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## **Phenotypic characteristics and prognosis of newly diagnosed diabetes in hospitalized patients with COVID-19: results from the CORONADO study.**

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## **ABSTRACT**

In patients with diabetes hospitalized for COVID-19 in CORONADO study, 2.8% had a newly discovered

diabetes (NDD): mean age  $60.2 \pm 12.5$  years and HbA<sub>1c</sub>  $9.0 \pm 2.5$  %. When compared with center, age and sex-matched patients with established type 2 diabetes, NDD was not significantly associated with a more severe COVID-19 prognosis.

**Key words:** COVID-19, new-onset diabetes, hospital, death, tracheal intubation

## **1. INTRODUCTION**

It is now well-established that diabetes is a risk factor for increased coronavirus disease 2019 (COVID-19) severity, including higher mortality rate (1-4). Since the beginning of the pandemic some cases of newly-diagnosed diabetes (NDD) had been observed in patients with COVID-19 (5-7), highlighting a bidirectional relationship between COVID-19 and diabetes (8). Moreover, it has been suggested that patients with NDD had a worsen prognosis than those with previously established diabetes (3, 9, 10).

The aim of the current post-hoc analysis is to describe the phenotypic characteristics of subjects with NDD in the nationwide CORONADO study (11).

## **2. MATERIAL AND METHODS**

### **2.1. Study design and participants**

The aim of the CORONADO study (clinicaltrials.gov NCT04324736) was to describe the phenotypic characteristics and prognosis of patients with diabetes admitted with COVID-19 between March 10 and April 10, 2020 in 68 French centers. The protocol obtained all regulatory approvals and the design was previously reported (11). Briefly, inclusion criteria were (i) hospitalization for biologically (positive SARS-CoV-2 PCR) and/or clinically/radiologically confirmed COVID-19; (ii) personal history of diabetes (based on medical record and/or routine use of antidiabetic drugs) or NDD. NDD definition was based on HbA<sub>1c</sub>  $\geq$  6.5% [48 mmol/mol] measured during the first week of hospitalization and the absence of personal history of diabetes or diabetic retinopathy (Flow Chart in **Figure S1**).

### **2.2. Data collection and outcomes**

Data collection was retrospectively performed from medical files of all COVID-19 inpatients and by contacting the patient's general and/or specialist practitioners, regular pharmacist and biomedical laboratory. The primary outcome combined tracheal intubation for mechanical ventilation and/or death within 7 days of admission. Secondary outcomes notably included death and tracheal intubation taken separately, and hospital discharge. A secondary time point was considered at day 28 for all patients alive and not discharged within 7 days.

### **2.3. Statistical analysis**

NDD patients were matched with up to three patients with T2D on center, sex and age ( $\pm$  5 y). Characteristics are presented as mean  $\pm$  SD, median [25<sup>th</sup>-75<sup>th</sup> percentile] or N (%). P-values were

computed using Student-t tests, Mann-Whitney-Wilcoxon tests or Fisher tests. In the matched sample, we used logistic regression models to estimate ORs with 95%CI. Analyses were performed using statistical software R, version 4.0.2.

### 3. RESULTS

#### 3.1. Phenotypic characteristics of patients with NDD

Among 2,951 CORONADO participants, 2,820 could be analyzed regarding the primary outcome. After a careful review of the medical files, 80 patients (2.8%) were identified as having NDD (**Figure S1**).

The main clinical characteristics of all NDD patients are shown in **supplemental Table 1**. Median BMI (25<sup>th</sup>-75<sup>th</sup> percentile) was 27.7 (24.9-31.2) kg/m<sup>2</sup> and mean HbA<sub>1c</sub> was 9.0±2.5 % [75.1±27.2 mmol/mol]. Compared to patients with established T2D (n=2237), those with NDD were younger (60.2 ± 12.5 vs 70.5 ± 12.3 yrs, p<0.001) and more frequently from African or Caribbean origin (31.1 vs 16.7%, p=0.0055).

In order to identify specific phenotypic characteristics associated to NDD, we have been able to match 67 patients with NDD to 176 patients with established T2D on age, sex and center. As shown in **Table 1**, the median diabetes duration of patients with T2D was 9 years, with 35.8% under insulin therapy. Patients with NDD had less comorbidities than those with T2D with significantly less hypertension, dyslipidemia and CV diseases, as well as anti-hypertensive drugs and statins. Median BMI was numerically lower in NDD (27.9 vs 29.9 kg/m<sup>2</sup> in T2D, p=0.11), while HbA<sub>1c</sub> was numerically higher (8.9% vs 8.4% in T2D, p=0.29). The time between the onset of COVID-19 symptoms and hospitalization was longer in NDD compared to T2D (6 vs 5 days, P=0.019). The CRP level was significantly higher in patients with NDD, while plasma glucose levels on admission was not different (**Table 1**).

#### 3.2. COVID-19-related outcomes in patients with NDD

Finally, we compared the occurrence of major clinical outcomes within 7 and 28 days between patients with NDD and with established T2D. As shown in **Figure 1**, there was no statistically significant difference regarding the composite primary outcome, as well as tracheal intubation or

death, between the two groups. There was significantly less discharge in NDD group within 7 days (OR: 0.39 [0.17-0.96]), but the difference was not significant within 28 days (OR: 0.69 [0.37-1.31]).

#### 4. DISCUSSION

In the present analysis of the CORONADO study, we found that NDD occurred in only 2.8% of patients with diabetes hospitalized for COVID-19. This frequency is much lower than those previously reported in Chinese studies, ranging from 16% (12) to 21% (9), but closer to that of 5 % reported in a study from Italy (13). Of note, ethnicity data showed that NDD was more prevalent than T2D in African-Caribbean people but this needs to be confirmed in larger cohorts.

Importantly, we found that the severity of COVID-19 was not different in patients with NDD and age-, center- and sex-matched subjects with established T2D. In contrast to previous reports (9, 13), our results did not confirm a worsened COVID-19 prognosis in NDD compared to established T2D. It should be underlined, however, that patients with NDD had significantly less comorbidities (*i.e.* CV diseases, hypertension or dyslipidemia) than those with established T2D. These potential confounding factors were not taken into account in our matching process. Another potential explanation for this discrepancy is the severity of the COVID-19 in T2D which appears more pronounced in CORONADO with a mortality rate of 17.6% within 28 days compared to 11.2% in the study of Li et al. (9) and 14.0% in those of Fadini et al. (13). It should be underlined however that the mortality rate was also similar in NDD and established diabetes in the latter study in which the severity was mainly driven by admission in ICU (13). We also found that tracheal intubation was numerically, but not statistically, higher and that early discharge was significantly lower in NDD compared to established T2D. In accordance with the prominent role of hyperglycemia *per se* as a prognosis factor for COVID-19 (14), the admission plasma glucose levels were not different between NDD and T2D groups. Some differences regarding routine treatments between patients with NDD or T2D might also have impacted the outcomes. For instance, metformin was associated with a reduced risk of death in patients with T2D in CORONADO (15). Conversely, statin use was reported to be associated with a worse prognosis in CORONADO (16).

Our study displays some limitations, notably its observational and post-hoc design. Since we cannot guarantee that biological screening with HbA<sub>1c</sub> was systematically performed in all patients, an underestimation of the NDD frequency cannot be excluded. Finally, information on diabetes

management and evolution following the admission are lacking, especially regarding the use and the dose of glucose lowering therapies as well as the quality of glycemic control.

As highlighted by some authors (8,17), some dedicated prospective studies are warranted to assess more precisely the link between NDD and COVID-19 and to limit confounding biases due to observational design.

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## **CONFLICT OF INTEREST**

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**Table 1: Clinical characteristics of CORONADO participants in the matched sample**

Patient characteristics	NDD patients (n = 80)	Matched Sample (n = 243)		OR or delta (95% CI)	p-value	SMD
		Exposed: NDD patients (n = 67)	Controls: patients with T2D (n = 176)			
Sex	26/80 (32.5%)	24/67 (35.8%)	62/176 (35.2%)	1.03 (0.57-1.85)	0.9311	1.2
Age	60.2+/-12.5	61.9+/-11.3	64.1+/-10.7	0.98 (0.96-1.01)	0.1711	19.2
Ethnical origin					0.1982	138.7
EU	29/61 (47.5%)	27/51 (52.9%)	55/146 (37.7%)	1.00		
MENA	11/61 (18%)	9/51 (17.6%)	38/146 (26%)	0.48 (0.20-1.14)	0.0968	
AC	19/61 (31.1%)	13/51 (25.5%)	40/146 (27.4%)	0.66 (0.30-1.44)	0.2981	
AS	2/61 (3.3%)	2/51 (3.9%)	13/146 (8.9%)	0.31 (0.07-1.49)	0.1445	
BMI (kg/m <sup>2</sup> )	27.7 [24.9; 31.2]	27.9 [25.2; 31.7]	29.9 [26.2; 33.9]	0.77 (0.56-1.06)	0.1092	27.9
HbA <sub>1c</sub> (mmol)	75.1+/-27.2	73.8+/-27.4	68.8+/-26.2	1.01 (0.99-1.02)	0.2912	18.6
HbA <sub>1c</sub> (%)	9.0+/-2.5	8.9+/-2.5	8.4+/-2.4	1.07 (0.94-1.23)	0.2912	18.6
Hypertension	30/78 (38.5%)	27/65 (41.5%)	139/175 (79.4%)	0.18 (0.10-0.34)	<10 <sup>-4</sup>	84.1
Dyslipidemia	10/78 (12.8%)	8/65 (12.3%)	85/173 (49.1%)	0.15 (0.07-0.32)	<10 <sup>-4</sup>	87.1
Current tobacco use	3/66 (4.5%)	2/55 (3.6%)	12/148 (8.1%)	0.43 (0.09-1.98)	0.2766	19.1
Cardiovascular diseases <sup>a</sup>	9/69 (13.0%)	8/58 (13.8%)	62/170 (36.5%)	0.28 (0.12-0.63)	0.002	54.2
Active cancer	3/76 (3.9%)	3/64 (4.7%)	10/172 (5.8%)	0.80 (0.21-2.99)	0.7364	5.1
COPD	3/77 (3.9%)	3/64 (4.7%)	21/173 (12.1%)	0.36 (0.10-1.24)	0.1041	27.1
Treated OSA	3/72 (4.2%)	2/60 (3.3%)	25/164 (15.2%)	0.19 (0.04-0.84)	0.0279	41.9
Diabetes duration (years)	-	-	9 [5; 15]	-	-	-
<b>Routine medication</b>						
Metformin	-	-	121/176 (68.8%)	-	-	-
Sulfonylureas	-	-	47/176 (26.7%)	-	-	-
DPP4 inhibitors	-	-	42/176 (23.9%)	-	-	-
GLP-1 RA	-	-	26/176 (14.8%)	-	-	-
Insulin therapy	-	-	63/176 (35.8%)	-	-	-
Thiazide diuretics	7/80 (8.8%)	5/67 (7.5%)	41/176 (23.3%)	0.27 (0.1-0.7)	0.0077	45
Loop diuretics	3/80 (3.8%)	2/67 (3.0%)	24/176 (13.6%)	0.19 (0.04-0.85)	0.0294	39.3
Potassium-sparing diuretics	1/80 (1.2%)	1/67 (1.5%)	10/176 (5.7%)	0.25 (0.03-2.00)	0.1923	22.7
ARBs and/or ACE inhibitors	18/80 (22.5%)	15/67 (22.4%)	100/176 (56.8%)	0.22 (0.11-0.42)	<10 <sup>-4</sup>	75.2
Beta-blockers	5/80 (6.2%)	4/67 (6.0%)	54/176 (30.7%)	0.14 (0.05-0.41)	< 0.001	67.4
Calcium-channel inhibitor	8/80 (10.0%)	6/67 (9.0%)	57/176 (32.4%)	0.21 (0.08-0.50)	< 0.001	60.4
Statins	8/80 (10.0%)	7/67 (10.4%)	83/176 (47.2%)	0.13 (0.06-0.30)	< 0.001	88.7
Anti-platelet agent	8/80 (10.0%)	7/67 (10.4%)	70/176 (39.8%)	0.18 (0.08-0.41)	< 0.001	71.9
Anticoagulant	1/80 (1.2%)	1/67 (1.5%)	23/176 (13.1%)	0.10 (0.01-0.76)	0.0262	45.7
Oral corticosteroids	3/80 (3.8%)	3/67 (4.5%)	11/176 (6.2%)	0.70 (0.19-2.6)	0.5979	7.9
<b>Symptoms on admission</b>						
Positive SARS-CoV-2 PCR	71/78 (91.0%)	59/65 (90.8%)	166/175 (94.9%)	0.53 (0.18-1.56)	0.2514	15.9

COVID-related symptoms	77/80 (96.2%)	64/67 (95.5%)	174/176 (98.9%)	0.25 (0.04-1.5)	0.1284	20.3
Duration of symptoms on admission	7 [4; 9]	6 [4; 8]	5 [3; 7.2]	1.08 (1.01-1.16)	0.0185	34.1
Fever	67/78 (85.9%)	56/66 (84.8%)	133/173 (76.9%)	1.68 (0.79-3.60)	0.1789	20.4
Asthenia	51/77 (66.2%)	43/65 (66.2%)	112/165 (67.9%)	0.92 (0.5-1.70)	0.8016	3.7
Cough	64/78 (82.1%)	53/65 (81.5%)	117/172 (68.0%)	2.08 (1.03-4.20)	0.0419	31.5
Cephalalgia	14/76 (18.4%)	11/64 (17.2%)	34/162 (21.0%)	0.78 (0.37-1.66)	0.5199	9.7
Dyspnoea	58/79 (73.4%)	50/66 (75.8%)	126/173 (72.8%)	1.17 (0.61-2.24)	0.6465	6.7
Rhinitis and/or pharyngeal symptoms	8/71 (11.3%)	7/62 (11.3%)	19/161 (11.8%)	0.95 (0.38-2.39)	0.9152	1.6
Ageusia and/or anosmia	17/69 (24.6%)	14/59 (23.7%)	31/159 (19.5%)	1.28 (0.63-2.63)	0.4934	10.3
Digestive disorder	24/76 (31.6%)	19/63 (30.2%)	46/169 (27.2%)	1.15 (0.61-2.18)	0.6576	6.5
<b>Biological parameters</b>						
Plasma glucose on admission (mg/dL)	173 [129; 28]	170 [128; 256]	173 [131; 231]	1.25 (0.91-1.71)	0.1623	28.8
eGFR (CKD-EPI, mL/min)	87.4 [68.9; 99.1]	87.8 [68.3; 99.5]	77.4 [51.8; 96.3]	1.59 (1.1-2.29)	0.0131	39
ALT (% ULN)	0.79 [0.50; 1.34]	0.84 [0.52; 1.36]	0.77 [0.48; 1.21]	1.05 (0.79-1.39)	0.7495	7.7
AST (% ULN)	1.27 [0.85; 2.3]	1.26 [0.85; 2.3]	1.2 [0.91; 1.75]	1.06 (0.8-1.4)	0.702	9.4
Hemoglobin (g/dL)	14.0 [13; 15.3]	13.9 [13; 15.2]	13.1 [11.7; 14.4]	1.88 (1.31-2.69)	0.0006	56
White cells count (G/L)	6960 [5440; 8500]	7040 [5810; 8890]	6490 [5000; 8480]	1.28 (0.96-1.70)	0.0955	22.7
Lymphocyte count (G/L)	1020 [785; 1300]	1000 [740; 1300]	1150 [820; 1622]	0.79 (0.58-1.07)	0.1345	31.1
Platelelet count (G/L)	204 [159; 258]	204 [161; 256]	203 [166; 246]	1.12 (0.84-1.5)	0.4316	13.8
CRP (mg/L)	107 [2; 179]	108 [6; 189]	95 [4; 153]	1.37 (1.00-1.88)	0.0492	20
LDH (UI/L)	484 [363; 647]	484 [359; 647]	397 [300; 534]	1.66 (0.93-2.94)	0.0855	2.5
CPK (UI/L)	139 [87; 290]	136 [82; 304]	154 [87; 421]	0.87 (0.6-1.26)	0.4555	22.6

Characteristics are presented as N (%) for categorical variables and as mean  $\pm$  SD. for continuous variables or median [IQR] if non-normally distributed. Univariable associations were estimated using Fisher exact tests, Student-t tests or Mann-Whitney-Wilcoxon tests, respectively.

Abbreviations: EU (Europid); MENA (Middle East North Africa); AC (African or Caribbean); AS (Asian); HbA1c corresponds to the glycated hemoglobin determined in the 6 months prior to or in the first 7 days following hospital admission; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; DPP4-inhibitors, Dipeptidyl peptidase 4-inhibitors; GLP-1RA, Glucagon-Like Peptide 1-Receptor Agonist; CCB, calcium channel blocker; ARB, angiotensin-2 receptor blocker; ACE-Inhibitors, angiotensin converting enzyme-inhibitors; eGFR, estimated glomerular filtration rate, according to the CKD-EPI formula; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; ULN, Upper limit of normal; SMD, Standardized Mean Difference.

<sup>a</sup>Cardiovascular diseases were defined as history of one or more of the following comorbidities: acute coronary syndrome, coronary artery disease revascularization, transient ischemic attack and/or lower limb artery revascularization

**Figure 1**

