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ABSTRACT

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

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 6,314 consecutive patients hospitalized for COVID-19 between February and June 30 2020, and follow-up recorded until 30 September 2020, in the Paris metropolitan area, France.

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 (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 in those with diabetes. In direct comparison between patients with and without diabetes, diabetes-associated risk was inversely proportional to age, highest in <50 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 under 50 (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.

INTRODUCTION

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, over 70, 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 EDS-COVID (Entrepôt de données de santé COVID) database from the Assistance Publique-Hôpitaux de Paris (AP-HP) Hospitals (regrouping 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 above 18 with confirmed positive SARS-CoV-2 PCR tested between February 6th (first positive PCR recorded) and June 30 2020 was retrieved from this database (n=10,448) and patients follow-up was recorded until 30 September 2020. Patients without available body mass index (BMI) (n=4,134) were excluded.

This study was approved by the institutional review board from the AP-HP CDW Scientific and Ethics Committee (IRB 00011591). All subjects included in this study were informed about the

reuse of their data for research and subjects that objected to the reuse of their data were excluded in accordance with French legislation.

Comorbidities

Chronic comorbidities were extracted using ICD-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 ICD-10 codes, treatment by an intermediate or long-acting insulin treatment (ATC codes A10AC, A10AD, A10AE) or other non-insulin blood glucose lowering drugs (ATC codes A10B) in any previous or current hospitalization, or having a hemoglobin A1c (HbA1c) level greater than 6.5% (48 mmol/mol) in any previous or current hospitalization. HbA1c within 1 year prior or 7 days after positive PCR result date was available for 1,892 patients.

Primary and Secondary Outcomes

The primary outcome was a composite of in-hospital mortality or intensive care unit (ICU) admission with oro-tracheal intubation (OTI) 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 two-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: *i)* patients with and without diabetes analyzed separately; and *ii)* 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 in order 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 hospitalisation. R (https://www.R-project.org/) was used for statistical analysis.

RESULTS

Among the 6,314 included individuals, 2,459 (39%) had a diagnosis of diabetes. The characteristics of participants at baseline were presented in Table 1. Compared to 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/m², 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 2,197 (35%) individuals and increased by age categories from 26% among patients under < 50 to 35% among those over > 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 seventh decade in those with diabetes (Figure 1A).

Diabetes was significantly associated with a higher risk of primary outcome (970/2,459, 39%) compared to those without diabetes (1,227/3,855, 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, Figure 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 under 50 years to 1.30 [1.08-1.57] for patients aged 60-70 years, and was no longer significant for those over 70 (Figure 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 under 50 (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 under 50, 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 6,314 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 to 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 (1, 3, 5). Older people, especially after 70 years, are facing the highest burden of COVID-19 mortality (6). Beyond 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 under 70 years and, even more so, among those under 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 while 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 sixth 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 over 50, 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 prior to and given 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, since out-of-hospital deaths were not recorded in our data, we cannot exclude that this unavailable information may have impacted our results.

To conclude, our study suggests physicians dealing with SARS-CoV-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.

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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.

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Duality of interest

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

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.

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FIGURE LEGENDS

Figure 1: Orotracheal intubation and mortality risk in patients with COVID-19 according to diabetes status. Five age categories are shown on the y-axis. A: primary composite outcome reported as percentage for patients with (grey circles) or without (black circles) diabetes. B: corresponding multi-adjusted hazard ratio and confidence-interval 95% for presence of diabetes compared with no diabetes within each age category. HR: Hazard ratio.

Table 1: Baseline characteristics of participants

	No Diabetes (n = 3855)	Diabetes (n = 2459)	P-value
Age (years)	70 (54-83)	69 (58-79)	0.476
Sex: 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) or n (%). BMI: body mass index, CVD: cardiovascular disease, COPD: chronic obstructive pulmonary disease