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Research Article

The incidence and mortality of COVID-19 related TB infection in Sub-Saharan Africa: A systematic review and meta-analysis

Jacques L Tamuzi[1]*; Gomer Lulendo[2]; Patrick Mbuesse[2]

[1]Division of Epidemiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.

[2]Africa Centre for HIVAIDS management, Stellenbosch University, Cape Town, South Africa.

Abstract

Background

Coronavirus disease 2019 (COVID-19) is also associated with other co-morbidities among with previous and current pulmonary tuberculosis (PTB). PTB is a risk factor for COVID-19, both in terms of severity and mortality, regardless of human immunodeficiency virus (HIV) status. However, there is less information available on COVID-19 associated with PTB in point of view incidence and mortality rates in sub-Saharan Africa (SSA) as a high burden TB region. This systematic review served to provide data synthesis of available evidence on COVID-19/PTB incidence and case fatality rates, and mortality rate found in clinical and post-mortem COVID-19/PTB diagnostics in SSA.

Methods

We conducted a systematic electronic search in the PubMed, Medline, Google Scholar, Medrxix and COVID-19 Global literature on coronavirus disease databases for studies including COVID-19 associated with PTB in sub-Saharan Africa. The main outcomes were the proportion of people with COVID-19 associated to current /or previous PTB and the case fatality associated to COVID-19/PTB. The combination method was based on methodological similarities in the included random effect model studies using Prometa 3 software. We further undertook sensitivity analysis and meta-regression.

Results

From the 548 references extracted by the literature search, 25 studies were selected and included in the meta-analysis with a total of 191, 250 COVID-19 infected patients and 11, 452 COVID-19 deaths. The pooled COVID-19/PTB incidence was 2% [1%-3%] and mortality of 10% [4%-20%]. The pooled estimates for case fatality rate among COVID-19/PTB were 6% [3%-11%] for clinical PTB diagnostic and 26% [14%-48%] for post-mortem PTB diagnostic. Meta-regression model including the effect sizes and cumulative COVID-19 cases (P= 0.032), HIV prevalence (P= 0.041) and TB incidence (P= 0.002) to explained high heterogeneity between studies.

Conclusion

As a summary, the incidence of TB associated with COVID-19 and case fatality rates are higher in SSA. However, COVID-19 associated to TB may be underreported in the studies conducted in SSA as the post-mortem TB diagnostic was higher. Large-scale cohort studies that adequately clear tool on previous and/or current TB diagnostic tools are required to confirmed COVID-19/TB incidence and case fatality in SSA.

Keywords: COVID-19; PTB; Incidence; Mortality; sub-Saharan Africa Review registration: PROSPERO (CRD42021233387).

Background

The coronavirus disease 2019 (COVID-19) pandemic has caused significant morbidity and mortality all over the world, with total confirmed cases of 296,496,809 globally and 5,462,631 deaths in January 2022 [1]. In African region, 7,493,439 confirmed cases are already recorded, among them, 154, 837 deaths in January 2022 [1]. Though it is reported that the African region showed a decreasing trend in the number deaths over the past several weeks compared to other WHO regions [1]. The age groups at highest risk of severe COVID-19 disease and death (those >60 years old) [2-4] may be proportionately less in many SSA countries than in other parts of the world [4]. In contradistinction to potential health vulnerabilities, sub-Saharan African

***Corresponding Author:** Jacques L Tamuzi, Division of Epidemiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.Email: drjacques.tamuzi@gmail.com

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countries could be "protected" from COVID-19 mortality by an age structure differing significantly from countries where morbidity and mortality has been particularly high such as Italy, Spain, the United States, and in Hubei Province in China [5-7].

However, COVID-19 is also associated with other co-morbidities among with previous and current pulmonary tuberculosis (PTB) [8]. A recent review has shown that TB is a risk factor for COVID-19, both in terms of severity and mortality, regardless of HIV status [8]. Geographically, most people who developed TB are in South-East Asia (44%), Africa (25%) and the Western Pacific (18%) [9]. It is estimated that 94% of all TB infections and deaths occur appropriately in low- and middle-income countries, including sub-Saharan Africa (SSA) [10]. An observational study from the epicenter of the pandemic in Wuhan, suggested that individuals with latent or active TB were more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [11]. This study found infection with Mycobacterium tuberculosis to be a more common co-morbidity for COVID-19 (36%) [11]. They also found Mycobacterium tuberculosis co-infection to be linked to more severe COVID-19 and more rapid progression [12]. Another study conducted in Zambia, revealed that 31.4% post-mortem PTB diagnostic in COVID-19 deaths [13]. In countries where tuberculosis (TB) risk factors for mortality are highly prevalent among young individuals (poverty, overcrowding, diabetes mellitus, smoking, alcohol and substance abuse, HIV co-infection, among others), particularly in the presence of drug resistance and difficult access to diagnosis (delayed diagnosis) [14, 15], COVID-19 incidence and mortality associated to TB may be hypothesized as significant. However, COVID-19 associated to previous, current or both TB has been lower in high burden TB countries. Both active and previous history of TB may play a deleterious synergism SARS-CoV-2, increasing then the risk of COVID-19 associated mortality, and for patients with PTB may increase the severity of COVID-19 and of death due to chronic lung disease and immunosuppression [8]. This may contribute to higher than expected mortality in high TB burden region such as SSA.

Therefore, there is less information available on COVID-19 associated to TB in point of view incidence and fatality rates in SSA. This systematic review served to provide data synthesis of available evidence on COVID-19/TB incidence and case fatality rates, and case fatality rates found in clinical and post-mortem COVID-19/TB diagnostics in SSA.

Methods

The review followed a predesigned protocol registered in PROSPERO (CRD42021233387). The systematic review met the criteria outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16].

Search strategy and eligibly criteria

A search of the literature was systematically conducted using Pubmed, Medline, Google Scholar, Medrxix and COVID-19 Global literature on coronavirus disease. All searches were limited to articles written in English given that such language restriction does not alter the outcome of systematic reviews and meta-analyses. The search was restricted to studies related to the incidence and fatality rates of COVID-19 related to TB in SSA since December 2019 to November 2021 including the key words and term as follows: "Covid-19 or 2019-nCoV or coronavirus disease 2019 or Novel coronavirus or SARS-CoV-2 " and "tuberculosis or PTB or TB or Mycobacterium tuberculosis infection" and "mortality rate or death rate or case fatality rate" and "incidence or Incidence proportions or Incidence rate or incidence rate or attack rate" and "Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Cape Verde or "Central African republic" or Chad or Congo or "Democratic Republic of Congo" or DRC or Djibouti or Equatorial guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Bissau or Ivory coast or ""Cote d' ivoire" or Kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mayotte or Mozambique or Namibia or Niger or Nigeria or Principe or Reunion or Rhodesia or Rwanda or "Sao Tome" or Senegal or "Sierra Leone" or Somalia or "South Africa" or Swaziland or Tanzania or Togo or Uganda or Zambia or Zimbabwe or "Central Africa" or "Sub-Saharan Africa" or "East Africa" or "Southern Africa" or "South Africa", without language restrictions to identify citations from prior to January 2020. The review included observational studies conducted in Sub-Saharan Africa, including the incidence and mortality related to COVID-19 and TB. We included confirmed COVID-19 participants with TB diagnosed previously, currently or in post-mortem.

Study quality and risk of bias assessment

The methodological quality of the included studies was independently assessed by two of the authors (JLT and GL). Any inconsistencies were resolved by consensus, and if no agreement was reached yet again, the case was resolved by seeking the views of a third author (PB). The Newcastle-Ottawa scale (NOS) [17] was used by two reviewers (JTL and GL) to independently assess study quality. The NOS evaluated the case series, cross-sectional, case-control study's selection, comparability, and exposure, as well as the cohort study's selection, comparability, and outcome. The sample with more than 6 stars was considered to be of reasonably high quality, and the sample with nine stars reflects the highest ranking. Any discrepancies in the content of the included studies were resolved with the help of another reviewer (PB).

Data extraction

Three levels of screening were performed. The first and second rounds of screening were based on titles and abstracts only while the third round consisted of a review of full text articles. The first screening was performed by JTL and excluded references that did not contain information on the pathogens of interest or those that were not the study designs of interest (included observational studies only). The second screening was performed independently by JLT and GL with differences solved by consensus. The third level of screening identified those publications related COVID-19 incidence and mortality associated to PTB in SSA and data extraction was performed on those that met the criteria. Screening and data extraction were performed by JLT and GL independently reviewing each full text article. Conflicts were resolved via discussion to achieve consensus, with any remaining disagreements resolved by a third reviewer. Included studies were observational studies that included COVID-19 incidence and/or mortality

sons, and 25 studies were selected and included in the meta-analysis and six studies were excluded as they were study protocols. We included a total of 191, 250 COVID-19 infected patients and 11, 452 COVID-19 deaths. The selected articles reported data from South Africa (n = 9), Nigeria (n = 4), Democratic Republic of Congo (n = 2), Angola (n=1), Uganda (n = 1), Zambia (n = 5), Ethiopia (n=2) and Kenya (n = 1) (**Figure 2**).

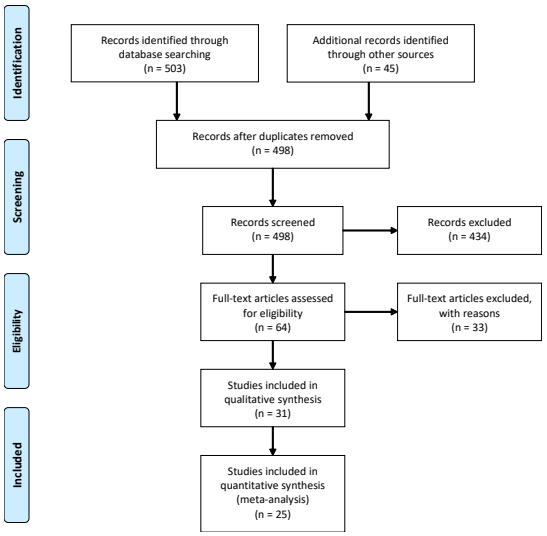

Figure 1: Flow chart of TB incidence and mortality proportions associated to COVID-19 in Sub-Saharan Africa.

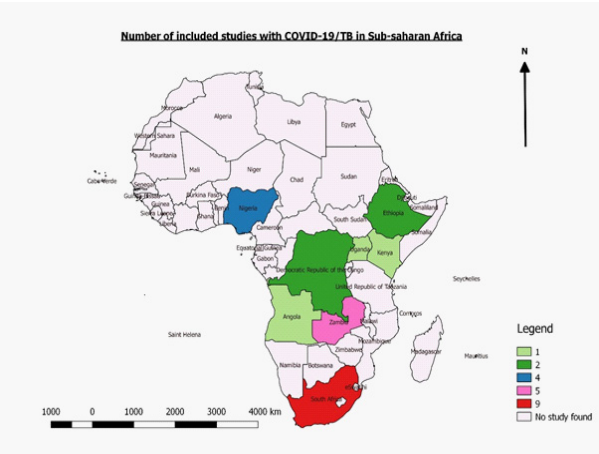

Figure 2: Distribution of included studies in Sub-Saharan African countries.

Included studies

Twenty-five studies were included for quantitative analysis. All the studies analysed clinical characteristics and co-morbidities of COVID-19 patients in SSA. Among them, twenty studies included the incidence proportion of COVID-19 associated to TB [20-39], and nine studies included the case fatality rate of COVID-19 associated to TB [13, 20, 30, 33, 38, 40-43]. The minimum age for the study population was 13 years and the maximum was 72 years. Incidence and mortality of TB associated to COVID-19, stratified by sex were not obvious as all the studies included common co-morbidities associated to COVID-19 without sex stratification. The median study duration was 15 months (range, 4 months to 45 years) and the study period ranged from 2020 to 2021. Eleven studies used retrospective case identification [13, 30-37, 40, 43], six prospective case identification [20-24, 39], and three were Case series [25, 41, 42], three Cross-sectional studies [26-28], one cross-sectional and retrospective cohort study [38] and one case control study [29] (Supplementary material **Table 1**).

Study quality

The NOS [17] was used to determine the methodological validity of included research for determining the consistency of cohort, case-control, and descriptive studies in meta-analyses. The three essential components of this strategy are range, comparability, and exposure. For case–control and cohort studies, the NOS employs a star system with ratings ranging from 0 to 9. We considered a study with a higher score than the six of each type of study to be a high-quality study because the criteria for determining whether a study is high or poor quality are unknown. Two studies received an eight, five received a seven, eight received a six, five received a five, and one received a four. Supplementary material **Table 2** shows the NOS scores for the studies that were included.

Supplementary material Table 1: Characteristics of included studies in the incidence and mortality of COVID-19 related TB infection in Sub-Saharan Africa.

Study ID	Country	Population/Sample size	Study design	Mortality rates	Incidence
Jassat et al., 2020	South Africa	41,845 COVID-19 hospitalized patients including HIV+ and -. Median age: 52 years (IQ: 40-63) 54.4% of patients were females 5 March-11 August 2020	Retrospective analysis	P=353/7,662	P = 1325/35,509
Mwananyanda et al., 2021	Zambia	372 deceased individuals of COVID-19. Median age: 48 years (IQR 36-72 years) June and September 2020	Retrospective analysis	P=117/372	
Boulle et al., 2020	South Africa	1, 2020, 22,308 were diagnosed with COVID-19 including HIV + and COVID-19 deceased cases were older than surviving cases (median age [interquartile range] 63 years [54-71] vs. 37 [30-48]) March 1, 2020	Population prospective cohort study	P=85/625	P=2,128/22,308
Hassan et al., 2020	Nigeria	25,695 confirmed COVID-19 participants. March-April 2020	Retrospective analysis		P=732/25,694

Nachega et al., 2020	Democratic republic of Congo	766 confirmed COVID-19 participants. The median (IQR): 46 (34–58) years March 10, 2020–July 31, 2020	Prospective analysis		P=19/745
Wyk et al., 2020	South Africa	A total of 2,457 COVID-19 deaths Male: 52% and female: 48%). Only 20.3% of the deaths were in individuals aged <50 years, and 29.4% of those who died were aged ≥70 years. 28 March and 3 July 2020	Retrospective analysis	P= 81/2457	
Zamparini et al., 2020	South Africa	single-centre case series on the first 100 adult patients with reverse-transcriptase polymerase chain reaction (RT-PCR)-confirmed COVID-19	Single-centre case series		P=2/100
van der Zalm et al., 2020	South Africa	159 children aged 0-13 years with a laboratory-confirmed SARS-CoV-2 presenting to Tygerberg Hospital (TBH). 17 April to 24 July 2020	Observational cohort study		P=2/159
Hesse et al., 2020	South Africa	98,335 individuals with positive SARS-CoV-2 PCR test. The mean age was 42.3±15.0 years. 4-month period in 2020	Retrospective analysis		P=395/98,335
Kirenga et al., 2020	Uganda	56 confirmed COVID-19 participants. 67.9% of the patients were male. The mean age: 34.2 years with an SD of 15.5 years	prospective cohort study		P=1/56
Otuonye et al., 2020	Nigeria	154 COVID-19 confirmed patients. The mean age (SD) was 46.16(13.701)	Descriptive study		P=2/154
Mash et al., 2021	South Africa	1376 COVID-19 positive patients. The mean age of patients was 46.3 years (SD 16.3 years). March and June 2020	Descriptive observational cross-sectional Study by means of a retrospective audit of medical records.	P=20/151	P=84/1,376
Parker et al., 2020	South Africa	113 patients with confirmed COVID-19/ HIV + and -. The mean (SD) age of patients was 48 (14) years. Females (n=71; 61%) and males (n=45; 39%).	Single-centre descriptive study		P=13/113
Ombajo et al., 2020	Kenya	787 confirmed SARS-CoV2. Median age: 43 years. 64% were male. 14th March 2020 and 17th September 2020	Multi-center cohort study	P=1/107	P=8/787
Osibogun et al., 2021	Nigeria	2075 COVID-19 confirmed participants The median age of the patients was 40 (IQR=32 - 50) years. The male to female ratio was 2:1. From 27 February to 6 July 2020	Retrospective observational study		P=7/2,075
Abraha et al., 2021	Ethiopia	2617 patients confirmed COVID-19 positive. The median age of the cohort was 29 (IQR 24–38) years. The majority of our study population were male (63.3%)	Retrospective cohort study		P=8/2,503
Bepouka et al., 2020	Democratic republic of Congo	141 COVID-19 patients admitted at the Kinshasa University Hospital from March 23 to June 15, 2020 were included in the study. their average age was 49.6±16.5 years. 67.4 % were men (sex ratio 2H: 1F)	Retrospective cohort study		P=1/141
Sebastião et al., 2021	Angola	622 individuals tested for the SARS-CoV-2 infection between January to September 2020. The age range varied between 1–92 years old, with an average of 32.3±18.7. 244/622 (39.2%) were female and 378/622 (60.8%) were male.	A cross-sectional study		P=1/88
Ibrahim et al., 2020	Nigeria	45 patients with the diagnosis of COVID-19. Patients were young and predominantly male.	Retrospective study		P=2/45
Gebrecherkos et al., 2021	Ethiopia	515 individuals enrolled The majority of our study population were male (62.5%). The median age of the cohort was 32 (IQR 26–43) years, the majority (60.7%) being in the age range 24 to 44 years.	Prospective observational cohort study		P=1/515
Himwaze et al., 2021	Zambia	29 whole body autopsies we had performed of COVID-19 inpatient. mean age=44 ± 15.8years; age range=19-82; 17/29 [58.8%] males	Retrospective descriptive study	P= 3/29	
Mucheleng'anga et al., 2021	Zambia		Retrospective case series	P =1/21	

Du Bruyn et al., 2021	South Africa	104 SARS-CoV-2 RT-PCR positive	single-centre observational case-control study		P=22/104
Mudenda et al., 2021	Zambia	29 deceased individuals	Retrospective case series	P = 16/28	
Chanda et al., 2021	Zambia	443 patients	Prospective cohort study		P=21/443

Supplementary material Table 2: Results of Assessment of Study Quality and Risk of Bias.

N	Study ID	Quality assessment of included studies.				
		Study designs	Selection	Comparability	Outcome/ exposure	Overall quality
1	Jassat et al., 2020	Retrospective analysis	**	**	***	7
2	Mwananyanda et al., 2020	Retrospective analysis	**	*	***	6
3	Boulle et al., 2020	Population prospective cohort study	****	*	***	8
4	Hassan et al., 2020	Retrospective analysis	**	*	***	6
5	Nachega et al., 2020	Prospective analysis	***	*	***	7
6	Wyk et al., 2020	Retrospective analysis	**	*	***	6
7	Zamparini et al., 2020	Single-centre case series	**	*	**	5
8	Van Der Zalm et al., 2020	Observational cohort study	**	*	***	6
9	Hesse et al., 2020	Retrospective analysis	***	*	**	6
10	Kirenga et al., 2020	prospective cohort study	***	**	**	7
11	Otuonye et al., 2020	Descriptive study	**	*	***	6
12	Mash et al., 2020	Descriptive observational cross-sectional Study and retrospective	***	*	***	7
13	Parker et al., 2020	Single-centre descriptive study	**	*	**	5
14	Ombajo et al., 2020	Multi-center cohort study	***	*	***	7
15	Osibogun et al., 2021	Retrospective observational study	**	*	***	6
16	Abraha et al., 2021	Retrospective cohort study	**	*	***	6
17	Bepouka et al., 2020	Retrospective cohort study	**	*	**	5
18	Sebastião et al., 2021	A cross-sectional study	***	*	**	6
19	Ibrahim et al., 2020	Retrospective study	**	*	**	5
20	du Bruyn et al., 2021	single-centre observational case-control study	**	*	**	5
21	Chanda et al., 2021	Prospective cohort study	****	*	***	8
22	Mudenda et al., 2021	Retrospective case series	**	*	**	5
23	Mucheleng'anga et al., 2021	Retrospective case series	*	*	**	4
24	Himwaze et al., 2021	Retrospective descriptive study	**	*	**	5
25	Gebrecherkos et al., 2021	Prospective observational cohort study	**	*	***	6

Newcastle-Ottawa Scale was obtained to assess the selection, comparability and exposure of the case-control study, while the selection, comparability and outcome for the cohort study. -: no point; *: one point; **: two points; ***: three points; ****: four points.

Outcomes measurement

In this review, we defined the incidence proportion as the number of new cases of COVID-19 associated to TB over the total number of people in the population at risk for having COVID-19 during a specified period. The case fatality rate was defined as total number of new deaths due to COVID-19 associated to TB divided by the total number of COVID-19 associated to TB. The incidence and case fatality rates were summarized as specific period cases per 100.

Meta-analysis and meta-regression

Incidence proportion of COVID-19 associated to TB

In total, 20 studies were identified for incidence proportion of COVID-19 associated to TB in SSA. The pooled RR-P [95% CI] was 2% [1%-3%]. The test for heterogeneity was statistically significant with (I2 = 93.53 P<0.0001) (**Figure 3**).

Case fatality rate of COVID-19 associated to TB

We identified nine studies [13, 20, 30, 33, 38, 40-43] meeting the inclusion criteria relating mortality proportion of COVID-19 associated to TB in SSA. The pooled RR-P [95%CI] estimates for mortality proportion among patients with COVID-19 associated to TB were 6% [3%-11%] for clinical TB diagnostic and 26% [14%-48%] for post-mortem TB diagnostic. The overall pooled RR-P was 10% [4%-20%]. Hetero-

geneity between studies was high (I2 = 98.82, P <0.001) however, the test for subgroup analysis did not show any difference between the groups (**Figure 4**).

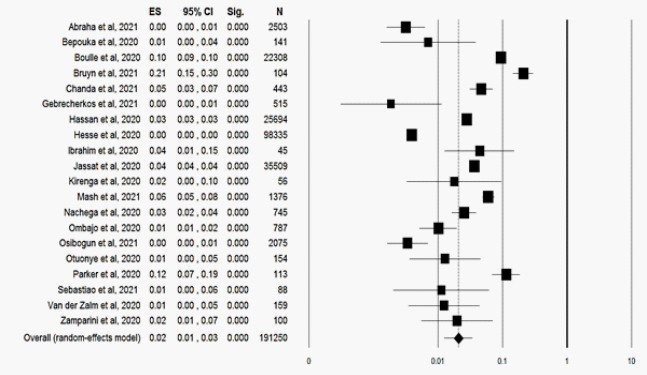

Figure 3: pooled incidence proportion of COVID-19 associated to TB in sub-Saharan Africa.

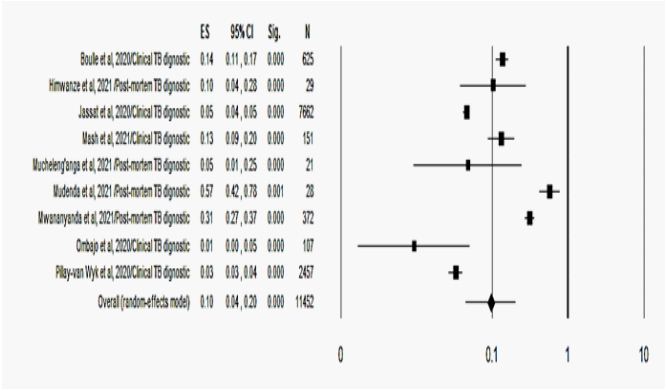

Figure 4: pooled case fatality rate of COVID-19 associated to TB

Meta-regression

We built multivariate meta-regression model including cumulative COVID-19 cases, HIV prevalence and TB incidence to explore heterogeneity between studies. People living with HIV (all ages), TB incidence rate and cumulative COVID-19 cases were (7, 800, 000; 360 in thousands; 3, 533, 106) for South Africa, (1, 700, 000; 440 in thousands; 231, 413) for Nigeria, (1 700 000; 59 in thousands, 221, 880) for Zambia, (1, 500, 000; 157 in thousands; 382, 371) for Ethiopia, (510, 000; 278 in thousands; 70, 059) for Democratic republic of Congo, (1, 400, 000; 140 in thousands; 270, 899) for Kenya, (340, 000; 112 in thousands; 65, 938) for Angola and (1, 400, 000 ; 253 in thousands; 130, 178) for Uganda [1, 44, 45]. This model showed that the variability across studies was explained by COVID-19 cumulative cases by countries (P= 0.032), HIV prevalence (P= 0.041) and TB incidence (P= 0.002)

Egger's and Mazumdar's rank correlation test and Begg's funnel plot were used to evaluate publication bias quantitatively and qualitatively respectively. Asymmetry was found in the plot including COVID-19/TB incidence proportion (**Figure 5**). Both Egger's and Mazumdar's rank correlation tests did not exhibit obvious publication bias in different studies included in the review because the P-values of both tests for COVID-19/TB incidence rate were (-1.10, P = 0.285) and (-0.26, P = 0.795), respectively. Furthermore, P-values of both tests for COVID-19/TB mortality rate were [Egger's test (t = 0.49, p = 0.642)] 0.173 and [Begg and Mazumdar's rank correlation test (z = -0.83, p = 0.404)], respectively.

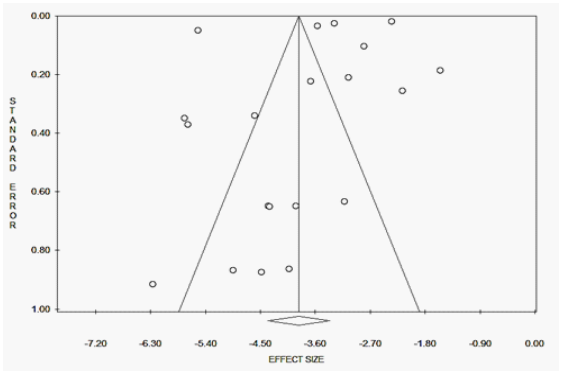

Figure 5: Funnel plot of incidence proportion of COVID-19 associated to TB in sub-Saharan Africa

Sensitivity Analysis

For all the studies including in COVID-19/TB incidence and mortality rates in SSA, sensitivity analysis was performed by sequential omission of every study respectively Prometa 3. For every incidence and mortality rates, the RR-P was not significantly influenced by omitting any single study.

Discussion

The objective of this review was to help us to estimate the burden of COVID-19 associated with TB in SSA; the meta-analysis including twenty studies and 191, 250 COVID-19 infected cases demonstrated that the overall pooled incidence proportion was 2% [1%-3%]. Our COVID-19/TB incidence was higher than the incidence found in a recent meta-analysis forty-three studies which showed the pooled estimate for proportion of active pulmonary tuberculosis was 1.07% [0.81%-1.36%] [46]. This systematic review included more studies conducted in low and moderate TB prevalence compared to our review which included studies in high burden TB countries in SSA. Additionally, this review only included active TB associated with COVID-19, compared to our study which included COVID-19 cases with previous and/or active TB.

The case fatality rate of COVID-19/TB including nine studies and 11,452 COVID-19 deaths was 10% [4%-20%]. However, the meta-analysis of subgroup analysis (clinical vs post-mortem TB diagnostics) showed post-mortem TB diagnostic counted higher case fatality rate than clinical TB diagnostic with 26% [14%-48%] for post-mortem TB diagnostic compared to 6% [3%-11%] for TB clinical diagnostic. Our case fatality rate was higher than a meta-analysis including seventeen studies with 42,321 COVID-19 patients, of whom 632 (1.5%) had tuberculosis, reported on deaths due to COVID-19 [46]. Our high case fatality rate may be justified by same reasons referred to COVID-19/TB incidence. Interestingly, our review has shown that TB was among the commonest co-morbidity in COVID-19 patients in sub-Saharan Africa. This is consistent with findings in other studies including high TB post-mortem diagnostic in sub-Saharan Africa [47, 48]. Referring to a meta-analysis showing that TB exposure was high-risk COVID-19 group (OR 1.67, 95% CI 1.06–2.65, P = 0.03) [8]. COVID-19/TB clinical diagnostic may be underestimated in SSA as post-mortem TB diagnostic has shown high mortality rate. Tamuzi et al. have suggested

an algorithm for suspected COVID-19/TB diagnostic in high burden HIV/TB countries. This algorithm may reflect the true COVID-19/TB incidence in high burden TB countries and reduce COVID-19/TB severity rate OR 4.50 (95% CI 1.12–18.10, P = 0.03) and mortality (OR 2.23, 95% CI 1.83–2.74, P < 0.001) compared to non-TB group [8].

This deleterious synergism of SARS-CoV-2 and Mycobacterium tuberculosis increases the risk of COVID-19-associated morbidity and mortality [8], and patients with PTB may increase the severity of COVID-19 and death due to chronic lung disease and immunosuppression. In fact, advanced PTB is characterized by significant collagen deposition and fibrosis [49-49], although tissue remodelling during fibrosis is a healing process, extensive fibrosis with scar formation impairs lung function [51]. A study reported a series of 454 cases of massive fibrosis with evidence of tuberculosis in 40% [52]. Furthermore, ACE2 has been reported to play a protective role in lung fibrosis [53]. In lung biopsy specimens of patients with lung fibrosis, ACE2 mRNA and enzyme activity decreased significantly [53, 54]. Interestingly, SARS-CoV-2 spike protein decrease the amount of ACE2 expression during viral infection [55]. Decreased ACE2 expression results in increased ANG-II levels and contributes to lung fibrosis and pulmonary failure [53]. In three different acute lung injury models, loss of ACE2 expression precipitated serious acute lung failure, while RhACE2 attenuated ARDS and further decreased Angiotensin II levels in the lungs [56, 57]. In addition to TGF- β and ACE2, other pathways can contribute to SARS-CoV-2 mediated lung fibrosis. MCP-1 is a chemokine that causes lung fibrosis. In addition, there are permanent changes in lung architecture after TB due, in part, to aberrant wound healing processes [58]. Regulation of the TGF-β signalling pathway was also associated with elevated levels of collagen in lung lesions prior to and during TB [58, 59]. The TGF-β activation pathways in both SARS-CoV and PTB contribute to the production of fibrin, collagen and secreted proteases (Matrix metalloproteinases) associated with human cavities involved in the formation of fibrosis and tissue remodelling [51]. As a summary the presence of cavitary lesions, fibrosis and extensive lung pathology was then identified as a major risk factor for poor COVID-19/TB outcomes, which could be explained by reduced drug penetration due to minimal blood supply in fibrotic lungs sites [60]. Lastly, the transient immunosuppression characterized both conditions, a reason for poorer IgG antibody response and a delayed viral clearance in co-infected SARS-CoV-2 patients and the use of corticoid therapy in SARS added even more on immunosuppression [8].

There are several implications to our findings in screening TB concomitantly to COVID-19 in SSA. Our findings indicate that the risks of COVID-19 associated to previous and/or current TB may be underestimated in SSA, as this co-infection is poorly reported. Although there is a paucity of accurate epidemiological data about COVID-19 associated to previous and/or current TB, the fatality rate is estimated high. Therefore, COVID-19 associated to TB should be taken in a context of proper history taking, accurate diagnostic tools and clear management [8]. Then, clinicians dealing with a possible SARS-CoV-2 patient from high burden TB region, one should never forget TB as a coexisting pathology.

High heterogeneity was observed between studies exploring the incidence and mortality rates. This heterogeneity may be explained by a model including the cumulative COVID-19 cases, HIV prevalence and TB incidence which varied considerably across the countries. Meta-regression has shown statistically significant p-values between the effect size and our model. Besides, sensitivity analysis performed by sequential omission of every study for every incidence and mortality rates, the RR-P was not significantly influenced by omitting any single study. Egger's and Mazumdar's rank correlation test and Begg's funnel plot were used to evaluate publication bias quantitatively and qualitatively respectively. Asymmetry was found in the plot including COVID-19/TB incidence proportion (Fig 5). Both Egger's and Mazumdar's rank correlation tests did not exhibit obvious publication bias in different studies included in the review because the P-values of both tests for COVID-19/TB incidence rate were (-1.10, P = 0.285) and (-0.26, P = 0.795), respectively. Furthermore, P-values of both tests for COVID-19/TB mortality rate were [Egger's test (t = 0.49, p = 0.642)] 0.173 and [Begg and Mazumdar's rank correlation test (z = -0.83, p = 0.404)], respectively.

Our systematic review is limited by the quality of the included studies: first, the majority involved retrospective data analyses, which increase the risk of bias associated with the recording of baseline data, the need for imputation, and potential selection bias. Retrospective studies did not report how missing data were handled or if imputation was used. High risk of selection bias was noted in retrospective and cross-sectional studies. Finally, the results of the case fatality meta-analysis should be interpreted with caution because data pooling the post-mortem PTB diagnostic were all extracted in studies conducted in Zambia [13, 41-43]. This could limit the external validity of the review. Future studies should be properly designed with high-quality and systematic methods of TB diagnostic associated with COVID-19. This will play a substantial role in reflecting the true incidence and mortality rates of COVID-19/TB in SSA.

Conclusion

This systematic review of the incidence proportion and case fatality rate of COVID-19 associated to TB in SSA. This analysis showed that the incidence of TB associated with COVID-19 and case fatality rates are higher in SSA. However, COVID-19 associated to TB may be underreported in the studies conducted in SSA due to no specific COVID-19/TB diagnostic tools. This is strengthened by high case fatality rate of COVID-19/TB in post-mortem diagnostic. Large-scale cohort studies that adequately clear tool on previous and/or current TB diagnostic tools are required to confirmed COVID-19/TB incidence and case fatality.

Footnotes

Contributions: JLT conceived the study and developed the protocol. JLT did the literature search and selected the studies. JLT and GL reviewed the methodological quality of the study and extracted the relevant information. JLT synthesized the data. JLT wrote the first draft of the paper. GL and PB revised successive drafts of the paper. All the authors approved its final version. JLT is the guarantor of the study.

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