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 Témoin Représentatif 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 (± SD) age of 56.0 (± 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)

			Primary outcome on day 7					
					No adjustment		Adjusted on age	
Clinical features	Available data (*N*)	All	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.)			
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 m^2, 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/m^2. 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 time 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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References

1. Richardson S, Hirsch JS, Narasimhan M, et al.; Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020; 323:2052–2059

2. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. J Clin Virol 2020;127:104354

3. Cariou B, Hadjadj S, Wargny M, et al.; CORONADO investigators. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63:1500–1515

4. Lecomte P, Romon I, Fosse S, Simon D, Fagot-Campagna A. Self-monitoring of blood glucose in people with type 1 and type 2 diabetes living in France: the Entred study 2001. Diabetes Metab 2008;34:219–226

5. Santé Publique France. Échantillon national témoin représentatif des personnes diabétiques, Entred 2007-2010. Caractéristiques, état de santé, prise en charge et poids économique des personnes diabétiques. Saint-Maurice: Institut de veille sanitaire. 2013, 140 pp. Accessed 13 May 2020. Available from https://www.santepubliquefrance.fr/maladies-et-traumatismes/diabete/documents/rapport-synthese/etude-entred-2007-2010

6. Barron E, Bakhai C, Kar P, et al. Association of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol. 13 August 2020 [Epub ahead of print]. DOI: 10.1016/S2213-8587(20)30272-2