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LETTER TO THE EDITOR

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

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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 I^2 was < 50% and the random-effects model was used if 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. 1 a 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], $I^2 = 58.2\%$, random-effects model) (Fig. 1a) and nine studies reporting adjusted HR (HR = 1.37, 95% CI [1.19–1.57]; $I^2 = 29.2\%$, 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–

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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 PMID: 32173725	China	155	54 (42–66)	86 (55.5)	R	15 (9.7)	NR	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 PMID: 32361738	China	323	61 (23–91)	166 (51.4)	R	47 (14.6)	NR	OR 3.109 (1.155–8.373)	Age, smoking, hypnotics, diagnosis of critical status, hypersensitive troponin I, WBC, neutrophil count
Huang R PMID: 32384078	China	202	44.0 (33.0–54.0)	116 (57.4)	R	19 (9.4)	OR 8.145 (2.842–23.342)	OR 4.326 (1.059–17.668)	Age, gender, BMI, HTN, smoking, WBC, neutrophils, lymphocyte, Hb, PLT, ALT, LDH, Tbil, ALB, CR, CRP, PT
Shi S PMID: 32391877	China	671	63 (50–72)	322 (48.0)	R	97 (14.5)	NR	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 PMID: 32351037	China	333	50 (35–63)	172 (51.7)	R	28 (8.4)	NR	OR 1.1 (0.3–3.6)	Age, gender, heart disease, HTN, respiratory disease
Cummings MJ PMID: 32442528	USA	257	62 (51–72)	171 (67)	P	92 (36)	HR 1.65 (1.11–2.44)	HR 1.31 (0.81–2.10)	Age, gender, symptom duration before hospital presentation, HTN, chronic cardiac disease, COPD or interstitial lung disease, CKD, BMI, interleukin-6, D-dimer
Zhang Y PMID: 32446795	China	258	64 (56–70)	138 (53.5)	R	63 (24.4)	NR	HR 2.840 (1.01–8.01)	Age, CVD, CKD
Phipps MM PMID: 32473607	USA	2273	65 (52–76)	1297 (57)	R	886 (39)	OR 1.65 (1.34–2.02)	OR 1.30 (1.02–1.68)	Age, peak ALT, BMI, HTN, intubation, renal replacement therapy
Galloway JB PMID: 32479771	UK	1157	71 (57–82)	666 (57.6)	R	408 (35.3)	NR	HR 1.20 (0.97–1.48)	Age, gender
Zhao M PMID: 32499448	China	1000	61 (46–70)	466 (46.6)	R	118 (11.8)	NR	HR 0.962 (0.576–1.608)	Age
Lim JH PMID: 32503180	Korea	160	NR	86 (53.8)	R	50 (31.3)	HR 1.55 (0.85–2.83)	HR 1.35 (0.72–2.56)	Age, gender, HTN
Lala A PMID: 32517963	USA	2736	66.4	1630 (59.6)	R	719 (26.3)	NR	OR 1.01 (0.80–1.27)	Age, gender, troponin strata, race, ethnicity, coronary artery disease, heart failure, HTN, atrial fibrillation, CKD, clinical variables
Cen Y PMID: 32526275	China	1007	61 (49–68)	493 (49.0)	P	119 (11.8)	HR 2.920 (2.224–3.835)	HR 1.816 (1.351–2.442)	Age, gender, smoking history, HTN, chronic obstructive lung disease, coronary artery disease, duration of antiviral therapy
Jang JG PMID: 32537954	Korea	110	56.9 (± 17.0)	48 (43.6)	R	29 (26.4)	OR 7.47 (2.73–20.04)	OR 19.15 (1.90–193.42)	Age, gender, HTN, body temperature, peripheral oxygen saturation, albumin, Tbil, CK-MB
Rath D PMID: 32537662	Germany	123	68 (±15)	77 (62.6)	P	30 (24.4)	NR	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	OR 0.21	

Table 1 (continued)

Author	Location	Case	Age (years)	Male (%)	Study design	DM	Unadjusted effect estimate (95% CI)	Adjusted effect estimate (95% CI)	Confounding factors
PMID:32564467							(0.06–1.35)	(0.02–1.85)	Gender, duration of symptoms, aCL IgG, CHD, HTN, chronic respiratory disease
Yu C PMID: 32564974	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)	Age, gender, HTN, lymphopenia, ALT, LDH, D-dimer, PCT
Bravi F PMID: 32579597	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 PMID: 12734147	Canada	144	45 (34–57)	56 (39)	R	16 (11)	NR	HR 3.1 (1.4–7.2)	Age, comorbidity
Han J PMID: 32580792	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 PMID: 32585065	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 PMID: 32597048	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 PMID: 32589784	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

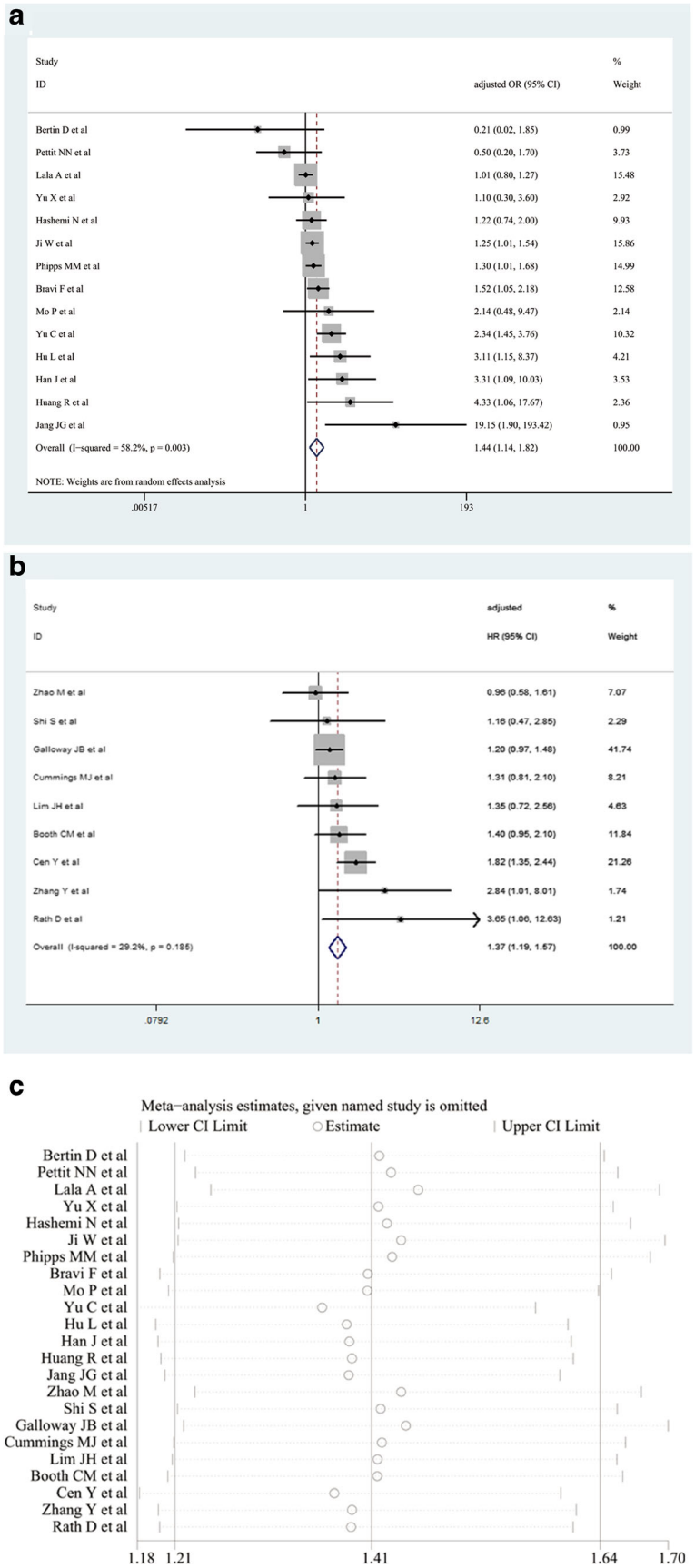

Fig. 1 The pooled odds ratio (OR) (**a**), hazard ratio (HR) (**b**), and their 95% confidence interval (CI) of the relationship between diabetes and the risk of disease severity in patients with COVID-19. Sensitivity analysis for evaluating the relationship between diabetes and the risk of disease severity 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 so as to prevent rapid deterioration of 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.

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Compliance with ethical standards

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

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