Diabetes and Risk of COVID-19 Mortality
A Systematic Review and Meta-Analysis

To the Editor

A growing body of evidence has suggested that patients with diabetes who developed the novel corona virus disease (COVID-19) might have shown increased mortality. Biologically, patients with diabetes have glycemic instability, impaired immune response, and associated comorbidities such as obesity and heart diseases, factors that could explain the high COVID-19 mortalities among patients with diabetes.[1] Epidemiologically, numerous studies assessed the possible relationship between diabetes and COVID-19 mortalities, but most of them were limited by the small sample size in addition to reaching inconsistent findings.[2–16] We, therefore, combined the results of the published studies via a meta-analysis to precisely detect the excess risk of COVID-19 mortality attributed to diabetes.

First, we searched MEDLINE (PubMed), Web of Science, and Scopus for potential studies published before May 31, 2020, using relevant search terms (diabetes OR diabetes mellitus OR type 2 diabetes OR DM) AND (COVID-19 OR SARS-COV 2 OR coronavirus) AND (outcomes OR mortality OR fatality OR deaths). The study was considered eligible if 1) it was published in English, 2) the exposure was COVID-19 patients with diabetes in comparison with COVID-19 patients without diabetes, 3) the outcome was COVID-19 mortality, and 4) the number of COVID-19 patients with diabetes is 50 or more.

After reviewing the abstracts of all studies detected by the primary search, we reached a shortlist of studies from which the following relevant information was extracted: last name of the first author, country, sample size, method of diabetes diagnosis, odds ratios (ORs) with corresponding 95% confidence intervals (CIs), and the quality of studies as determined using the modified Newcastle-Ottawa Scale (NOS) (Table 1). The fixed- or random-effects model was used to compute the pooled ORs. The I^2 was calculated to test the statistical heterogeneity across studies. A forest plot showing the ORs with their 95% CIs and study weights of the selected studies in addition to the pooled OR (95% CI) and I^2 was presented (Fig. 1). Sensitivity analysis was conducted to assess the influence of individual studies on the pooled OR and I^2 by leaving out one study and combining the remaining studies in separate analyses. Publication bias was assessed using the regression test for funnel plot asymmetry. R-3.2.0 statistical package (Metafor: A Meta-Analysis Package for R) was used for analysis.

Eventually, we retrieved a total of 831 studies before excluding 431 duplicates; 327 articles for being written in a non-English language, case reports, comments, reviews, or unrelated; 41 articles for not examining COVID-19 mortality or not including a comparison group; and 21 articles for including less than 50 COVID-19 patients with diabetes, leaving a shortlist of 15 studies for this meta-analysis. Most of the included studies were conducted in China, whereas only 5 studies were conducted out of China (3 studies in the United States and 1 study in each of Iran and Mexico). The studies included 75,200 COVID-19 patients, of which 13,609 had concomitant diabetes. According to the modified NOS, most studies were of average to good quality (Table 1).

A total of 8 studies showed statistically significant associations between diabetes and COVID-19 mortality, whereas 7 studies indicated no significant association. Combining the ORs of all studies revealed that COVID-19 patients with diabetes had an 87% higher risk of death than COVID-19 patients without diabetes (pooled OR,

TABLE 1. Characteristics of the Included Studies

Study	Country	Overall Patients	Diabetes Patients	Diabetes Diagnosis	Quality by Modified NOS
Zhu L	China	7337	952	Records based on the Chinese guidelines for type 2 diabetes prevention and control	8
Chen Y	China	904	136	Records based on the World Health Organization diagnostic criteria	7
Shi Q	China	306	153	Records based on the American Diabetes Association guidelines	7
Guan W	China	1590	130	Self-report	6
Wang L	China	339	54	Records	7
Nikpouraghdam M	Iran	2968	113	Records	5
Bode B	USA	1122	194	HbA1c ≥6.5%	7
Li H	China	453	192	FG ≥7 mmol/L and/or HbA1c ≥6.5%	7
Bello-Chavolla O	Mexico	51,633	9460	Medical history	7
Richardson S	USA	5700	1808	Records	7
Zhang Y	China	166	61	Self-report, high FG, and/or HbA1c ≥6.5%	8
Wang Y	China	344	64	Records	5
Chen R	China	1590	130	Records	7
Wang K	China	548	83	Records	5
Palaiodimos L	USA	200	79	Records	7

FG indicates fasting glucose.

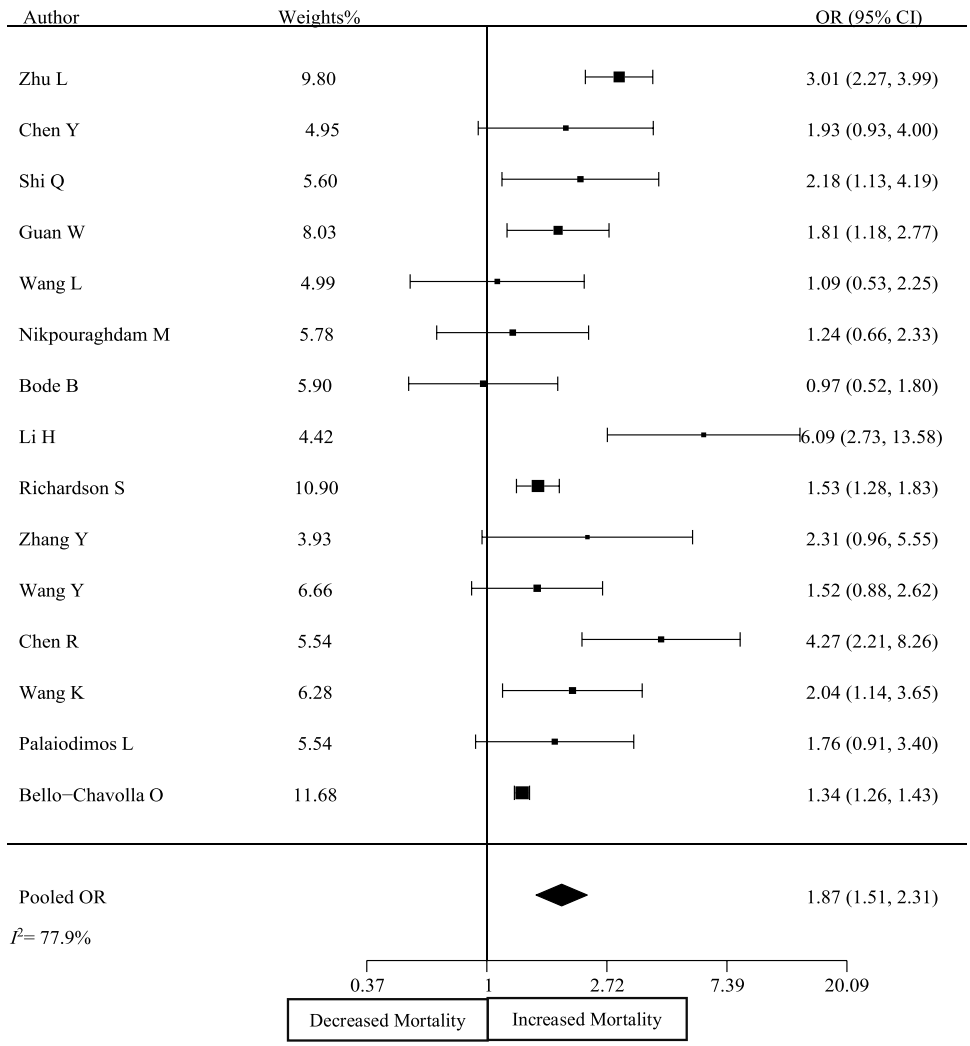

FIGURE 1. Meta-analysis of the included studies.

1.87; 95% CI, 1.51–2.31). However, we could notice a high degree of heterogeneity across studies (I^2 = 77.9%; P value for heterogeneity <0.001) (Fig. 1). This heterogeneity could be partially explained by the wide variation in the sample size among studies and the differences in the sociodemographic characteristics between study populations. Leaving out studies one by one and combining the remainders in separate analyses did not significantly affect the pooled risk or the heterogeneity across studies. No signs of publication bias could be detected (Z = 1.078; P value for publication bias = 0.281).

Our results came in line with similar meta-analyses that put the risk of COVID-19 mortality among patients with diabetes compared with COVID-19 patients without diabetes between 1.75 and 2.68 and showed moderate to high degrees of heterogeneity between their studies.[17–20] In conclusion, our results confirmed the previous findings indicating that COVID-19 patients with diabetes were highly vulnerable to a lethal outcome.

Hend Kandil, MD
Faculty of Medicine, Menoufia University
Menoufia, Egypt

Ahmed Elsayed Ibrahim, MD
Faculty of Medicine, Alexandria University
Alexandria, Egypt

Naglaa Afifi, MD, PhD
Department of Internal Medicine, Faculty of Medicine
Ain Shams University
Cairo, Egypt
Department of Internal Medicine
Armed Forces College of Medicine (AFCM)
Cairo, Egypt

Ahmed Arafa, MD, MSc
Department of Public Health
Graduate School of Medicine, Osaka University
Osaka, Japan
ahmed011172@med.bsu.edu.eg
Department of Public Health, Faculty of Medicine
Beni-Suef University
Beni-Suef, Egypt

Hend Kandil and Ahmed Elsayed Ibrahim contributed equally to this work.

The authors have no funding or conflicts of interest to disclose. We acknowledge Covid-19 MENA Response Research Team for their logistic support.

REFERENCES

1. Gupta R, Hussain A, Misra A. Diabetes and COVID-19: evidence, current status and unanswered research questions. *Eur J Clin Nutr.* 2020;1–7.
2. Zhu L, She Z, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab.* 2020;31:1068–1077.
3. Chen Y, Yang D, Cheng B, et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. *Diabetes Care*. 2020;43:1399–1407.
4. Shi Q, Zhang X, Jiang F, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. *Diabetes Care*. 2020;43:1382–1391.
5. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J.* 2020;55:2000547.
6. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020;80:639–645.
7. Nikpouraghdam M, Jalali Farahani A, Alishiri G, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in Iran: a single center study. *J Clin Virol*. 2020;127:104378.
8. Bode B, Garrett V, Messler J, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. *J Diabetes Sci Technol*. 2020;14:813–821.
9. Li H, Tian S, Chen T, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. *Diabetes Obes Metab.* 2020;22:1897–1906.
10. Bello-Chavolla O, Bahena-López J, Antonio-Villa N, et al. Predicting mortality due to SARS-CoV-2: a mechanistic score relating obesity and diabetes to COVID-19 outcomes in Mexico. *J Clin Endocrinol Metab.* 2020;105:2752–2761.
11. Richardson S, Hirsch J, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052–2059.
12. Zhang Y, Li H, Zhang J, et al. The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: A single-centre, retrospective, observational study in Wuhan. *Diabetes Obes Metab.* 2020;22:1443–1454.
13. Wang Y, Lu X, Li Y, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. *Am J Respir Crit Care Med*. 2020;201: 1430–1434.
14. Chen R, Liang W, Jiang M, et al. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. *Chest*. 2020;S0012–3692(20):30710–30718.
15. Wang K, Zhang Z, Yu M, et al. 15-day mortality and associated risk factors for hospitalized patients with COVID-19 in Wuhan, China: an ambispective observational cohort study. *Intensive Care Med*. 2020;1–3.
16. Palaiodimos L, Kokkinidis D, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism*. 2020;108:154262.
17. Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr.* 2020;14:535–545.
18. Huang I, Lim M, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia—a systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr.* 2020; 14:395–403.
19. Mantovani A, Byrne C, Zheng M, et al. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: a meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis*. 2020;30:1236–1248.
20. Wu Z, Tang Y, Cheng Q. Diabetes increases the mortality of patients with COVID-19: a meta-analysis. *Acta Diabetol*. 2020;1–6.