

LETTER TO THE EDITOR

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Diabetes and Covid-19: An interplay difficult to dissect

Recently, *Diabetes/Metabolism Research and Reviews* published a study by Guo et al,¹ dealing with the relevant question on whether diabetes might have a direct and independent impact on the clinical course of patients infected with SARS-CoV-2 virus. Diabetes is a common condition, associated with an increased mortality, particularly from cardiovascular diseases (CVD), and clarifying the role of the disease in the onset and/or the prognosis of Covid-19 might be of the greatest importance.

Furthermore, the search of the most appropriate treatment to control diabetes would become an important priority. The study by Guo et al¹ is a retrospective study on 174 patients admitted to the Wuhan Union hospital in February 2020. In this group of patients, 37 were diabetic. Compared with patients without diabetes, the diabetic patients had a more than double prevalence of cardiovascular disease (CVD), and 28% less frequently fever. In addition, diabetic patients had lower lymphocyte and red blood cell count, higher neutrophils count and D-dimer. Among the diabetic patients, mortality was 3-fold higher, but did not reach the threshold of statistical significance ($P = .185$). Since the more frequent coexistence of cardiovascular disease in the diabetic patients (32.4 vs 14.6%) made difficult to compare diabetic and non-diabetic patients, the authors excluded from the further analysis all the patients with coexisting comorbidities, that is, COPD, hypertension, malignancy, CVD, chronic kidney or liver or pulmonary disease, etc. As a result, the two groups of patients without comorbidities profoundly differ for age ($P < .01$), being the median age of the 24 diabetic patients 61 years (IQ range 57-69) vs 32 years (IQ range 30-37) of the 26 non-diabetic patients. Since age is the single most determinant prognostic factor for ICU admission, acute respiratory stress syndrome (ARDS), and mortality, any further comparison of the data would lose reliability.²⁻⁶ However, the authors continued the analysis. They observed that diabetic patients, compared with non-diabetic patients, had a worse mortality rate and unfavourable levels of many parameters associated with worse prognosis.

Several comments can be made regarding the manuscript by Guo et al.¹ First, the concept that age has a tremendous impact on prognosis and mortality in patients with Covid-19 has very solid evidences and has been constantly reported together with the presence of any coexisting illness.²⁻⁷ Among the coexisting illnesses, the most frequently associated with worse prognosis were hypertension, chronic obstructive pulmonary disease (COPD), cardio or cerebro-vascular diseases and diabetes.²⁻⁷ However, with ageing, the prevalence of chronic diseases increases and clusters, making difficult to dissect the increased risk of mortality due to the age per se from the risk linked to the coexisting diseases. Analysing the data relative to 355 patients

who died in Italy and whose mean age was 79.5 years, only one quarter of them had an isolated chronic illness, while 48.5% had three diseases, and the mean of chronic diseases present in the same individual was 2.7.⁵ However, in work, in which a multivariate analysis was performed, age was strongly and independently associated with death.² Therefore, the comparisons of two groups with ages so different should not have been done and the results are questionable. Furthermore, more details should have been provided to make the results useful, that is, the fever levels. The authors inform that diabetic patients had less frequently fever. Was the fever measured at the hospital admission? Was the fever reported the average of all the temperatures measured during the hospital staying? These are important differences, since less fever at the admission might just be the expression of major attention and early hospital referral in patients with diabetes and more comorbidities, rather than showing a true different onset of the disease. On the other hand, high fever has been associated with higher risk of ARDS, but with lower mortality in patients with Covid-19.⁴ Finally, for being an observational study, the number of patients studied is low and presence or absence of differences might be just fortuitous. By the way, a recent commentary on the pages of this journal⁸ had already raised the issue that the difference of age between the two groups of patients and the small sample size represent some limitations of the study by Guo et al.¹

Diabetes and Covid-19 have potentially many possible pathogenetic links through which diabetes could worsen the prognosis of Covid-19.⁸

However, although methodologically sound, there is potentially a conceptual flaw in the way of investigating the effects of diabetes on Covid-19 in the article by Guo et al.¹: thinking to dissect the effect of diabetes by removing all the comorbidities. Diabetes is a complex disease for which many comorbidities just represent its complications, the natural consequences of the disease, not an occasional event. They are, unfortunately, part of the syndrome we call diabetes. Micro- and macro-vascular complications are, with different degree, present in the diabetic patients and increase all-cause and cardiovascular mortality.^{9,10} Hypertension is present in at least half of the diabetic patients.¹¹ The fact that the population of diabetic patients had an increased prevalence of CVD simply means that they were diabetic. By removing the patients with comorbidities from the analysis, paradoxically, does not make the two groups equal. It just removes the most complicated form of the disease, the patients with longer duration of diabetes, the patients with worse blood glucose control, etc. Very recently, an increased mortality risk from Covid-19 associated with diabetes and independent from age has been demonstrated in a group of 7337 patients.¹² Interestingly, in this paper, the authors

decided not to adjust for CVD because, as they say, CVD coexist with diabetes. In addition, they show that poorly controlled diabetic patients had a worse prognosis.¹²

KEYWORDS

cardiovascular diseases, Covid-19, diabetes mellitus

CONFLICT OF INTEREST

The author declares no conflicts of interests related to this manuscript.

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REFERENCES

- Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020; e3319. <https://doi.org/10.1002/dmrr.3319>.
- 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. *Lancet*. 2020;395:1054-1062.
- 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.
- 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. <https://doi.org/10.1001/jamainternmed.2020.0994>.
- Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA*. 2020;323:1775-1776. <https://doi.org/10.1001/jama.2020.4683>.
- Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: prevalence, pathophysiology, prognosis and practical considerations. *Diabetes Metab Syndr Clin Res Rev*. 2020;14:303-310.
- Guan W, Ni Z, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720. <https://doi.org/10.1056/NEJMoa2002032>.
- Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. *Diabetes Metab Res Rev*. 2020; e33213321. <https://doi.org/10.1002/dmrr.3321>.
- Rawshani A, Rawshani A, Franzen S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379:633-644. <https://doi.org/10.1056/NEJMoa1800256>.
- Rawshani A, Rawshani A, Franzen S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376:1407-1418. <https://doi.org/10.1056/NEJMoa1608664>.
- Horr S, Nissen S. Managing hypertension in type 2 diabetes mellitus. *Best Pract Res Clin Endocrinol Metab*. 2016;30:445-454. <https://doi.org/10.1016/j.beem.2016.06.001>.
- Zhu L, She Z-G, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 Diabetes. *Cell Metab*. 2020;31:1068-1077.e3.