatment and long-term outcome of TB–COVID coinfection.

In terms of global prevalence status, 19 countries reported coinfected patients, including low TB prevalence countries like Belgium and Switzerland, as well as high TB prevalence countries like China and India. Therefore, we assumed that the TB–COVID coinfection was common worldwide, which every country and region should be aware of. The only large-scale study about the prevalence rate came from West Cape Province, South Africa. The rate was 0.04% on 1 June 2020, and 0.06% on 9 June 2020, increasing by 50% within only 8 days, not to mention that the public sector tests were limited to patients >55 years of age or with comorbidity. From the perspective of hindsight, though the rate was low, considering it was at the beginning of the pandemic, the situation was still worrying. However, we cannot infer the global prevalence rate based on this very limited information, and we believe more studies are urgently needed,

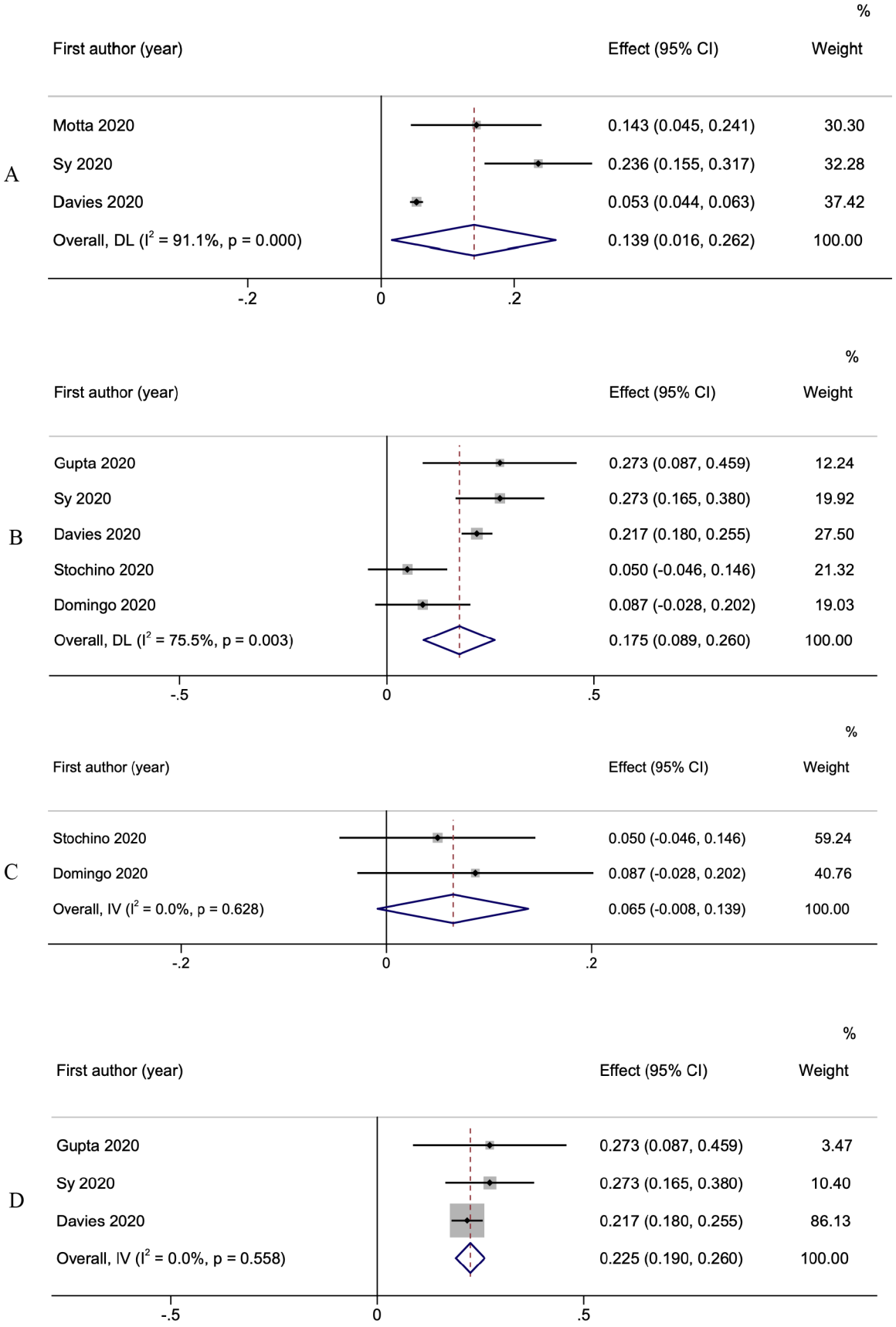

Figure 2 Forest plots of fatality rate accorting to hospitalisation, subgrouped according to economic status of regions: (A) overall fatality rate; (B) in-hospital fatality rate; (C) in-hospital fatality rate (high-income country subgroup); (D) in-hospital fatality rate (low/middle-income country subgroup).

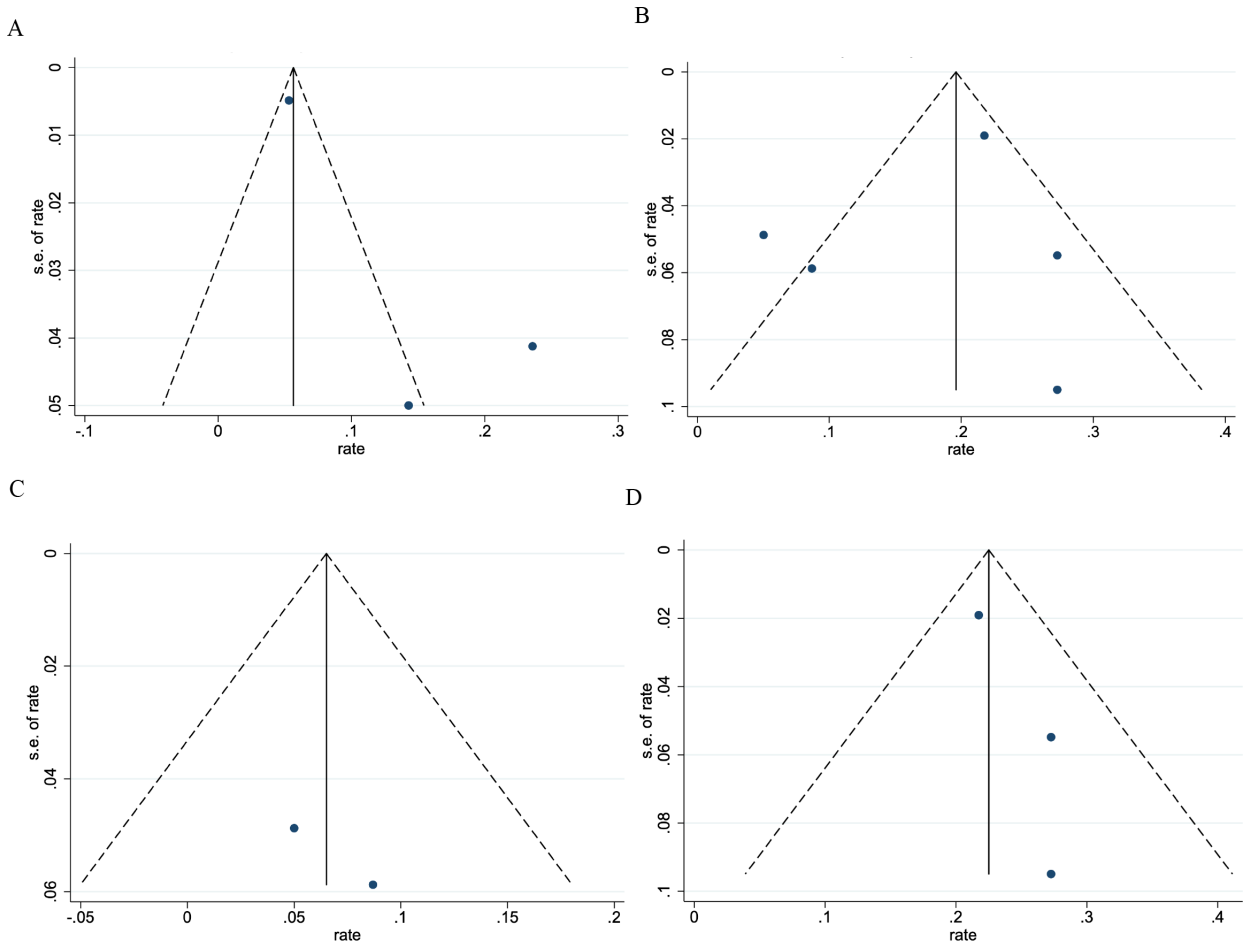

Figure 3 Funnel plots of fatality rate according to hospitalisation, subgrouped according to economic status of regions: (A) overall fatality rate; (B) in-hospital fatality rate; (C) in-hospital fatality rate (high-income country subgroup); (D) in-hospital fatality rate (low/middle-income country subgroup).

especially for countries with high COVID-19 cases and high TB prevalence.

Although a case report is not a very sound study design for us to evaluate treatment and outcome information, we did not find any other kinds of study design on this topic. The analysis of case reports showed the treatment for coinfection was of great heterogeneity, while we still identified four main paradigms: (1) simultaneous antiviral treatment and ATT, (2) only ATT, (3) only antiviral treatment, (4) no antiviral treatment and ATT. Some studies implied the doctor just followed the local clinical guidelines; however, very few studies mentioned regimen adjustments due to characteristics of TB and COVID-19 coinfected patients. Therefore, we assumed the current treatment plans were more like a mix of the suggested TB regimen and the COVID-19 regimen. Besides, we did not detect any specific treatment protocol for patients with inactive TB, namely the patients with previous TB or latent TB. Furthermore, HCQ, the most commonly used antiviral drug in these cases, was not taken by any patient in a Chinese study. Traditional Chinese medicine, which was widely used for patients with COVID-19 in China,[60] was also seldomly mentioned in these Chinese reports. The reason might be that these cases were reported at the beginning of the pandemic, and the doctors lacked the experience to deal with the situation. We tried multiple ways to explore the relationship between treatments and outcomes, but we did not find meaningful results. Therefore, we could not find evidence on which one is the best clinical practice due to a lack of sound investigation or experimental study, which suggested the urgency of further research.

The prolonged hospital stay for coinfected posed a significant challenge to the healthcare system, especially for those low-resource countries. Besides, the vaguely described health status at discharge and the absence of long-term outcomes are alarming. Moreover, for discharged patients who were still on ATT, the adverse impact of the pandemic on the delivery of TB care services, which had been confirmed in multiple countries,[61–63] might impede their accessibility to services.

We tried to conduct MA on overall and in-hospital fatality rates, and the estimated results were 13.9% and 17.5%. According to Meyerowitz-Katz and Merone, the fatality rate of patients with single COVID-19 was 0.68% (95% CI: 0.053% to ~0.82%),[64] which was relatively smaller. Therefore, we believe the coinfected patients faced more challenges and called for the need to refine medical equipment

and interventions. In addition, significant heterogeneity was detected in both MAs on overall and in-hospital fatality rates. In contrast, neither heterogeneity was detected in both subgroups' MAs on the in-hospital fatality rate. Based on case reports, we did not detect any pattern about treatment in both high-income countries and LMICs. Considering that patients in high-income countries are likely to receive care of better quality than patients in LMICs, we guess the different results of MAs' heterogeneity might hint that the quality of care is highly associated with outcomes. In other words, the patients in high-income countries shared a better condition than those in LMICs and were more likely to recover from TB–COVID coinfection. It is necessary to point out that the results of MA were based on a limited number of studies, of which defects in the quality were a frequent feature.

This systematic review has a few limitations. We did not include comorbidity as a keyword and MeSH term in the searching process, which might keep us from some relevant studies. All preprint and grey literature databases were not included in the search process. Besides, the diagnosis and testing criteria for COVID-19 and TB differ in countries and regions, and we were not able to transfer the data under a universal standard. Therefore, there might be some false-positive patients. Only six studies were included in MA, and significant heterogeneity was detected among them. Therefore, the results should be interpreted with caution.

In conclusion, the results of our systematic review show coinfection was not rare worldwide, and outcomes based on current evidence shared significant differences between high-income countries and LMICs. However, current evidence is insufficient to evaluate the treatment and outcome or estimate the prevalence rate of TB–COVID coinfection globally. More study about this field is urgently needed, especially an experimental study and cohort study. Given that some countries have higher TB and COVID-19 prevalence simultaneously, global efforts are needed to work collaboratively on TB–COVID coinfection, especially in response to those with limited medical resources.

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