Diabetes increases severe COVID-19 outcomes primarily in younger adults Age and diabetes in COVID-19 severity

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56 **ABSTRACT**

57 **Context.** Diabetes is reported as a risk factor for severe COVID-19, but whether this risk is

58 similar in all categories of age remains unclear.

59 **Objective**. To investigate the risk of severe COVID-19 outcomes in hospitalized patients with

60 and without diabetes according to age categories.

61 **Design Setting and Participants.** We conducted a retrospective observational cohort study of

62 6,314 consecutive patients hospitalized for COVID-19 between February and June 30 2020, and

63 follow-up recorded until 30 September 2020, in the Paris metropolitan area, France.

64 **Main Outcome Measure(s)**. The main outcome was a composite outcome of mortality and

65 orotracheal intubation in subjects with diabetes compared with subjects without diabetes, after

66 adjustment for confounding variables and according to age categories.

67 **Results**. Diabetes was recorded in 39% of subjects. Main outcome was higher in patients with

68 diabetes, independently of confounding variables (HR 1.13 [1.03-1.24]) and increased with age

69 in individuals without diabetes, from 23% for those <50 to 35% for those >80 years but reached

70 a plateau after 70 in those with diabetes. In direct comparison between patients with and without

71 diabetes, diabetes-associated risk was inversely proportional to age, highest in <50 and similar

72 after 70 years. Similarly, mortality was higher in patients with diabetes (26%) than in those

73 without diabetes (22%, p<0.001), but adjusted HR for diabetes was significant only in patients

74 under 50 (HR 1.81 [1.14-2.87]).

75 **Conclusions**. Diabetes should be considered as an independent risk factor for the severity of

76 COVID-19 in young adults more so than in older adults, especially for individuals younger than

77 70 years.

78

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

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101 reuse of their data for research and subjects that objected to the reuse of their data were excluded

102 in accordance with French legislation.

Comorbidities

104 Chronic comorbidities were extracted using ICD-10 codes in any previous or current

105 hospitalization: C00 to D49 for malignancies, E78 for dyslipidemia, G473 for sleep apnea, I10

106 for high blood pressure, I20 to I25, I63, I64 and I70 to I79 for cardiovascular disease, I50 for

107 heart failure, J44 for chronic obstructive pulmonary disease and N18 for chronic kidney disease.

108 Smoking status was defined as a binary variable by extracting mentions of both current and

109 history of smoking from free-text electronic health records using a dedicated pipeline.

110 Diabetes was defined as being diagnosed a E10 to E14 ICD-10 codes, treatment by an

111 intermediate or long-acting insulin treatment (ATC codes A10AC, A10AD, A10AE) or other

112 non-insulin blood glucose lowering drugs (ATC codes A10B) in any previous or current

113 hospitalization, or having a hemoglobin A1c (HbA1c) level greater than 6.5% (48 mmol/mol) in

114 any previous or current hospitalization. HbA1c within 1 year prior or 7 days after positive PCR

115 result date was available for 1,892 patients.

Primary and Secondary Outcomes

117 The primary outcome was a composite of in-hospital mortality or intensive care unit (ICU)

118 admission with oro-tracheal intubation (OTI) within 90 days of first admission with positive

119 PCR. The secondary outcome was in-hospital mortality at 90 days alone.

Statistical analysis

121 Continuous variables are presented as median (interquartile range) and categorical variables as

122 number (percentage). Baseline characteristics were compared with the two-sided t-test for

123 continuous variables and χ^2 test for categorical variables.

124 Multivariate Cox Proportional Hazards Models assessed the risk of primary and secondary

125 outcomes according to age categories in: *i)* patients with and without diabetes analyzed

126 separately; and *ii)* between patients with and without diabetes. Models included age (except for

127 subgroup analysis), BMI (classes), sex, smoking status and all aforementioned comorbidities.

128 Considering that intermediate or long-acting insulin may be prescribed to treat stress- or

129 glucocorticoid-induced acute hyperglycemia in patients with COVID-19 in order to minimize

130 contact with the patients, we also performed a sensitivity analysis in which we excluded patients

131 for whom diabetes had been defined only by prescription of intermediate or long-acting insulin

132 during hospitalisation. R (https://www.R-project.org/) was used for statistical analysis.

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134

135 **RESULTS**

136 Among the 6,314 included individuals, 2,459 (39%) had a diagnosis of diabetes. The

137 characteristics of participants at baseline were presented in Table 1. Compared to patients

138 without diabetes, patients with diabetes had comparable age (69 [58-79] *vs* 70 [54-83], p = 0.48),

139 comprised a higher proportion of men (65 *vs* 54%, p <0.001), and presented with higher rate of

140 associated comorbidities: higher BMI (27.4 [23.9-31.2] *vs* 25.3 [22.0-29.3] kg/m², p<0.001),

141 previous arterial hypertension (62 *vs* 43%, p<0.001), dyslipidemia (21 *vs* 8%, p <0.001),

142 cardiovascular diseases (34 *vs* 19%, p <0.001), heart failure (19 *vs* 15%, p <0.001) and chronic

143 kidney disease (26 *vs* 17%, p <0.001).

144 During a 90-day follow-up period from first admission with positive PCR, primary outcome

145 occurred in 2,197 (35%) individuals and increased by age categories from 26% among patients

146 under < 50 to 35% among those over > 80 years. In subgroup analyses according to age and

7

147   diabetes status, we observed a progressive increased incidence of primary outcomes with age in

148   all age groups in patients without diabetes whereas a plateau was reached from the seventh

149   decade in those with diabetes (Figure 1A).

150   Diabetes was significantly associated with a higher risk of primary outcome (970/2,459, 39%)

151   compared to those without diabetes (1,227/3,855, 32%) with an adjusted hazard ratio (HR) of

152   1.13 [95%CI 1.04-1.25]. The incidence rate difference between people with and without diabetes

153   decreased with age (interaction p-value 0.002, Figure 1A). Accordingly, the adjusted HR for the

154   risk of primary outcome between groups decreased with age from 1.52 [1.18-1.97] for patients

155   under 50 years to 1.30 [1.08-1.57] for patients aged 60-70 years, and was no longer significant

156   for those over 70 (Figure 1B).

157   Similar results were obtained for mortality alone, with a mortality rate higher in patients with

158   diabetes (n=637, 26%) than in those without (n=831, 22%, p< 0.001). Mortality rate increased in

159   both groups with age, but adjusted HR for diabetes remained significant only in patients under 50

160   (HR 1.81 [1.14-2.87]).

161   In sensitivity analysis without inclusion of patients with diabetes defined only by prescription of

162   intermediate or long-acting insulin during hospitalization, we found similar results for primary

163   outcomes and mortality in the whole population (adjusted HR for the risk of primary outcome:

164   1.10 [95%CI 1.01-1.21]) and for each age category: in patients under 50, the adjusted HR for the

165   risk of primary outcome is 1.45 [1.11-1.89] but was no longer significant for those over 70 (1.03

166   [95%CI 0.85-1.23]).

167

168   **DISCUSSION**

169   In this cohort of 6,314 patients hospitalized for COVID-19, we found that diabetes was an

170   independent factor of severe outcomes after adjustment for comorbidities. In subgroup analyses

171   by age categories, we showed that increasing age tends to alleviate the higher risk of severity

172   observed in patients with diabetes compared to patients without diabetes.

173   Trends in COVID-19 deaths by age have been clear since early in the pandemic with a risk of

174   death increasing from the age of 50 (1, 3, 5). Older people, especially after 70 years, are facing

175   the highest burden of COVID-19 mortality (6). Beyond age, people living with diabetes have

176   been identified as people at high risk. However, whether diabetes is an independent factor for

177   severe outcomes remains unclear (2, 7–10). Here, in the whole population of analysis, we found

178   that diabetes was associated with a higher risk of severe outcomes after adjustment for

179   confounders. However, diabetes-associated risk was only observed in the younger categories of

180   age suggesting that diabetes should be considered as an independent risk factor for severity

181   mainly in people under 70 years and, even more so, among those under 50 years. In line with our

182   findings, a recent meta-analysis found that the increased diabetes related mortality was

183   attenuated in older patients (11). Similarly, Gregory *et al.* reported that risk of hospitalization for

184   COVID-19 according to age increased from the 5th decade of age in subjects with no diabetes

185   while the risk increased from 20 to 50 and then reached a plateau in those with type 2 diabetes

186   (12). Deduced from their figure, the highest difference between HR for hospitalization of people

187   with diabetes and no diabetes was in the sixth decade. Moreover, Legris et al has recently shown

188   that diabetes is not associated with COVID-19-related mortality in older institutionalized people

189   (13). Taken together, these results might suggest that over 50, diabetes-related risk is weakened

190   by all other comorbidities or conditions associated with age. These findings are consistent with

191   previous observational data in the general population of type 2 diabetes, beyond the scope of

192   COVID-19, showing that diabetes-associated risk of death decreased in a stepwise fashion from

193   younger to older age groups (14).

194   One strength of our study is the number of patients included, covering a wide range of

195   individuals hospitalized for COVID-19 in the same area, while associated with detailed clinical

196   information. On the other hand, there are several limitations. First, glucose-lowering treatment

197   prior to and given during hospitalization was not known. Furthermore, type of diabetes was not

198   reliably indicated, making it impossible to determine which type of diabetes is associated with a

199   poor prognosis. Similarly, no information regarding the duration of diabetes is available in our

200   study. However, duration of diabetes has not been shown to be associated with poor prognosis in

201   patients with diabetes hospitalized for COVID-19 (15). Finally, since out-of-hospital deaths were

202   not recorded in our data, we cannot exclude that this unavailable information may have impacted

203   our results.

204   To conclude, our study suggests physicians dealing with SARS-CoV-2 infected subjects should

205   consider diabetes as an independent risk factor for the severity of COVID-19 in young adults

206   more so than in older adults.

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230   the integrity of the data and the accuracy of the data analysis. The corresponding author attests

231   that all listed authors meet authorship criteria and that no others meeting the criteria have been

232   omitted.

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FIGURE LEGENDS

313 **Figure 1**: Orotracheal intubation and mortality risk in patients with COVID-19 according to

314 diabetes status. Five age categories are shown on the y-axis. A: primary composite outcome

315 reported as percentage for patients with (grey circles) or without (black circles) diabetes. B:

316 corresponding multi-adjusted hazard ratio and confidence-interval 95% for presence of diabetes

317 compared with no diabetes within each age category. HR: Hazard ratio.

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320 **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

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322 Median (Interquartile) or n (%). BMI: body mass index, CVD: cardiovascular disease, COPD:
323 chronic obstructive pulmonary disease