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Associations of microvascular complications with all-cause death in patients with diabetes and COVID-19: The CORONADO, ABCD COVID-19 UK national audit and AMERICADO study groups

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Abstract

Aim: To provide a detailled analysis of the microvascular burden in patients with diabetes hopitalized for COVD-19.

Materials and Methods: We analysed data from the French CORONADO initiative and the UK Association of British Clinical Diabetologists (ABCD) COVID-19 audit, two nationwide multicentre studies, and the AMERICADO, a multicentre study conducted in New York area. We assessed the association between risk of all-cause death during hospital stay and the following microvascular complications in patients with diabetes hospitalized for COVID-19: diabetic retinopathy and/or diabetic kidney disease and/or history of diabetic foot ulcer.

Results: Among 2951 CORONADO, 3387 ABCD COVID-19 audit and 9327 AMERICADO participants, microvascular diabetic complications status was ascertained for 1314 (44.5%), 1809 (53.4%) and 7367 (79.0%) patients, respectively: 1010, 1059 and 1800, respectively, had ≥1 severe microvascular complication(s) and 304, 750 and 5567, respectively, were free of any complications. The patients with isolated diabetic kidney disease had an increased risk of all-cause death during hospital stay: odds ratio [OR] 2.53 (95% confidence interval [CI] 1.66-3.83), OR 1.24 (95% CI 1.00-1.56) and OR 1.66 (95% CI 1.40-1.95) in the CORONADO,

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the ABCD COVID-19 national audit and the AMERICADO studies, respectively. After adjustment for age, sex, hypertension and cardiovascular disease (CVD), compared to those without microvascular complications, patients with microvascular complications had an increased risk of all-cause death during hospital stay in the CORONADO, the ABCD COVID-19 diabetes national audit and the AMERICADO studies: adjusted OR ($_{adj}$OR) 2.57 (95% CI 1.69-3.92), $_{adj}$OR 1.22 (95% CI 1.00-1.52) and $_{adj}$OR 1.33 (95% CI 1.15-1.53), respectively. In meta-analysis of the three studies, compared to patients free of complications, those with microvascular complications had an unadjusted OR for all-cause death during hospital stay of 2.05 (95% CI 1.42-2.97), which decreased to 1.62 (95% CI 1.19-2.119) after adjustment for age and sex, and to 1.50 (1.12-2.02) after hypertension and CVD were further added to the model.

Conclusion: Microvascular burden is associated with an increased risk of death in patients hospitalized for COVID-19.

KEYWORDS

chronic kidney disease, COVID-19, diabetic foot, microvascular complications, mortality, retinopathy

1 | INTRODUCTION

Since the identification of the first case of COVID-19 in Wuhan, China in December 2019, the disease has become one of the top three causes of death, possibly exceeding cardiovascular disease (CVD) and malignant neoplasms in the United States.[1] Epidemiological studies have quickly and consistently identified diabetes as one of the major comorbidities associated with COVID-19 that affects its severity[2]: the risk of intensive care unit admission is more than doubled and the risk of death is more than tripled in patients with diabetes compared with those without diabetes.[3]

Although diabetes status has been reported in an impressive number of studies, data regarding diabetes-associated microvascular complications and the severity of COVID-19 are very limited. Evidence for a deleterious role of diabetic microvascular complications in patients with diabetes mellitus during the COVID-19 pandemic was recently reported in a large-scale nationwide study in Scotland,[4] as well as by the CORONADO study[5] and in people with type 1 diabetes across the United Kingdom.[6] Chen et al and others have also highlighted the deleterious effect of chronic kidney disease, at least in univariate analysis, on prognosis in patients with COVID-19, although diabetes mellitus has not been specifically studied.[7] In another study, renal failure and proteinuria were associated with poor COVID-19 prognosis[8] but, again, diabetes mellitus was not studied. Because renal status has emerged as a key predictive factor,[9] the impact of microvascular history regarding the prognosis of patients with diabetes needs to be carefully evaluated.

It has been shown that ACE2 receptor expression in the kidneys, involved in SARS-CoV-2 entry into host cells, is increased in diabetic kidney disease (DKD), providing clues to increased susceptibility to SARS-CoV-2.[10] Whether the impact of COVID-19 on mortality is solely related to renal disease or more broadly to microvascular complications has therefore not been fully established. To answer this question, we studied which components of diabetic microvascular complications (renal, retinal and neurological complications) contributed to the association with all-cause death during hospital stay. For this purpose, we used the full set of patients with COVID-19 and diabetes in France who were included in the CORONADO (CORONAvirus-SARS-CoV-2 and Diabetes Outcomes) study, the UK Association of British Clinical Diabetologists (ABCD) COVID-19 study and the AMERICADO (American Corona Analysis/Diabetes Outcomes) study, conducted in New York, United States.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

2.1.1 | CORONADO study

The CORONADO initiative has previously been described.[5,11] Briefly, CORONADO is a retrospective study including a total of 68 French hospitals that have volunteered to share data, collected in a consistent manner, on hospitalized COVID-19 patients with diabetes. The study was sponsored by Nantes University Hospital and designed in accordance with the Declaration of Helsinki. It obtained all regulatory approvals (detailed in supplementary material regulatory considerations). The aim of the CORONADO study was to describe the phenotypic characteristics and prognosis of patients with diabetes admitted with COVID-19 between March 10 and April 10, 2020.

2.1.2 | ABCD COVID-19 audit

Data for the retrospective analysis conducted by the ABCD were collected through a nationwide audit and full details have been described previously.[12] The National Health Service (NHS) supports audit with clear guidance for the contributing centres on the use of routine clinical practice data submitted in anonymized form via the secure NHS network. As the study was retrospective, and comprised routinely collected healthcare data only, there was no requirement for approval by a research ethics committee. The centres in the United Kingdom submitted demographic and clinical characteristics up to December 8, 2020 to the ABCD COVID-19 diabetes national audit.

2.1.3 | AMERICADO study

The AMERICADO study participants were previously reported.[13] This study includes all patients with diagnoses of type 2 diabetes and COVID-19 who were treated in Northwell Health System hospitals in the New York area. The primary outcomes of the study were death and delivery of mechanical ventilation. Inclusion dates ranged from January 1 to May 31, 2020.

2.2 | Patient follow-up and clinical outcomes

For all participants (CORONADO, ABCD COVID-19 audit and AMERICADO), follow-up ended at the time of hospital discharge or transfer to another hospital, rehabilitation centre or death within hospital. For CORONADO participants, follow-up ended not more than 28 days after admission, in case the patient remained hospitalized. Patients discharged before Day 7 or their families were systematically contacted to check for the nonoccurrence of death or readmission by Day 7. Follow-up ended on Day 7 for those discharged before Day 7 and at discharge or not later than Day 28 for the others.

TABLE 1 Clinical and biological characteristics of CORONADO participants according to complications

	No MICRO (n = 304)	Any MICRO (n = 1010)	Specific MICRO (DR), (n = 275)	*P* value (no MICRO vs. any MICRO)	*P* value (no MICRO vs. specific MICRO)
Sex: male, n (%)	191 (63)	628 (62)	174 (63)	0.84	0.91
Age, years	65 (56-72)	75 (66-83)	69 (61-77)	<0.0001	<0.0001
Type of diabetes, n (%)				0.74	0.0005
Type 1	8 (3)	33 (3)	29 (11)		
Type 2	278 (91)	909 (90)	231 (84)		
Other	18 (6)	68 (7)	15 (5)		
BMI, kg/m^2	28.9 (25.5-33.8)	28.5 (25.2-32.5)	28.3 (24.6-31.8)	0.07	0.0243
HbA1c, mmol/mol	60.7 (50.8-72.7)	59.6 (50.8-71.6)	65.6 (55.2-79.2)	0.69	0.0030
HbA1c, %	7.7 (6.8-8.8)	7.6 (6.8-8.7)	8.1 (7.2-9.4)	0.69	0.0030
Hypertension, n (%)	198 (65)	895 (89)	248 (91)	<0.0001	<0.0001
Smoking status, n (%)			164 (62)	0.06	0.97
Never	183 (65)	496 (58)	158 (65)		
Former or current	99 (35)	352 (42)	85 (35)		
Positive SARS-CoV-2 PCR, n (%)	288 (97)	925 (95)	249 (93)	0.15	0.0641
Admission plasma glucose, mmol/L	9.6 (6.8-12.9)	9.4 (6.9-13.5)	10.1 (7.1-14.1)	0.66	0.37
eGFR (CKD-EPI), mL/min/1.73 m^2	90.4 (79.6-102.2)	39.9 (24.9-53.1)	40.9 (18.0-67.8)	<0.0001	<0.0001
Haemoglobin, g/L	135 (122-145)	120 (107-134)	117 (103-129)	<0.0001	<0.0001
White blood cell count, G/L	5.85 (4.60-8.28)	6.70 (5.10-9.16)	6.31 (4.87-8.66)	<0.0001	0.14
Lymphocyte count, G/L	1.10 (0.78-1.50)	0.92 (0.62-1.36)	1.00 (0.66-1.46)	<0.0001	0.0394
Platelet count, G/L	203 (160-244)	198 (150-260)	193 (145-261)	0.93	0.61
C-reactive protein, mg/L	77 (38-136)	86 (42-147)	75 (40-130)	0.16	0.98
Death by Day 28 after admission, n (%)	31 (10)	308 (30)	66 (24)	<0.0001	<0.0001

"no MICRO", denotes patients with ascertained microvascular status and no severe DR and no DKD and no DFU; "any MICRO" denotes patients with ascertained microvascular status and at least one complication among DR, DKD and DFU; "specific MICRO" denotes patients who are part of the "any MICRO" population and have DR with or without additional microvascular complication; DR corresponds to active or past DR (any stage); DKD was defined as proteinuria (when available) and/or eGFR below 60 mL/min. DFU, active or past diabetic foot ulcer (see definitions in methods). Of note, the AMERICADO population comprised patients living with type 2 diabetes. As microvascular burden was defined on claimed billing codes, all patients were considered as ascertained.
Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DFU, diabetic foot ulcer; DKD, diabetic kidney disease; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; NA, not available.

2.3 | Definition of microvascular and macrovascular burden

Microvascular burden was defined according to the presence of retinal, renal and peripheral neuropathic complications. Diabetic retinopathy (DR) was staged as present (history of retinopathy, whether DR was active or not), or absent otherwise.[14] History of diabetic foot ulcer (DFU) was established using an internationally accepted definition,[15] after the questioning of patients and their general practitioners (GPs), if appropriate, and after careful review of their previous hospitalization records when available. DKD was defined as proteinuria (albumin excretion rate- ≥ 300 mg/24 h; urinary albumin/creatinine ratio ≥ 300 mg/g; urinary albumin/creatinine ratio ≥ 30 mg/mmol; proteinuria ≥500 mg/24 h), assessed on previous routine determination, and/or estimated glomerular filtration rate (eGFR) equal to or lower than 60 mL/min/1.73 m,[2] using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula,[16] according to routine plasma creatinine determination in the 18 months prior to admission.

In CORONADO participants, DR data were obtained from ophthalmologist routine examination files, DKD and DFU data were obtained from routine determination in the 6 months prior to admission and/or at admission and by interview of GPs/specialists. In the United Kingdom, all microvascular complications were obtained from hospital in-patient records. In the United States, AMERICADO participants' microvascular diagnoses were based on International Classification of Diseases-10 billing codes. Urinary albumin excretion was not available for the ABCD COVID-19 audit or AMERICADO participants and DKD was defined as eGFR equal to or lower than 60 mL/min/1.73 m^2.

We defined specific microvascular disease controls as persons with ascertained data, with eGFR equal to or higher than 60 mL/min/1.73 m^2 and no DR and no moderately or severely increased albumin excretion and no history of DFU. Specific microvascular disease cases were defined as having DR with or without any additional complications, since DR can be considered as more specific to diabetic microvascular disease compared to DKD or DFU. To homogenize our approach in the three cohorts, we considered decreased renal function but not albuminuria to define cases, thus leaving DR patients with or without associated DKD. Cases with altered renal function and/or DFU without DR were not classified as cases or controls.

Cardiovascular disease was defined as patient's personal history of heart failure and/or ischaemic heart disease (myocardial infarction/angina and/or coronary artery revascularization) and/or cerebrovascular disease (stroke/transient ischaemic attack and/or carotid artery revascularization).

TABLE 2 Clinical and biological characteristics of ABCD COVID-19 diabetes national audit participants according to microvascular complications status

	No MICRO (n = 750)	Any MICRO (n = 1059)	Specific MICRO (DR), (n = 417)	*P* value (no MICRO vs. any MICRO)	*P* value (no MICRO vs. specific MICRO)
Sex (male), n (%)	465 (62)	646 (61)	250 (60)	0.50	0.34
Age, years	69 (58-79)	78 (69-85)	74 (67-84)	<0.0001	<0.01
Type of diabetes, n (%)				0.15	0.09
Type 1	3 (4)	74 (7)	38 (9)		
Type 2	720 (96)	985 (93)	379 (91)		
BMI, kg/m^2	28.8 (24.5-34.2)	27.8 (24.1-32.9)	28.7 (24.1-33.8)	0.04	0.24
HbA1c, mmol/mol	55.0 (47.0-70.0)	59.0 (48.0-75.0)	64.0 (52.0-79.0)	0.008	<0.01
HbA1c, %	7.2 (6.5-8.6)	7.6 (6.5-9.0)	8.0 (6.9-9.4)	0.008	<0.01
Hypertension, n (%)	438 (64)	710 (74)	319 (77)	<0.0001	<0.01
Smoking status, n (%)*				0.54	0.24
Never	371 (91)	620 (92)	245 (93)		
Former or current	36 (9)	51 (8)	19 (7)		
Positive SARS-CoV-2 PCR, n (%)	750 (100)	1059 (100)	417 (100)	1	1
Admission plasma glucose, mmol/L	9.2 (7.0-13.2)	9.2 (6.7-13.6)	10.1 (7.2-14.0)	0.14	<0.01
eGFR (CKD-EPI), mL/min/1.73 m^2	72.8 (55.9-91.5)	34.7 (21.1-52.1)	50.3 (31.1-72.1)	<0.0001	<0.01
Death (in-hospital), n (%)	225 (30.0)	453 (42.8)	170 (40.8)	<0.0001	<0.01

"no MICRO", denotes patients with ascertained microvascular status and no severe DR and no DKD and no DFU; "any MICRO" denotes patients with ascertained microvascular status and at least one complication among DR, DKD and DFU; "specific MICRO" denotes patients who are part of the "any MICRO" population and have DR with or without additional microvascular complication; DR corresponds to active or past DR (any stage); DKD was defined as proteinuria (when available) and/or eGFR below 60 mL/min. DFU, active or past diabetic foot ulcer (see definitions in methods). Of note, the AMERICADO population comprised patients living with type 2 diabetes. As microvascular burden was defined on claimed billing codes, all patients were considered as ascertained.

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DFU, diabetic foot ulcer; DKD, diabetic kidney disease; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; NA, not available.

2.4 | Statistical analysis

Quantitative data were expressed as mean ± standard deviation (SD) or median [25th-75th percentile]. Categorical variables were given as number (percentage) of participants. The characteristics of patients were compared using traditional statistical tests (ANOVA, Kruskal-Wallis test or χ^2 test).

A univariate logistic regression model was used to assess the association between microvascular status and death within 28 days. Adjustment for age, sex, hypertension and CVD were also considered in the models. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. We analysed each study population separately, and performed a meta-analysis based on a random-effects model by pooling ORs. We identified heterogeneity by visual inspection of the forest plots and calculation of the I^2 statistic.

Since DFU and DKD can be multifactorial, particularly in people with type 2 diabetes, we performed an additional sensitivity analysis on those patients with specific microvascular disease, that is, DR with or without additional microvascular complications.

P values <0.05 were taken to indicate statistical significance. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina), R statistical software version 3.6.3, GraphPad Prism software version 8.0 (La Jolla, California) and RevMan software (version 5.4; The Cochrane Collaboration).

3 | RESULTS

3.1 | Study populations

Flow charts for the present study are presented in Figure S1A-C, for the CORONADO, ABCD COVID-19 audit and AMERICADO study populations, respectively. Among 2951 CORONADO, 3387 ABCD COVID-19 audit and 9327 AMERICADO patients, microvascular diabetic complications status was ascertained for 1314 (44.5%), 1809 (53.4%) and 7367 (79.0%), respectively, of whom 1010, 1059 and 1800, respectively, had ≥1 severe microvascular complication(s) and 304, 750 and 5567, respectively, were free of any complications. In addition, focusing on patients with specific microvascular complications, for the CORONADO, ABCD COVID-19 audit and AMERICADO study populations we found specific microvascular disease in 275 (70 DR+/DKD− and 205 DR+/DKD+), 417 (96 DR+/DKD− and 321 DR+/DKD+) and 903 patients (580 DR+/DKD− and 323 DR+/DKD+), respectively.

TABLE 3 Clinical and biological characteristics of AMERICADO participants according to microvascular complications status

	No MICRO (n = 5567)	Any MICRO (n = 1800)	Specific MICRO (DR), (n = 903)	*P* value (no MICRO vs. any MICRO)	*P* value (no MICRO vs. specific MICRO)
Sex: male, n (%)	3126 (56)	1020 (57)	485 (53)	0.70	0.17
Age, years	68 (14)	68 (13)	67 (13)	0.39	0.18
BMI, kg/m^2	30.5 (25.1- 33.9)	30.0 (24.8- 33.4)	30.6 (25.4- 33.9)	0.07	0.57
HbA1c, %	7.4 (4.5)	7.7 (4.5)	8.3 (2.3)	0.13	<0.001
HbA1c, mmol/mmol	57 (26)	61 (26)	67 (10)	0.13	<0.001
Hypertension, n (%)	4461 (80)	1719 (95)	859 (95)	<0.0001	<0.001
Smoking status, n (%)				<0.0001	<0.001
Never	4674 (84)	646 (62)	545 (60)		
Former or current	892 (16)	399 (38)	358 (40)		
Positive SARS-CoV-2 PCR, n (%)	5567 (100)	1800 (100)	903 (100)	1	1
Admission plasma glucose (mmol/L)	9.8 (6.9-12.8)	9.3 (6.9-13.6)	10.8 (6.8-14.0)	0.03	0.001
eGFR (CKD-EPI), mL/min/1.73 m^2	65.9 (59.2-93.2)	38.6 (17.7-62.4)	42.5 (19.5-70.6)	<0.0001	<0.001
Haemoglobin, g/L	126 (115-141)	116 (99-130)	115 (101-132)	<0.0001	<0.01
White blood cell count, G/L	8.19 (5.24-9.69)	8.15 (5.47-9.81)	7.12 (5.29-9.70)	0.84	0.24
Lymphocyte count, G/L	1.16 (0.64-1.34)	1.09 (0.59-1.33)	1.10 (0.62-1.37)	0.23	0.60
Platelet count, G/L	213 (164-275)	232 (153-267)	210 (155-279)	0.004	0.83
C-reactive protein, mg/L	40 (11 -70)	29 (11 -49)	10 (4 -22)	<0.001	<0.001
Death (in-hospital), n (%)	851 (15)	400 (22)	151 (17)	<0.001	0.82

"no MICRO", denotes patients with ascertained microvascular status and no severe DR and no DKD and no DFU; "any MICRO" denotes patients with ascertained microvascular status and at least one complication among DR, DKD and DFU; "specific MICRO" denotes patients who are part of the "any MICRO" population and have DR with or without additional microvascular complication; DR corresponds to active or past DR (any stage); DKD was defined as proteinuria (when available) and/or eGFR below 60 mL/min. DFU, active or past diabetic foot ulcer (see definitions in methods). Of note, the AMERICADO population comprised patients living with type 2 diabetes. As microvascular burden was defined on claimed billing codes, all patients were considered as ascertained.

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DFU, diabetic foot ulcer; DKD, diabetic kidney disease; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; NA, not available.

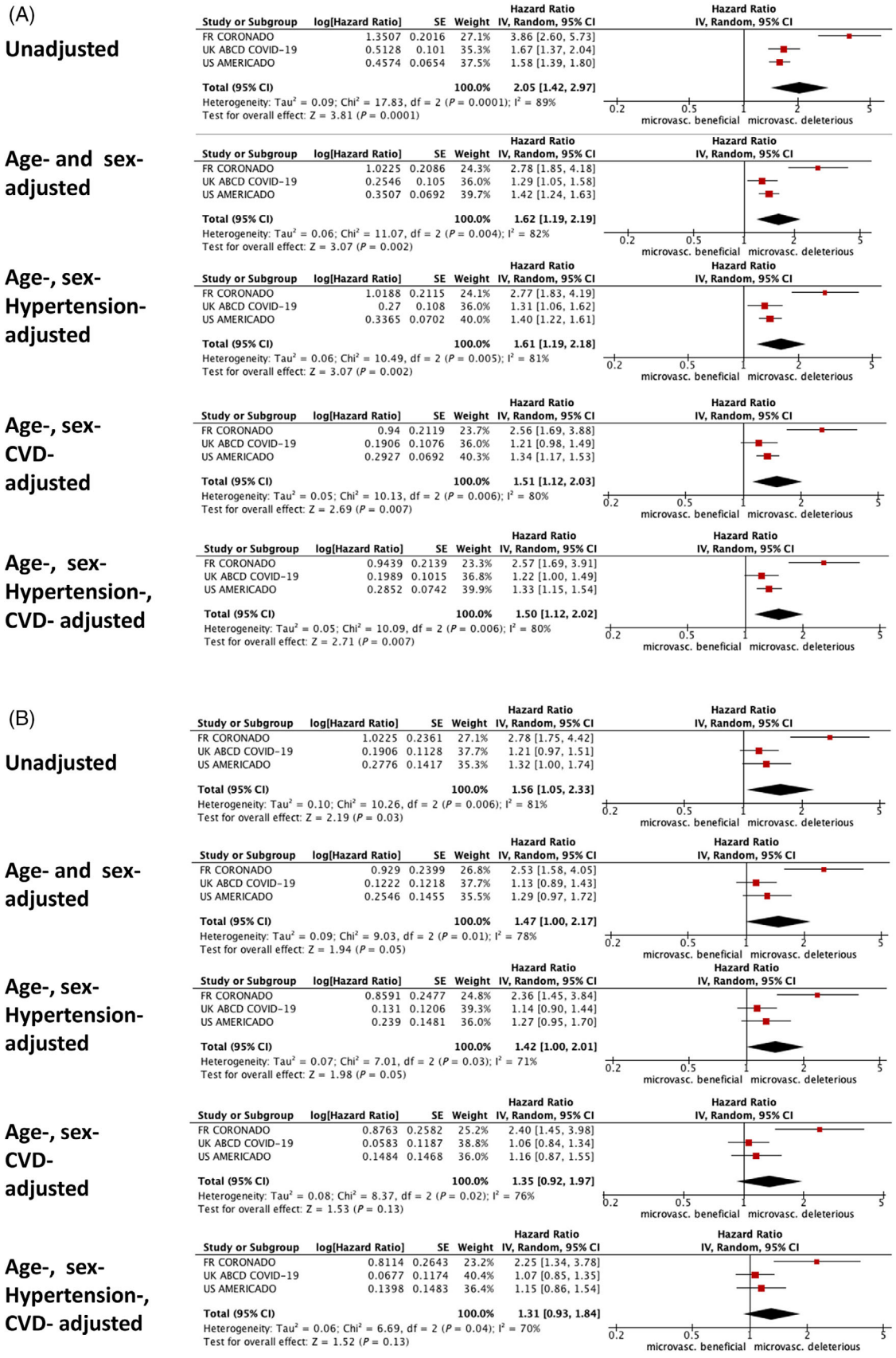

FIGURE 1 Forest plot of odds ratio for in-hospital death in patients with COVID-19 and diabetes: Individual cohorts and meta-analysis in the whole population of patients with microvascular disease (A) and in the subpopulation of patients with diabetic retinopathy, with or without additional microvascular complications (B). CI, confidence interval; CVD, cardiovascular disease.

3.2 | Baseline characteristics

Tables 1 to 3 detail the participants' clinical and biological characteristics, comparing those with and without microvascular complications, with a special focus on those with specific microvascular complications (namely, DR with or without other microvascular burden involvement), in the CORONADO, ABCD COVID-19 national audit and AMERICADO study populations, respectively, while Tables S1 and S2 detail the clinical and biological characteristics of all participants, according to their microvascular status.

Briefly, patients with microvascular complications were older, had longer diabetes duration, and higher C-reactive protein levels, lymphocyte and platelet counts than controls without microvascular complications, while sex, body mass index and glycated haemoglobin (HbA1c) concentration were not significantly different between the two groups. When comparing patients with specific microvascular complications (ie, DR with or without additional microvascular complications), those with specific microvascular damage consistently were older and had higher HbA1c concentration and lower eGFR compared to those without microvascular complications.

As depicted in Figure S2A-C, and as expected, there was a large overlap among the different components of severe microvascular complications. DKD was found in 931/1010 patients (87.6%), including 672 (66%) with isolated renal involvement, in the CORONADO study, 989/1129 patients (96.2%), including 595 (52.7%) with isolated renal involvement, in the ABCD COVID-19 national audit study, and 1121/1800 patients (62.3%), including 942 (52.3%) with isolated renal involvement, in the AMERICADO study.

3.3 | Risk of all-cause death during hospital stay: Association with diabetic microvascular complications

In the CORONADO, the ABCD COVID-19 national audit and the AMERICADO studies, 339/1314 (25.8%), 800/1950 (41.0%) and 1251/7367 patients (17.0%) had died during hospital stay, respectively (see Figures S1-S3). In the CORONADO, the ABCD COVID-19 national audit and the AMERICADO studies, the unadjusted OR of all-cause death during hospital stay in those patients with any microvascular involvement compared to those free of microvascular complications was 3.86 (95% CI 2.60-5.73), 1.67 (95% CI 1.37-2.04) and 1.58 (95% CI 1.39-1.81), respectively.

The relationship between the number of microvascular complications and all-cause death during hospital stay is shown in Figure S3A-C. Figure S4 shows the association between mortality and type of microvascular complication. Very consistently in all three study populations, patients with isolated DKD had an increased risk for all-cause death during hospital stay: OR 2.53 (95% CI 1.66-3.83), OR 1.24 (95% CI 1.00-1.56) and OR 1.66 (95% CI 1.40-1.95), in the CORONADO (panel A), the ABCD COVID-19 national audit (panel B) and the AMERICADO studies (panel C), respectively.

In meta-analysis of the three studies, compared to those patients free of complications, those with microvascular complications had an unadjusted OR for all-cause death during hospital stay of 2.05 (95% CI 1.42-2.97), which decreased to 1.62 (95% CI 1.19-2.119) after adjustment for age and sex and to 1.50 (1.12-2.02) after further adjustment for hypertension and CVD (Figure 1A). Figure 1B shows results for the same approach in those patients with specific microvascular complications.

4 | DISCUSSION

The current analysis focused on the association of microvascular complications with all-cause death during hospital stay in patients with diabetes hospitalized for COVID-19. Patients with microvascular complications were older and more often hypertensive. The current study enabled us to establish that microvascular burden was associated with all-cause death during hospital stay even after adjustment for age, sex, hypertension and CVD. Of note, renal and neurological microvascular complications were associated with all-cause death, while DR did not significantly contribute to the primary outcome.

In this international joint effort, we were able to collect data regarding microvascular burden from three different sources. Data are similar in the CORONADO and ABCD COVID-19 audit participants because these were collected after medical examination. Conversely, data from the AMERICADO participants were obtained from electronic health records mostly using billing codes, probably leading to the lowest incidence of microvascular disease in this cohort compared to the other two cohorts. However, as expected, microvascular burden was associated with age or hypertension while HbA1c did not substantially contribute to this risk in this cross-sectional analysis. Focusing on patients with DR, HbA1c concentration was higher in those with specific microvascular complications than in those without, in good accordance with the established literature on this topic.

Our results on the impact on in-hospital death of microvascular burden are consistent with previous reports, suggesting a deleterious role of microvascular complications in patients with diabetes hospitalized for COVID-19. Our results extend novel findings to those patients with history of DFU, which has not been previously reported to the best of our knowledge. The association between death and DKD was confirmed when considering renal function very consistently in all three cohorts, as well as urinary albumin excretion in the CORONADO study. Accordingly, in a nationwide population of patients with diabetes, Holman et al reported a very clear graded relationship between decrease in eGFR and COVID-19-related mortality[2]—in line with the current findings. This finding was also recently reported in a nationwide analysis of diabetes patients in Scotland.[4] Importantly, such an association between microvascular disease and death remained significant and consistent after adjustment of hypertension and CVD on top of age and sex.

Our results were consistent regarding the deleterious association of DKD and/or DFU (whether individually or combined) but not DR, although microvascular involvement was differently represented, particularly comparing the AMERICADO study and the CORONADO/ABCD COVID-19 national audit populations. The relationship between

renal complications and COVID-19-related deaths was well established in our study and in the literature for patients with or without diabetes. However, our study went further by showing that the microvascular burden was not solely related to DKD. It is by far the most prevalent complication since it is surely the easiest to establish—particularly in times of emergency such as the first COVID-19 wave in Spring 2020. However, we also found DR and history of DFU ranging from 27% to 50% and 13% to 19% of the microvascular participants, respectively. Indeed, the analysis of patients with a history of DFU supported the theory that neuropathy also contributed to hospital deaths in patients with diabetes hospitalized for COVID-19.

We then focused our analysis on participants with specific microvascular disease (DR with or without additional complications) in order to precisely measure the impact of microvascular burden. Indeed, DFU and DKD are not as related to microvascular lesions as DR. This sensitivity analysis led to a reduction of included patients and thus a possible lack of statistical power. The results were unchanged regarding French participants because participants in the CORONADO study had a significantly higher adjusted risk of death compared to participants without microvascular disease. However, such a deleterious effect of DR was not evidenced in the ABCD COVID-19 national audit and AMERICADO studies.

Diabetic retinopathy was not significantly associated with all-cause death during hospital stay. This result extends the previous findings of the Steno cohort, showing that kidney and neuropathic complications but not retinal disease are associated with premature mortality in patients with type 1 diabetes established before the pandemic.[17] Our results require further confirmation but identified microvascular disease beyond kidney and eye disease as significant risk factors for death in COVID-19 patients with diabetes.

So far, the exact cause of the poor prognosis associated with COVID-19 in patients with diabetes is unknown. The involvement of kidney and neurological microvascular complications suggests a generalized inability to respond to the cytokine storm associated with the severe forms of COVID-19. Interestingly, it has also been reported that diabetic microvascular complications may affect microvascular pulmonary vasculature.[18] Other data also suggest that respiratory disease is associated with both type 1 and type 2 diabetes compared with non-diabetic counterparts.[19,20] We found that participants with microvascular complications did not differ from participants without microvascular complications with regard to the frequency of dyspnoea on admission. Neuropathy leading to a positive history of DFU could be one of the missing links between lung function and diabetes prognosis in COVID-19 since lung autonomic neuropathy could predispose those patients to severe respiratory failure. An alternative hypothesis is that microvascular complications are a manifestation of endothelial disease as proposed more than 30 years ago by the Steno hypothesis.[21] Since COVID-19 is associated with endothelitis,[9] it can be speculated that an altered endothelium, of which microvascular complication is an indication, could be more prone to viral infection than a healthier vascular bed. Previous studies have shown that cumulative burden of microvascular complications is associated with increased cardiovascular risk in people with type 2 diabetes.[22] We did not have data on cause of mortality, but risk of myocardial infarction and stroke are increased in people with COVID-19.[23] People with microvascular complications may therefore be a high-risk population for mortality due to cardiovascular events.

Our study has some limitations that must be acknowledged. Microvascular status could not be established in the entire population of participants in the CORONADO and ABCD COVID-19 national audit studies, leaving some uncertainty regarding the precision of our findings. In addition, DKD was not defined using the same criteria in all three studies, with urinary albumin/creatinine ratio missing in the ABCD COVID-19 national audit study, leading to a likely underestimation of renal involvement and possibly narrowing the difference between those with and without microvascular complications. The AMERICADO data are limited by the fact that complications were based on billing codes and not on laboratory tests or physical examination findings, which may underestimate the cases of microvascular disease in this population. This difficulty in establishing microvascular status was also encountered in other registry data-based studies.[4] New additional studies examining our research hypothesis could help to better establish our findings. As already noted, DKD is much easier to establish since it only requires an inquiry into routine biological data. Data on DR and on history of DFU might be harder to collect. However, some assets must also be considered with a good consistency with previous reports on microvascular disease since traditional risk factors are associated with microvascular disease (including diabetes duration). In addition, we considered severe forms of microvascular disease, with eGFR below 60 mL/min and/or proteinuria for renal involvement and severe peripheral neuropathy (with a history of DFU). This could lead not only to a low prevalence of such complications but also to a very specific evaluation of complications since such severe types of complication are more often noted by GPs and patients compared with less severe complications. It should also be noted that DFU and DKD do not exclusively refer to microvascular disease but might be multifactorial, including macrovascular disease. In this context, adjustment for CVD helped to better address their association with all-cause death. Results obtained in a study sample recruited from hospitalized patients must be interpreted with caution as there might be a collider bias, even if our data also fit well with population-based studies.[9] Lastly, the current data were generated at the end of the first phase of the pandemic and current treatment strategy and mortality rates could be quite different from what they were in the period March to June 2020. However, the risk factors have not changed greatly and the current paper should nevertheless encourage a focus on microvascular disease in diabetes COVID-19 patients.

The strengths of this study should also be noted, including its international evaluation of a significant number of patients. The data used originated from patients from three countries with different healthcare systems. Despite the differences in healthcare provision and in the prevalence of microvascular complications, our findings were consistent among the three study populations.

In conclusion, the relationship between microvascular complications and COVID-related death is established, beyond hypertension and CVD. This strongly justifies the systematic search for

microvascular complications in any patient with diabetes and COVID-19 to identify those at high mortality risk. The results were inconsistent among the three study populations for patients with DR with or without additional microvascular complications, which merits further research. The COVID-19 outbreak can be seen as an opportunity to learn about diabetes in an acute situation and our results are likely to go well beyond COVID-19, even if this speculation will require future confirmation in other infectious and noninfectious acute situations.

AUTHOR CONTRIBUTIONS

M. Wargny, P. Gourdy, S. Hadjadj and B. Cariou designed the CORONADO study. R. Rea, Emma G. Wilmot, Sarah H. Wild, Sophie Harris, Benjamin C.T Field, Robert E J Ryder, Parth Narendran, Y. Ruan and K. Khunti designed the ABCD COVID-19 national audit study (see contributors in the ABCD Audit steering committee). Alyson K. Myers, X. Zhu and R. Pekmezaris, designed the AMERICADO study. P.-J. Saulnier conducted the statistical analysis for the CORONADO study and for joint analysis. Y. Ruan conducted the statistical analysis for the ABCD study. S. Hadjadj, J. M. Halimi and P.-J. Saulnier drafted the first version of the manuscript. All authors approved the final manuscript. P.-J. Saulnier and S. Hadjadj 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. Xu Zhu conducted the statistical analysis for the AMERICADO study

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CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported. B. Cariou reports grants and personal fees from Amgen, Sanofi and Regeneron, and personal fees from Astra-Zeneca, Akcea, Genfit, Gilead, Eli Lilly, Novo Nordisk and Merck (MSD). P. Gourdy reports personal fees from Abbott, Amgen, Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, MSD, Mundipharma, Sanofi and Servier, and grants and personal fees from Novo Nordisk. S. Hadjadj reports personal fees and non-financial support from Astra Zeneca, MSD, Servier and Sanofi, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, Eli Lilly, Valbiotis and Novartis, grants from Dinno Santé and Pierre Fabre Santé, and non-financial support from LVL. P. J. Saulnier reports personal fees from Astra Zeneca and non-financial support from Abbott. M. Wargny reports personal fees from Novo Nordisk. R. Rea has acted as a consultant, speaker or received grants from Novo Nordisk, Eli Lilly and Boehringer Ingelheim. K. Khunti has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG / Menarini Group, Janssen, and Napp. All other authors declare no competing interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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