LETTER TO THE EDITOR

The association of diabetes with COVID-19 disease severity: evidence from adjusted effect estimates

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Received: 5 August 2020 / Accepted: 4 November 2020 / Published online: 25 November 2020
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To the Editor,

Diabetes, which is one of the leading causes of mortality and morbidity worldwide with increasing prevalence, is a well-known risk factor for various infections, post-infection complications, and increased mortality secondary to infections [1]. Diabetes has now been shown to be among the most common medical conditions in patients who develop coronavirus disease 2019 (COVID-19) [2] and has been associated with higher mortality in patients with this disease [3]. Zheng et al. reported that diabetes is associated with an almost fourfold greater risk for severe disease and death in patients with COVID-19 (odds ratio (OR) = 3.68, 95% confidence interval (CI) [2.68–5.03]; \( P < 0.001 \)) [4]. However, although a significant association was observed between diabetes and disease severity (including severe and critical conditions and mortality) among COVID-19 patients based on the data of unadjusted effect estimates (hazard ratio (HR)) in the study by Cummings et al., this disappeared based on the data of the adjusted effect estimates [5], which suggest that several factors such as age, gender, and underlying diseases might modulate the relationship between diabetes and COVID-19 disease severity. Therefore, it was evident that the association between diabetes and severe COVID-19 disease needed to be investigated via a quantitative meta-analysis based on the data of adjusted effect estimates.

A systematic literature search was conducted for studies published from January 1, 2020, to July 25, 2020, in the PubMed, Chinese National Knowledge Infrastructure (CNKI), and Web of Science databases. According to the indices of the various databases, we used the search terms “coronavirus disease 2019,” “2019-nCoV, SARS-CoV-2,” “COVID-19,” and “diabetes,” and “diabetes mellitus.” Only articles reporting adjusted effect estimates (adjusted OR or HR) for diabetes and severity of disease in COVID-19 patients were considered eligible. There was no restriction on country or location. All calculations were carried out with Stata 11.2 software. The pooled OR and pooled HR with their corresponding 95% CI were applied to evaluate the risk of severity in diabetic patients with COVID-19. The choice of the appropriate effects model was based on the analysis results, as follows: the fixed effect model was used if \( \hat{I}^2 \) was < 50% and the random-effects model was used if \( \hat{I}^2 \) was ≥ 50% [6]. Sensitivity analysis was conducted to evaluate the robustness of the results. Publication bias among the included studies was assessed by employing Begg’s funnel plot and Egger’s test.

A total of 1057 studies were identified using the search algorithm. Twenty-three studies [5, 7–28], comprising a total of 22,359 patients, were considered to be eligible for inclusion (Table 1). The median age of the patients ranged from 44 to 71 years; 4407 (20%) of them had diabetes. Among the 23 included articles, there were 19 retrospective studies and four prospective studies.

The forest plot of the association between diabetes and the severity of COVID-19 symptoms is shown in Fig. 1a and b. Diabetes was found to be associated with an increased risk of disease severity in COVID-19 patients on the basis of 14 studies reporting adjusted OR (OR = 1.44, 95% CI [1.14–1.82], \( \hat{I}^2 = 58.2\% \), random-effects model) (Fig. 1a) and nine studies reporting adjusted HR (HR = 1.37, 95% CI [1.19–1.57]; \( \hat{I}^2 = 29.2\% \), fixed-effects model) (Fig. 1b). In the 23 studies we included, only 11 studies reported both unadjusted and adjusted effect estimates (HR or OR) simultaneously. We calculated the pooled unadjusted and adjusted effect estimates (HR or OR) separately, and the pooled results based on unadjusted effect estimates showed that diabetes was associated with greater risk for disease severity in patients with COVID-19 compared to the pooled results based on adjusted effect estimates (HR unadjusted = 2.04 (95% CI: 1.30–3.19) and OR unadjusted = 2.98 (95% CI: 1.75–5.05); HR adjusted = 1.61 (95% CI: 1.28–2.04) and OR adjusted = 1.58 (95% CI: 1.07–
Table 1  Characteristics of the included studies

| Author | Location | Case | Age (years) | Male (%) | Study design | DM | Unadjusted effect estimate (95% CI) | Adjusted effect estimate (95% CI) | Confounding factors |
|--------|----------|------|-------------|----------|--------------|----|-----------------------------------|----------------------------------|-------------------|
| Mo P   | China    | 155  | 54 (42–66)  | 86 (55.5)| R            |    | 15 (9.7)                         | OR 2.138 (0.483–9.471)          | Age, male, CVD, fever, shortness of breath, anorexia, blood test, chest CT or X-ray, treatment |
| Hu L   | China    | 323  | 61 (23–91)  | 166 (51.4)| R            |    | 47 (14.6)                        | OR 3.109 (1.155–8.373)          | Age, smoking, hypnotics, diagnosis of critical status, hypersensitive troponin I, WBC, neutrophil count |
| Huang R| China    | 202  | 44.0 (33.0–54.0) | 116 (57.4)| R            |    | 19 (9.4)                         | OR 8.145 (2.842–23.342)         | Age, gender, BMI, HTN, smoking, WBC, neuphilops, lymphocyte, Hb, PLT, ALT, LDH, Tbil, ALB, CR, CRP, PT |
| Shi S  | China    | 671  | 63 (50–72)  | 322 (48.0)| R            |    | 97 (14.5)                        | HR 1.16 (0.47–2.85)             | Age, gender, HTN, CHD, chronic renal disease, CHD, cerebrovascular diseases, PCT, cTnI, myoglobin; CRP; NT-proBNP; MYO, CK-MB |
| Yu X   | China    | 333  | 50 (35–63)  | 172 (51.7)| R            |    | 28 (8.4)                         | OR 1.1 (0.3–3.6)                | Age, gender, heart disease, HTN, respiratory disease |
| Cummings MJ | USA | 257  | 62 (51–72)  | 171 (67)  | P            |    | 92 (36)                          | HR 1.65 (1.11–2.44)             | Age, gender, symptom duration before hospital presentation, HTN, chronic cardiac disease, COPD or interstitial lung disease, CKD, BMI, interleukin-6, D-dimer |
| Zhang Y| China    | 258  | 64 (56–70)  | 138 (53.5)| R            |    | 63 (24.4)                        | HR 2.840 (1.01–8.01)            | Age, CVD, CKD |
| Phipps MM | USA    | 2273 | 65 (52–76)  | 1297 (57) | R            |    | 886 (39)                         | OR 1.65 (1.34–2.02)             | Age, peak ALT, BMI, HTN, intubation, renal replacement therapy |
| Galloway JB | UK    | 1157 | 71 (57–82)  | 666 (57.6)| R            |    | 408 (35.3)                       | HR 1.20 (0.97–1.48)             | Age, gender |
| Zhao M | China    | 1000 | 61 (46–70)  | 466 (46.6)| R            |    | 118 (11.8)                       | HR 0.962 (0.576–1.608)          | Age, gender, HTN |
| Lim JH | Korea    | 160  | NR          | 86 (53.8) | R            |    | 50 (31.3)                        | HR 1.55 (0.85–2.83)             | Age, gender, troponin strata, race, ethnicity, coronary artery disease, heart failure, HTN, atrial fibrillation, CKD, clinical variables |
| Lala A | USA      | 2736 | 66.4        | 1630 (59.6)| R            |    | 719 (26.3)                       | OR 1.01 (0.80–1.27)             | Age, gender, smoking history, HTN, chronic obstructive lung disease, coronary artery disease, duration of antiviral therapy |
| Cen Y | China    | 1007 | 61 (49–68)  | 493 (49.0) | P            |    | 119 (11.8)                       | HR 2.920 (2.224–3.835)          | Age, gender, smoking history, HTN, chronic obstructive lung disease, coronary artery disease, duration of antiviral therapy |
| Jang JG| Korea    | 110  | 56.9 (±17.0)| 48 (43.6) | R            |    | 29 (26.4)                        | OR 7.47 (2.73–20.04)            | Age, gender, HTN, body temperature, peripheral oxygen saturation, albumin, Tbil, CK-MB |
| Rath D | Germany  | 123  | 68 (±15)    | 77 (62.6) | P            |    | 30 (24.4)                        | HR 3.65 (1.06–12.63)            | Age, arterial HTN, LVEF, RV-function, tricuspid regurgitation >1 |
| Bertin D| France  | 56   | NR          | 33 (58.9) | P            |    | 10 (17.9)                        | OR 0.33 (0.21)                  | Age, gender, smoking history, HTN, chronic obstructive lung disease, coronary artery disease, duration of antiviral therapy |
| Author       | Location   | Case | Age (years) | Male (%) | Study design | DM | Unadjusted effect estimate (95% CI) | Adjusted effect estimate (95% CI) | Confounding factors                                                                 |
|--------------|------------|------|-------------|----------|--------------|----|-------------------------------------|-----------------------------------|-------------------------------------------------------------------------------------|
| Yu C        | China      | 1464 | 64.0 (51.0–71.0) | 736 (50.3) | R            | 211 (14.4) OR 3.77 (2.70–5.28) | OR 2.34 (1.45–3.76) | Gender, duration of symptoms, aCL IgG, CHD, HTN, chronic respiratory disease         |
| Bravi F     | Italy      | 1603 | 58.0 (20.9)   | 758 (47.3) | R            | 194 (12.1) NR | OR 1.52 (1.05–2.18) | Age, gender, HTN, CVD, cancer, COPD, renal disease                                    |
| Booth CM    | Canada     | 144  | 45 (34–57)    | 56 (39)   | R            | 16 (11)   NR | HR 3.1 (1.4–7.2)    | Age, comorbidity                                                                   |
| Han J       | China      | 185  | 44 (±17.88)   | 95 (51.4)  | R            | 28 (15.1) OR 5.792 (2.366–14.176) | OR 3.311 (1.093–10.031) | Age, time from symptoms onset to treatment, PaO2/FiO2 on admission, NLR, PLT          |
| Hashemi N   | USA        | 363  | 63.4 (± 16.5) | 201 (55.4) | R            | 117 (32.2) NR | OR 1.22 (0.74–2.00) | Age, gender, HTN, obesity, cardiac diseases, hyperlipidemia, pulmonary disorders     |
| Ji W        | Korea      | 7541 | 47.05 (± 19.0) | 2970 (40.5) | R            | 1043 (14.2) OR 4.646 (3.984–5.418) | OR 1.247 (1.009–1.543) | Comorbidity                                                                         |
| Pettit NN   | USA        | 238  | 58.5 (±17)    | 113 (47.5) | R            | 68 (28.6) OR 0.8 (0.3–2.2) | OR 0.5 (0.2–1.7) | Age, gender, HTN, obesity, pulmonary disease, CVD, kidney disease, cancer, stroke, hyperlipidemia, VTE |

All values are n (%), mean (standard deviation, SD), or median (interquartile range, IQR). USA, United States of America; NR, not reported; DM, diabetes mellitus; P, prospective; R, retrospective; HR, hazard ratio; OR, odds ratio; CVD, cardiovascular diseases; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; PCT, procalcitonin; COPD, chronic obstructive pulmonary diseases; HTN, hypertension; BMI, body mass index; CRP, C-reactive protein; CHD, coronary heart disease; WBC, white blood cell; PLT, platelet; Tbil, total bilirubin; ALB, albumin; CR, creatinine; PT, prothrombin time; Hb, hemoglobin; NT-proBNP, amino-terminal pro-brain natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatinine kinase-myocardial band; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; aCL: anti-cardiolipin antibodies; NLR, neutrophil-to-lymphocyte ratio; VTE: venous thromboembolism.
Fig. 1 The pooled odds ratio (OR) (a), hazard ratio (HR) (b), and their 95% confidence interval (CI) of the relationship between diabetes and the risk of disease severity in patients with COVID-19. Sensitivity analysis for evaluating the relationship between diabetes and the risk of disease severity in patients with COVID-19 (c)
2.32), respectively) (Fig. S1). Sensitivity analysis indicated that our results were robust and stable (Fig. 1c). There was no significant publication bias, as determined by Begg’s test ($P = 0.224$) and Egger’s test ($P = 0.065$).

Although previous meta-analyses have demonstrated that diabetes was positively associated with an increased risk of severity and mortality in COVID-19 patients, these studies did not uniformly address the influences of several factors, including age, gender, and underlying diseases, on the results [4, 29–33]. Therefore, our present study investigated the relationship between diabetes and disease severity in COVID-19 patients based on adjusted effect estimates: the results demonstrated that diabetes was an independent predictor of COVID-19 disease severity.

Some limitations should be considered in our study. Firstly, the definitions of severity of COVID-19 varied among the included studies. Secondly, the type of diabetes and whether it was with good or with poor glycemic control are also unknown. Because the selected studies did not adequately present data on the treatment of diabetes and blood glucose control, these could not be evaluated. Finally, all selected studies presented adjusted effect estimates, but the adjusted confounders among the studies were not completely consistent: for example, the number and kinds of adjusted confounders are different among the included studies.

In conclusion, our findings indicated that diabetes is an independent risk factor for predicting COVID-19 disease severity in these patients. These results clearly underscore the necessity to increase our focus in clinical practice on COVID-19 patients with diabetes to stabilize their condition.

Given the limited level of evidence, further well-designed studies with larger samples are needed to confirm our current results.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s42000-020-00259-x.

Funding This study was supported by a grant from the National Natural Science Foundation of China (No. 81973105). The funder has no role in data collection and analysis, manuscript preparation, and decision to submission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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