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1 **Diabetes increases severe COVID-19 outcomes primarily in younger adults**

2 **Short title: Age and diabetes in COVID-19 severity**

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51

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53

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55

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

79 **INTRODUCTION**

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

89

90 **METHODS**

91 This observational study used the EDS-COVID (Entrepôt de données de santé COVID) database
92 from the Assistance Publique-Hôpitaux de Paris (AP-HP) Hospitals (regrouping 39 French
93 public hospitals), aggregating on a daily basis hospitalization-related electronic health records
94 since the beginning of the COVID-19 epidemic (4). Data for all patients above 18 with
95 confirmed positive SARS-CoV-2 PCR tested between February 6th (first positive PCR recorded)
96 and June 30 2020 was retrieved from this database (n=10,448) and patients follow-up was
97 recorded until 30 September 2020. Patients without available body mass index (BMI) (n=4,134)
98 were excluded.

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

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.

103 **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.

116 **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.

120 **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.

133

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

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.

207

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210 research collaboration and AP-HP Covid Clinical Data Warehouse (CDW) Initiative. Data used
211 in preparation of this article were obtained from the AP-HP Covid CDW. As such, the members
212 of the AP-HP Covid CDW initiative contributed to the design and implementation of the
213 database but did not participate in analysis or writing of this report. A complete listing of
214 members can be found at: <https://eds.aphp.fr/covid-19>.

215 **Data Availability**

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

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223 **Duality of interest**

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

225 **Authors contributions**

226 M.D. designed the study, conducted analysis and wrote the manuscript. E.D. structured the
227 database, conducted analysis and wrote the manuscript. L.P. designed the study, conducted
228 analysis and wrote the manuscript. Critical revision of the manuscript for important intellectual
229 content: all authors. L.P. had full access to all the data in the study and takes responsibility for

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
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233

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312 **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.

318

319

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

321

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