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RESEARCH LETTER

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Diabetes mellitus association with coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis

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Highlights

- There are ~ 2-fold increased odds of severe coronavirus disease 2019 (COVID-19) and a ~ 2-fold increased risk of odds of mortality in patients with history of diabetes mellitus compared to those without diabetes mellitus.
- Patients with a history of diabetes mellitus should be closely monitored if they get infected with COVID-19.

To the Editor

Coronavirus disease 2019 (COVID-19) is a viral infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Because of the huge pressure that this pandemic infectious disorder is placing on healthcare services worldwide, better knowledge of factors influencing the evolution into unfavorable outcomes is urgently needed to help in appropriate allocation of residual resources. Diabetes mellitus (DM), another current epidemic around the world, is associated with high mortality and morbidity burden. Because the prevalence of DM has been reported to be high among COVID-19 patients,[2] we carried out a pooled analysis of current studies for evaluating potential associations between DM and infection severity outcomes in COVID-19 patients.

TABLE 1 Characteristics of the studies included

		Severe patients/non-survivors				Non-severe patients/survivors			
Study	**Total sample size**	**n (%)**	**Age (yrs)[a]**	**Women (%)**	**Diabetes n (%)**	**n (%)**	**Age (yrs)[a]**	**Women (%)**	**Diabetes n (%)**
Chen et al 2020[a18]	150	24 (16%)	68.5	6 (25%)	5 (20.8%)	126 (84%)	57.1	60 (47.6%)	15 (11.9%)
Deng et al 2020[3]	225	109 (48.5%)	69 (62-74)	36 (33%)	17 (15.6%)	116 (51.5%)	40 (33-57)	65 (56%)	9 (7.8%)
Guan et al 2020[4]	1099	173 (15.7%)	52 (40-65)	73 (42%)	28 (16.2%)	926 (84.3%)	45 (34-57)	386 (42%)	53 (5.7%)
Huang et al 2020[10]	41	13 (31.7%)	49 (41-61)	2 (15%)	1 (8%)	28 (68.3%)	49 (41-57.5)	9 (32%)	7 (25%)
Liu et al 2020[6]	78	11 (14.1%)	66 (51-70)	4 (52.2%)	2 (18.2%)	67 (85.9%)	37 (32-41)	35 (36.4%)	6 (9.0%)
Liu et al 2020[a7]	12	6 (50%)	64	3 (50%)	1 (16%)	6 (50%)	43.3	1 (16%)	1 (16%)
Qin et al 2020[8]	452	286 (63.3%)	61 (51-69)	131 (45.8%)	53 (18.5%)	166 (36.7%)	53 (41.25-62)	86 (51.8%)	22 (13.3%)
Ruan et al 2020[9]	150	68 (45.3%)	67 (15-81)	19 (28%)	12 (18%)	82 (54.6%)	50 (44-81)	29 (35%)	13 (16%)
Tianxin et al[a14]	49	9 (18.3%)	53	1 (11.1%)	2 (2.2%)	40 (81.7%)	40.6	15 (37.5%)	0 (0%)
Wan et al 2020[10]	135	40 (29.6%)	56 (52-73)	19 (47.5%)	9 (22.5%)	95 (70.4%)	44 (33-49)	43 (45.3%)	3 (3.1%)
Wang et al 2020[11]	138	36 (26.1%)	66 (57-78)	14 (39%)	8 (22.2%)	102 (73.9%)	51 (37-62)	49 (48%)	6 (5.9%)
Wang et al 2020[12]	69	14 (20.3%)	70.5 (62-77)	7 (50%)	6 (43%)	55 (79.7%)	37 (32-51)	30 (55%)	1 (2%)
Wu et al 2020[13]	201	84 (41.7%)	58.5 (50-69)	24 (28.6%)	16 (19%)	117 (58.3%)	48 (40-54)	49 (41.9%)	6 (5.1%)
Yang et al 2020[15]	52	32 (61.5%)	64.6 (11.2)	11 (34%)	7 (22%)	20 (38.5%)	51.9 (12.9)	6(30%)	2 (10%)
Zhang et al 2020[16]	140	58 (41.4%)	64 (25-87)	25 (43%)	8 (13.8%)	82 (58.6%)	52 (26-78)	44 (54%)	9 (11%)
Zhou et al 2020[17]	191	54	69 (63-76)	16 (30%)	17 (31%)	137	52 (45-58)	56 (41%)	19 (14%)

Abbreviation: ICU, intensive care unit; MV, mechanical ventilation; NR, not reported.
[a]Age data presented as median (interquartile range [IQR]) or mean (SD). Studies marked with (a) report age as mean (yrs).

1. | METHODS

We searched PUBMED, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) for studies published until March 31, 2020. We also searched major infectious disease, endocrinology, and general medicine journals and then performed a hand search of the bibliography of included studies.

Studies were included if they fulfilled the following criteria: (a) report history of DM in COVID-19 patients; (b) report outcomes of interest; and (c) sample size >10. A meta-analysis was performed to estimate the odds ratio (OR) and 95% confidence interval (CI) of DM in COVID-19 patients with or without severe disease and in non-survivors vs survivors. The statistical analysis was carried out using MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia), with inverse variance model. Finally, we performed a random effects meta-regression using log OR to evaluate the impact of mean age and gender on association of DM with disease severity and mortality in patients with COVID-19.

2. | RESULTS

An initial search identified 348 publications. After removing duplicated or overlapping publications, and excluding reviews and editorials, 202 documents could be initially identified. A total number of 187 studies were excluded because they did not provide the rate of DM in COVID-19 patients with different disease severity. Fifteen articles were hence selected. During hand search of the bibliography, one additional study was identified, so that our final pooled analysis included 16 studies.[3-18] Twelve studies reported history of DM in severe vs non-severe cases, with a sample of 2564 confirmed COVID-19 patients (754, 29.4% being severe cases). A total number of 265 patients (10.3%) were classified as having a history of DM. Four studies with 618 patients (307, 42.5% of non-survivors) compared the rate of DM between survivors and non-surviving COVID-19 patients, 96 (15.5%) of them previously diagnosed with DM. Details of the included studies are listed in Table 1.

The results of the pooled analysis are presented in Figure 1. COVID-19 patients previously diagnosed with DM were found to be associated with a statistically significant increased risk of worse COVID-19 infection (OR: 2.60 [95% CI: 1.96 to 3.45], $I^2 = 56\%$, Cochran's Q = 24.9, $P = 0.01$). In the pooled analysis of the four studies reporting mortality data, significant association was found with increased risk of mortality in COVID-19 patients previously diagnosed with DM (OR: 2.03 [95% CI: 1.29-3.20] $I^2 = 0\%$, Cochran's Q = 2.63, $P = 0.45$).

Meta-regression analysis showed no effect of age (Figure S1) or gender (Figure S2) on the association of DM with COVID-19 infection severity or mortality.

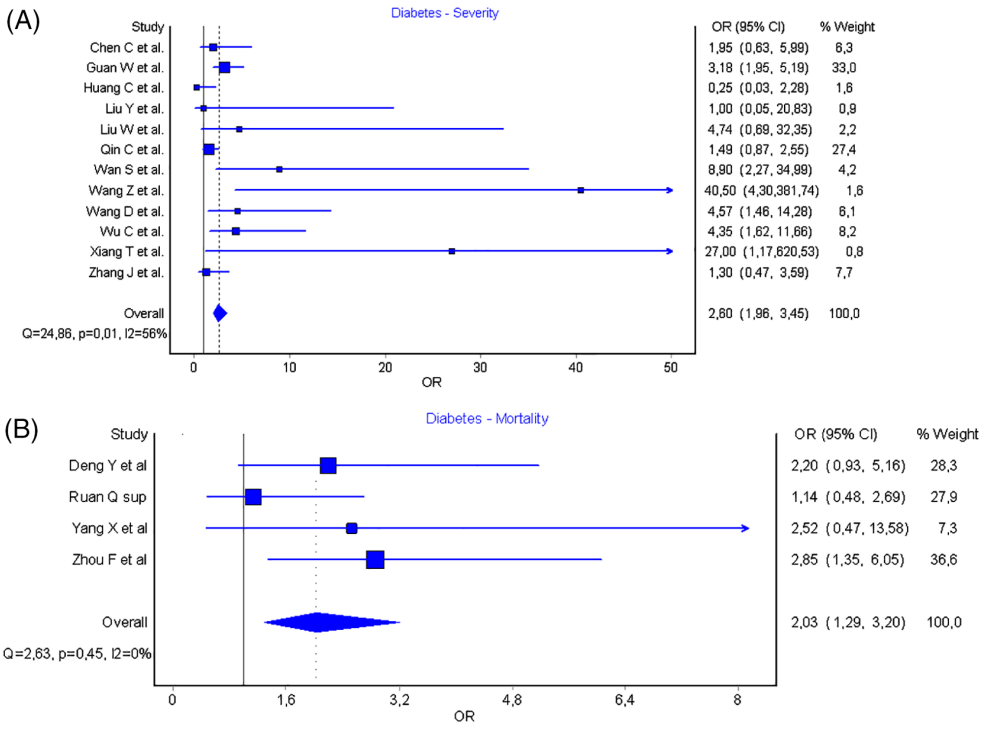

FIGURE 1 Results of meta-analysis showing association of diabetes mellitus with severity (Panel A) of disease and mortality (Panel B) in coronavirus disease 2019 (COVID-19) patients

3. | COMMENT

The results of our pooled analysis demonstrate that the presence of DM may significantly worsen the clinical course of COVID-19. Overall, we found a ~ 2-fold increased odds of severe COVID-19 and a ~ 2-fold increased odds of mortality in DM patients with this infection compared to non-DM patients.

There are several possible mechanisms explaining these findings. Patients with DM have been inherently known to have higher cumulative mortality, mostly owing to cardiovascular and renal disease.[19] DM has also been previously associated with worse outcomes in patients with SARS infection.[20] The circulating levels of some cytokines such as interleukin-6 (IL-6) were found to be higher in COVID-19 patients with DM, which suggests the presence of an underlying proinflammatory milieu as one mechanism linking DM to worse severity outcomes in COVID-19 patients.[21] It is also noteworthy that DM patients are more frequently overweight or have a higher prevalence of obesity, which could also contribute to worsen the prognosis of restrictive lung diseases.

A limitation of our analysis is in the fact that we could not use exclusion criteria to obtain data from the largest possible number of studies. We did perform sensitivity analysis and analysis for publication bias to assess for heterogeneity. To assess the effect of age and gender as confounding variables in our analysis, we also performed a meta-regression that showed no impact on association of DM with disease severity or mortality in COVID-19 patients. Because the included studies were observational, we cannot rule out possibility of confounding and reverse causation. We did not have data on use of antihyperglycemic agents, duration of diabetes, and associated diabetic micro- and macrovascular complications. Owing to the limited number of studies and small sample size, large prospective studies would be advisable to confirm our findings, data regarding COVID-19 are still in nascent stage and our findings may help clinicians and policymakers implement risk stratification models and put the limited healthcare resources to judicious use.

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DISCLOSURE

None declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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