The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 9, e3364–e3368
doi:10.1210/clinem/dgab393
Clinical Research Article

Clinical Research Article

Diabetes Increases Severe COVID-19 Outcomes Primarily in Younger Adults

Marc Diedisheim,[1,2] Etienne Dancoisne,[3,4] Jean-François Gautier,[1,5] Etienne Larger,[2] Emmanuel Cosson,[6,7] Bruno Fève,[8,9,10] Philippe Chanson,[11,12] Sébastien Czernichow,[13,14] Sopio Tatulashvili,[6,7] Marie-Laure Raffin-Sanson,[15,16] Kankoé Sallah,[4] Muriel Bourgeon,[17] Christiane Ajzenberg,[18] Agnès Hartemann,[19] Christel Daniel,[3,20] Thomas Moreau,[21] Ronan Roussel,[1,22] and Louis Potier[1,22]

[1]Cordeliers Research Centre, ImMeDiab team, INSERM, Université de Paris, 75006 Paris, France; [2]Hôpital Cochin, APHP, Diabetology Department, 75014 Paris, France; [3]Assistance Publique-Hôpitaux de Paris, DSI WIND, Web Innovation Données, 75012 Paris, France; [4]Hôpital Bichat - Claude-Bernard, APHP, URC PNVS, CIC-EC 1425, INSERM, 75018 Paris, France; [5]GH Lariboisiere Fernand-Widal, APHP, Department of Diabetes and Endocrinology, 75010 Paris, France; [6]Hospital Avicenne, APHP, Department of Endocrinology-Diabetology-Nutrition, CRNH-IdF, CINFO, 93000 Bobigny, France; [7]Université Sorbonne Paris Cité, UMR U557 INSERM/U11125 INRAE, Unité de Recherche Epidémiologique Nutritionnelle, 93000 Bobigny, France; [8]Hôpital Saint-Antoine, APHP, Department of Endocrinology-Diabetology, 75012 Paris, France; [9]Institut Hospitalo-Universitaire ICAN, 75013 Paris, France; [10]Sorbonne Université, INSERM, UMR_S938, CRMR PRISIS, 75012 Paris, France; [11]Hôpital Bicêtre, APHP, Service d'Endocrinologie et des Maladies de la Reproduction, 94270 Le Kremlin-Bicetre, France; [12]Université Paris-Saclay, INSERM, Physiologie et Physiopathologie Endocriniennes, 94270 Le Kremlin-Bicetre, France; [13]Hôpital Européen Georges Pompidou, APHP, Service de Nutrition, Centre Spécialisé Obésité, 75015 Paris, France; [14]Université de Paris, INSERM, UMR1153, Epidemiology and Biostatistics Sorbonne Paris Cité Centre (CRESS), 75015 Paris, France; [15]Hospital Ambroise Paré, APHP, Service d'Endocrinologie Diabétologie et Nutrition, 92100 Boulogne-Billancourt, France; [16]Université de Versailles Saint-Quentin-en-Yvelines, 78000 Versailles, France; [17]Hôpital Antoine-Béclère, APHP, Service de Médecine Interne, 92140 Clamart, France; [18]Hôpital Henri Mondor, APHP, Service de Médecine Interne, 94000 Creteil, France; [19]Hôpital Pitié Salpêtrière, APHP, Diabetology Department, 75013 Paris, France; [20]Sorbonne Université, University Paris 13, Sorbonne Paris Cité, INSERM UMR_S 1142, 75006 Paris, France; [21]Université Paris-Saclay, INRIA, CEA, 91120 Palaiseau, France; and [22]Hôpital Bichat - Claude-Bernard, APHP, Department of Diabetology, 75018 Paris, France

ORCiD numbers: 0000-0002-0418-1107 (M. Diedisheim); 0000-0001-5096-5722 (P. Chanson); 0000-0001-6268-7360 (L. Potier).

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; HR, hazard ratio

Received: 8 March 2021; Editorial Decision: 27 May 2021; First Published Online: 1 June 2021; Corrected and Typeset: 2 July 2021.

Abstract

Context: Diabetes is reported as a risk factor for severe coronavirus disease 2019 (COVID-19), but whether this risk is similar in all categories of age remains unclear.

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Objective: To investigate the risk of severe COVID-19 outcomes in hospitalized patients with and without diabetes according to age categories.
Design Setting and Participants: We conducted a retrospective observational cohort study of 6314 consecutive patients hospitalized for COVID-19 between February and 30 June 2020 in the Paris metropolitan area, France; follow-up was recorded until 30 September 2020.
Main Outcome Measure(s): The main outcome was a composite outcome of mortality and orotracheal intubation in subjects with diabetes compared with subjects without diabetes, after adjustment for confounding variables and according to age categories.
Results: Diabetes was recorded in 39% of subjects. Main outcome was higher in patients with diabetes, independently of confounding variables (hazard ratio [HR] 1.13 [1.03-1.24]) and increased with age in individuals without diabetes, from 23% for those <50 to 35% for those >80 years but reached a plateau after 70 years in those with diabetes. In direct comparison between patients with and without diabetes, diabetes-associated risk was inversely proportional to age, highest in <50 years and similar after 70 years. Similarly, mortality was higher in patients with diabetes (26%) than in those without diabetes (22%, $P < 0.001$), but adjusted HR for diabetes was significant only in patients younger than age 50 years (HR 1.81 [1.14-2.87]).
Conclusions: Diabetes should be considered as an independent risk factor for the severity of COVID-19 in young adults more so than in older adults, especially for individuals younger than 70 years.

Key Words: diabetes, covid-19, mortality, age

For the past year, the coronavirus disease 2019 (COVID-19) pandemic has spread around the world, leading to more than 2.0 million deaths, with higher risk of severe illness in older adults and those with comorbidities including diabetes (1, 2), leading to increasing anxiety in this population. It is becoming increasingly evident that the main risk factor for severe outcomes is age: elderly people, older than age 70 years, had the highest burden of risk associated with COVID-19 (3). In contrast, diabetes is prevalent in people from a wide range of ages and whether it is associated with severe outcomes in all age groups is not known. The aim of this study was to compare severe outcomes among patients with and without diabetes hospitalized for COVID-19 according to age in a large French repository database.

Methods

This observational study used the Entrepôt de données de santé COVID database from the Assistance Publique-Hôpitaux de Paris Hospitals (a group of 39 French public hospitals), aggregating on a daily basis hospitalization-related electronic health records since the beginning of the COVID-19 epidemic (4). Data for all patients older than 18 years of age with confirmed positive severe acute respiratory syndrome coronavirus 2 PCR tested between 6 February 2020 (first positive PCR recorded) and 30 June 2020 was retrieved from this database (n = 10 448); patient follow-up was recorded until 30 September 2020. Patients without available body mass index (BMI) (n = 4134) were excluded.

This study was approved by the institutional review board from the Assistance Publique-Hôpitaux de Paris CDW Scientific and Ethics Committee (IRB 00011591). All subjects included in this study were informed about the reuse of their data for research; subjects that objected to the reuse of their data were excluded in accordance with French legislation.

Comorbidities

Chronic comorbidities were extracted using International Classification of Diseases-10 codes in any previous or current hospitalization: C00 to D49 for malignancies; E78 for dyslipidemia; G473 for sleep apnea; I10 for high blood pressure; I20 to I25, I63, I64, and I70 to I79 for cardiovascular disease; I50 for heart failure; J44 for chronic obstructive pulmonary disease; and N18 for chronic kidney disease. Smoking status was defined as a binary variable by extracting mentions of both current and history of smoking from free-text electronic health records using a dedicated pipeline.

Diabetes was defined as being diagnosed a E10 to E14 International Classification of Diseases-10 codes, treatment by an intermediate or long-acting insulin treatment

(Anatomical Therapeutic Chemical codes A10AC, A10AD, A10AE) or other noninsulin blood glucose-lowering drugs (Anatomical Therapeutic Chemical codes A10B) in any previous or current hospitalization, or having a hemoglobin A1c level greater than 6.5% (48 mmol/mol) in any previous or current hospitalization. Hemoglobin A1c within 1 year before or 7 days after positive PCR result date was available for 1892 patients.

Primary and secondary outcomes

The primary outcome was a composite of in-hospital mortality or intensive care unit admission with orotracheal intubation within 90 days of first admission with positive PCR. The secondary outcome was in-hospital mortality at 90 days alone.

Statistical analysis

Continuous variables are presented as median (interquartile range) and categorical variables as number (percentage). Baseline characteristics were compared with the 2-sided *t* test for continuous variables and χ^2 test for categorical variables.

Multivariate Cox proportional hazards models assessed the risk of primary and secondary outcomes according to age categories in: (1) patients with and without diabetes analyzed separately; and (2) between patients with and without diabetes. Models included age (except for subgroup analysis), BMI (classes), sex, smoking status, and all aforementioned comorbidities.

Considering that intermediate or long-acting insulin may be prescribed to treat stress- or glucocorticoid-induced acute hyperglycemia in patients with COVID-19 to minimize contact with the patients, we also performed a sensitivity analysis in which we excluded patients for whom diabetes had been defined only by prescription of intermediate or long-acting insulin during hospitalization. R (https://www.R-project.org/) was used for statistical analysis.

Results

Among the 6314 included individuals, 2459 (39%) had a diagnosis of diabetes. The characteristics of participants at baseline were presented in Table 1. Compared with patients without diabetes, patients with diabetes had comparable age (69 [58-79] vs 70 [54-83], $P = 0.48$), comprised a higher proportion of men (65% vs 54%, $P < 0.001$), and presented with higher rate of associated comorbidities: higher BMI (27.4 [23.9-31.2] vs 25.3 [22.0-29.3] kg/m^2, $P < 0.001$), previous arterial hypertension (62% vs 43%, $P < 0.001$), dyslipidemia (21% vs 8%, $P < 0.001$), cardiovascular diseases (34% vs 19%, $P < 0.001$), heart failure (19% vs 15%, $P < 0.001$), and chronic kidney disease (26% vs 17%, $P < 0.001$).

During a 90-day follow-up period from first admission with positive PCR, primary outcome occurred in 2197 (35%) individuals and increased by age categories from 26% among patients younger than 50 years to 35% among those > 80 years. In subgroup analyses according to age and diabetes status, we observed a progressive increased incidence of primary outcomes with age in all age groups in patients without diabetes, whereas a plateau was reached from the 7th decade in those with diabetes (Fig. 1A).

Diabetes was significantly associated with a higher risk of primary outcome (970/2459, 39%) compared with those without diabetes (1227/3855, 32%) with an adjusted hazard ratio (HR) of 1.13 (95% CI, 1.04-1.25). The incidence rate difference between people with and without diabetes decreased with age (interaction *P* value 0.002, Fig. 1A). Accordingly, the adjusted HR for the risk of primary outcome between groups decreased with age from 1.52 (1.18-1.97) for patients younger than 50 years to 1.30 (1.08-1.57) for patients aged 60 to 70 years, and was no longer significant for those older than 70 years (Fig. 1B).

Similar results were obtained for mortality alone, with a mortality rate higher in patients with diabetes (n = 637, 26%) than in those without (n = 831, 22%, $P < 0.001$). Mortality rate increased in both groups with age, but adjusted HR for diabetes remained significant only in patients younger than 50 years (HR 1.81 [1.14-2.87]).

In sensitivity analysis without inclusion of patients with diabetes defined only by prescription of intermediate or long-acting insulin during hospitalization, we found similar results for primary outcomes and mortality in the whole population (adjusted HR for the risk of primary outcome: 1.10 [95% CI, 1.01-1.21]) and for each age category: in patients younger than 50 years, the adjusted HR for the risk of primary outcome is 1.45 [1.11-1.89] but was no longer significant for those over 70 (1.03 [95% CI, 0.85-1.23]).

Discussion

In this cohort of 6314 patients hospitalized for COVID-19, we found that diabetes was an independent factor of severe outcomes after adjustment for comorbidities. In subgroup analyses by age categories, we showed that increasing age tends to alleviate the higher risk of severity observed in patients with diabetes compared with patients without diabetes.

Trends in COVID-19 deaths by age have been clear since early in the pandemic, with a risk of death increasing from the age of 50 years (1, 3, 5). Older people, especially those older than 70 years, are facing the highest burden of COVID-19 mortality (6). Beyond

Table 1. Baseline characteristics of participants

	No Diabetes (n = 3855)	Diabetes (n = 2459)	*P* value
Age, y	70 (54-83)	69 (58-79)	0.476
Female	1760 (46)	866 (35)	<0.001
BMI	25 (22-29)	27 (24-31)	<0.001
Smoking	617 (16)	470 (19)	0.001
Hypertension	1656 (43)	1513 (62)	<0.001
CVD	739 (19)	825 (34)	<0.001
Heart failure	567 (15)	470 (19)	<0.001
Renal failure	648 (17)	650 (26)	<0.001
COPD	281 (7)	166 (7)	0.416
Dyslipidemia	326 (8)	523 (21)	<0.001
Sleep apnea	199 (5)	256 (10)	<0.001

Median (interquartile range) or n (%).
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

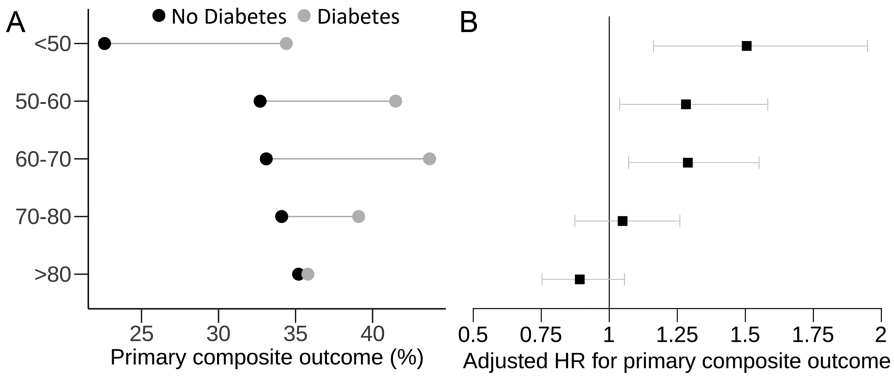

Figure 1. Orotracheal intubation and mortality risk in patients with coronavirus disease 2019 according to diabetes status. Five age categories are shown on the y-axis. (A) Primary composite outcome reported as percentage for patients with (gray circles) or without (black circles) diabetes. (B) Corresponding multiadjusted HR and 95% confidence interval for presence of diabetes compared with no diabetes within each age category. HR, hazard ratio.

age, people living with diabetes have been identified as people at high risk. However, whether diabetes is an independent factor for severe outcomes remains unclear (2, 7-10). Here, in the whole population of analysis, we found that diabetes was associated with a higher risk of severe outcomes after adjustment for confounders. However, diabetes-associated risk was only observed in the younger categories of age, suggesting that diabetes should be considered as an independent risk factor for severity mainly in people younger than 70 years and, even more so, among those younger than 50 years. In line with our findings, a recent meta-analysis found that the increased diabetes-related mortality was attenuated in older patients (11). Similarly, Gregory et al reported that risk of hospitalization for COVID-19 according to age increased from the 5th decade of age in subjects with no diabetes, whereas the risk increased from 20 to 50 and then reached a plateau in those with type 2 diabetes (12). Deduced from their figure, the highest difference between HR for hospitalization of people with diabetes and no diabetes was in the 6th decade. Moreover, Legris et al has recently shown that diabetes is not associated with COVID-19-related mortality in older institutionalized people (13). Taken together, these results might suggest that after age 50 years, diabetes-related risk is weakened by all other comorbidities or conditions associated with age. These findings are consistent with previous observational data in the general population of type 2 diabetes, beyond the scope of COVID-19, showing that diabetes-associated risk of death decreased in a stepwise fashion from younger to older age groups (14).

One strength of our study is the number of patients included, covering a wide range of individuals hospitalized for COVID-19 in the same area, while associated with detailed clinical information. On the other hand, there are several limitations. First, glucose-lowering

treatment before and during hospitalization was not known. Furthermore, type of diabetes was not reliably indicated, making it impossible to determine which type of diabetes is associated with a poor prognosis. Similarly, no information regarding the duration of diabetes is available in our study. However, duration of diabetes has not been shown to be associated with poor prognosis in patients with diabetes hospitalized for COVID-19 (15). Finally, because out-of-hospital deaths were not recorded in our data, we cannot exclude that this unavailable information may have affected our results.

To conclude, our study suggests physicians dealing with severe acute respiratory syndrome coronavirus 2–infected subjects should consider diabetes as an independent risk factor for the severity of COVID-19 in young adults more so than in older adults.

Acknowledgment

This manuscript has been submitted on the behalf of Assistance Publique-Hôpitaux de Paris (AP-HP)/Universities/Inserm COVID-19 research collaboration and AP-HP Covid Clinical Data Warehouse (CDW) Initiative. Data used in preparation of this article were obtained from the AP-HP Covid CDW. As such, the members of the AP-HP Covid CDW initiative contributed to the design and implementation of the database but did not participate in analysis or writing of this report. A complete listing of members can be found at: https://eds.aphp.fr/covid-19.

Authors Contributions: M.D. designed the study, conducted analysis, and wrote the manuscript. E.D. structured the database, conducted analysis, and wrote the manuscript. L.P. designed the study, conducted analysis, and wrote the manuscript. Critical revision of the manuscript for important intellectual content: all authors. L.P. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Financial Support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Additional Information

Correspondence: Louis Potier, MD, Diabetology, Endocrinology and Nutrition Department, Bichat Hospital, AP-HP, 46 rue Henri Huchard 75018 Paris, France. Email: louis.potier@aphp.fr.

Conflict of Interest: All authors had no conflict of interest to disclose related to this work.

Data Availability: Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

References

1. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *Bmj*. 2020;**369**:m1966.
2. Docherty AB, Harrison EM, Green CA, et al.; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *Bmj*. 2020;**369**:m1985.
3. Perez-Saez J, Lauer SA, Kaiser L, et al.; Serocov-POP Study Group. Serology-informed estimates of SARS-CoV-2 infection fatality risk in Geneva, Switzerland. *Lancet Infect Dis*. 2021;**21**(4):e69-e70.
4. Czernichow S, Beeker N, Rives-Lange C, et al.; AP-HP / Universities / INSERM COVID-19 research collaboration and AP-HP COVID CDR Initiative. Obesity doubles mortality in patients hospitalized for severe acute respiratory syndrome coronavirus 2 in Paris hospitals, France: a cohort study on 5795 patients. *Obesity (Silver Spring)*. 2020;**28**(12):2282-2289.
5. Pastor-Barriuso R, Pérez-Gómez B, Hernán MA, et al.; ENE-COVID Study Group. Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study. *Bmj*. 2020;**371**:m4509.
6. Ward H, Atchison C, Whitaker M, et al. SARS-CoV-2 antibody prevalence in England following the first peak of the pandemic. *Nat Commun*. 2021;**12**(1):905.
7. Xu J, Yang X, Yang L, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. *Crit Care*. 2020;**24**(1):394.
8. Sutter W, Duceau B, Vignac M, et al.; Critical COVID-19 France Investigators. Association of diabetes and outcomes in patients with COVID-19: Propensity score-matched analyses from a French retrospective cohort. *Diabetes Metab*. 2020;**47**(4):101222.
9. de Jong M, Woodward M, Peters SAE. Diabetes and COVID-19-related mortality in women and men in the UK biobank: comparisons with influenza/pneumonia and coronary heart disease. *Diabetes Care*. 2021;**44**(2):e22-e24.
10. Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol*. 2020;**8**(10):813-822.
11. Corona G, Pizzocaro A, Vena W, et al. Diabetes is most important cause for mortality in COVID-19 hospitalized patients: systematic review and meta-analysis. *Rev Endocr Metab Disord*. 2021;**22**(2):275-296.
12. Gregory JM, Slaughter JC, Duffus SH, et al. COVID-19 severity is tripled in the diabetes community: a prospective analysis of the pandemic's impact in type 1 and type 2 diabetes. *Diabetes Care*. 2021;**44**(2):526-532.
13. Legris P, Vaillard L, Nonciaux C, et al. Diabetes is not associated with COVID-19-related mortality in older institutionalized people. *Diabetes Metab*. 2021;**47**(3):101235.
14. Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;**376**(15):1407-1418.
15. Wargny M, Potier L, Gourdy P, et al.; CORONADO investigators. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. *Diabetologia*. 2021;**64**(4):778-794.