Diabetologia (2022) 65:1436–1449
https://doi.org/10.1007/s00125-022-05734-1

ARTICLE

Impact of diabetes on COVID-19 prognosis beyond comorbidity burden: the CORONADO initiative

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Received: 18 November 2021 / Accepted: 6 April 2022 / Published online: 15 June 2022

Abstract

Aims/hypothesis Diabetes has been recognised as a pejorative prognostic factor in coronavirus disease 2019 (COVID-19). Since diabetes is typically a disease of advanced age, it remains unclear whether diabetes remains a COVID-19 risk factor beyond advanced age and associated comorbidities. We designed a cohort study that considered age and comorbidities to address this question.

Methods The Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) initiative is a French, multicentric, cohort study of individuals with (exposed) and without diabetes (non-exposed) admitted to hospital with COVID-19, with a 1:1 matching on sex, age (±5 years), centre and admission date (10 March 2020 to 10 April 2020). Comorbidity burden was assessed by calculating the updated Charlson comorbidity index (uCCi). A predefined composite primary endpoint combining death and/or invasive mechanical ventilation (IMV), as well as these two components separately, was assessed within 7 and 28 days following hospital admission. We performed multivariable analyses to compare clinical outcomes between patients with and without diabetes.

Results A total of 2210 pairs of participants (diabetes/no-diabetes) were matched on age (mean±SD 69.4±13.2/69.5±13.2 years) and sex (36.3% women). The uCCi was higher in individuals with diabetes. In unadjusted analysis, the primary composite endpoint occurred more frequently in the diabetes group by day 7 (29.0% vs 21.6% in the no-diabetes group; HR 1.43 [95% CI 1.19, 1.72], $p<0.001$). After multiple adjustments for age, BMI, uCCi, clinical (time between onset of COVID-19 symptoms and dyspnoea) and biological variables (eGFR, aspartate aminotransferase, white cell count, platelet count, C-reactive protein) on admission to hospital, diabetes remained associated with a higher risk of primary composite endpoint within 7 days (adjusted HR 1.42 [95% CI 1.17, 1.72], $p<0.001$) and 28 days (adjusted HR 1.30 [95% CI 1.09, 1.55], $p=0.003$), compared with individuals without diabetes. Using the same adjustment model, diabetes was associated with the risk of IMV, but not with risk of death, within 28 days of admission to hospital.

Conclusions/interpretation Our results demonstrate that diabetes status was associated with a deleterious COVID-19 prognosis irrespective of age and comorbidity status.

Trial registration ClinicalTrials.gov NCT04324736

Keywords Charlson index · Comorbidity · COVID-19 · Death · Diabetes · Invasive mechanical ventilation · Prognosis

PG and SH contributed to the work equally and should be regarded as co-last authors.

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Abbreviations

AST	Aspartate aminotransferase
CCi	Charlson comorbidity index
CKD-EPI	Chronic Kidney Disease EPIdemiology collaboration
CORONADO	Coronavirus SARS-CoV-2 and Diabetes Outcomes
COVID-19	Coronavirus disease 2019

Research in context

What is already known about this subject?

- Diabetes is recognised as a pejorative prognostic factor for coronavirus disease 2019 (COVID-19)
- The relative weight of diabetes per se compared with that of its associated comorbidities on COVID-19-related outcomes remains unclear

What is the key question?

- Does diabetes remain associated with a pejorative prognosis of COVID-19 beyond age and associated comorbidities?

What are the new findings?

- Hospitalised individuals with diabetes had a worse COVID-19 prognosis than age- and sex-matched individuals without diabetes
- Diabetes, as compared with no diabetes, was associated with a deleterious COVID-19 prognosis independently of the comorbidity burden assessed by the updated Charlson comorbidity index

How might this impact on clinical practice in the foreseeable future?

- These data reinforce the need for a specific management of COVID-19 in individuals with diabetes

CRP	C-reactive protein
DAG	Directed acyclic graph
deCCi	Diabetes excluded CCi
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
PSM	Propensity score matching
uCCi	Updated CCi

Introduction

Early in the coronavirus disease 2019 (COVID-19) pandemic in China, diabetes was associated with an increased risk of severe outcomes, including death [1]. This initial finding was then confirmed by several studies, including analyses of whole-population health data showing an increased risk of COVID-19-related mortality in England [2] and of COVID-19-related deaths or intensive care unit (ICU) admission in Scotland [3] in individuals with diabetes compared with those without diabetes. However, the specific influence of diabetes beyond the burden of associated comorbidities on COVID-19 prognosis remains an unresolved issue. Diabetes, and more specifically type 2 diabetes, is associated with a reduced lifespan including an increased risk of death from pneumonia [4, 5]. On the other hand, type 2 diabetes, the most prevalent type of diabetes, segregates with many important determinants of COVID-19 prognosis such as advanced age and various comorbidities [2]. When analysing data released by the Center for Disease Control in the USA [6], the most frequent conditions related to COVID-19 death in adults were metabolic diseases, making it important to precisely establish their specific contribution in COVID-19 prognosis. Even though a previous meta-analysis has suggested that the association between diabetes and COVID-19 death was independent of sex and age [7], major potential confounders such as obesity [8, 9], or other frequent comorbidities have not been taken into account.

So far, most of the published studies have considered each specific comorbidity separately but did not include the impact of multimorbidity. Emphasising the need for dedicated studies taking into account the overall burden of comorbidities, a systematic review and meta-analysis of observational studies suggested that individuals with a more severe course of diabetes, and thus more pre-existing comorbidities, have a poorer prognosis of COVID-19 compared with individuals with a milder course of the disease [10]. In this context, the Charlson comorbidity index (CCi), initially developed to establish risk factors for hospital death, is of great interest since it can help to capture significant comorbidities associated with mortality risk [11].

The objective of the present study was to determine whether diabetes is an independent prognostic factor for COVID-19 severity beyond advanced age and associated comorbidities. To address this question, we designed a cohort study to compare individuals with diabetes from the Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study [12] (exposed) with age-, sex- and centre-matched individuals without diabetes (non-exposed) who were also hospitalised

for COVID-19 during the same period, to determine whether the individual comorbidity burden assessed using the CCi altered the influence of diabetes status on COVID-19-related severe outcomes.

Methods

Study design and population of diabetic participants The design of the CORONADO study has already been described elsewhere (ClinTrials.gov registration no. NCT04324736) [13]. Briefly, CORONADO is a French nationwide, multicentric, cohort study with both retrospective and prospective data collection, aiming to describe the phenotypic characteristics and prognosis of individuals with diabetes admitted to hospital with COVID-19 between 10 March 2020 and 10 April 2020. The main inclusion criteria were as follows: clinical and/or biological and/or radiological COVID-19 diagnosis; known diabetes mellitus before admission to hospital and/or HbA_{1c} ≥48 mmol/mol (6.5%) during hospital stay; and no opposition of the individual to participate in the study. The study was approved by the local ethics committee (IRB/IEC – GNEDS; ref. CORONADOV2), the national ethics committee (CEREES, INDS no. 1544730) and the French data protection authority (CNIL, DR-2020-155/920129). Due to the emergency setting, informed consent was primarily waived by regulatory authorities. Secondarily, for all individuals remaining alive during their hospital stay, a postal mail was sent to record their non-opposition.

Non-diabetic participants A non-exposed (i.e. without diabetes) cohort study was created based on the CORONADO population. Each centre was asked to produce a list of all individuals hospitalised for COVID-19 during the same period of interest, excluding the individuals with diabetes. At the centre level, the non-exposed population was matched 1:1 with CORONADO participants with diabetes on sex, age (same year of birth ± 5 years) and date of admission to hospital (10 March 2020 to 10 April 2020). In the event of multiple matching, centres were asked to choose the individual without diabetes with the closest admission date (1 unit = 1 day), and then with the closest date of birth. Eligibility criteria were the same as for the participants with diabetes, except, obviously, that they should not have a known history of diabetes defined by a statement of diabetes in the medical file and/or treatment for diabetes and/or HbA_{1c} ≥48 mmol/mol (6.5%). If a non-exposed individual was secondarily excluded (e.g. because of a diagnosis of diabetes during hospitalisation), then he/she was replaced by the nearest matching candidate. A detailed flow chart is provided in Fig. 1.

Data collection: updated CCi Participants' data were collected from medical files by physicians, nurses and clinical research assistants. Investigators were asked to contact patients' general practitioners, external analysis laboratories and pharmacists to complete the clinical histories. The clinical history was recorded in two ways on the electronic case report form: using closed questions (e.g. 'does the patient have a history of myocardial infarction? Yes/No/Not known') or verbatim. All verbatims were carefully and independently read by two senior clinicians in order to assess items for both CCi (8) and updated CCi (uCCi) [14]. Where there was a difference of opinion between clinicians, the item was discussed by a steering committee composed of four senior clinicians (BC, PG, SH and MW). The uCCi was privileged over CCi as it does not include diabetes status. In accordance with the design of our study, a cohort study of diabetic (exposed) and non-diabetic (non-exposed) individuals, we also calculated a 'diabetes excluded' CCi (deCCi), defined as the classical CCi excluding the item 'diabetes without complications', for sensitivity analyses purposes. The verbatim retained for each item is presented in the electronic supplementary material (ESM) Methods.

Outcomes We examined the different outcomes prespecified in our original protocol assessed within 7 days and within 28 days following hospital admission: first a composite endpoint defined as death and/or invasive mechanical ventilation (IMV); then death alone; and finally IMV alone [13]. These time frames were selected to account for short- and middle-term COVID-19-related prognosis. All participants were followed until day 7. After day 7, if an individual was discharged from hospital, we considered her/his data as right-censored after this date.

Statistical analyses Categorical data are expressed as *n* (%). Quantitative data are expressed as mean±SD or median (25th–75th percentile) according to their distribution. Comparisons between groups are based on data availability within pairs, so if the data were missing for an individual with diabetes or his/her non-diabetic pair, the matched pair was removed from the comparison. For categorical data, between-group comparisons were tested using McNemar's test for binary data or Fisher's exact test if not applicable. For quantitative data, between-group comparisons were tested using the sign test.

For multivariable analyses, Cox proportional hazards models were fitted to compare outcomes between individuals with diabetes vs those without diabetes, with different levels of adjustments. The covariates of interest were established from background knowledge (i.e. clinician perspective): age (to account for possible imperfect matching); BMI; uCCi (categorical approach: 0, 1, 2, 3 or ≥4); and seven hospital-admission variables, both clinical (time between symptom onset and admission, dyspnoea) and biological (white cell count, platelet count, C-reactive protein [CRP], eGFR according to Chronic Kidney Disease EPIdemiology collaboration (CKD-EPI) formula and aspartate aminotransferase [AST]).

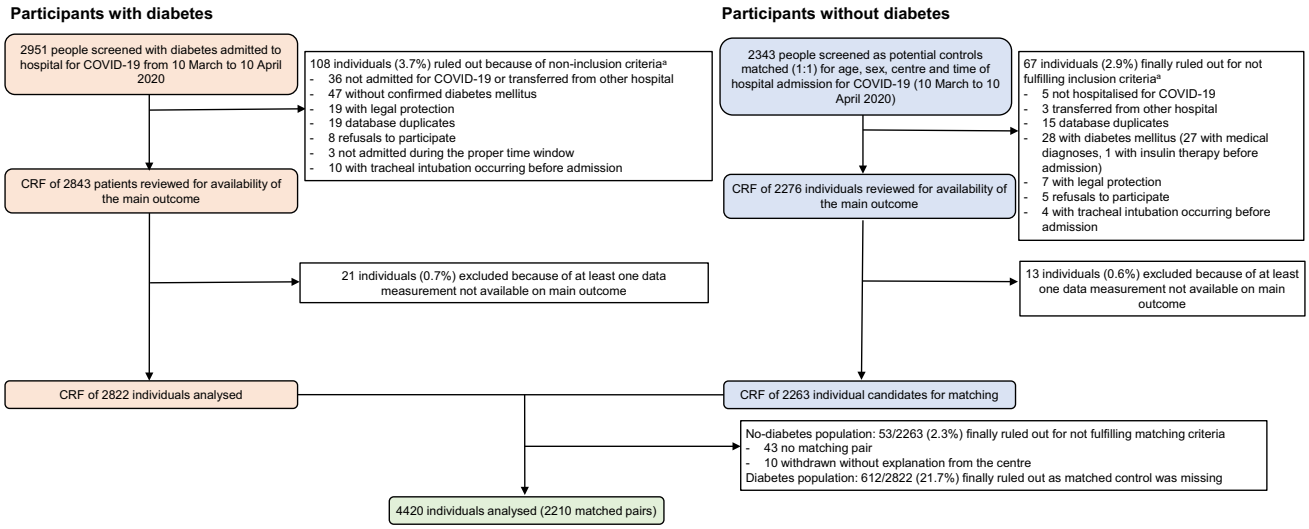

Fig. 1 Flow chart of study. [a]Non-inclusion criteria were not mutually exclusive; therefore, the same individual could be non-included for one or more reasons. CRF, case report form

To clarify the way we should account for these potential confounders, we proposed to summarise the associated causation hypotheses using directed acyclic graphs (DAGs) [15]. The two DAGs are shown in ESM Fig. 1a,b. These DAGs were performed on www.daggity.net [16] (accessed 15 February 2022) and can be produced directly with the code provided in ESM Methods B. Based on these DAGs, the direct effect of diabetes exposure or the total effect (direct and mediated through uCCi or through the clinical or biological hospital-admission variables) can be captured by Models 2, 3 or 4 of the following models: Model 1, adjusted only on age, corresponds to the raw effect accounting only for the matching set; Model 2, as for Model 1 and further adjusted for BMI; Model 3, as for Model 2 and further adjusted for uCCi; and Model 4, as for Model 3 and further adjusted for the clinical or biological hospital-admission variables. In addition, interactions between diabetes status and age and uCCi were tested, with a significance threshold of 0.05 (likelihood-ratio test). Kaplan–Meier survival curves according to the three different outcomes were plotted for the diabetes and no-diabetes groups, and these curves were compared using logrank tests.

We proposed different sensitivity analyses derived from the main analysis: (1) the uCCi was replaced by the deCCi, to assess the robustness of the results with a different comorbidity burden estimation; (2) the ethnicity was added in the model, as a potential confounding factor; and (3) a propensity score matching (PSM) approach based on the individual characteristics of individuals, using a 1:1 ratio (without replacement), an exact matching for both sex and uCCi, and an 'optimal matching' process for age, BMI, time between symptoms onset and admission to hospital, dyspnoea on admission, eGFR (CKD-EPI), AST, white cell count, platelet count and CRP.

All analyses were performed without imputation, using statistical software R, version 4.0.3, particularly using packages 'MatchIt' and 'optmatch' [17, 18].

A p value <0.05 was considered as statistically significant, without correction for multiple testing.

Results

Study population and baseline characteristics In total, 2210 participants with diabetes from the CORONADO study (i.e. exposed) were matched with 2210 individuals without diabetes (i.e. non-exposed). The groups were not different for age (mean±SD 69.4±13.2 vs 69.5±13.2 years for diabetes vs no-diabetes, respectively) or sex (36.3% women in both groups) (Table 1), validating an appropriate matching. Among participants with diabetes, diabetes was categorised as type 1 in 49 (2.2%), type 2 in 1983 (89.7%) and other or unknown types in 178 (8.1%) individuals.

Compared with non-diabetic participants, individuals with diabetes more frequently were obese and had hypertension, dyslipidaemia and cardiovascular disease (Table 2). The comorbidity burden assessed either with uCCi or deCCi was also higher in individuals with diabetes. For instance, 39.6% of the individuals with diabetes had uCCi ≥ 2 compared with 27.5% of non-exposed. The frequency of each CCi and/or uCCi item in both groups is detailed in Table 2.

Regarding biological values on admission to hospital, individuals with diabetes exhibited higher plasma glucose levels and lower eGFR, compared with non-exposed individuals. In addition, they had slightly lower plasma levels of transaminases and lactate dehydrogenase as well as higher lymphocyte counts than non-exposed individuals (Table 1).

Table 1 Characteristics according to diabetes status

Characteristic	Pairs with available data, *n* (%)	All participants (*n*=4420)[a]	No diabetes (*n*=2210)	Diabetes (*n*=2210)	*p* value
Sex, female	4420 (100)	1604/4420 (36.3)	802/2210 (36.3)	802/2210 (36.3)	NR
Age	4420 (100)	69.4±13.2	69.5±13.2	69.4±13.2	NR
Ethnicity	3150 (71.3)				<0.001
African or Caribbean		508/3560 (14.3)	171/1575 (10.9)	287/1575 (18.2)	
Middle-Eastern/North African		607/3560 (17.1)	212/1575 (13.5)	323/1575 (20.5)	
Asian		123/3560 (3.5)	38/1575 (2.4)	59/1575 (3.7)	
Europid		2322/3560 (65.2)	1154/1575 (73.3)	906/1575 (57.5)	
BMI, kg/m^2	3152 (71.3)	27.5 (24.2–31.2)	26.3 (23.5–29.5)	28.7 (25.0–32.5)	<0.001
Obesity (BMI ≥30 kg/m^2)	3152 (71.3)	1189/3704 (32.1)	367/1576 (23.3)	621/1576 (39.4)	<0.001
Hypertension	4338 (98.1)	2734/4377 (62.5)	1043/2169 (48.1)	1667/2169 (76.9)	<0.001
Dyslipidaemia	4190 (94.8)	1473/4303 (34.2)	461/2095 (22.0)	972/2095 (46.4)	<0.001
Active smoker	2874 (65.0)	216/3501 (6.2)	94/1437 (6.5)	74/1437 (5.1)	0.14
Clinical variables on admission					
Time between symptoms onset and admission, days	4224 (95.6)	6 (3–9)	7 (3–10)	6 (2–9)	<0.001
Dyspnoea	4310 (97.5)	2796/4365 (64.1)	1370/2155 (63.6)	1390/2155 (64.5)	0.54
Biology on admission					
Positive SARS-CoV-2 PCR	4134 (93.5)	4020/4270 (94.1)	1950/2067 (94.3)	1950/2067 (94.3)	1
Plasma glucose, mmol/l	2256 (51.0)	7.20 (5.91–10.40)	6.20 (5.50–7.10)	9.40 (7.00–13.18)	<0.001
Plasma creatinine, μmol/l	3848 (87.1)	85 (68–115)	81 (66–103)	91 (69–132)	<0.001
eGFR (CKD-EPI), ml min^{-1} [1.73 m]$^{-2}$	3848 (87.1)	75 (50–91)	79 (59–92)	69 (43–90)	<0.001
ALT, %ULN	3454 (78.1)	0.68 (0.45–1.09)	0.73 (0.47–1.16)	0.64 (0.44–1.02)	<0.001
AST, %ULN	3350 (75.8)	1.12 (0.80–1.71)	1.19 (0.83–1.78)	1.09 (0.76–1.63)	<0.001
GGT, %ULN	3128 (70.8)	0.95 (0.56–1.78)	0.97 (0.56–1.80)	0.93 (0.57–1.78)	0.87
Haemoglobin, g/l	4196 (94.9)	131 (118–144)	134 (122–145)	128 (114–142)	<0.001
White cell count, 10^9/l	4060 (91.9)	6.450 (4.860–8.820)	6.290 (4.602–8.600)	6.600 (5.022–9.000)	0.002
Lymphocyte count, 10^9/l	3776 (85.4)	0.920 (0.655–1.300)	0.890 (0.620–1.212)	0.990 (0.690–1.380)	<0.001
Platelet count, 10^9/l	4154 (94.0)	201 (154–261)	199 (153–262)	203 (156–260)	0.64
D-dimers, nmol/l	938 (21.2)	6078 (3450–11527)	5476 (3340–10240)	6188 (3565–11828)	0.083
CRP, mg/l	3886 (87.9)	84.0 (38.7–146.8)	82.5 (36.3–144.0)	86.0 (41.0–149.1)	0.072
LDH, μkat/l	1404 (31.8)	6.11 (4.58–8.62)	6.25 (4.79–8.80)	6.08 (4.56–8.60)	0.039
CPK, μkat/l	1466 (33.2)	2.20 (1.10–4.81)	2.19 (1.09–4.66)	2.12 (1.10–4.58)	0.75
Fibrinogen, g/l	1378 (31.2)	6.2 (5.0–7.3)	6.1 (5.0–7.3)	6.2 (4.9–7.4)	0.24
Outcomes within 7 days					
Composite endpoint[b]	4420 (100)	1119/4420 (25.3)	478/2210 (21.6)	641/2210 (29.0)	<0.001
Death	4420 (100)	426/4420 (9.6)	184/2210 (8.3)	242/2210 (11.0)	0.003
IMV	4420 (100)	754/4420 (17.1)	320/2210 (14.5)	434/2210 (19.6)	<0.001
Discharged alive	4348 (98.4)	1320/4383 (30.1)	750/2174 (34.5)	560/2174 (25.8)	<0.001
Outcomes within 28 days					
Composite endpoint[b]	4420 (100)	1396/4420 (31.6)	627/2210 (28.4)	769/2210 (34.8)	<0.001
Death	4420 (100)	822/4420 (18.6)	378/2210 (17.1)	444/2210 (20.1)	0.007
IMV	4420 (100)	794/4420 (18.0)	340/2210 (15.4)	454/2210 (20.5)	<0.001
Discharged alive	4354 (98.5)	3108/4386 (70.9)	1612/2177 (74.0)	1473/2177 (67.7)	<0.001
Time of discharge (days)[c]	2226 (71.7)	9 (5–14)	8 (5–12)	9 (6–15)	<0.001

Data are presented as *n* (%), mean±SD or median (25th–75th percentile)

[a] Results are presented for the whole population with available data, before pair selection. This implies that the presented populations might be greater than the no-diabetes and diabetes populations added together

[b] Composite endpoint defined as death and/or IMV

[c] In the population discharged alive within 28 days

p values are calculated using McNemar's or, if not applicable, Fisher's exact test (categorical variables) or sign test (quantitative variables)

%ULN, % of the upper limit of normal; ALT, alanine aminotransferase; CPK, creatine phosphokinase; GGT, γ-glutamyl transferase; LDH, lactate dehydrogenase; NR, not relevant

Table 2 CCi: detail of the items according to diabetes status

Item	Item's weight		All participants (*n*=4420)	No diabetes (*n*=2210)	Diabetes (*n*=2210)	*p* value
	CCi	uCCi				
Charlson's items						
Myocardial infarction	1	-	839/4420 (19.0)	303/2210 (13.7)	536/2210 (24.3)	<0.001
Congestive heart failure	1	2	409/4420 (9.3)	165/2210 (7.5)	244/2210 (11.0%)	<0.001
Peripheral vascular disease	1	-	337/4420 (7.6)	97/2210 (4.4)	240/2210 (10.9%)	<0.001
Cerebrovascular disease	1	-	469/4420 (10.6)	204/2210 (9.2)	265/2210 (12.0)	0.002
Dementia	1	2	21/4420 (0.5)	12/2210 (0.5)	9/2210 (0.4)	0.66
Chronic pulmonary disease	1	1	904/4420 (20.5)	430/2210 (19.5)	474/2210 (21.4)	0.11
Rheumatic disease	1	1	171/4420 (3.9)	83/2210 (3.8)	88/2210 (4.0)	0.75
Peptic ulcer disease	1	-	20/4420 (0.5)	12/2210 (0.5)	8/2210 (0.4)	0.50
Renal disease	1	1	1018/4420 (23.0)	322/2210 (14.6)	696/2210 (31.5)	<0.001
Liver disease						
Mild	1	2	194/4420 (4.4)	49/2210 (2.2)	145/2210 (6.6)	<0.001
Moderate to severe	3	4	70/4420 (1.6)	18/2210 (0.8)	52/2210 (2.4)	<0.001
Hemiplegia / paraplegia	2	2	13/4420 (0.3)	6/2210 (0.3)	7/2210 (0.3)	1
Any malignancy without metastasis	2	-	554/4420 (12.5)	274/2210 (12.4)	280/2210 (12.7)	0.82
Any malignancy without metastasis, including leukaemia and lymphoma	-	2	650/4420 (14.7)	330/2210 (14.9)	320/2210 (14.5)	0.70
Leukaemia	2	-	69/4420 (1.6)	40/2210 (1.8)	29/2210 (1.3)	0.22
Lymphoma	2	-	46/4420 (1.0)	28/2210 (1.3)	18/2210 (0.8)	0.18
Metastatic solid tumour	6	6	44/4420 (1.0)	19/2210 (0.9)	25/2210 (1.1)	0.44
AIDS	6	4	1/4420 (<0.1)	1/2210 (<0.1)	0/2210 (0)	1
Diabetes with chronic complication	2	1	-	-	227/2210 (10.3)	-
uCCi categories						<0.001
0			2091/4420 (47.3)	1214/2210 (54.9)	877/2210 (39.7)	
1			847/4420 (19.2)	389/2210 (17.6)	458/2210 (20.7)	
2			659/4420 (14.9)	300/2210 (13.6)	359/2210 (16.2)	
3			422/4420 (9.5)	185/2210 (8.4)	237/2210 (10.7)	
≥4			401/4420 (9.1)	122/2210 (5.5)	279/2210 (12.6)	
deCCi categories						<0.001
0			1717/4420 (38.8)	1033/2210 (46.7)	684/2210 (31.0)	
1			785/4420 (17.8)	413/2210 (18.7)	372/2210 (16.8)	
2			728/4420 (16.5)	339/2210 (15.3)	389/2210 (17.6)	
3			441/4420 (10.0)	177/2210 (8.0)	264/2210 (11.9)	
≥4			749/4420 (16.9)	248/2210 (11.2)	501/2210 (22.7)	

Data are presented as *n* (%)

Mutually exclusive categories: liver diseases ('mild' OR 'moderate to severe'); 'any malignancy' OR 'metastatic solid tumour'

p values are calculated using McNemar's or, if not applicable, Fisher's exact test

COVID-19 related outcomes in individuals with diabetes and matched individuals without diabetes Regarding the clinical outcomes, unadjusted analyses confirmed that individuals with diabetes had a worse COVID-19 prognosis than those without diabetes. The primary composite endpoint (IMV and/or death) occurred in 29.0% (641/2210) of individuals with diabetes compared with 21.6% (478/2210) of those without diabetes ($p<0.001$) within 7 days of admission to hospital, and in 34.8% (769/2210) vs 28.4% (627/2210), respectively, within 28 days ($p<0.001$) (Table 1). Each outcome (i.e. IMV and death) occurred more frequently in individuals with diabetes than in those without diabetes. The Kaplan–Meier survival curves for each outcome in individuals with and without diabetes are shown in Fig. 2. Within 7 days of admission to

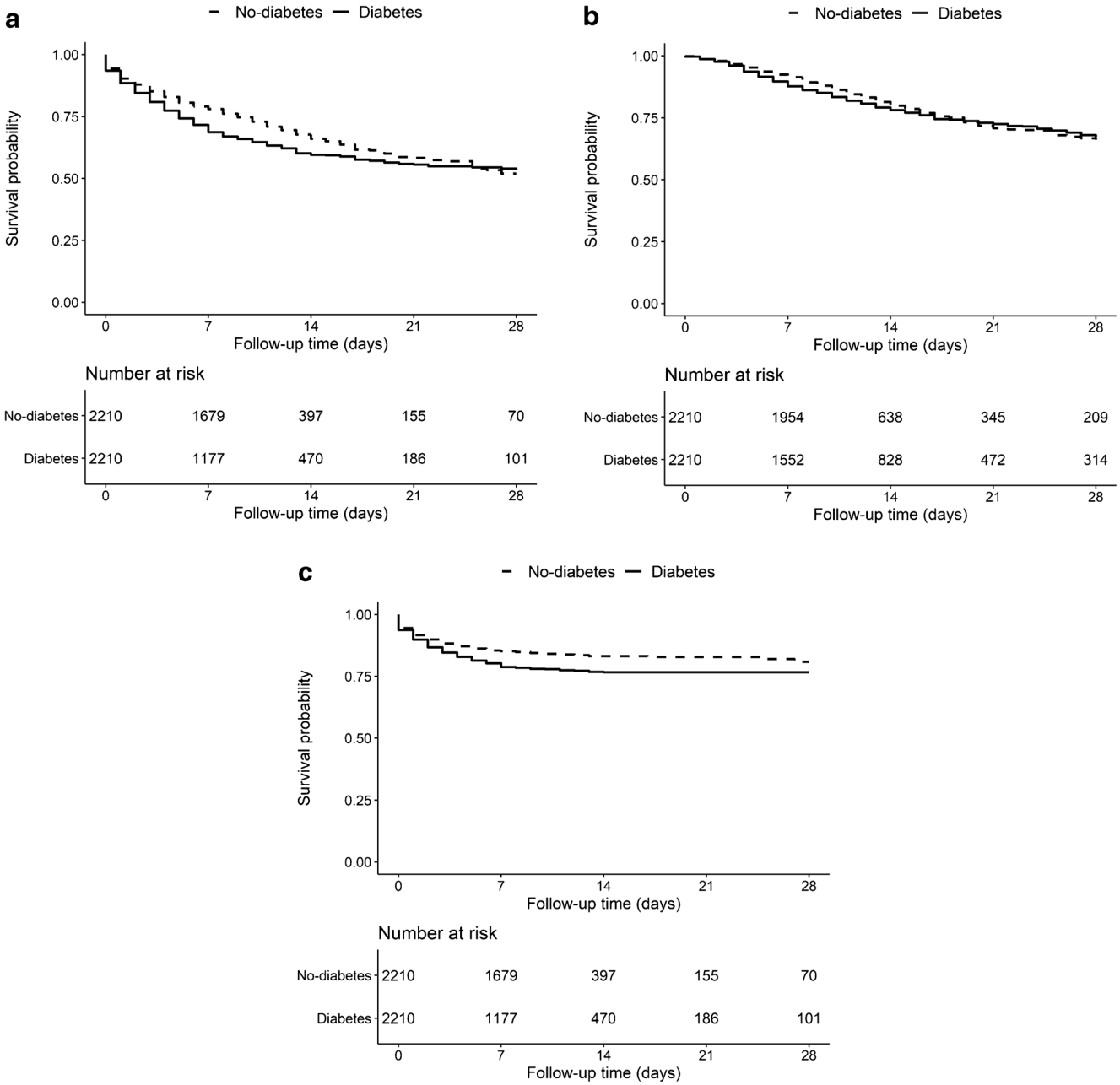

Fig. 2 Kaplan–Meier survival curves for the composite endpoint (**a**), death (**b**) and IMV (**c**) within 28 days according to diabetes status. *p* values were calculated using logrank test, within 28 days: $p<0.0001$ (**a**); $p=0.16$ (**b**); and $p<0.0001$ (**c**)

hospital, the outcomes of interest occurred more in people with diabetes; only the composite endpoint and IMV occurred more frequently within 28 days. For death within 28 days, the survival curves for the diabetes and no-diabetes groups crossed each other.

Impact of diabetes status on COVID-19 prognosis To measure the specific effect of diabetes status as a prognostic factor, we performed multivariable logistic regression models using different levels of adjustment (Table 3).

A DAG approach summarises the causation hypotheses we made to assess the specific impact of diabetes on COVID-19 related outcomes (ESM Fig. 1a,b). Importantly, the risk of occurrence of the primary composite endpoint remained statistically significantly higher in individuals with diabetes than in those without diabetes, after sequential adjustment on age (Model 1), BMI (Model 2) and uCCi (Model 3). After further adjustment on both clinical (time between onset of COVID-19 symptoms and admission to hospital, dyspnoea) and biological (eGFR, AST, white cell count, platelets count, CRP)

Table 3 Survival analyses of the composite endpoint, death and IMV according to diabetes status

Endpoint	Events, *n* (%)		Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
	No diabetes	Diabetes	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Events within 7 days										
Composite endpoint[e]	205/940 (21.8)	272/940 (28.9)	1.43 (1.19, 1.72)	<0.001	1.35 (1.13, 1.63)	0.001	1.40 (1.16, 1.69)	<0.001	1.42 (1.17, 1.72)	<0.001
Death	54/940 (5.7)	85/940 (9.0)	1.68 (1.19, 2.36)	0.003	1.58 (1.11, 2.23)	0.010	1.47 (1.03, 2.09)	0.035	1.44 (1.00, 2.06)	0.049
IMV	161/940 (17.1)	201/940 (21.4)	1.28 (1.04, 1.57)	0.021	1.21 (0.98, 1.50)	0.074	1.31 (1.05, 1.62)	0.015	1.37 (1.10, 1.70)	0.005
Events within 28 days										
Composite endpoint[e]	255/940 (27.1)	321/940 (34.1)	1.31 (1.11, 1.54]	0.001	1.26 (1.07, 1.49)	0.007	1.28 (1.07, 1.51)	0.005	1.30 (1.09, 1.55)	0.003
Death	126/940 (13.4)	163/940 (17.3)	1.27 (1.00, 1.60)	0.048	1.22 (0.96, 1.55)	0.10	1.15 (0.90, 1.46)	0.26	1.19 (0.93, 1.53)	0.16
IMV	170/940 (18.1)	209/940 (22.2)	1.30 (1.06, 1.59)	0.011	1.24 (1.01, 1.52)	0.043	1.32 (1.07, 1.63)	0.009	1.38 (1.11, 1.70)	0.003

All presented HRs are calculated comparing diabetes vs no-diabetes population

[a] Model 1: multivariable Cox proportional hazards model adjusted for age and diabetes status only

[b] Model 2: as for Model 1 plus adjusted for BMI

[c] Model 3: as for Model 2 plus adjusted for uCCi (categorical approach, 0/1/2/3/4 or more)

[d] Model 4: as for Model 3 plus adjusted for admission variables, both clinical (time between symptom onset and admission, dyspnoea on admission) and biological (eGFR [CKD-EPI], AST, white cell count, platelets, CRP). Population with full data for Model 4: *N*=2847/4420 (64.4%), of which 1880/2847 (66.0%) were analysed after selection on complete pairs

[e] Composite endpoint defined as death and/or IMV

p values are calculated using Wald test

variables on admission to hospital (Model 4), the primary composite endpoint occurred more frequently in the diabetes group than in the no-diabetes group both within 7 days (adjusted HR 1.42 [1.17, 1.72], $p<0.001$) and within 28 days (adjusted HR 1.30 [1.09, 1.55], $p=0.003$).

As a next step, we considered the components of the primary composite endpoint separately.

After adjustment for BMI, the observed difference in the risk of IMV between the two groups was not statistically significant within 7 days, although it reached significance within 28 days (Model 2, $p=0.074$ and $p=0.043$, respectively). However, when the uCCi (Model 3) and hospital-admission variables (Model 4) were considered in addition to age and BMI, an increased risk of IMV was found in the diabetes group both within 7 and 28 days after admission (Table 3). An increased risk of death was observed within 7 days in the diabetes group compared with the no-diabetes group, in Models 1–4; after 28 days, the adjusted risks were no longer significant in Models 2–4 (Model 4: adjusted HR 1.19 [95% CI 0.93, 1.53], $p=0.16$).

In sensitivity analyses, similar results were obtained when replacing uCCi with deCCi (ESM Table 1). Moreover, adding ethnicity to Model 4 did not alter the association between diabetes and the different outcomes (ESM Table 2). For the PSM approach, the selection of the analysed population is presented in a specific flow chart (ESM Fig. 2). The characteristics of the PSM population were similar to those of the original population (ESM Table 3). The quality of the matching can be appreciated on the Love plot (ESM Fig. 3). In this sensitivity analysis, diabetes remained a risk factor for both the composite endpoint (adjusted HR 1.17 [1.01, 1.35], $p=0.04$) and IMV (adjusted HR 1.30 [1.09, 1.55], $p=0.003$) within 28 days, but not for death (adjusted HR 0.94 [0.76, 1.16], $p=0.70$) (ESM Table 4).

Interactions between age, uCCi and diabetes on COVID-19-related outcomes When focusing on the two key variables, namely age class and uCCi categories, using a regression model with full adjustment (same as Model 4), we found no interaction between uCCi and diabetes status for the three outcomes. However, an interaction was found between diabetes status and age for the primary composite endpoint and for IMV, both after 7 days and after 28 days of follow-up (ESM Fig. 4). All these interactions were negative, suggesting a less deleterious impact of diabetes with older age. This interaction was not observed when death was the event of interest.

Discussion

This new CORONADO cohort analysis shows that diabetes status is independently associated with worse COVID-19 prognosis beyond comorbidity burden, in individuals hospitalised for COVID-19 in France during the first wave of the pandemic. Interestingly, in-hospital mortality by day 28 was associated with diabetes status in univariate analysis but this association was partly dependent on the comorbidity burden. Conversely, diabetes status was associated with the primary composite endpoint, combining death and IMV, thus accounting for the overall severity of the disease, even after adjustment on BMI, uCCi and relevant hospital-admission variables. Altogether, these data suggest that diabetes status is associated with worse COVID-19 prognosis irrespective of comorbidity status.

The unadjusted comparison between participants with and without diabetes is of clinical interest in this age- and sex-matched population. The risk factors associated with diabetes were well-established, including BMI, which was on average 2.4 kg/m^2 higher in individuals with diabetes than in those without. We also found that the prevalence of non-Europid ethnicity was higher in people with diabetes, which is in line with previous findings on the prevalence of diabetes worldwide [19]. The addition of ethnicity data to our multivariate analysis models did not alter the association between diabetes status and the outcomes of interest. Additionally, the prevalence of myocardial infarction in people with diabetes was twofold that seen in people without diabetes, in line with the RR found in a nationwide study in Sweden [20]. To the best of our knowledge, our study is the first to consider the association between diabetes and the detailed items of the comorbidity burden as assessed by the uCCi. We found that the participants with diabetes less-frequently presented with a zero uCCi compared with matched participants without diabetes (Table 2), arguing for the importance of considering comorbidity in evaluating the effect of diabetes status. We also found that the items differing between those with and without diabetes correspond to long-term established complications of diabetes such as cardiovascular and renal complications. Of note, liver diseases were also more often encountered in individuals living with diabetes. We thus believe that the participants included in the current analysis are representative of age- and sex-matched individuals with and without diabetes.

The demonstration that diabetes is a risk factor for severe COVID-19-related outcomes extends previous findings showing that individuals with diabetes have a higher risk of infectious diseases, especially influenza and pneumonia [5]. Such an increased susceptibility was also reported during the 2009 H1N1 influenza pandemic and, more recently, the Middle East respiratory syndrome-related coronavirus (MERS-CoV) outbreak [21, 22].

Epidemiological studies have quickly and consistently highlighted that diabetes is one of the major comorbidities associated with COVID-19 and affects its severity. We found an independent effect of diabetes on the composite endpoint (IMV and/or death), while the impact of diabetes on death was related to comorbidity and also to clinical and biological

features present on admission to hospital. Then, our results on the primary composite endpoint consistently support the hypothesis that diabetes burden remains associated with pejorative prognosis of COVID-19 beyond its related comorbidities as this relationship remained statistically significant after multiple adjustments, including uCCi and biological variables associated with COVID-19 severity. However, the data for each individual component of the primary outcome provided more contrasted results. The adjustment on age and BMI (Model 2) attenuated the deleterious effect of diabetes on the risk of IMV. This observation is in accordance with previous studies that highlighted the deleterious impact of obesity on the risk of IMV in individuals hospitalised for COVID-19 [8, 23, 24]. However, after further adjustments for uCCi and admission variables, diabetes was still associated with an increased risk of IMV, suggesting that obesity and diabetes synergistically increase the severity of COVID-19. Accordingly, the p value for interaction between diabetes status and BMI was not statistically significant regarding the different outcomes (data not shown). Thus, people with both obesity and diabetes, especially younger individuals, require a tight monitoring when they are hospitalised for COVID-19. In contrast, the increased risk of death observed in people with diabetes was mitigated after adjustments for uCCi and hospital-admission variables. This was more marked for the risk of death at day 28 as compared with early mortality at day 7. There are several potential explanations for this relative difference between the risk of IMV and death. First, it is plausible that indication of IMV was restricted to younger individuals with some withdrawal of life support in older individuals. Indeed, there were very few IMV events in individuals older than 80 years (4.6% and 4.0% in diabetes and no-diabetes groups, respectively). Thus, the respective weight of comorbidities on the risk of either death or IMV was not the same. Second, a higher discharge rate and a shorter time to discharge were observed in individuals without diabetes, in favour of a better prognosis. Since the follow-up was censored after discharge from hospital, our data are limited to in-hospital mortality and we cannot exclude that we have missed information on post-discharge mortality.

Our findings regarding mortality rate within 28 days do not fully agree with nationwide data from England, Scotland and France, which all demonstrated a deleterious influence of diabetes status on COVID-19-related mortality rate, even if adjustment for CCi was not so easily readable [2, 3, 25]. However, our results are in line with those of another study from the UK [26] that found no effect of diabetes status on COVID-19-related mortality rate whereas age, male sex, obesity, and other comorbidities were significant risk factors in individuals admitted to hospital in a similar time window to our study, corresponding to the first phase of the pandemic. Similarly, a French study also suggested no specific effect of diabetes on severe COVID-19 outcomes, from analyses on 603 pairs of patients derived by a matched propensity score approach [27].

Explaining the impact of diabetes on morbidity and mortality rates is well beyond the scope of this paper. However, we found that comorbidity, as captured by uCCi, did not fully account for the deleterious effect of diabetes. The specific role of hyperglycaemia has already been questioned. Although the Scottish nationwide survey reported a weak but statistically significant correlation between HbA_{1c} and COVID-19 severity (death or ICU admission), we did not find any relationship between HbA_{1c} level and COVID-19 outcomes in the CORONADO study, suggesting that chronic glucose control is not a crucial determinant of COVID-19 prognosis when focusing on hospitalised individuals [13]. Accordingly, an increased risk of death related to COVID-19 was observed in people with diabetes from the UK population, irrespective of HbA_{1c} level (below or above 58 mmol/mol [7.5%]) [28]. In contrast, we and others identified the predictive value of plasma glucose at admission [12, 29] which probably reflects the severity of the infectious process but may also interfere with pathophysiological mechanisms such as immune responses. Some authors have suggested an abnormal immunological response in individuals with diabetes admitted to hospital with COVID-19, possibly contributing to their worse prognosis [30]. However, whether these immune features result from diabetes status beyond classical micro- and macrovascular complications or from other comorbidities remains uncertain.

Some limitations must be considered. First, the data were established in the first phase of the pandemic, when prevention and treatment of COVID-19 were in their first steps. Whether the improvement of patient care has led to less difference in prognosis between individuals with and without diabetes will require future investigation. Second, the way multimorbidity was addressed in our analysis using CCi can also be disputed. Some Danish colleagues reported that consensus-based 50 multiple conditions were a good way to show the prevalence of multimorbidity in a nationwide population [31]. However, it has previously been shown that CCi has good clinical value in patients with diabetes [32]. Third, we considered a very specific population, namely people hospitalised for COVID-19, corresponding to severely ill patients. Thus, caution must be taken in interpreting our findings as they may be mitigated if the entire population of people infected with COVID-19 had been studied. In this context, whether diabetes is associated with paucisymptomatic forms of the disease is an interesting question, so far unresolved to our best knowledge. Fourth, statistical power could be an important explanation to discriminate between the lack of effect in small- or middle-sized studies vs bigger nationwide studies or registries. Finally, our results must be considered cautiously as residual confounding may

have contributed to the persistence of a statistically significant association between diabetes and worse COVID-19 prognosis in our models. However, the data presented here were generated after clinical examination of patients and not using electronic Health Records, which might be regarded as an asset, beyond sample size. Indeed, along with this careful clinical approach, one main strength of our study was the ability to perform a 1:1 pairing of diabetic vs non-diabetic individuals, not only based on age and sex but also on admission period and clinical centre. Furthermore, the PSM approach allowed a better pairing on individual characteristics, specifically on the comorbidity burden, even though losing centre-pairing. This sensitivity analysis showed very similar results regarding the three outcomes, the HR for death alone coming closer to 1.

In conclusion, our data support the hypothesis that diabetes is associated with severe COVID-19 outcomes, particularly the risk of IMV, irrespective of the associated comorbidity burden. Biological factors and/or pathways associated with such deleterious outcomes are important to establish in order to target specific interventions to reduce COVID-19 morbidity and mortality rates in the large and specific population of people living with diabetes.

Supplementary Information The online version of this article (https://doi.org/10.1007/s00125-022-05734-1) contains peer-reviewed but unedited supplementary material.

Acknowledgements We thank the sponsor (DRCI CHU Nantes) Clinical Project Manager (M. Saignes) and assistant (J. Saunier), Clinical Research Associates (S. El Andaloussi, J. Martin-Gauthier, E. Rebouilleau) and data managers (B. Guyomarc'h, T. Roman). We acknowledge all medical staff involved in the diagnosis and treatment of patients with COVID-19 in the participating centres. We thank all GPs, specialists, pharmacists and biological laboratories in charge of hospitalised individuals for providing additional medical information to investigators. We thank the Société Francophone du Diabète (SFD) and Société Française d'Endocrinologie (SFE) for disseminating the study design and organisation, and the Fédération Française des Diabétiques (FFD) for participating in the study organisation. Finally, we wish to thank all staff involved in the study and mentioned in the investigator list (ESM CORONADO investigators).

Data availability No sharing of participant data is allowed by our regulatory authorities. So far, French regulations have not validated de-identified data or avatars for data sharing. This statement might be modified in the event of changes in French law.

Funding The CORONADO study received the following funding: the Fondation Francophone de Recherche sur le Diabète (FFRD), supported by Novo Nordisk, Merck Sharpe Dome (MSD), Abbott, AstraZeneca, Lilly and FFD (Fédération Française des Diabétiques) (CORONADO initiative emergency grant); Société Francophone du Diabète (SFD) (CORONADO initiative emergency grant); and Fonds de dotation du CHU de Nantes (CORONADO project: Sanofi, Air Liquid Healthcare, Novo Nordisk, NHC, Allergan, Lifescan). The CORONADO control leg of the study was supported by a grant from the French Ministry of Health (PHRC COVID-19-20-0138). The funders had no role either in the design or in the conduct of the study. Particularly, they had no role in the collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript or the decision to submit the manuscript for publication.

Authors' relationships and activities BC reports grants and personal fees from Amgen and Sanofi, and personal fees from AstraZeneca, Akcea, Genfit, Gilead, Eli Lilly, Novo Nordisk, Merck (MSD) and Regeneron. J-BJ reports personal fees from Eli Lilly, Novo Nordisk, MSD and Sanofi. PG reports personal fees from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Mundipharma, Sanofi and Servier, and grants and personal fees from Novo Nordisk. SH reports personal fees and non-financial support from Astra Zeneca, MSD, Sanofi and Servier, grants from Dinno Santé and Pierre Fabre Santé, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, Novartis, Valbiotis and Eli Lilly, and non-financial support from LVL. PW reports personal fees from Sanofi, Novo Nordisk, Astra Zeneca, MSD and Novartis, and non-financial support from Novo Nordisk, Eli Lilly and MSD. MW reports personal fees from Novo Nordisk. All other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement BC, MW, PG and SH designed the study. Acquisition, analysis and interpretation of data were carried out on behalf of the scientific committee of the study (the list of the scientific committee members is available as ESM). B Balkau, DS and MW designed the statistical analysis. MW performed the statistical analyses. BC, A-SB, SS, BT, RD, ML, CA, DA, LB, SB, MB, OB, EC, ME, CG-L, J-BJ, L Marchand, L Meyer, DS-B, AS, CT, AV, CV, PW, P-JS, B Bauduceau, PG and SH recruited study patients and made a substantial contribution to the acquisition and interpretation of data. BC, PG, SH and B Bauduceau conducted the fundraising for the study. BC, MW, PG and SH drafted the first version of the manuscript. All co-authors critically reviewed and edited the manuscript for important intellectual content, and approved the final version. BC, MW and SH are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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