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 coronavirus 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. 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. 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 I² 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 I² was presented (Fig. 1). Sensitivity analysis was conducted to assess the influence of individual studies on the pooled OR and I² 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 outside 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.

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.

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                       |
| Palaidimos L | USA    | 200             | 79                | Records                                                                             | 7                       |

FG indicates fasting glucose.
However, we could notice a high degree of heterogeneity across studies (I² = 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. In conclusion, our results confirmed the previous findings indicating that COVID-19 patients with diabetes were highly vulnerable to a lethal outcome.

### Table

| Author                  | Weights% | OR (95% CI)     |
|-------------------------|----------|-----------------|
| Zhu L                   | 9.80     | 3.01 (2.27, 3.99) |
| Chen Y                  | 4.95     | 1.93 (0.93, 4.60) |
| Shi Q                   | 5.60     | 2.18 (1.13, 4.19) |
| Guan W                  | 8.03     | 1.81 (1.18, 2.77) |
| Wang L                  | 4.99     | 1.09 (0.53, 2.25) |
| Nikpouraghdam M         | 5.78     | 1.24 (0.66, 2.33) |
| Bode B                  | 5.90     | 0.97 (0.52, 1.80) |
| Li H                    | 4.42     | 6.09 (2.73, 13.58) |
| Richardson S            | 10.90    | 1.53 (1.28, 1.83) |
| Zhang Y                 | 3.93     | 2.31 (0.96, 5.55) |
| Wang Y                  | 6.66     | 1.52 (0.88, 2.62) |
| Chen R                  | 5.54     | 4.27 (2.21, 8.26) |
| Wang K                  | 6.28     | 2.04 (1.14, 3.65) |
| Palaiodimos L           | 5.54     | 1.76 (0.91, 3.40) |
| Bello-Chavolla O        | 11.68    | 1.34 (1.26, 1.43) |

| Pooled OR | ± 77.9% | 1.87 (1.51, 2.31) |

**FIGURE 1.** Meta-analysis of the included studies.
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