



Type 1 Diabetes in People Hospitalized for COVID-19: New Insights From the CORONADO Study

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Since the start of the coronavirus disease 2019 (COVID-19) pandemic, patients with diabetes were rapidly recognized as a high-risk population for severe disease. Indeed, a high prevalence of diabetes among patients with COVID-19 who required hospitalization has been consistently reported, reaching 33.8% in 5,700 people hospitalized for COVID-19 in the New York City area (1). In addition, diabetes was associated with more than a doubled risk of intensive care unit (ICU) admission and more than a tripled risk of death (2). However, precise data regarding the type of diabetes are scarce. We report here the clinical characteristics and early prognosis of patients with type 1 diabetes (T1D) hospitalized for COVID-19 in the nationwide multicenter observational CORONADO (Coronavirus SARS-CoV-2 and Diabetes Outcomes) study (3).

The aim of the CORONADO study was to describe the phenotypic characteristics and prognosis of patients with diabetes admitted with COVID-19 between 10 March and 10 April 2020 in 68 French hospitals. The protocol (ClinicalTrials.gov reg. no. NCT04324736) obtained all regulatory approvals as recently described (3). Inclusion criteria were 1) hospitalization for biologically and/or clinically/radiologically attested COVID-19 and 2) personal history of diabetes or newly diagnosed diabetes on admission. The composite primary end point combined tracheal intubation for mechanical ventilation and/or death on day 7 (D7). Secondary outcomes included death, tracheal intubation, and discharge on D7. Classification of diabetes was recorded in the electronic case report form as noted in the medical file by the physician in charge of the patient. In the present subanalysis,

patients in whom diabetes was diagnosed on admission were excluded since the etiological diagnosis had not been formally established. All cases noted as T1D were carefully reviewed by local investigators and the steering committee based on clinical and biological information. As an additional control, we applied the ENTRED (Échantillon National Témoignatif des Personnes Diabétiques) study algorithm (4) and systematically reviewed diabetes classification of all individuals diagnosed under 45 years of age and treated with insulin within 2 years of diagnosis.

Among the patients with previously established diabetes and with data availability for the primary outcome ($n = 2,608$), 56 had T1D (2.1%). Their main clinical characteristics are shown in Table 1, with male predominance (55.4%), mean (\pm SD) age of 56.0 (\pm 16.4)

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Table 1—Clinical characteristics of CORONADO participants with T1D according to the primary outcome (tracheal intubation and/or death on D7)

| Clinical features | Available data (N) | All | Primary outcome on day 7 | | | No adjustment | | Adjusted on age | |
|---|--------------------|-------------------|--------------------------|-------------------|------------------|---------------|------------------|-----------------|--|
| | | | No (N = 43) | Yes (N = 13) | OR (95% CI) | P value | OR (95% CI) | P value | |
| Sex (female/male) | 56 | 25/56 (44.6) | 20/43 (46.5) | 5/13 (38.5) | 0.72 (0.20–2.55) | 0.6097 | 0.73 (0.19–2.78) | 0.6415 | |
| Age (years) | 56 | 56.0 ± 16.4 | 53.2 ± 15.5 | 65.3 ± 16.3 | 1.05 (1.01–1.10) | 0.0260 | NA | — | |
| Age (categories) | | | | | | 0.0664 | NA | — | |
| <55 years | | 25/56 (44.6) | 22/43 (51.2) | 3/13 (23.1) | 1 (ref.) | | NA | — | |
| 55–74 years | | 21/56 (37.5) | 16/43 (37.2) | 5/13 (38.5) | 2.29 (0.48–11.0) | 0.3004 | NA | — | |
| ≥75 years | | 10/56 (17.9) | 5/43 (11.6) | 5/13 (38.5) | 7.33 (1.30–41.4) | 0.0240 | NA | — | |
| Diabetes duration (years) | 50 | 26.0 [15.0; 39.5] | 25.0 [15.0; 34.5] | 40.0 [20.5; 52.0] | 1.22 (0.57–2.62) | 0.6071 | 0.78 (0.34–1.76) | 0.5457 | |
| BMI (kg/m ²) | 52 | 25.8 [22.5; 29.8] | 25.1 [22.3; 29.5] | 26.3 [23.5; 32.0] | 1.45 (0.75–2.80) | 0.2706 | 1.91 (0.86–4.23) | 0.1102 | |
| Obesity (yes) | 52 | 13/52 (25.0) | 9/40 (22.5) | 4/12 (33.3) | 1.72 (0.42–7.06) | 0.4502 | 2.34 (0.50–11.0) | 0.2805 | |
| HbA _{1c} (mmol/mol) | 41 | 68.3 [59.6; 80.3] | 73.2 [62.3; 82.0] | 65.0 [53.0; 68.3] | 0.52 (0.23–1.18) | 0.1174 | 0.48 (0.19–1.21) | 0.1188 | |
| HbA _{1c} (%) | 41 | 8.4 [7.6; 9.5] | 8.8 [7.9; 9.7] | 8.1 [7.0; 8.4] | 0.50 (0.21–1.18) | 0.1126 | 0.46 (0.17–1.21) | 0.1149 | |
| Long-term diabetes complications | | | | | | | | | |
| Microvascular complications | 51 | 25/51 (49.0) | 18/38 (47.4) | 7/13 (53.8) | 1.30 (0.37–4.58) | 0.6871 | 1.01 (0.26–3.89) | 0.9942 | |
| Severe diabetic retinopathy | 52 | 19/52 (36.5) | 14/40 (35.0) | 5/12 (41.7) | 1.33 (0.35–4.96) | 0.6745 | 1.19 (0.30–4.76) | 0.8065 | |
| Diabetic kidney disease | 49 | 14/49 (28.6) | 10/36 (27.8) | 4/13 (30.8) | 1.16 (0.29–4.62) | 0.8379 | 0.71 (0.15–3.44) | 0.6712 | |
| Macrovascular complications | 52 | 17/52 (32.7) | 13/39 (33.3) | 4/13 (30.8) | 0.89 (0.23–3.44) | 0.8645 | 0.47 (0.10–2.07) | 0.3156 | |
| Ischemic heart disease (ACS/CAR) | 54 | 13/54 (24.1) | 9/41 (22.0) | 4/13 (30.8) | 1.58 (0.39–6.35) | 0.5190 | 0.90 (0.20–4.07) | 0.8901 | |
| Cerebrovascular disease (stroke or TIA) | 55 | 5/55 (9.1) | 3/42 (7.1) | 2/13 (15.4) | 2.36 (0.35–16.0) | 0.3775 | 1.13 (0.15–8.44) | 0.9028 | |
| Comorbidities | | | | | | | | | |
| Hypertension | 54 | 26/54 (48.1) | 16/41 (39.0) | 10/13 (76.9) | 5.21 (1.24–21.9) | 0.0242 | 3.33 (0.71–15.5) | 0.1259 | |
| Dyslipidemia | 55 | 27/55 (49.1) | 19/42 (45.2) | 8/13 (61.5) | 1.94 (0.54–6.91) | 0.3083 | 0.99 (0.24–4.18) | 0.9945 | |
| Tobacco use (former or current vs. never) | 48 | 18/48 (37.5) | 13/37 (35.1) | 5/11 (45.5) | 1.54 (0.39–6.03) | 0.5363 | 0.91 (0.20–4.09) | 0.9035 | |
| Active cancer | 56 | 6/56 (10.7) | 3/43 (7.0) | 3/13 (23.1) | 4.00 (0.70–22.9) | 0.1192 | 2.24 (0.36–14.0) | 0.3876 | |
| COPD | 54 | 2/54 (3.7) | 1/42 (2.4) | 1/12 (8.3) | 3.73 (0.22–64.5) | 0.3657 | 3.93 (0.18–84.6) | 0.3824 | |
| Treated OSA | 52 | 6/52 (11.5) | 4/40 (10.0) | 2/12 (16.7) | 1.80 (0.29–11.3) | 0.5304 | 1.59 (0.24–10.5) | 0.6323 | |
| Routine treatment before admission | | | | | | | | | |
| Metformin | 56 | 7/56 (12.5) | 4/43 (9.3) | 3/13 (23.1) | 2.92 (0.56–15.2) | 0.2024 | 2.93 (0.51–16.7) | 0.2270 | |
| Insulin pump (yes/no) | 53 | 6/53 (11.3) | 4/40 (10.0) | 2/13 (15.4) | 1.64 (0.26–10.2) | 0.5972 | 3.15 (0.41–24.3) | 0.2706 | |
| Insulin (daily dose) | 45 | 41 [25; 60] | 41 [26; 55] | 42 [21; 77] | 1.29 (0.63–2.66) | 0.4877 | 1.61 (0.70–3.69) | 0.2583 | |
| ARBs and/or ACE inhibitors | 56 | 22/56 (39.3) | 15/43 (34.9) | 7/13 (53.8) | 2.18 (0.62–7.66) | 0.2252 | 1.69 (0.44–6.39) | 0.4426 | |
| Statins | 56 | 23/56 (41.1) | 16/43 (37.2) | 7/13 (53.8) | 1.97 (0.56–6.90) | 0.2895 | 1.28 (0.33–4.91) | 0.7189 | |

Data are presented as numbers (%), mean ± SD, or, if not normally distributed, median [25th; 75th percentile]. P values are calculated using Wald test in logistic regression model before/after adjustment on age. BMI, diabetes duration, HbA_{1c}, and insulin (daily dose) were natural-log transformed before OR calculation, and the OR are calculated for an increase of 1 SD. ACS, acute coronary syndrome; ARB, angiotensin 2 receptor blocker; CAR, coronary artery revascularization; COPD, chronic obstructive pulmonary disease; NA, not applicable; OSA, obstructive sleep apnea; TIA, transient ischemic attack. HbA_{1c} corresponds to the HbA_{1c} value determined in the 6 months prior to or in the first 7 days following hospital admission. Microvascular complications were defined as severe diabetic retinopathy (proliferative retinopathy and/or laser photocoagulation and/or clinically significant macular edema requiring laser and/or intravitreal injections) and/or diabetic kidney disease (proteinuria [albumin excretion rate ≥300 mg/24 h; urinary albumin-to-creatinine ratio ≥300 mg/g; urinary albumin-to-creatinine ratio >30 mg/mmol creatinine; proteinuria ≥500 mg/24 h] and/or estimated glomerular filtration rate ≤60 mL/min/1.73 m², using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) and/or history of diabetic foot ulcer. Macrovascular complications were defined as ischemic heart disease (ACS and/or CAR) and/or cerebrovascular disease (stroke or TIA) and/or peripheral artery disease (amputation owing to ischemic disease and/or lower-limb artery revascularization).

Table 2—Clinical outcomes on D7 in patients with T1D and patients with T2D, according to age strata

| | T1D (n = 56) | | | T2D (n = 2,373) | | |
|---------------|-----------------|---------------------|-------------|------------------|---------------------|------------------|
| | Primary outcome | Tracheal intubation | Death | Primary outcome | Tracheal intubation | Death |
| All | 13/56 (23.2) | 11/56 (19.6) | 3/56 (5.4) | 657/2,373 (27.7) | 436/2,373 (18.4) | 251/2,373 (10.6) |
| Age subgroups | | | | | | |
| <55 years | 3/25 (12.0) | 3/25 (12.0) | 0/25 (0) | 78/256 (30.5) | 76/256 (29.7) | 5/256 (2.0) |
| 55–74 years | 5/21 (23.8) | 5/21 (23.8) | 1/21 (4.8) | 333/1,168 (28.5) | 290/1,168 (24.8) | 62/1,168 (5.3) |
| ≥75 years | 5/10 (50.0) | 3/10 (30.0) | 2/10 (20.0) | 246/949 (25.9) | 70/949 (7.4) | 184/949 (19.4) |

Data are number of events/total number of participants (%).

years, and median (25th; 75th percentile) BMI of 25.8 (22.5; 29.9) kg/m². In patients with T1D, 13 (23.2%) met the primary outcome, 11 (19.6%) required tracheal intubation for mechanical ventilation, 3 (5.4%) died, and 9 (16.1%) were discharged on D7, compared with 657/2,373 (27.7%), 436/2,373 (18.4%), 251/2,373 (10.6%), and 483/2,363 (20.4%) in patients with T2D, respectively. As shown in Table 1, patients with T1D who met the primary outcome were older (65.3 vs. 53.2 years, $P = 0.026$) and more frequently hypertensive (odds ratio [OR] 5.21 [95% CI 1.24–21.9], $P = 0.024$) than the others. Hypertension was no longer associated with the primary outcome after adjustment for age (OR 3.33 [95% CI 0.71–15.5], $P = 0.13$). In order to further determine the impact of age on COVID-19 severity in people with T1D and type 2 diabetes (T2D), we analyzed the occurrence of major clinical outcomes on D7 by age strata (<55, 55–74, and ≥75 years) (Table 2). As expected, patients with T1D were significantly younger than those with T2D (56.0 ± 16.4 vs. 70.5 ± 12.5 years, $P < 0.0001$). In patients <55 years of age, those with T1D met the primary outcome three times less than those with T2D, without such a difference in those ≥75 years.

For the first time, we show a prevalence of T1D among patients with diabetes hospitalized for COVID-19 (2.1%) that is lower than expected in the general population. Indeed, a previous epidemiological study in the general population reported that T1D accounts for 5.6% of people with diabetes in France (5). Notably, such a low prevalence of T1D among patients admitted with COVID-19 is primarily observed in people <55 years (7.8% in CORONADO vs. 23.2% in the French general population [5]). In addition, early severity of COVID-19 in patients with T1D was mainly influenced by age, with no deaths occurring in

patients <65 years. Hypertension was associated with the severity of COVID-19 prognosis, but this association was partly driven by age. Finally, neither long-term glucose control assessed by HbA_{1c} nor history of micro- or macrovascular complications was identified as a risk factor of early COVID-19 severity in inpatients with T1D. Importantly, the severity of COVID-19 appeared less marked in patients with T1D than in those with T2D, with half the risk of death on D7. This lower severity is prominent in the younger group, mostly due to a reduced rate of tracheal intubation. Obesity, more frequent in patients with T2D (55.1% vs. 34.8% for T1D in subjects <55 years), might explain this poorer prognosis, but this will deserve further studies.

While our paper was under review, a National Health Service (NHS) population cohort study including 61,414,470 individuals in England showed that people with T1D ($n = 263,830$; 0.4%) exhibited an increased risk of in-hospital death due to COVID-19 compared with those without known diabetes (OR 3.50 [95% CI 3.15–3.89], after adjustment for age, sex, deprivation, ethnicity, and geographical region). The apparent discrepancy regarding the severity of COVID-19 between the two studies could be explained by some differences in anthropometric characteristics of people with T1D between the two countries (i.e., patients with T1D have a lower BMI in France compared with England) but also by differences in study design (medico-administrative vs. investigator-checked data). In accordance with the strong impact of the age on the severity of COVID-19 in T1D, the NHS study reported no deaths in patients younger than 50 years ($n = 142,440$) (6).

Our study displays some limitations. Only inpatients were recruited and the results cannot be generalized to people with T1D and less severe forms of COVID-19. In addition, we did not

directly compare patients with T1D with matched subjects without diabetes. The size of our study population is limited and the results should be replicated in other larger studies and/or meta-analyses.

In conclusion, among patients with diabetes requiring hospitalization for COVID-19, the present data suggest a lower risk of severe prognosis in those with T1D, especially in the younger ones.

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