**Associations of microvascular complications with death in patients with diabetes: the CORONADO and** ABCD Covid-19 audit study groups.

Authors please could you suggest some authors and positions. It is fair to mention some back to back positions with some mention such as equally contributed or so. Fine if Kamlesh is last author with Bertrand as equal contributor. It seems that Yue and Pierre Jean were very active regarding analysis. Yue could thus be placed between PJ and my-self with the \* also

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Abstract: 290 words; Manuscript word count: – words

4 Figures; 2 tables; 1 supplementary table

**ABSTRACT**

**OBJECTIVE**

The prognostic role of microvascular complications for all-cause death in patients with diabetes hospitalized for coronavirus disease-2019 (COVID-19) has been suggested. However, no detailed analysis of the microvascular burden in these patients is available so far.

**RESEARCH DESIGN AND METHODS**

Participants from the French CORONADO initiative (Coronavirus SARS-CoV-2 and Diabetes Outcomes) and the United Kingdom Association of British Clinical Diabetologist (ABCD) Covid-19 audit, two nationwide multicenter studies, were analyzed, during the first phase of the pandemic. In patients with diabetes hospitalized for COVID-19 within a 28-day follow-up (CORONADO) or during the inpatient stay (UK ABCD) , we assessed the association between the risk of deathand microvascular complications which included diabetic retinopathy (DR) and/or diabetic kidney disease (DKD) proteinuria and/or eGFR<60 ml/min/1.73m2, and/or history of diabetic foot ulcer (DFU).

**RESULTS**

Among 2,796 CORONADO and 3,528 ABCD Covid-19 audit patients, the status for microvascular diabetic complications was ascertained for 1,314 (47.0%) and 1,809 (51,3%) patients: 968 and 1,030 with ≥1 severe microvascular complication(s) and 346 and 779 free of any complications, respectively. Compared with patients without microvascular complications, those with microvascular complications were older and had higher HbA1c, AST/ALT, lymphocyte and platelet counts, while sex, type of diabetes and CRP were not significantly different between the 2 groups. After adjustment for age and sex, patients with one or more microvascular complications had an increased risk of death (OR: 2.54 (1.94-3.31, *P* < 0.0001). Isolated DKD (adjusted OR: 2.57 (1.91-3.46)) and DFU (adjusted OR: 4.13 (1.15-14.83)), combined DKD and DFU (2.41 [1.26-4.59], combined DKD and DR (4.20 [2.28-7.74]), combined DFU and DR (OR: 6.38 [1.02-39.84]) but not isolated DR (adjusted OR: 0.88 (0.19-1.91)) were associated with the risk of death.

**CONCLUSIONS**

Diabetic kidney disease or diabetic foot ulcer, alone or combined are associated with an increased risk of death in patients hospitalized for COVID-19. These findings support systematic search for specific diabetic complication phenotyping in diabetic COVID-19 patients.

**Key words:** COVID-19, chronic kidney disease, diabetic foot, retinopathy, microvascular complications, mortality

The pandemic of Coronavirus Disease-2019 (COVID-19), a disease caused by the coronavirus Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) has impacted our societies in a brutal way since the identification of the first case in Wuhan, China in December 2019. COVID-19 has become one of the top 3 causes of death, possibly exceeding heart diseases and malignant neoplasms in the US (1).

COVID-19 is particularly severe in patients with diabetes. Indeed, epidemiological studies have quickly and consistently identified diabetes as one of the major comorbidities associated with COVID-19 affecting its severity (2): the risk of ICU 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. The deleterious role of diabetic microvascular complications in patients with diabetes mellitus during the COVID-19 pandemic was recently suggested in a large-scale nationwide study in Scotland (4) and by the CORONADO study (5) and in people with Type 1 diabetes across the UK (<https://doi.org/10.1007/s00125-021-05463-x>). Chen et al. and others have also highlighted the deleterious effect of chronic kidney disease (CKD), at least in univariate analysis, on the prognosis in patients with COVID-19 but diabetes mellitus has not been specifically studied (6). In another paper, renal failure and proteinuria were associated with poor COVID-19 prognosis (7) but again, diabetes mellitus was not studied. Since renal prognosis has appeared as a key prognostic factor, the impact of microvascular history regarding the prognosis of patients with diabetes needs to be carefully evaluated.

Recent histological findings have evidenced a localization of SARS-CoV-2 in the kidneys of patients deceased from COVID-19, particularly in case of multiple comorbidities (8) but also in endothelial cells (9). It has been shown that entry machinery in diabetic kidney disease (DKD) provides 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 microvascular complications (renal, retinal and neurological complications) contributed to the association with the 28-day risk of death. For this purpose, we used the full set of CORONADO (CORONAvirus-SARS-CoV-2 and Diabetes Outcomes) participants, a nationwide multicenter observational study across France, together with the ABCD COVID-19 study, a nationwide multicentre observational study across the UK.

**RESEARCH DESIGN AND METHODS**

**Study design and participants**

CORONADO study

The CORONADO study initiative has previously been described (5,11). Briefly, CORONADO is a retrospective study including a total of 68 French hospitals volunteering to share data 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 diabetic patients admitted with COVID-19 between March 10 and April 10, 2020. Inclusion criteria were (i) hospitalization in a dedicated COVID-19 unit for biologically- (SARS-CoV-2 PCR) and/or clinically/radiologically-attested COVID-19, i.e., ground-glass opacity and/or crazy paving on chest CT scan; (ii) personal history of diabetes or newly diagnosed diabetes on admission (i.e., HbA1c ≥48 mmol/mol [6.5% during hospitalization).

ABCD COVID-19 Audit

Data for this retrospective analysis were collected through a nationwide audit conducted by the Association of British Clinical Diabetologists (ABCD) and full details have been described previously. The NHS supports audit with clear guidance for the contributing centres on the use of routine clinical practice data submitted in anonymised 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 UK submitted demographic and clinical characteristics upto 8 December 2020 to the ABCD COVID-19 diabetes national audit.

**Patient follow-up and clinical outcomes**

CORONADO participants discharged before day 7 or their families were systematically contacted to check for the non-occurrence of death or readmission by day 7. Follow-up ended on day 7 for those discharged before day 7.

For all participants (CORONADO and ABCD COVID 19 Audit), follow-up ended at the time of hospital discharge or transfer to another hospital, rehabilitation center or death within hospital. Follow-up was considered up to day 28. In this analysis, death rate refers to in-hospital mortality up to day 28.

**Definition of microvascular burden**

Microvascular burden was defined according to the presence of retinal, kidney and peripheral neuropathic complications. In France, details on diabetic retinopathy (DR) were obtained from files on routine examination by an ophthalmologist. DR staging was performed according to the French-speaking diabetes society – SFD – classification: absent; mild/moderate non-proliferative retinopathy; severe non-proliferative; proliferative retinopathy (12). In the current study, we considered patients with history of retinopathy, whether DR was active or not. A history of diabetic foot ulcer (DFU) was established, using internationally accepted definition (13), after the questioning of patients and their general practitioners (GPs) if appropriate and careful review of their previous hospitalization records when available. DKD was defined as proteinuria (albumin excretion rate ≥300 mg/24h; urinary albumin/creatinine ratio ≥300 mg/g; urinary albumin/creatinine ratio >30 mg/mmol creatinine; proteinuria ≥500 mg/24h), assessed on previous routine determination and/or eGFR equal to or lower than 60 ml/min/1.73 m2, using the CKD-EPI formula (14), according to the routine plasma creatinine determination in the 18 months prior to admission. In the UK, all microvascular complications were obtained from hospital in-patient records. Urinary albumin excretion was not available for ABCD-COVID19 Audit participants and DKD was defined as eGFR equal to or lower than 60 ml/min/1.73 m2, in this population.

**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 χ2 test).

Univariate logistic regression model was used to assess the association between microvascular status and death within 28 days. Adjustment for age and sex were also performed. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated.. a meta-analysis based on a random-effects mode by pooling ORs. We identified heterogeneity by visual inspection of the forest plots and calculation of I2 statistic.

*P* values < 0.05 were considered statistically significant Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC), R statistical software version 3.6.3, GraphPad Prism software version 8.0 (La Jolla, CA) and RevMan software (Version 5.4. The Cochrane Collaboration).

**RESULTS**

**Study populations**

The flow chart of the present study is presented in Fig. 1 A and B, for both CORONADO and ABCD-COVID-19 Audit populations. Among 2,796 CORONADO and 3,528 ABCD Covid-19 audit patients, the status for microvascular diabetic complications was ascertained for 1,314 (47.0%) and 1,809 (51,3%) patients: 1,010 and 1,030 with ≥1 severe microvascular complication(s) and 304 and 779 free of any complications, respectively. Among 3,528 ABCD-COVID-19 patients, the status for microvascular diabetic complications was ascertained for 3,349 (95%) patients: 1,870 with ≥1 severe microvascular complication(s) and 1,479 free of any complications.

**Baseline characteristics**

Table 1 and 2 detail the clinical and biological characteristics of participants according to their microvascular status. Briefly, patients with microvascular complications were older, presented longer diabetes duration, higher CRP, lymphocyte and platelet count than the other patients without severe microvascular complications, while sex, type of diabetes and HbA1c were not significantly different between the 2 groups.

Details on the specific components of the microvascular disease according to microvascular status are presented in Table 3 and 4, and the Supplementary Tables 1-2. Patients with severe microvascular complications were more likely to be treated by insulin, statins and renin angiotensin aldosterone system (RAAS) blockers than patients without.

As depicted in Fig. 2 A and B and as expected, there was a large overlap among the different components of severe microvascular complications. In CORONADO participants, DKD was present in 931/1,010 (96.2%) patients, DR in 275/1,010 (14.6%) patients and a history of DFU in 124/1,010 (13.8%).

**Risk of death by day 28: association with diabetic microvascular complications**

In CORONADO, by day 28, 339/1314 (25.8%) patients had died. The incidence of death was higher in patients with severe microvascular complications than in those without (308/1,010 (30.5%) vs. 31/304 (10.2%), unadjusted OR: 3.86 (95% CI: 2.60-5.73, *P* < 0.0001). The relationship between the number of microvascular complications and mortality by day 28 is depicted in Fig. 3. After adjustment for age and sex, patients with severe microvascular complications had a 2.78-fold increased risk of death (95% CI: 1.73-3.76, *P* < 0.0001) compared to those without.

As shown in Fig. 3, the presence of one or more microvascular complications was associated with higher day 28-death. Of note and as depicted in Fig. 4, patients with isolated DKD (OR: 2.53 [95% CI: 1.66-3.83]) or isolated DFU (OR: 6,91 [95% CI: 1.70-28,13]) had an increased adjusted risk of death but not those with isolated DR (0.98 [95% CI: 0.39-2,52]). Moreover, combined DKD and DFU (2.40 [95% CI: 1.19-4.83], combined DKD and DR (2.75 [95% CI: 1.62-4.65]) and combined DFU and DR (OR: 2.95 [95% CI: 0.56-15.45]) were so associated with an increased risk of death.

**DISCUSSION**

The current analysis focused on the association of microvascular complications on death within 28 days in patients with diabetes or during the hospital admission when hospitalized for COVID-19. Patients with microvascular complications were older with a longer diabetes duration. Our current report enabled us to establish that kidney and neuropathic microvascular complications were associated with all-cause death, while retinopathy did not significantly contribute to the primary outcome.

Our results are in agreement with previous reports, suggesting a deleterious role of microvascular complications (renal and retinal) in patients with diabetes hospitalized for COVID-19. Our results extend novel finding to those patients with histories of DFU, which has not been previously reported to the best of our knowledge. The association between death and DKD was confirmed by renal function as well as urinary albumin excretion in the French cohort. 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 our current findings. This finding was also recently found in a nationwide analysis of diabetes patients in Scotland (4). The more severe the kidney function, the higher the urinary albumin and the higher the OR for in-hospital mortality. The impact of DR defined as "referable or eye clinic" was positive but of rather weak magnitude, in accordance with our findings where we showed a non-significant association of severe DR and death by day 28.

The relationship between renal complications and COVID-19 related deaths is 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 France and the UK in the Spring of 2020. However, we also found DR and history of DFU in 18.8% and 19.2% (add UK data) of the participants with ascertained microvascular status. Indeed, the analysis of patients with a history of DFU supported that neuropathy also contributed to hospital deaths in patients with diabetes hospitalized for COVID-19. Conversely, diabetic retinopathy was not significantly associated with death within 28 days following admission. 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 (15). Our results require further confirmation but clearly identified microvascular disease beyond kidney and eye disease as a significant risk factor 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 COVID-19. Of great interest, it has also been reported that diabetic microvascular complications may affect microvascular pulmonary vasculature (16). Other data also suggest that respiratory disease is associated with both type 1 and type 2 diabetes compared with non-diabetic counterparts (17,18). We found that participants with microvascular complications did not differ from participants without microvascular complications with regard to the frequency of dyspnea on admission.

Of interest, 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 as the Steno hypothesis (19). Since COVID-19 is associated with endotheliitis (9), it can be speculated that an altered endothelium, for 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 are associated with increased cardiovascular risk in people with type 2 diabetes. We did not have data on cause of mortality but risk of myocardial infarction and stroke are increased in people with COVID-19. People with microvascular complications may therefore be a high risk population for mortality due to cardiovascular events.

Our study has some limitations which must be acknowledged. The microvascular status could not be established in the entire population of participants, leaving some uncertainty on the precision of our findings even if spurious results are unlikely. Such a difficulty to establish 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 mentioned, diabetic kidney disease is much easier to establish since it only requires an inquiry into routine biological data. Data on diabetic retinopathy and on history of DFU are harder to collect. However, some reassuring facts must be considered since traditional risk factors are associated with microvascular disease (including diabetes duration). Secondly, we considered severe forms of microvascular disease, with eGFR below 60 ml/min and/or proteinuria for renal involvement, severe diabetic retinopathy (severe non-proliferative or proliferative retinopathy) and severe peripheral neuropathy (with a history of DFU). This could lead to a low prevalence of such complications but also lead to a very specific evaluation of complications since such severe forms of complications are often mentioned to GPs and patients compared with developing less severe complications. 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 March - June 2020. However, the risk factors have not changed that much even though our current paper should encourage a focus on microvascular disease in diabetes COVID-19 patients.

Some strengths must also be mentioned such as the fine phenotyping of the participants with an effective collection of microvascular disease- a novel finding in itself. We also report data from a large number of centres in two countries with different health care provisions. The UK has a national health service with free universal coverage of medical care. France…. The size of our study population and particularly the number of deaths was adequate to examine the impact of microvascular burden and its components on all-cause death by day 28 or during the inpatient admission. Despite the differences in health care provision, our findings were consistent between the two countries.

In conclusion, the relationship between microvascular complications and COVID-related death by day 28 is not limited to diabetic kidney disease but to all microvascular complications. This strongly justifies the systematic search for microvascular complications for any patient with diabetes and COVID-19 to identify patients at high mortality risk.

**ACKNOWLEDGMENTS**

See contributors of the CORONADO initiative in supplementary material.

We thank the sponsor (DRCI, Nantes University Hospital), Clinical Project Manager (Maëva Saignes) and assistant (Jeanne Saunier), Clinical Research Associates (Selma El Andaloussi, Joëlle Martin-Gauthier, Emily Rebouilleau) and data manager (Tanguy Roman). We thank the Communication Manager of l’Institut du Thorax (Vimla Mayoura). We acknowledge all medical staff involved in the diagnosis and treatment of patients with COVID-19 in participating centers. We thank all GPs, specialists, pharmacists and biological laboratories in charge of hospitalized patients for providing additional medical information to our investigators. We thank the Société Francophone du Diabète (SFD) and Société Française d’Endocrinologie (SFE) for disseminating study design and organization, the Fédération Française des Diabétiques (FFD) for participating in the organization of the study.

**Funding**

This study received the following funding: the Fondation Francophone de Recherche sur le Diabète (FFRD), supported by Novo Nordisk, MSD, Abbott, AstraZeneca, Lilly and FFD (Fédération Française des Diabétiques) – CORONADO initiative emergency grant; Société Francophone du Diabète (SFD) – CORONADO initiative emergency grant; Air Liquide Health Care international. CORONADO initiative emergency grant; Allergan. CORONADO initiative emergency grant; AstraZeneca. CORONADO initiative emergency grant; Elivie. CORONADO initiative emergency grant; Fortil. CORONADO initiative emergency grant; Lifescan. CORONADO initiative emergency grant; CORONADO initiative emergency grant; Nantes Métroplole. NHC. CORONADO initiative emergency grant; Novo Nordisk. CORONADO initiative emergency grant; Sanofi. CORONADO emergency grant; PHRC National COVID-19 Hospitalization and Care Organization Division (DGOS) as part of the Hospital Clinical Research Program (PHRC COVID-19-20-0138). All research facilities are acknowledged for providing research associates and research technicians for clinical investigations pro bono. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

BC reports grants and personal fees from Amgen, personal fees from Astra-Zeneca, personal fees from Akcea, personal fees from Genfit, personal fees from Gilead, personal fees from Eli Lilly, personal fees from Novo Nordisk, personal fees from Merck (MSD), grants and personal fees from Sanofi, grants and personal fees from Regeneron.

PD reports personal fees from Novo Nordisk, Sanofi, Eli Lilly, MSD, Novartis, Abbott, Astra Zeneca, Boehringer Ingelheim, Mundipharma.

JFG reports Personal fees and non-financial support from Eli Lilly, Novo Nordisk, and AstraZeneca, Personal fees from Bristol-Myers Squibb, Gilead and Bayer, all disclosures above unrelated to this presentation.

PG reports personal fees from Abbott, personal fees from Amgen, personal fees from Astra-Zeneca, personal fees from Boehringer Ingelheim, personal fees from Eli Lilly, personal fees from MSD, personal fees from Mundipharma, grants and personal fees from Novo Nordisk, personal fees from Sanofi, personal fees from Servier.

SH reports personal fees and non-financial support from Astra Zeneca, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, grants from Dinno Santé, personal fees from Eli Lilly, non-financial support from LVL, personal fees and non-financial support from MSD, personal fees from Novartis, grants from Pierre Fabre Santé, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Servier, personal fees from Valbiotis.

PJS reports personal fees from Astra Zeneca and non-financial support from Abbott.

MP reports personal fees and non-financial support from Novo Nordisk, non-financial support from Sanofi, non-financial support from Amgen.

RR reports grants, personal fees and non-financial support from Sanofi, grants, personal fees and non-financial support from Novo Nordisk, personal fees and non-financial support from Eli Lilly, personal fees from Mundipharma, personal fees from Janssen, personal fees from Servier, grants and personal fees from Astra-Zeneca, personal fees from MSD, personal fees from Medtronic, personal fees from Abbott, grants from Diabnext, personal fees from Applied Therapeutics.

MW reports personal fees from Novo Nordisk. All other authors declare no competing interests.

**Author Contributions.**

M.W, P.G., S.H., and B.C. designed the study.

P.G., L.K., B.G., B.L., M.E., C.A., F.O., N.G., I.J., I.M., E.L., L.A.B., O.B., P.M., C.V, D.D, A.Z., D.S.B., M.L., P.S., R.R., J-F.G., P-J.S., S.H., and B.C. participated in patient recruitment. PJS. conducted the statistical analysis. SH, JMH and PJS drafted the manuscript. All of the authors approved the final manuscript. PJS 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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**Table 1. Clinical and biological characteristics of CORONADO participants according to microvascular status**

|  | **Lacking** | **All (n=2713)** | | **no MICRO (n=304)** | **any MICRO (n=1010)** | **not ascertained (n = 1,399)** | | | ***P* value**  (**all 3 groups)** | ***P* value**  **(no MICRO vs. any MICRO)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sex (male), n (%) | 0 | 1725 (64%) | | 191 (63%) | 628 (62%) | 906 (65%) | | | 0.4121 | 0.8374 |
| Age (years) | 0 | 71 (61-80) | | 65 (56-72) | 75 (66-83) | 70 (60-78) | | | **<0.0001** | **<0.0001** |
| Type of diabetes, n (%) | 0 |  | |  |  |  | | | **0.0115** | 0.7438 |
| type 1 |  | 58 (2%) | | 8 (3%) | 33 (3%) | 17 (1%) | | |  |  |
| type 2 |  | 2466 (91%) | | 278 (91%) | 909 (90%) | 1279 (91%) | | |  |  |
| Other |  | 189 (7%) | | 18 (6%) | 68 (7%) | 103 (7%) | | |  |  |
| BMI (kg/m2) | 321 | 28.4 (25.0-32.4) | | 28.9 (25.5-33.8) | 28.5 (25.2-32.5) | 28.3 (25.0-32.0) | | | **0.0472** | 0.0743 |
| diabetes duration (years) | 1020 | 11.0 (5.0-20.0) | | 9.0 (5.0-14.0) | 16.0 (10.0-24.0) | 9.0 (4.0-16.0) | | | **<0.0001** | **<0.0001** |
| HbA1c (%) | 996 | 7.7 (6.8-8.9) | | 7.7 (6.8-8.8) | 7.6 (6.8-8.7) | 7.8 (6.8-9.1) | | | 0.1736 | 0.6875 |
| HbA1c (mmol) |  | 60.7 (50.8-73.8) | | 60.7 (50.8-72.7) | 59.6 (50.8-71.6) | 61.6 (50.8-76.0) | | | 0.1736 | 0.6875 |
| Hypertension, n (%) | 26 | 2093 (78%) | | 198 (65%) | 895 (89%) | 1000 (73%) | | | **<0.0001** | **<0.0001** |
| Smoking status, n (%) | 496 |  | |  |  |  | | | 0.1449 | 0.0572 |
| never- |  | 1343 (61%) | | 183 (65%) | 496 (58%) | 664 (61%) | | |  |  |
| former or current |  | 874 (39%) | | 99 (35%) | 352 (42%) | 423 (39%) | | |  |  |
| Time between symptom onset and hospital admission (days) | 52 | 5.0 (2.0-9.0) | | 7.0 (3.0-10.0) | 4.0 (2.0-7.0) | 6.0 (2.0-9.0) | | | **<0.0001** | **<0.0001** |
| Dyspnea, n (%) | 40 | 1713 (64%) | | 201 (67%) | 626 (63%) | 886 (64%) | | | 0.3884 | 0.1833 |
| Positive SARS-CoV-2 PCR, n (%) | 89 | 2474 (94%) | | 288 (97%) | 925 (95%) | 1261 (94%) | | | 0.1001 | 0.1500 |
| Admission plasma glucose (g/L) | 1215 | | 9.4 (7.0-13.3) | 9.6 (6.8-12.9) | 9.4 (6.9-13.5) | | 9.4 (7.0-13.4) | | 0.8304 | 0.6565 | |
| Plasma creatinine (µmol/L) | 193 | | 89 (66-131) | 69 (56-84) | 134 (103-194) | | 77 (62-95) | | **<0.0001** | **<0.0001** | |
| eGFR (CKD-EPI) (ml/min/1.73 m²) | 193 | | 67.7 (41.1-89.3) | 90.4 (79.6-102.2) | 39.9 (24.9-53.1) | | 81.7 (65.9-94.8) | | **<0.0001** | **<0.0001** | |
| AST (ULN) | 474 | | 1.1 (0.7-1.6) | 1.1 (0.8-1.7) | 1.0 (0.7-1.6) | | 1.1 (0.8-1.6) | | 0.3766 | 0.1797 | |
| ALT (ULN) | 439 | | 0.6 (0.4-1.0) | 0.8 (0.5-1.2) | 0.6 (0.4-0.9) | | 0.6 (0.5-1.0) | | **<0.0001** | **<0.0001** | |
| GGT (ULN) | 592 | | 0.9 (0.5-1.8) | 1.0 (0.6-2.0) | 0.9 (0.5-1.7) | | 0.9 (0.6-1.8) | | **0.0357** | **0.0184** | |
| Hemoglobin (g/dL) | 67 | | 12.7 (11.3-14.2) | 13.5 (12.2-14.5) | 12.0 (10.7-13.4) | | 13.0 (11.7-14.4) | | **<0.0001** | **<0.0001** | |
| White blood cell count (103/mm3) | 70 | | 6570 (5000-8820) | 5850 (4600-8280) | 6700 (5100-9160) | | 6600 (5000-8790) | | **0.0004** | **<0.0001** | |
| Lymphocyte count (103/mm3) | 150 | | 990 (690-1400) | 1100 (780-1500) | 920 (620-1365) | | 1000 (700-1400) | | **<0.0001** | **<0.0001** | |
| Platelet count (103/mm3) | 71 | | 201 (155-260) | 203 (160-244) | 198 (150-260) | | 203 (158-263) | | 0.1775 | 0.9227 | |
| LDH (UI/L) | 1328 | | 348 (262-494) | 336 (268-462) | 341 (261-469) | | 360 (260-504) | | 0.2477 | 0.6903 | |
| CPK (UI/L) | 1376 | | 132 (66-305) | 107 (59-234) | 165 (73-350) | | 117 (63-279) | | **0.0002** | **0.0005** | |
| C-reactive protein (mg/L) | 184 | | 86 (40-148) | 77 (38-136) | 86 (42-147) | | 88 (41-151) | | 0.2285 | 0.1566 | |
| Fibrinogen (g/L) | 1339 | | 6.3 (5.0-7.4) | 6.2 (5.0-7.4) | 6.1 (4.8-7.3) | | 6.3 (5.0-7.5) | | 0.2703 | 0.6901 | |
| Death by day 28 after admission | 0 | 569 (21%) | | 31 (10%) | 308 (30%) | | | 230 (16%) | **<0.0001** | **<0.0001** |

## No Micro – patients with ascertained microvascular status and no severe diabetic retinopathy (DR) and no diabetes kidney disease (DKD) and no diabetic foot ulcer (DFU). Any Micro – patients with ascertained microvascular status and at least one complication among severe DR, DKD and DFU. DR corresponds to active or past severe non-proliferative or proliferative DR. DKD, diabetic kidney disease, defined as proteinuria and/or eGFR below 60 ml/min. DFU, active or past diabetic foot ulcer (see definitions in methods). Also applies to subsequent tables.

## AST/ALT: aspartate/alanine aminotransferase; GGT: gamma glutamyl transferase; LDH: lactodehydrogenase; CPK: creatine phosphokinase

**Table 2. Clinical and biological characteristics of ABCD COVID-19 participants according to microvascular status**

|  | **Lacking** | **All (n=2713)** | | **no MICRO (n=346)** | **any MICRO (n=968)** | ***P* value**  **(no MICRO vs. any MICRO)** |
| --- | --- | --- | --- | --- | --- | --- |
| Sex (male), n (%) | 0 | 1725 (64%) | | 213 (62%) | 606 (63%) | 0.7312 |
| Age (years) | 0 | 71 (61-80) | | 64 (56-72) | 75 (66-83) | **<0.0001** |
| Type of diabetes, n (%) | 0 |  | |  |  | 0.8414 |
| type 1 |  | 58 (2%) | | 12 (3%) | 29 (3%) |  |
| type 2 |  | 2466 (91%) | | 313 (90%) | 874 (90%) |  |
| Other |  | 189 (7%) | | 21 (6%) | 65 (7%) |  |
| BMI (kg/m2) | 321 | 28.4 (25.0-32.4) | | 28.9 (25.6-33.5) | 28.4 (25.1-32.5) | 0.0647 |
| diabetes duration (years) | 1020 | 11.0 (5.0-20.0) | | 10.0 (5.0-16.0) | 15.0 (10.0-23.0) | **<0.0001** |
| HbA1c (%) | 996 | 7.7 (6.8-8.9) | | 7.8 (6.8-9.0) | 7.6 (6.8-8.7) | 0.1319 |
| HbA1c (mmol) |  | 60.7 (50.8-73.8) | | 61.8 (50.8-74.9) | 59.6 (50.8-71.6) | 0.1319 |
| Hypertension, n (%) | 26 | 2093 (78%) | | 234 (68%) | 859 (89%) | **<0.0001** |
| Smoking status, n (%) | 496 |  | |  |  | 0.0508 |
| never- |  | 1343 (61%) | | 208 (65%) | 471 (58%) |  |
| former or current |  | 874 (39%) | | 114 (35%) | 337 (42%) |  |
| Time between symptom onset and hospital admission (days) | 52 | 5.0 (2.0-9.0) | | 7.0 (3.0-10.0) | 4.0 (2.0-7.0) | **<0.0001** |
| Dyspnea, n (%) | 40 | 1713 (64%) | | 230 (67%) | 597 (62%) | 0.0991 |
| Positive SARS-CoV-2 PCR, n (%) | 89 | 2474 (94%) | | 323 (95%) | 890 (95%) | 0.8292 |
| Admission plasma glucose (g/L) | 1215 | | 9.4 (7.0-13.3) | 9.8 (6.9-12.8) | 9.3 (6.9-13.6) | 0.8734 | | |
| Plasma creatinine (µmol/L) | 193 | | 89.0 (66.0-130.7) | 70.0 (56.0-84.0) | 135.9 (106.8-197.0) | **<0.0001** | | |
| eGFR (CKD-EPI) (ml/min/1.73 m²) | 193 | | 67.7 (41.1-89.3) | 90.1 (78.7-102.5) | 38.8 (24.5-51.2) | **<0.0001** | | |
| AST (ULN) | 474 | | 1.1 (0.7-1.6) | 1.1 (0.8-1.6) | 1.0 (0.7-1.6) | 0.2146 | | |
| ALT (ULN) | 439 | | 0.6 (0.4-1.0) | 0.8 (0.5-1.1) | 0.6 (0.4-0.9) | **<0.0001** | | |
| GGT (ULN) | 592 | | 0.9 (0.5-1.8) | 1.0 (0.6-2.0) | 0.9 (0.5-1.7) | 0.1433 | | |
| Hemoglobin (g/dL) | 67 | | 12.7 (11.3-14.2) | 13.4 (12.2-14.5) | 12.0 (10.6-13.4) | **<0.0001** | | |
| White blood cell count (103/mm3) | 70 | | 6570 (5000-8820) | 6000 (4670-8550) | 6700 (5100-9130) | **0.0006** | | |
| Lymphocyte count (103/mm3) | 150 | | 990 (690-1400) | 1100 (785-1505) | 910 (600-1340) | **<0.0001** | | |
| Platelet count (103/mm3) | 71 | | 201 (155-260) | 203 (164-248) | 197 (149-258) | 0.5355 | | |
| LDH (UI/L) | 1328 | | 348 (262-494) | 336 (268-454) | 342 (261-476) | 0.6558 | | |
| CPK (UI/L) | 1376 | | 132 (66-305) | 110 (60-262) | 168 (74-349) | **0.0012** | | |
| C-reactive protein (mg/L) | 184 | | 86 (40-148) | 77 (37-130) | 87 (42-149) | **0.0329** | | |
| Fibrinogen (g/L) | 1339 | | 6.3 (5.0-7.4) | 6.2 (5.0-7.4) | 6.1 (4.8-7.3) | 0.6396 | | |
| Death by day 28 after admission | 0 | 569 (21.0%) | | 35 (10.1 %) | 304 (31.4 %) | **<0.0001** | |

## No Micro – patients with ascertained microvascular status and no severe diabetic retinopathy (DR) and no diabetes kidney disease (DKD) and no diabetic foot ulcer (DFU). Any Micro – patients with ascertained microvascular status and at least one complication among severe DR, DKD and DFU. DR corresponds to active or past severe non-proliferative or proliferative DR. DKD, diabetic kidney disease, defined as proteinuria and/or eGFR below 60 ml/min. DFU, active or past diabetic foot ulcer (see definitions in methods). Also applies to subsequent tables.

## AST/ALT: aspartate/alanine aminotransferase; GGT: gamma glutamyl transferase; LDH: lactodehydrogenase; CPK: creatine phosphokinase

**Table 3. Details of microvascular status in CORONADO patients**

|  | **All (n=2,713)** | **no MICRO (n = 304)** | **any MICRO (n = 1,010)** | **not ascertained (n = 1,399)** |
| --- | --- | --- | --- | --- |
| Diabetic retinopathy, n (%) |  |  |  |  |
| No DR | 1798 (66%) | 304 (100%) | 735 (73%) | 759 (54%) |
| Non-severe DR | 160 (6%) | 0 (0%) | 134 (13%) | 26 (2%) |
| Severe DR | 152 (6%) | 0 (0%) | 141 (14%) | 11 (1%) |
| not ascertained | 603 (22%) | 0 (0%) | 0 (0%) | 603 (43%) |
| Diabetic kidney disease, n (%) |  |  |  |  |
| DKD | 1183 (44%) | 0 (0%) | 931 (92%) | 252 (18%) |
| no DKD | 451 (17%) | 304 (100%) | 79 (8%) | 68 (5%) |
| not ascertained | 1079 (40%) | 0 (0%) | 0 (0%) | 1079 (77%) |
| Diabetic foot ulcer, n (%) |  |  |  |  |
| DFU | 185 (7%) | 0 (0%) | 124 (13%) | 61 (4%) |
| no DFU | 2414 (89%) | 346 (100%) | 844 (87%) | 1224 (87%) |
| not ascertained | 114 (4%) | 0 (0%) | 0 (0%) | 114 (8%) |
| Albuminuria, n (%) |  |  |  |  |
| normo- | 484 (18%) | 207 (68%) | 190 (18%) | 87 (6%) |
| micro- | 318 (12%) | 97 (32%) | 186 (18%) | 35 (3%) |
| macro- | 131 (5%) | 0 (0%) | 123 (12%) | 8 (1%) |
| not available | 1780 (66%) | 0 (0%) | 511 (52%) | 1269 (90%) |
| Altered renal function - eGFR < 60 ml/min/1.73 m2, n (%) |  |  |  |  |
| No | 1501 (55%) | 304 (100%) | 112 (11%) | 1085 (78%) |
| Yes | 1148 (43%) | 0 (0%) | 898 (89%) | 250 (18%) |
| not available | 64 (2%) | 0 (0%) | 0 (0%) | 64 (4%) |

## DR (Diabetic retinopathy) Non-severe DR, active or past mild or moderate non proliferative DR ; Severe DR, active or past severe non proliferative or proliferative DR. DKD, diabetic kidney disease, defined as proteinuria and/or eGFR below 60 ml/min. DFU, active or past diabetic foot ulcer (see definitions in Methods)

**Table 4. Details of microvascular status in ABCD COVID-19 patients**

|  | **All (n=2713)** | **no MICRO (n = 304)** | **any MICRO (n = 1010)** | **not ascertained (n = 1,399)** |
| --- | --- | --- | --- | --- |
| Diabetic retinopathy, n (%) |  |  |  |  |
| No DR | 1798 (66%) | 304 (88%) | 735 (76%) | 759 (54%) |
| Non-severe DR | 160 (6%) | 42 (12%) | 92 (10%) | 26 (2%) |
| Severe DR | 152 (6%) | 0 (0%) | 141 (15%) | 11 (1%) |
| not ascertained | 603 (22%) | 0 (0%) | 0 (0%) | 603 (43%) |
| Diabetic kidney disease, n (%) |  |  |  |  |
| DKD | 1183 (44%) | 0 (0%) | 931 (96%) | 252 (18%) |
| no DKD | 451 (17%) | 346 (100%) | 37 (4%) | 68 (5%) |
| not ascertained | 1079 (40%) | 0 (0%) | 0 (0%) | 1079 (77%) |
| Diabetic foot ulcer, n (%) |  |  |  |  |
| DFU | 185 (7%) | 0 (0%) | 124 (13%) | 61 (4%) |
| no DFU | 2414 (89%) | 346 (100%) | 844 (87%) | 1224 (87%) |
| not ascertained | 114 (4%) | 0 (0%) | 0 (0%) | 114 (8%) |
| Albuminuria, n (%) |  |  |  |  |
| normo- | 484 (18%) | 236 (68%) | 161 (16%) | 87 (6%) |
| micro- | 318 (12%) | 110 (32%) | 173 (18%) | 35 (3%) |
| macro- | 131 (5%) | 0 (0%) | 123 (13%) | 8 (1%) |
| not available | 1780 (66%) | 0 (0%) | 511 (53%) | 1269 (90%) |
| Altered renal function - eGFR < 60 ml/min/1.73 m2, n (%) |  |  |  |  |
| No | 1501 (55%) | 346 (100%) | 70 (7%) | 1085 (78%) |
| Yes | 1148 (43%) | 0 (0%) | 898 (93%) | 250 (18%) |
| not available | 64 (2%) | 0 (0%) | 0 (0%) | 64 (5%) |

## DR (Diabetic retinopathy) Non-severe DR, active or past mild or moderate non proliferative DR ; Severe DR, active or past severe non proliferative or proliferative DR. DKD, diabetic kidney disease, defined as proteinuria and/or eGFR below 60 ml/min. DFU, active or past diabetic foot ulcer (see definitions in Methods)

**Figure legends**

## Figure 1 – Flow chart of the study population

## Figure 2 – Prevalence of components of microvascular complications status among 968 participants with microvascular complications

## Figure 3 – Day-28 death rate according to number of microvascular complications

## Figure 4 – Age- and sex-adjusted odds ratio for death within 28 days after admission