Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

ELSEVIER

Archives of Medical Research 51 (2020) 700–709

Archives of Medical Research

EPIDEMIOLOGICAL

Diabetes Mellitus is Associated with Severe Infection and Mortality in Patients with COVID-19: A Systematic Review and Meta-analysis

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Received for publication May 1, 2020; accepted July 24, 2020 (ARCMED_2020_603).

Background and Aim. Currently, the number of patients with coronavirus disease 2019 (COVID-19) infection is increasing rapidly worldwide. In this study, we aimed to assess whether diabetes mellitus (DM) would increase the risk of severe infection and death in patients with COVID-19.

Methods. We systematically searched the PubMed, Web of Science, MedRxiv and COVID-19 academic research communication platform for studies reporting clinical severity and/or overall mortality data on DM in patients with COVID-19 published up to July 10, 2020. The primary outcome was to compare the severe infection rate and mortality rate in COVID-19 patients with and without DM, and to calculate the odds ratio (*OR*) and 95% confidence interval (CI).

Results. A total of 76 studies involving 31,067 patients with COVID-19 were included in our meta-analysis. COVID-19 patients with DM had higher severe infection and case-mortality rates compared with those without DM (21.4 vs. 10.6% and 28.5 vs. 13.3%, respectively, all $p < 0.01$). COVID-19 patients with DM were at significantly elevated risk of severe infection ($OR = 2.38$, 95% CI: 2.05–2.78, $p < 0.001$) and mortality ($OR = 2.21$, 95% CI: 1.83–2.66, $p < 0.001$).

Conclusion. DM is associated with increased risk of severe infection and higher mortality in patients with COVID-19. Our study suggests that clinicians should pay more attention to the monitoring and treatment of COVID-19 patients with DM.

Key Words: COVID-19, Diabetes mellitus, Disease severity, Mortality, Meta-analysis.

Introduction

Since first reported in December 2019, coronavirus disease 2019 (COVID-19), caused by the new corona virus SARS-CoV-2, has spread all over the world and has been defined as a global pandemic by the World Health Organization (WHO) (1). COVID-19 is now a worldwide public health concern, the number of confirmed cases is increasing exponentially worldwide (2). By July 1, 2020, there were more than ten million confirmed cases and half a million deaths from COVID-19 in more than 200 countries (3).

The clinical manifestations of patients after SARS-CoV-2 infection are heterogeneous. Mild cases are mainly characterized by flu-like symptoms, such as cough and fever. However, patients with severe cases may die due to severe pneumonia, acute respiratory distress syndrome, multiple organ failure, or sepsis (4). According to a report from

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0188-4409/$ - see front matter.
https://doi.org/10.1016/j.arcmed.2020.07.005

the Chinese Center for Disease Control and Prevention, the case-fatality rate was 2.3% in 44,672 patients with confirmed cases of COVID-19, and all death cases were among critical patients (5). Therefore, it is very important to identify predictors of severe infection and mortality for effective treatment and therapeutic intervention.

Diabetes mellitus (DM) is a common underlying disease in patients with COVID-19. A meta-analysis including 76,993 patients with confirmed cases showed that the prevalence of DM in patients with COVID-19 was 7.87% (95% confidence interval [CI]: 6.57% - 9.28%) (6). Emerging evidence suggests that COVID-19 patients with DM have an increased risk of complications and poor prognosis (7). A recent study showed that COVID-19 patients with DM had higher levels of serum inflammation-related biomarkers and increased risk of severe pneumonia, excessive uncontrolled inflammatory responses, and hypercoagulability compared with non-diabetic patients (8). In the present study, we performed a systematic review and meta-analysis to investigate the association of DM with disease severity and mortality in patients with COVID-19 and to provide reliable evidence for improved treatment and control of COVID-19.

Methods

Our literature search was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (9) and was performed following the Preferred Reporting Items for Meta-Analyses (PRISMA) statement (10).

Search Strategy

We searched PubMed, the Web of Science, MedRxiv (https://www.medrxiv.org) and COVID-19 academic research communication platform (http://medjournals.cn/2019NCP/index.do) on March 31, 2020 and up-dated the search on July 10, 2020. The search was limited to papers published in English or Chinese language. The following mesh-terms and free words were used: ''COVID-19'', ''coronavirus disease 2019'', ''novel coronavirus pneumonia'', ''2019-nCoV'', ''SARS-CoV-2'', ''clinical characteristics'', ''clinical features'', ''outcome'', ''severe infection'', ''severe illness'', ''severity'', ''alive'', ''death'', ''mortality'', ''non-survivor'', and ''deceased'', alone and in combination. The title, abstract, and full text of all documents identified with the search criteria were assessed. The reference lists of all studies were also analyzed to identify additional eligible studies. Only those research articles that reported data of DM and at least one outcome of interest were included in this meta-analysis. The primary outcomes were the pooled severe infection and mortality risk in COVID-19 patients with DM. Studies were excluded if they included duplicated results, reported insufficient data, or were case reports, case series with less than 20 patients, letters, review articles, editorial comments, guidelines or studies with animals. Studies that reported only deaths or critically ill cases were excluded. When single-center studies from the same hospital reported the same outcome with the study period overlapping by at least 50%, outcome from the study with the largest number of patients was extracted.

Study Selection

Two investigators (MJS and LXS) independently scanned all the titles, abstracts and full text to identify studies that met the inclusion criteria and extracted data from these studies. Discrepancies between reviewers were resolved by discussion with a third reviewer (QLG) or by consensus. In this study, patients with severe infection were defined as those who met the diagnostic criteria of the Guidelines on the Diagnosis and Treatment of Novel Coronavirus Pneumonia (11) or were admitted to intensive care units.

Data Collection and Quality Assessment

Data extraction and quality assessment of the included studies were also performed by two investigators (MJS and LXS) who performed the literature search. Data were collected and entered into a spreadsheet. We extracted the following variables: first author, study period, location, sample size, patient age range, sex, the number of participants with severe infection and/or death, and the prevalence of comorbidities. We used the Newcastle-Ottawa Scale (NOS) to assess the risk of bias of the included studies, and a NOS score >7 was considered good quality (12).

Statistical Analysis

Statistical analysis was performed using the Meta package within *R* software (version 3.6.3). The *OR* and its 95% CI were used to estimate the corelation between DM and severe infection and mortality in patients with COVID-19. We used a random-effects model to synthesize data for the relevant outcomes. Heterogeneity was evaluated using the χ^2 test and the I^2 statistic. For the χ^2 test, the significant heterogeneity among studies was indicated with a Cochran's Q p-value of <0.10. I^2 values of 25%, 25−50%, or 50% indicated low, moderate, or high heterogeneity, respectively (13). If there was high heterogeneity, a sensitivity analysis was performed by removing each study from the meta-analysis (14). Forest plots visually showed effect estimates of the included studies. We used funnel plots, Begg's test, and Egger's test to evaluate potential publication bias. A two tailed p <0.05 was considered statistically significant.

Results

The flow of studies through our meta-analysis is depicted in Figure 1. A total of 76 studies with 31,067 patients were eventually included in our study (8,15–89). The characteristics of the included studies are described in Supplementary Table 1. The number of confirmed COVID-19 cases in each study ranged from 41–3,841. The proportion of diabetic patients ranged from 3.3–68.5%. As outlined in Supplementary Table 2, all articles included in the meta-analysis had high quality according to the NOS tool.

Pooled Analysis of Severe Infection

There were 54 studies reported the association between DM and severe infection in patients with COVID-19. COVID-19 patients with DM had higher severe infection rate compared with those non-diabetic patients (21.4 vs. 10.6%, $p < 0.01$). DM was found to be associated with a significantly greater risk of severe COVID-19 infection (pooled $OR = 2.38$, 95% CI: 2.05–2.78, $p < 0.001$; $I^2 = 39\%$, $p < 0.01$, Figure 2). The result remained similar for subgroup analysis according to study location ($p = 0.24$).

Pooled Analysis of Mortality

A total of 28 studies reported an association between DM and mortality in patients with COVID-19. COVID-19 patients with DM had higher mortality rate compared with those non-diabetic patients (28.5 vs. 13.3%, $p < 0.01$). COVID-19 patients with DM had a higher risk of death (pooled $OR = 2.21$, 95% CI: 1.83–2.66, $p < 0.001$; $I^2 = 50\%$, $p < 0.01$, Figure 3). The subgroup analyses in different locations showed similar result ($p = 0.93$).

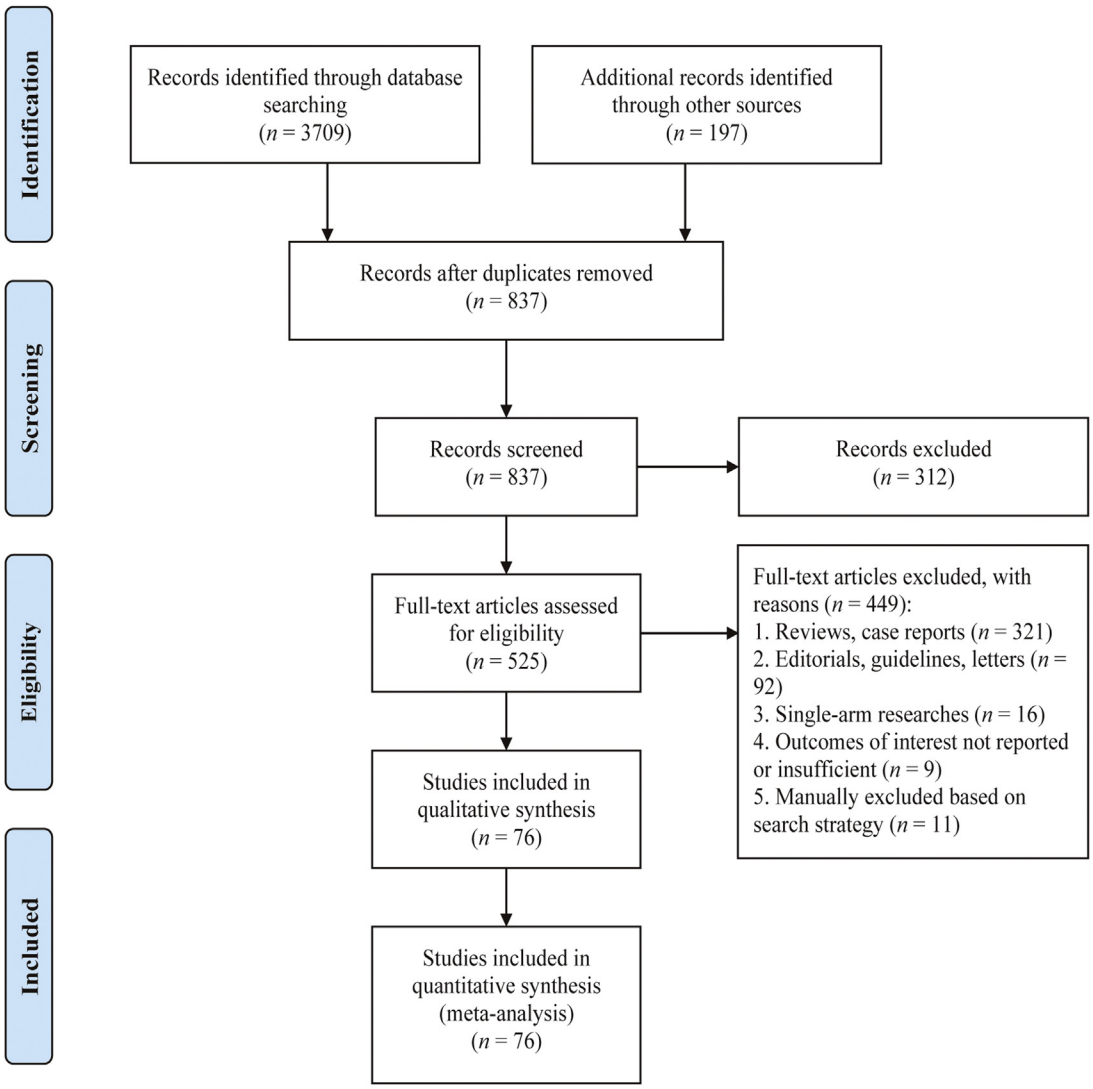

Figure 1. Flow diagram for literature selection.

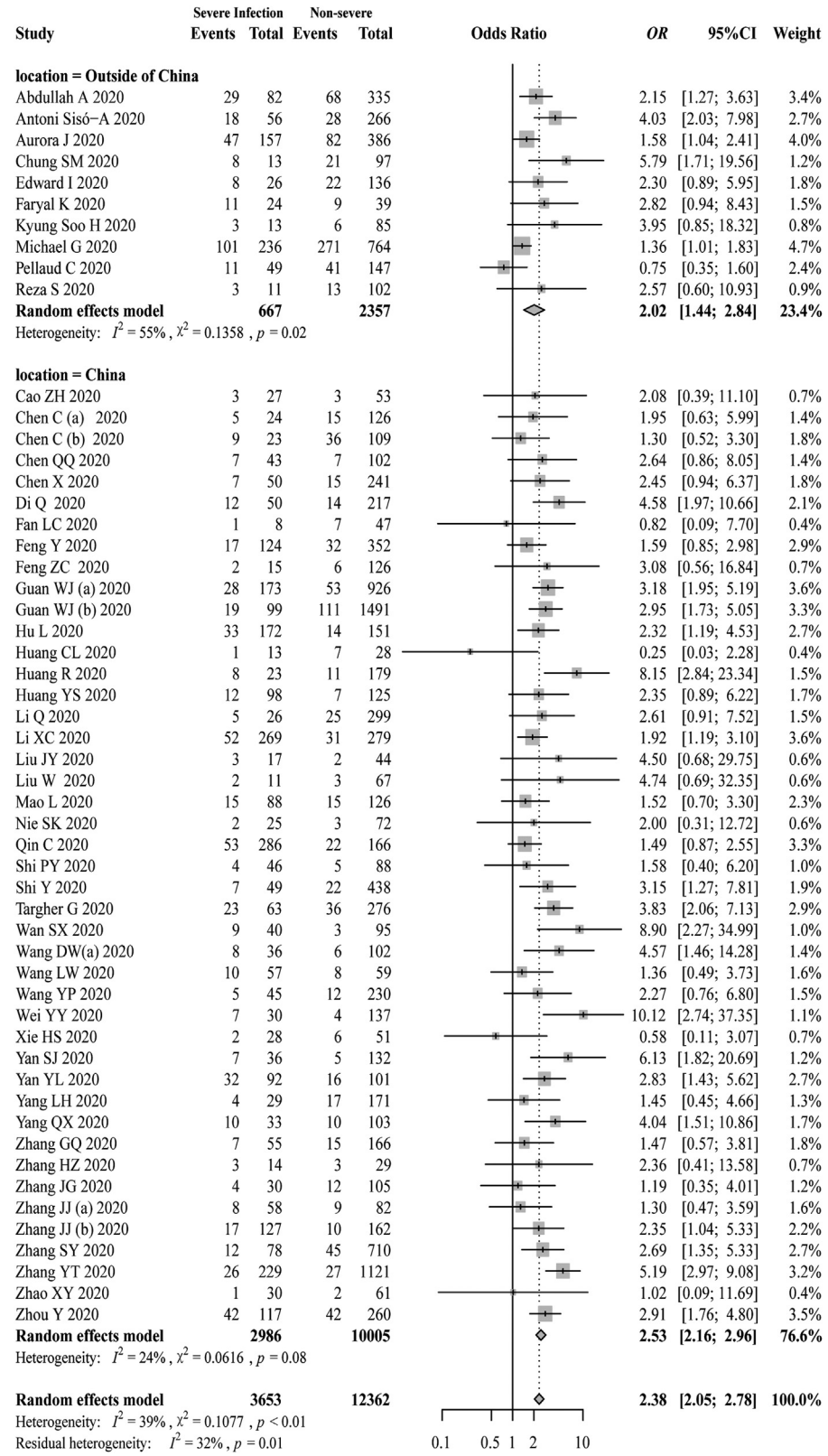

Figure 2. Forest plot for the association of DM and disease severity in patients with COVID-19.

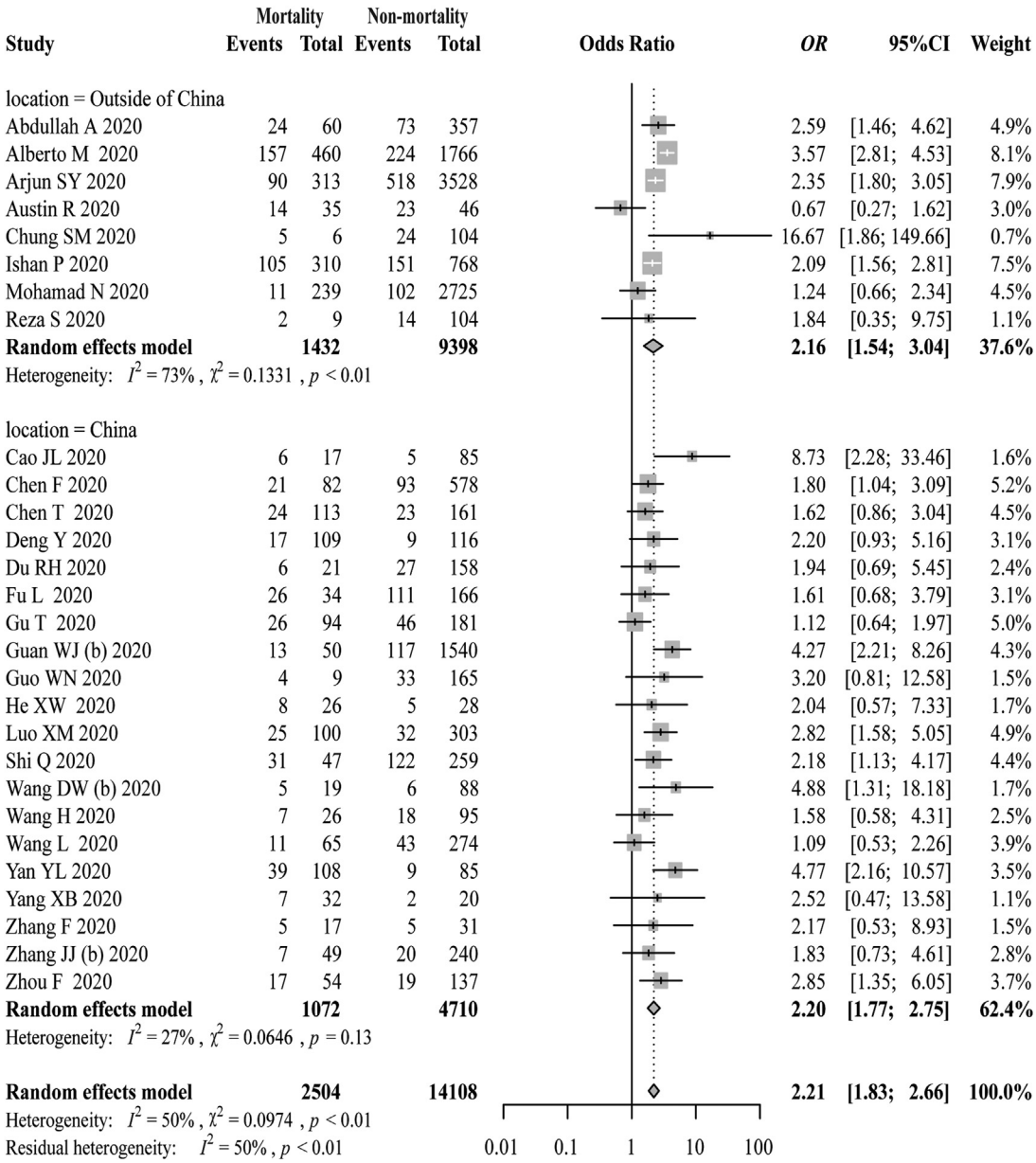

Figure 3. Forest plot for the association of DM and mortality in patients with COVID-19.

Sensitivity Analysis and Publication Bias

The sensitivity analysis showed that none of the studies remarkably affected the pooled ORs and CIs (Supplementary Figure 1). Visual inspection of the both funnel plots revealed symmetry, indicating a low risk of publication bias (Figure 4). The Begg's test and Egger's test for the severe infection outcome (Begg's test: $p = 0.96$, Egger's test: $p = 0.18$) and for mortality outcome (Begg's test: $p = 0.25$, Egger's test: $p = 0.48$), respectively, confirmed that there was no statistically publication bias.

Discussion

To our knowledge, this meta-analysis used the largest number of studies and the largest sample size so far to evaluate the correlation between DM and the risk of disease severity and death in COVID-19. Our results showed that diabetic patients with COVID-19 had higher severe infection and case-fatality rates compared with non-diabetic patients, and DM was associated with an increased risk of severe infection and mortality in patients with COVID-19.

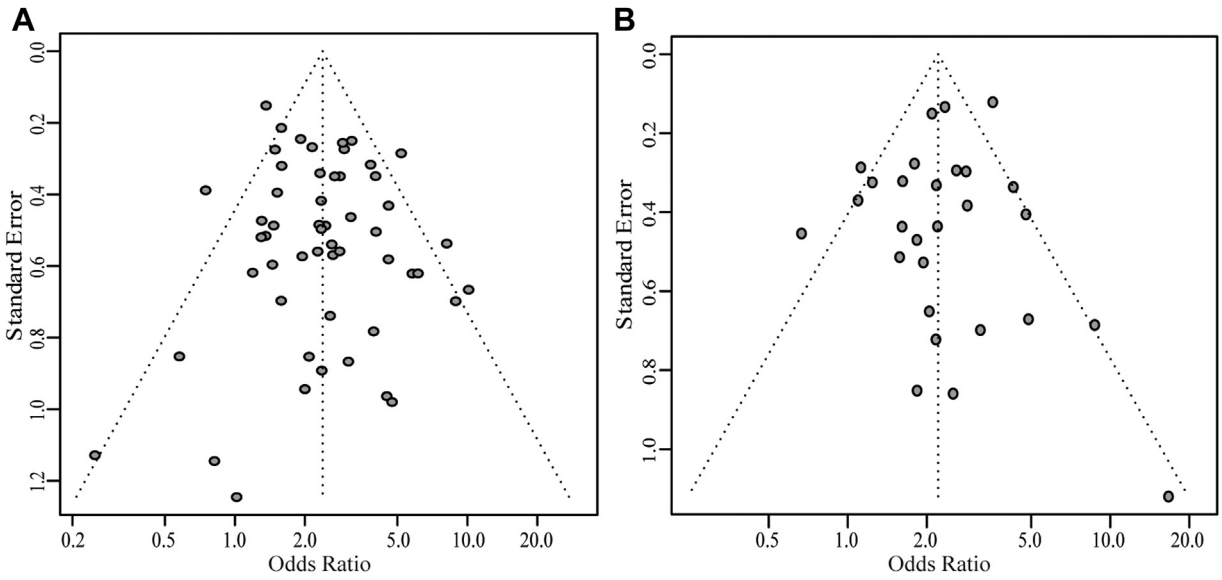

Figure 4. Funnel plot for the assessment of publication bias. (A) Outcome of severe infection; (B) Outcome of mortality.

It remains unclear whether DM would increase the risk of SARS-CoV-2 infection, however, it has been observed that DM is a common underlying disease in patients with COVID-19. An early meta-analysis of 6 studies with 1,527 patients showed that hypertension (17.1%), cardio-cerebrovascular disease (16.4%), and DM (9.7%) were the most prevalent cardiovascular metabolic comorbidities in COVID-19 patients (7). An updated meta-analysis, including 83 studies and nearly 79,000 patients with laboratory-confirmed cases of COVID-19 showed that the prevalence of DM among COVID-19 patients was 14.34% (95% CI: 12.62−16.06 %) (90). Therefore, patients with DM are suggested to pay attention to self-protection, and maintain good blood glucose control to reduce the risk of infection.

Our results showed that diabetic patients with COVID-19 had higher severe infection and case-fatality rates. A retrospective review of 25 patients with COVID-19 who died showed that all had one or more underlying diseases, of which DM accounted for 40% (91). An analysis from Italy showed that the average number of complications is 2.7 in patients who died from COVID-19, and this study suggests that the high prevalence of complications is one of the important reasons for the high mortality of COVID-19 patients in Italy (92). Our results support most of the current research conclusions (93,94) and highlight the importance of DM in the stratification of critical illness and death risk in patients with COVID-19.

However, so far, the mechanism leading to worse clinical outcomes in COVID-19 patients with DM has not been fully clarified. One possible reason is that DM is related to the activation of the renin-angiotensin system, and patients with DM are often treated with angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs), which may both lead to the increased expression of ACE2 in tissues, promoting virus absorption and increasing the risk of severe infection in patients with DM (95). Secondly, DM may induce the hypercoagulable state in patients with COVID-19, resulting in worse outcomes of these patients. Studies have reported that diabetic patients with COVID-19 had increased risk of hypercoagulability, and many severe and fatal patients with COVID-19 seemed to eventually die of small pulmonary embolism (96). Futhermore, DM patients are in a state of chronic inflammation. Inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate and interleukin-6 are elevated in diabetic patients with COVID-19, which may contribute to a cytokine storm and in turn, lead to severe pneumonia and the eventual death outcome (97).

At present, experts from all over the world are providing advice on the management of diabetic patients with COVID-19. The suggestion from the Chinese Diabetes Society points out that hospitalized COVID-19 patients with DM should receive individualized blood glucose control goals and treatment strategies according to their condition (98). Klonoff DC, et al. (99) pointed out the importance of careful use of glucocorticoids, strengthened blood glucose monitoring, strengthened contacts with health-care staff, and cautious cessation of ACEIs or ARBs. Advice from China called for the ‘‘Seven Treasures’’ policy for DM management, including health education, balanced nutrition, physical activity, standardized medication, blood glucose monitoring, regular schedule, and care for mental health (100). The European Society of Endocrinology also suggested that endocrinologists provide online/email/phone consultation services and closely monitor glycemic control

in patients with DM during the COVID-19 pandemic (101). However, in view of the pandemic state of COVID-19, the evidence available at present is still limited. More studies are needed to determine the best treatment for COVID-19 patients with DM in the future, and the current clinical management should be revised promptly according to the latest evidence.

This study has several limitations. First, while we excluded some studies manually to avoid including any duplicate studies, it is still possible that some overlapping patients were included in our meta-analysis, which might have some slight impact on our results. Second, the patients with COVID-19 in our meta-analysis had a high case-fatality rate, which may be due to these included studies during the early stages of the outbreak involving a higher proportion of severely ill patients. Therefore, the relationship between DM and mortality risk in mildly ill patients still needs to be evaluated. Third, different studies have different definitions of severe infection; at the same time, most studies were not adjusted for various confounding factors, such as data on diabetic medications, which might both cause bias in the results. Forth, the majority of the included studies in our meta-analysis were retrospective case-control studies, as the disease spreads around the world, it is hoped that other cohort studies and randomized studies will report more clinical data to verify our results, and further examine the effect of DM type, DM duration, presence of DM-related complications and glycaemic controls on prognosis of COVID-19.

In conclusion, DM is related to a higher risk of severe infection and mortality. Therefore, it is needed to protect DM population from COVID-19 infection. Meanwhile, special care and monitoring are required in COVID-19 patients with DM to improve prognosis.

Conflicts of Interest

All authors report no conflicts of interest related to this manuscript.

Acknowledgments

This study was supported by National Key R&D Program of China (Grant number: 2016YFC0900905). We thank AJE (American Journal Experts) and ‘‘HOME for Researchers’’ for linguistic assistance.

Funding: National Key R&D Program of China (2016YFC0900905).

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.arcmed.2020.07.005.

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