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

Gaurav Aggarwal1 | Giuseppe Lippi2 | Carl J. Lavie3 | Brandon Michael Henry4 | Fabian Sanchis-Gomar5,6

1Department of Medicine, Jersey City Medical Center, Jersey City, New Jersey
2Section of Clinical Biochemistry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy
3John Ochsner Heart and Vascular Institute, Ochsner Clinical School - The University of Queensland School of Medicine, New Orleans, Louisiana
4Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio
5Department of Physiology, Faculty of Medicine, University of Valencia and INCLIVA Biomedical Research Institute, Valencia, Spain
6Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California

Correspondence
Brandon Michael Henry, Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children’s Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH, 45229.
Email: brandon.henry@cchmc.org

Funding information
Subprograma Atracció de Talent - Contractes Postdoctorals de la Universitat de València

KEYWORDS
coronavirus, COVID-19, diabetes mellitus

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). 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, 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

| Study          | Total sample size | Severe patients/non-survivors | Non-severe patients/survivors |
|----------------|-------------------|-------------------------------|-------------------------------|
|               | n (%)             | Age (yrs)* | Women (%) | Diabetes n (%) | n (%) | Age (yrs)* | Women (%) | Diabetes n (%) |
| Chen et al 2020 | 150               | 24 (16%) | 68.5      | 6 (25%)       | 5 (20.8%) | 126 (84%) | 57.1       | 60 (47.6%) | 15 (11.9%) |
| Deng et al 2020 | 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  | 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 | 41                | 13 (31.7%) | 49 (41-61) | 2 (1.5%)       | 1 (8%)     | 28 (68.3%) | 49 (41-57.5) | 9 (32%) | 7 (25%) |
| Liu et al 2019  | 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 2020a | 12                | 6 (50%) | 64        | 3 (50%)       | 1 (16%)    | 6 (50%) | 43.3       | 1 (16%) | 1 (16%) |
| Qin et al 2020  | 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  | 150               | 68 (45.3%) | 67 (15-81) | 19 (28%)       | 12 (18%)   | 82 (54.6%) | 50 (44-81) | 29 (35%) | 13 (16%) |
| Tianxin et al 2014 | 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   | 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  | 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 2020a | 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    | 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  | 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 | 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 2020a | 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.

*aAge data presented as median (interquartile range [IQR]) or mean (SD). Studies marked with (a) report age as mean (yrs).
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.

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. 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], I² = 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] I² = 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](image-url) 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.

ACKNOWLEDGEMENT

Fabian Sanchis-Gomar is supported by a postdoctoral contract granted by “Subprograma Attracció de Talent - Contractes Postdoctorals de la Universitat de València.” Other authors: No funding received.

DISCLOSURE

None declared.

REFERENCES

1. Lippi G, Sanchis-Gomar F, Henry BM. Coronavirus disease 2019 (COVID-19): the portrait of a perfect storm. Ann Transl Med. 2020;8:497. https://doi.org/10.21037/atm.2020.03.157.
2. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med. 2020;8(1):e35.
3. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J (Engl). 2020;133:1261-1267.
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-1720.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
6. Liu W, Tao ZW, Lei W, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl). 2020;133(9):1032-1038.
7. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63(3):364-374.
8. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020;71(15):762-768.
9. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-848.
10. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in Northeast Chongqing. J Med Virol. 2020;92:797-806.
11. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061.
12. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis. 2020;71(15):769-777.
13. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180:934.
14. Tianxin X, Jiaming L, Fei X, et al. Analysis of clinical characteristics of 49 patients with new type of coronavirus pneumonia in Jiangxi region. Chin J Resp Crit Care. 2020;19:154-160.
15. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan,
China: a single-centered, retrospective, observational study. \textit{Lancet Respir Med.} 2020;8:475-481.

16. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. \textit{Allergy.} 2020;75:1730-1741.

17. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. \textit{Lancet.} 2020;395(10229):1054-1062.

18. Chen C, Chen C, Jiangtao Y, Ning Z, Jianping Z, Daowen W. Analysis of myocardial injury and cardiovascular diseases in critical patients with new coronavirus pneumonia. \textit{Chin J Cardiovasc Dis.} 2020.

19. Rodriguez BL, Abbott RD, Fujimoto W, et al. The American Diabetes Association and World Health Organization classifications for diabetes. Their impact on diabetes prevalence and total and cardiovascular disease mortality in elderly Japanese-American men. \textit{Diabetes Care.} 2002;25(6):951-955.

20. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. \textit{JAMA.} 2003;289(21):2801-2809.

21. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. \textit{Lancet.} 2020;395(10229):1033-1034.

**SUPPORTING INFORMATION**

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

**How to cite this article:** Aggarwal G, Lippi G, Lavie CJ, Henry BM, Sanchis-Gomar F. Diabetes mellitus association with coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. \textit{Journal of Diabetes.} 2020;12:851–855. \url{https://doi.org/10.1111/1753-0407.13091}