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LETTER TO THE EDITOR

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An updated meta-analysis on the association between tuberculosis and COVID-19 severity and mortality

Recently, Gao et al. published a paper entitled "Association between tuberculosis and COVID-19 severity and mortality: A rapid systematic review and meta-analysis" in the Journal of Medical Virology.[1] Their findings demonstrated that tuberculosis was not significantly associated with the increased risk for severity (odds ratio [OR] = 2.10, 95% confidence interval (CI): 0.61–7.18) and mortality (OR = 1.40, 95% CI: 0.10–18.93) in a meta-analysis on the basis of six studies with 2765 COVID-19 patients.[1] This study was extremely interesting but had limited sample sizes. To our knowledge, a series of articles on this topic have been emerging since then. Therefore, we performed this updated meta-analysis to clarify the association between tuberculosis and COVID-19 severity and mortality based on the latest data.

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[2] The electronic databases including PubMed, Web of Science, and EMBASE were systematically searched to identify the eligible studies published between January 1, 2020 and May 14, 2021. The keywords used were: "coronavirus disease 2019", "COVID-19", "severe acute respiratory syndrome coronavirus 2", "SARS-CoV-2", "2019-nCoV", and "tuberculosis". The outcomes of interest were severity (severe, critical, intensive care unit [ICU] admission, invasive mechanical ventilation [IMV], intubation or death), and mortality. All peer-reviewed articles written in the English language reporting the association between tuberculosis and COVID-19 severity and mortality were eligibly included. Accordingly, repeated articles, case reports, review papers, comments, errata, and studies without sufficient data were excluded. The pooled OR and 95% CI were estimated using a random-effects meta-analysis model.[3] Heterogeneity across studies was evaluated using the I^2 statistic.[4,5] Egger's test and Begg's test were conducted to assess publication bias.[6–8] Leave-one-out sensitivity analysis was performed to evaluate the stability of our results.[9] The statistical analyses were performed by R software (Version 3.6.3). Statistical significance was defined as $p < 0.05$.

Thirty-six full-text articles with 60,103 COVID-19 patients were included in this study. Among them, 26 studies were from Asia (20 from China, three from Korea, and one each from Qatar, Turkey, and the Philippines), six studies were from Africa (two from Congo, two from South Africa, one from Ethiopia, and one from Nigeria), three studies came from Americas (two from Brazil and one from the United States) and one study was from multi-country. The baseline characteristics of the enrolled studies are summarized in Table 1.

Overall, we found that COVID-19 patients with tuberculosis tended to have an increased risk for the disease severity compared to those without tuberculosis (OR = 1.56, 95% CI: 1.13–2.16, Figure 1A). When we restricted the outcomes to mortality, the significant association was still present (OR = 1.94, 95% CI: 1.28–2.93, Figure 1B). Leave-one-out sensitivity analysis demonstrated that omitting each eligible study once had no obvious impacts on the overall results, which suggests that our results were robust and stable (Figure 1C for severity and 1D for mortality). There was no potential publication bias detected in Begg's test ($p = 0.558$) or Egger's test ($p = 0.293$).

There are several limitations in this current meta-analysis. First, the majority of the included studies are from Asia, especially from China. Thus, the findings of the present meta-analysis should be verified by future studies mainly from other regions. Second, the information on medications for tuberculosis is not available presently, thus we could not address the effects of medications on the association between tuberculosis and COVID-19 severity and mortality. Third, the association between tuberculosis and COVID-19 severity and mortality was estimated on the basis of crude OR. It is reported that age, gender, and several comorbidities had obvious effects on the clinical outcomes of COVID-19 patients,[10–12] therefore, a meta-analysis on this association based on risk factors adjusted-effect estimates should be performed to verify our findings in the future. Fourth, most of the included studies ($n = 25$) were retrospectively designed and only one study was prospectively designed. Therefore, well-designed studies with large sample-sized prospective articles are warranted to verify our findings in the future when more data are available.

In conclusion, our updated meta-analysis demonstrated that tuberculosis was significantly associated with an increased risk for severity and mortality among COVID-19 patients. Thus, several preventive measures should be taken to protect individuals with tuberculosis from SARS-CoV-2 infection and more clinical intervention and treatment also should be allocated to COVID-19 patients with tuberculosis to prevent disease progression. We hope that the updated data will contribute to the more accurate elaboration and substantiation of the findings reported by Gao et al.[1]

TABLE 1 General information of the included studies on the association between tuberculosis and severity and mortality among coronavirus disease 2019 (COVID-19) patients

Author	Country	Study design	Sample sizes	Male (%)	Age	Severe (TB/cases, %)	Non-severe (TB/cases, %)
Du RH	China	Prospective study	179	54.2	57.6 ± 13.7	Deceased (0/21, 0%)	Survival (8/158, 5.1%)
Mo P	China	Retrospective study	155	55.5	54 (42–66)	Refractory (3/85, 3.5%)	General (0/70, 0%)
Zeng JH	China	Retrospective study	416	47.6	46.58	ICU (0/35, 0%)	Non-ICU (8/381, 2%)
Sy KTL	Philippines	Cohort study	430	NR	NR	Died (25/71, 35.2%)	Recovery (57/359, 15.9%)
Li X	China	Ambispective study	548	50.9	60 (48–69)	Severe (4/269, 1.5%)	Non-severe (5/279, 1.8%)
Chen T	China	Case series	55	53.2	54 (20–91)	Died (1/19, 5.3%)	Survived (0/36, 0%)
Zhang JJ	China	Retrospective study	140	50.7	57 (25–87)	Severe (2/58, 3.4%)	Non-severe (0/82, 0%)
Pierrotti LC	Brazil	Retrospective study	51	49	51.9 (17–78)	ICU (1/23, 4.3%)	Non-ICU (1/28, 3.6%)
Song J	China	Retrospective study	961	52	63 (49–70)	Severe (2/242, 0.8%)	Non-severe (18/719, 2.5%)
Lee JY	Korea	Retrospective study	694	30.5	55.91	Severe (0/137, 0%)	Mild (2/557, 0.5%)
Miciel EL	Brazil	Cross-sectional study	416	NR	NR	Death (0/217, 0%)	Discharge (1/199, 0.5%)
Zhang J	China	Retrospective study	901	48.3	60.0 (49.0–69.0)	Severe/Critical (9/535, 1.7%)	Common (4/366, 1.1%)
Liu J	China	Retrospective study	1190	53.4	57 (47–67)	Non-survivor (5/157, 3.3%)	Survivor (10/1033, 1.4%)
Yu HH	China	Retrospective study	1561	50	62 (50–70)	Severe (2/365, 0.5%)	Mild (18/1196, 1.5%)
Boulle A	South Africa	Cohort study	22,308	31.6	NR	Deceased (103/625, 16.5%)	Not deceased (2015/21683, 9.3%)
Yang C	China	Retrospective study	104	61.5	44 (33–55)	Severe/Critical (0/36, 0%)	Moderate (2/68, 2.9%)
Nachega JB	Congo	Cohort study	766	65.6	46 (34–58)	Severe (4/191, 2.1%)	Non-severe (15/575, 2.6%)
Al Kuwari HM	Qatar	Case series	5462	88.9	35.8 ± 1.2	Severe/Critical (1/117, 0.9%)	Mild (12/5345, 0.2%)
Ibrahim OR	Nigeria	Retrospective study	145	86.7	43 ± 16.0	Non-survivor (1/7, 14.3%)	Survivor (1/138, 2.6%)
Dai M	China	Retrospective study	73	59	51 ± 13	Severe (0/26, 0%)	Non-severe (3/47, 6.4%)

(Continues)

TABLE 1 (Continued)

Author	Country	Study design	Sample sizes	Male (%)	Age	Severe (TB/cases, %)	Non-severe (TB/cases, %)
Parker A	South Africa	Retrospective study	113	38.9	48.5	Death (6/28, 21.4%)	Survivor (7/85, 8.2%)
Lee SG	Korea	Retrospective study	7339	40.1	47.1 ± 19.0	Deceased (4/227, 1.8%)	Survivor (24/7112, 0.3%)
Tahtasakal CA	Turkey	Retrospective study	534	56.4	59 (19–97)	Severe/Critical (1/136, 0.7%)	Mild/Moderate (1/398, 0.3%)
Li S	China	Retrospective study	2924	50.6	61.9 (49.7–69.5)	Death (8/257, 3.1%)	Survival (44/2667, 1.6%)
Wang W	China	Retrospective study	146	61.2	44 (33–50)	Severe (2/24, 8.3%)	Non-severe (1/122, 0.8%)
Yan B	China	Retrospective study	110	53.7	59.5 (14–86)	Critical (1/41, 2.4%)	Moderate (0/69, 0%)
Zheng B	China	Retrospective study	198	40.4	49.5	Severe (1/36, 2.8%)	Mild (0/162, 0%)
Lu Y	China	Retrospective study	77	65	59 (54–63)	Non-survivor (1/40, 2.5%)	Survivor (0/37, 0%)
Oh TK	Korea	Cohort study	7780	NR	NR	Mortality (OR = 1.65, 95% CI: 0.48 to 5.64)	
Bepouka BI	Congo	Retrospective study	141	67.4	49.6 ± 16.5	Non-survivor (0/41, 0%)	Survivor (1/100, 1%)
Yitao Z	China	Retrospective study	257	54	46 ± 17	Deterioration (0/49, 0%)	Non-deterioration (3/208, 1.4%)
Li G	Multi-country	NR	399	54	66 (58–74)	Non-survivor (3/157, 1.9%)	Survivor (3/242, 1.2%)
Mollalo A	USA	NR	NR	NR	NR	Mortality (OR = 0.094, 95% CI: 0.012–0.761)	
						Mortality (OR = 0.142, 95% CI: 0.026–0.784)	
Zhang W	China	Retrospective study	500	53.6	40.6	Critical (1/300, 0.3%)	General (2/200, 1%)
Abraha HE	Ethiopia	Retrospective study	2617	63.3	29 (24–38)	Severe (0/114, 0%)	Non-severe (8/2503, 0.3%)
Meng M	China	Retrospective study	413	58.8	62.6 ± 13.5	Non-survivor (5/218, 2.29%)	Survivor (3/195, 1.54%)

Note: The value of age (years) was presented as mean ± *SD* or median with interquartile range (IQR).

Abbreviations: CI, confidence interval; ICU, intensive care unit; NR, not clearly reported; OR, odds ratio; TB, tuberculosis; USA, United States of America.

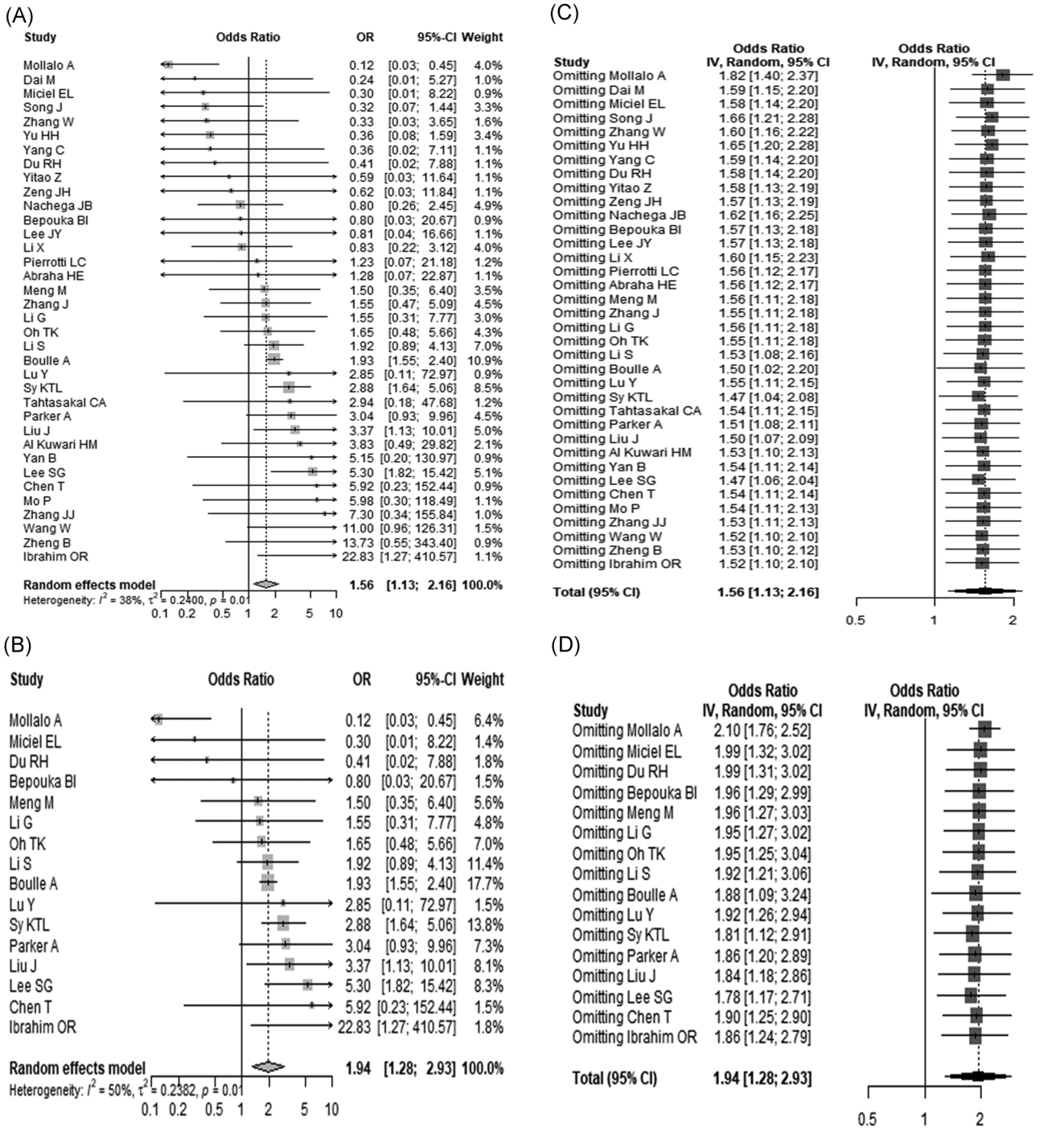

FIGURE 1 Forest plot indicated that there was a significant association between tuberculosis and the increased risk for severity (A) and mortality (B) among patients with coronavirus disease 2019 (COVID-19); Leave-one-out sensitivity analysis demonstrated that our results were stable and robust ((C) for severity and (D) for mortality). For Mollalo et al.'s study, the combined odds ratio was used

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AUTHOR CONTRIBUTIONS

Yadong Wang, Haiyan Yang, and Huifen Feng designed the study. Yadong Wang, Ruo Feng, Jie Xu, and Hongjie Hou searched articles and extracted the data. Jie Xu, Huifen Feng, and Haiyan Yang analyzed the data. Yadong Wang and Ruo Feng wrote and reviewed the manuscript. All the authors approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

All data relevant to this study are included in this article.

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