


## RESEARCH ARTICLE

# Characteristics and outcomes of COVID-19 in hospitalized patients with and without diabetes

Abdallah Al-Salameh<sup>1,2</sup>  | Jean-Philippe Lanoix<sup>3</sup> | Youssef Bennis<sup>4</sup> |  
 Claire Andrejak<sup>5</sup> | Etienne Brochot<sup>6</sup> | Guillaume Deschasse<sup>7</sup> | Hervé Dupont<sup>8</sup> |  
 Vincent Goeb<sup>9</sup> | Maité Jaureguy<sup>10</sup> | Sylvie Lion<sup>11</sup> | Julien Maizel<sup>12</sup> |  
 Julien Moyet<sup>7</sup> | Benoit Vaysse<sup>13</sup> | Rachel Desailoud<sup>1,2</sup> | Olivier Garry<sup>14</sup> |  
 Jean-Luc Schmit<sup>3</sup> | Jean-Daniel Lalau<sup>1,2</sup>

<sup>1</sup>Department of Endocrinology, Diabetes Mellitus and Nutrition, Amiens University Hospital, Amiens, France

<sup>2</sup>PériTox = UMR\_I 01, University of Picardy Jules Verne, Amiens, France

<sup>3</sup>Department of Infectious Diseases, Amiens University Hospital, Amiens, France

<sup>4</sup>Laboratory of Clinical Pharmacology, Amiens University Hospital, Amiens, France

<sup>5</sup>Department of Pulmonary diseases, Amiens University Hospital, Amiens, France

<sup>6</sup>Laboratory of Virology, Amiens University Hospital, Amiens, France

<sup>7</sup>Department of Geriatrics, Amiens University Hospital, Amiens, France

<sup>8</sup>Surgical Intensive Care Unit, Amiens University Hospital, Amiens, France

<sup>9</sup>Department of Rheumatology, Amiens University Hospital, Amiens, France

<sup>10</sup>Department of Nephrology, Amiens University Hospital, Amiens, France

<sup>11</sup>Department of Orthopaedics and Traumatology, Amiens University Hospital, Amiens, France

<sup>12</sup>Medical Intensive Care Unit, Amiens University Hospital, Amiens, France

<sup>13</sup>Department of Medical Informatics, Amiens University Hospital, Amiens, France

<sup>14</sup>Department of Epidemiology, Amiens University Hospital, Amiens, France

## Correspondence

Abdallah Al-Salameh, Department of Endocrinology, Diabetes Mellitus and Nutrition, Amiens University Hospital, F-80054, Amiens, France, PériTox = UMR\_I 01, University of Picardy Jules Verne, Amiens, France.  
 Email: al-salameh.abdallah@chu-amiens.fr

## Abstract

**Background:** Coronavirus disease 2019 (COVID-19) is a rapidly progressing pandemic, with four million confirmed cases and 280 000 deaths at the time of writing. Some studies have suggested that diabetes is associated with a greater risk of developing severe forms of COVID-19. The primary objective of the present study was to compare the clinical features and outcomes in hospitalized COVID-19 patients with vs without diabetes.

**Methods:** All consecutive adult patients admitted to Amiens University Hospital (Amiens, France) with confirmed COVID-19 up until April 21st, 2020, were included. The composite primary endpoint comprised admission to the intensive care unit (ICU) and death. Both components were also analysed separately in a logistic regression analysis and a Cox proportional hazards model.

**Results:** A total of 433 patients (median age: 72; 238 (55%) men; diabetes: 115 (26.6%)) were included. Most of the deaths occurred in non-ICU units and among older adults. Multivariate analyses showed that diabetes was associated neither with the primary endpoint (odds ratio (OR): 1.12; 95% confidence interval (CI): 0.66-1.90) nor with mortality (hazard ratio: 0.73; 95%CI: 0.40-1.34) but was associated with ICU admission (OR: 2.06; 95%CI 1.09-3.92,  $P = .027$ ) and a longer length of hospital stay. Age was negatively associated with ICU admission and positively associated with death.

**Conclusions:** Diabetes was prevalent in a quarter of the patients hospitalized with COVID-19; it was associated with a greater risk of ICU admission but not with a significant elevation in mortality. Further investigation of the relationship between COVID-19 severity and diabetes is warranted.

## KEYWORDS

acute respiratory distress syndrome, coronavirus disease 2019 (COVID-19), diabetes, intensive care, mortality, outcome

## 1 | INTRODUCTION

Since December 2019, more than 4 million persons have been infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 280 000 have been killed by the resulting coronavirus disease 2019 (COVID-19). Extrapolating these figures to the total number of people with diabetes worldwide (463 million in 2019<sup>1</sup>) gives a conservative global estimate of 230 000 SARS-CoV-2 infections and 15 000 deaths due to COVID-19 in this population. The actual numbers are probably higher because diabetes is generally reported in about 20% (7.4%-33.8%) of hospitalized patients with COVID-19.<sup>2-4</sup> In some studies in China and the USA, diabetes appears to be associated with more severe course of the COVID-19,<sup>2,5</sup> including poor survival.<sup>6</sup> However, people with diabetes have higher prevalence of hypertension and obesity, and a greater burden of cardiovascular disease than non-diabetic people. Indeed, hypertension and obesity are frequent among COVID-19 patients (50% and 40%, respectively)<sup>7,8</sup> and are associated with more severe course of COVID-19.<sup>8-10</sup> Cardiovascular disease is also associated with an elevated risk of inpatient death among inpatients with COVID-19.<sup>11</sup> Therefore, in order to characterize the probably complex associations between diabetes, co-existing conditions, and COVID-19, we decided to directly compare people with vs without diabetes within the same general population and same hospital context. In a rather small study from China, a comparison of 137 COVID-19 patients without diabetes with 37 COVID-19 patients with diabetes found that the disease was more severe in the diabetic group.<sup>12</sup> However, the characteristics and outcomes of patients in China might not apply to patients from other countries because of differences in ethnicity, genetic backgrounds, lifestyles and demographics. The goal of the present study was therefore to assess the characteristics and outcomes of consecutive hospitalized patients with COVID-19 as a function of the presence or absence of diabetes.

## 2 | PATIENTS AND METHODS

### 2.1 | Study population

We constituted an observational cohort in order to gather information about the possible impact of pretreatment with metformin on the clinical course of COVID-19. The cohort included all consecutive hospitalized adult patients with laboratory-confirmed COVID-19 at Amiens University Hospital (Amiens, France). Confirmed COVID-19 was defined as a nasopharyngeal swab specimen that tested positive in a reverse-transcriptase polymerase-chain-reaction assay. We included all confirmed COVID-19 cases up until April 21st, 2020. Hence, the main inclusion criteria were a confirmed diagnosis of COVID-19 and inpatient admission to Amiens University Hospital. The main exclusion criteria were past or present opposition to data collection by the patient or his/her legal

guardian, outpatient admission (even in confirmed cases of COVID-19), and age under 18.

### 2.2 | Data collection

Specifically trained physicians extracted data on demographics, risk factors, personal medical history, history of diabetes, antidiabetic drug use (including daily doses of metformin and dipeptidyl peptidase 4 inhibitors), medications of special concern (such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)<sup>13</sup>), the main clinical data, routine laboratory results, and outcomes from the hospital's electronic medical records. All data were double-checked by the first and last authors, who vouch for the accuracy of the data. The study was conducted in compliance with good clinical practice guidelines and the French legislation on clinical research and data protection. Furthermore, the study was approved by the local institutional review board (IRB) and registered with the French National Data Protection Commission (*Commission nationale de l'informatique et des libertés* [Paris, France]; reference: PI2020\_843\_0051). Although the requirement for written informed consent was waived by the IRB, patients who expressed their opposition to data collection were excluded. Patient confidentiality was protected by the assignment of an anonymous identifier to each enrolled participant. The identifier was attributed when the data were extracted, and only anonymized data were analysed. It should be noted that due to the study's retrospective, observational design and the inclusion of the entire cohort of consecutive adult patients admitted to Amiens University Hospital, it is probable that some patients had also been included in other studies—especially the CORONADO study (Coronavirus SARS-CoV2 and Diabetes Outcomes; ClinicalTrials.gov identifier NCT04324736) and the DISCOVERY trial (Trial of Treatments for COVID-19 in Hospitalized Adults; ClinicalTrials.gov identifier NCT04315948).

### 2.3 | Outcomes

In order to compare outcomes between the study groups (namely COVID-19 patients with vs without diabetes), we chose a composite primary endpoint comprising admission to the intensive care unit (ICU) or death. Both components were also analysed separately. The secondary endpoints were the need for mechanical ventilation, the occurrence of acute respiratory distress syndrome (ARDS, according to the Berlin definition<sup>14</sup>) recorded on the ICU discharge note, acute coronary syndrome (serum levels of high-sensitivity cardiac troponin I<sub>c</sub> above the 99th percentile for the normal population, with new-onset abnormal features on the electrocardiogram or echocardiogram), acute renal failure (according to the Kidney Disease Improving Global Outcomes guidelines) recorded on the ICU discharge note, documented secondary infection, and the overall length of hospital stay. Vital status and the occurrence of clinical outcomes were last checked on May 1, 2020, for patients who were still hospitalized.

**Statistical analysis:** The cohort was divided into two groups, according to the presence or absence of diabetes. Diabetes was defined as diagnosed, treated diabetes or a glycated haemoglobin (HbA1c) level  $\geq 6.5\%$  (48 mmol/mol) on admission. Baseline demographics and clinical characteristics were expressed as mean  $\pm$  SD or the median [interquartile range (IQR)] for continuous numerical variables and the frequency (percentage) for categorical variables. Between-group comparisons were performed with a Mann-Whitney-Wilcoxon test for numerical variables and a chi-squared test or Fisher's exact test for categorical variables.

Associations between diabetes and the primary endpoint and between diabetes and ICU admission were estimated in a logistic regression analysis. The results were expressed as an odds ratio (OR) [95% confidence interval (CI)]. Model adequacy was checked using the Hosmer and Lemeshow goodness-of-fit test. The variables considered in the multivariable model were sex, age, the presence/absence of hypertension, the presence/absence of cardiovascular or cardiac disease (coronary heart disease, arrhythmia or heart failure), the presence/absence of obesity, the BMI as a numerical variable, the presence/absence of chronic obstructive pulmonary disease (COPD) or sleep apnoea syndrome, a history of chronic kidney disease (CKD), a history of cancer, treatment with ACEIs or ARBs, glycaemia on admission, the white blood cell (WBC) count on admission, the glomerular filtration rate (GFR, estimated with the Modification of Diet in Renal Disease [MDRD] equation) on admission, the serum C-reactive protein (CRP) on admission, and abnormal liver function test results. Liver function tests were categorized according to the number of abnormalities. When liver function tests were not performed on admission, the first in-hospital evaluation was selected. Variables that were associated ( $P \leq .10$ ) with the study endpoints were tested in the multivariable model. The final (parsimonious) model contained the fewest possible number of independent variables besides age, sex and diabetes status.

The association between diabetes and death was assessed in a Cox proportional hazards model. Patients who had not been discharged from the hospital were censored on May 1, 2020. The results were expressed as a hazard ratio (HR) [95%CI]. The final Cox model was tested for violation of the proportional hazards assumption by plotting the scaled Schoenfeld residuals against survival time. The variables considered in the multivariable model were the same as in the logistic regression.

The threshold for statistical significance was set to  $P < .05$ . All statistical tests were two-sided and were performed with the R software (version 4.0.0, R Core Team, R Foundation for Statistical Computing, Vienna, Austria). The *survival* package was used to fit the Cox model and the *forestmodel* package was used to generate forest plots from the logistic regression and Cox models.

### 3 | RESULTS

From the start of the COVID-19 epidemic until April 21st, 2020, 433 patients were admitted to Amiens University Hospital with

COVID-19. The patients' baseline characteristics are summarized according to the presence or absence of diabetes in Table 1. There were 115 patients with diabetes (26.6%), 317 patients without diabetes; and 1 patient whose diabetes status was unknown. The proportion of males was 63% in the diabetic group and 52% the non-diabetic group. The mean  $\pm$  SD age was  $72 \pm 14.3$  years in the diabetic group (median: 72 years) and  $70.6 \pm 16.4$  years in the non-diabetic group (median: 73 years). Patients with diabetes had a significantly higher body mass index (BMI) than patients without diabetes. Furthermore, patients with diabetes were more likely to have hypertension, hyperlipidaemia, cardiovascular disease and chronic kidney disease and more likely to be treated with ARBs than those without diabetes. On admission, median glycaemia in the diabetic group (8.3 mmol/L) was higher than in the non-diabetic group (6.3 mmol/L;  $P < .001$ ), and the median GFR was lower ( $71.5$  vs  $85$  mL/min/1.73 m<sup>2</sup>, respectively;  $P < 0.001$ ). The two groups did not differ with regard to the other laboratory results (WBC count, lymphocyte count and CRP).

The diabetic group was composed of 111 patients (96.5%) with type 2 diabetes, three patients with type 1 diabetes, and one patient with gestational diabetes. The mean duration of diabetes was  $8 \pm 9.4$  years (median: 5 years) and mean HbA1c level was  $7.5\% \pm 1.67$  (median: 7.1%). Metformin was the most widely prescribed anti-diabetic medication (used by 71 patients [61.7%]), followed by insulin (33 patients [28.7%]) and dipeptidyl peptidase 4 inhibitors (27 patients [23.5%]). Glinides, sulphonylureas, and glucagon-like peptide-1 analogues were employed much less frequently (by 17, 15 and 9 patients, respectively). Forty-four patients were taking one antidiabetic medication (monotherapy), 32 were taking two medications, 16 were taking three medications, and four patients taking four medications. Lastly, 19 patients were being treated with lifestyle measures alone.

Over the study period, 181 patients met the primary endpoint: 51 in the diabetic group and 129 in the non-diabetic group (OR [95% CI] for the diabetic group: 1.16 [0.75-1.79];  $P = .50$ ; Table 2). A total of 114 patients were admitted to the ICU: 40 in the diabetic group (35.1% of those admitted to the ICU) and 73 in the non-diabetic group (OR: 1.78 [1.12-2.83];  $P = .015$ ). The diabetic and non-diabetic groups did not differ with regard to the Simplified Acute Physiology Score on admission to the ICU. The mean age of people admitted to the ICU was  $62.2 \pm 12.6$  (median [IQR]: 63.5 [55-71]). Overall, 89 patients died: 20 in the diabetic group, 68 in the non-diabetic group (OR: 0.77 [0.44-1.32];  $P = .36$ ), and the patient whose diabetes status was unknown. Twenty-one of the deaths (23.6%) occurred in the ICU. Overall, the mean age at death in hospital was  $80.5 \pm 10.9$  (median [IQR]: 83 [73-88]), which was considerably greater than the value for patients admitted to the ICU. Other outcomes are presented in Table 2. Patients with diabetes had higher risk of developing ARDS and acute renal injury, whereas the groups did not differ in terms of the incidence of cardiac injury and a documented secondary infection. The mean length of stay was  $17.1 \pm 11.7$  days in the diabetic group and  $13.5 \pm 9.1$  days in the non-diabetic group. As of May 1, 2020, 30 non-diabetic patients and 17 diabetic patients were still hospitalized.

**TABLE 1** Characteristics of patients with vs without diabetes at baseline

Characteristic	No diabetes (N = 317)		Diabetes (N = 115)		P value	Test
	Median [IQR] or n (%)	Missing data	Median [IQR] or n (%)	Missing data		
Age (year)	73 [59-84]		72 [63.5-83]		.64	Mann-Whitney-Wilcoxon test
Males	165 (52.1%)		73 (62.6%)		.051	Chi-squared test
BMI (kg/m <sup>2</sup> )	27.1 [22-32]	81	28.2 [25.6-31.9]	22	<b>.04</b>	Mann-Whitney-Wilcoxon test
BMI class		81		22	<b>.019</b>	Chi-squared test
<18.5	18 (5.7%)		2 (1.7%)			
18.5-24.99	75 (23.7%)		20 (17.4%)			
25-29.99	56 (17.7%)		34 (29.6%)			
>30	87 (27.4%)		37 (32.2%)			
Smoking history		103		36	.74	Fisher's exact test
Never	137 (43.2%)		51 (44.3%)			
Former smoker	63 (19.9%)		25 (21.7%)			
Current smoker	14 (4.4%)		3 (2.6%)			
Comorbidities						
Arterial hypertension	164 (51.7%)	1	91 (79.1%)		<b>&lt;.001</b>	Chi-squared test
Hyperlipidaemia	82 (25.9%)	1	64 (55.7%)		<b>&lt;.001</b>	
Total CVD	99 (31.2%)	1	49 (42.6%)		<b>.029</b>	
Atherosclerotic CVD	67 (21.1%)		33 (28.7%)		.10	
Cardiac disease	74 (23.3%)	1	40 (34.8%)	1	<b>.016</b>	
SAS	14 (4.4%)		7 (6.1%)		.48	
COPD	33 (10.4%)		6 (5.2%)		.10	
CKD	33 (10.4%)		33 (28.7%)		<b>&lt;.001</b>	
Cancer	52 (16.4%)		20 (17.4%)	1	.78	
Main symptoms of COVID-19						
Cough	150 (47.3%)	8	52 (45.2%)	2	.65	Chi-squared test
Fever	217 (68.5%)	9	69 (60%)	2	.067	
Renin-angiotensin-aldosterone system inhibitors						
ACEIs	54 (17%)		28 (24.3%)		.087	Chi-squared test
ARBs	35 (11%)		24 (20.9%)		<b>.009</b>	
Main laboratory findings						
HbA1c	7.1% [6.5-8.1]		NA		NA	NA
Glycemia (mmol/l)	6.3 [5.6-7.3]	30	8.3 [6.5-11.8]	9	<b>&lt;.001</b>	Mann-Whitney-Wilcoxon test
GFR (MDRD) (ml/min/1.73 m <sup>2</sup> )	85 [60-111]	4	71.5 [40.5-88.5]	1	<b>&lt;.001</b>	
ALAT > 40 U/L	98 (30.9%)	30	29 (25.2%)	12	.27	Chi-squared test
ASAT > 40 U/L	161 (50.8%)	32	50 (43.5%)	13	.19	
GGT > ULN	147 (45.4%)	38	37 (32.2%)	20	<b>.033</b>	
WBC count (per mm <sup>3</sup> )	6400 [4800-9100]	5	6700 [5425-8900]	1	.36	Mann-Whitney-Wilcoxon test
Lymphocyte count (per mm <sup>3</sup> )	800 [600-1200]	5	900 [600-1200]	1	.95	
CRP mg/L	87 [35.1-152]	5	83.1 [32.6-162.7]	2	.87	

Note: Bold values represent statistically significant p values.

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ALAT, alanine transaminase; ARB, angiotensin-receptor blocker; ASAT, aspartate transaminase; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; GFR (MDRD), glomerular filtration rate as estimated by the Modification of Diet in Renal Disease equation; GGT, gamma-glutamyltranspeptidase; IQR, interquartile range; NA, not applicable; SAS, sleep apnoea syndrome; ULN, upper limit of normal; WBC, white blood cell.

**TABLE 2** Disease outcomes and important findings in people with and without diabetes

Characteristics	No diabetes N = 317		Diabetes N = 115		P value	Test	OR <sup>a</sup> [95%CI]	
	n (%) or median [IQR]	Missing data	n (%) or median [IQR]	Missing data				
<b>Main outcomes</b>								
Composite endpoint	<b>129 (40.7%)</b>		<b>51 (44.3%)</b>		.50	Chi-squared test	<b>1.16 (0.75-1.79)</b>	
Death	<b>68 (21.5%)</b>		<b>20 (17.4%)</b>		.36	Chi-squared test	<b>0.77 (0.44-1.32)</b>	
In the ICU	12 (3.8%)		9 (7.8%)					
Outside the ICU	56 (17.7%)		11 (9.6%)					
ICU admission	<b>73 (23%)</b>		<b>40 (34.8%)</b>		.015	Chi-squared test	<b>1.78 (1.12-2.83)</b>	
Intubation	49 (15.5%)	7	30 (26.1%)	1	.014			
<b>Clinical severity</b>								
SAPS II score	43.5 [30-67.3]	13	55.5 [32.5-68.3]	10	.43	Mann-Whitney-Wilcoxon test	NA	
<b>Secondary endpoints</b>								
ARDS	<b>49 (15.5%)</b>	<b>1</b>	<b>31 (27%)</b>		.007	Chi-squared test	<b>2.01 (1.20-3.35)</b>	
Acute renal injury	<b>62 (19.6%)</b>	<b>1</b>	<b>36 (31.3%)</b>		.01		<b>1.87 (1.15-3.01)</b>	
Documented secondary infection	<b>72 (22.7%)</b>	<b>2</b>	<b>25 (21.7%)</b>	<b>1</b>	.84		0.95 (0.56-1.57)	
Cardiac injury	<b>26 (8.2%)</b>	<b>1</b>	<b>11 (9.6%)</b>		.66		1.18 (0.54-2.41)	
Troponin I c > ULN (53 ng/L for men, 38 ng/L for women)	65 (20.5%)	133	29 (25.2%)	48	.30		NA	
<b>Length of stay</b>								
Length of stay for all patients		<b>11 (7-18)</b>		<b>14 (8-25)</b>		.007	Mann-Whitney-Wilcoxon test	NA
Length of stay for discharged patients		10 (6-15)	30 <sup>b</sup>	11 (86-18)	17 <sup>b</sup>	.069		NA

Note: Bold values represent statistically significant *p* values.

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; IQR, interquartile range; NA, not applicable; OR, odds ratio; SAPS, simplified acute physiology score; ULN, upper limit of normal.

<sup>a</sup>The ORs [95%CI] were obtained in univariable logistic regressions.

<sup>b</sup>These numbers refer to non-discharged patients.

Diabetes was not associated with the primary outcome in the non-adjusted analysis or in the multivariable logistic regression analysis (OR [95%CI]: 1.12 [0.66-1.90]; *P* = .67). Variables that were significant in the parsimonious model are shown in Figure 1. It should be noted that the removal of obesity from the parsimonious model did not modify the results significantly (Figure S1).

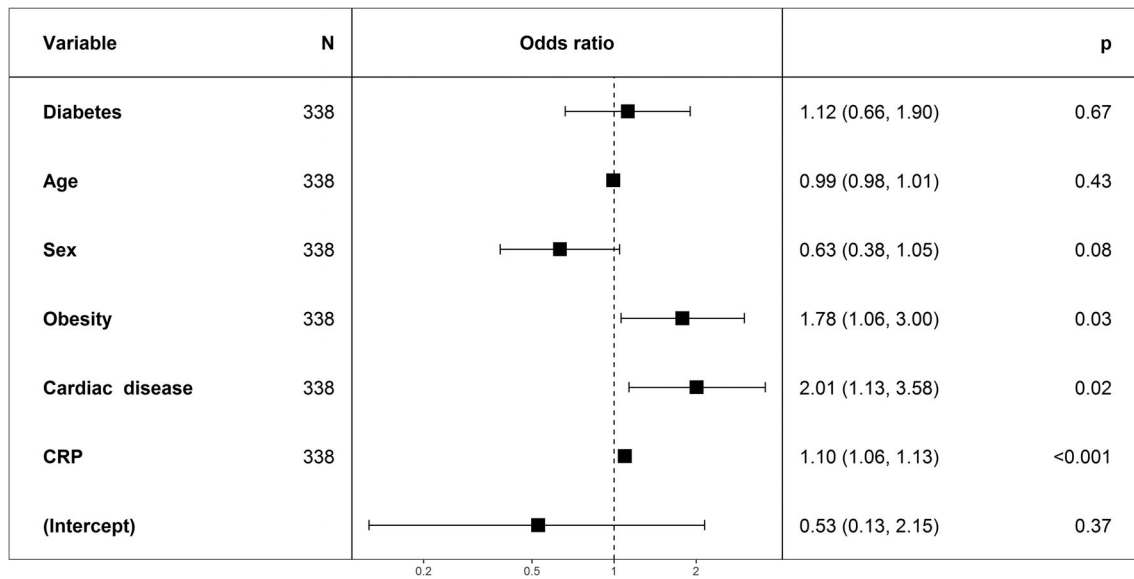
Diabetes was associated with ICU admission in the non-adjusted analysis (OR [95%CI]: 1.78 [1.12-2.83]; *P* = .015) and remained a significant factor in the multivariable model (OR [95%CI]: 2.06 [1.09-3.92]; *P* = .027; Figure 2).

Diabetes was not associated with death in the non-adjusted analysis or in the multivariable Cox model (HR [95%CI]: 0.73 [0.40-1.34]; *P* = .32). Variables that remained significant in the final model are shown in Figure 3, and survival curves from the multivariable model (stratified by the presence/absence of diabetes) are shown in Figure S2. It is noteworthy that glycaemia on admission did not emerge as a significant outcome predictor in any of the multivariable models. Moreover, none of the antidiabetic medications was significantly associated with the primary endpoint in the univariable analysis (Table S1).

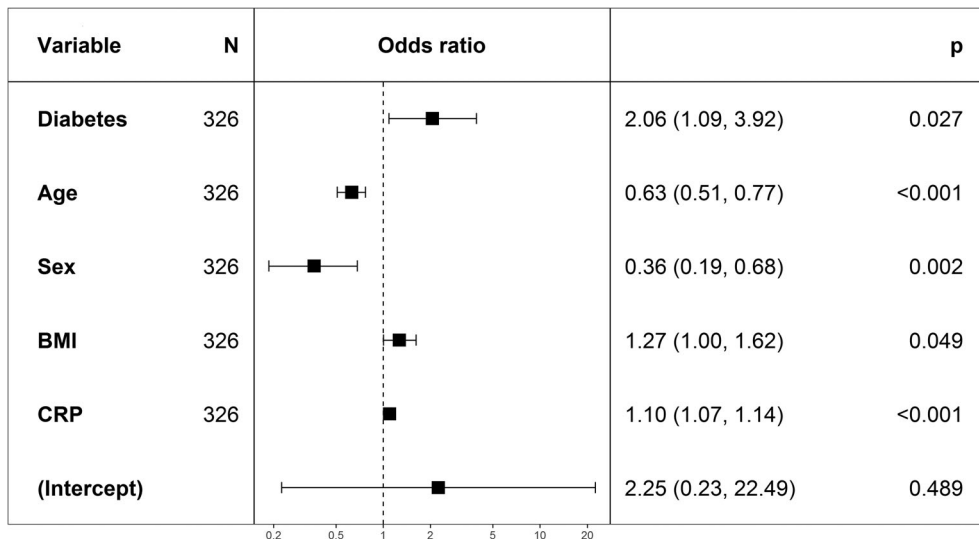
## 4 | DISCUSSION

The main findings of our study are as follows. Firstly, diabetes was present in 26.6% of patients hospitalized with COVID-19; this proportion is considerably higher than the prevalence of diabetes in Amiens University Hospital's referral area (5.53% in 2013 and ≈6% in 2016). Secondly, COVID-19 with diabetes was significantly associated with a greater likelihood of admission to the ICU (relative to COVID-19 without diabetes) but was not associated with increased mortality. Thirdly, COVID-19 with diabetes was also associated with a higher risk of developing ARDS and acute renal injury, relative to COVID-19 without diabetes. Lastly, the median length of stay was longer in COVID-19 patients with diabetes than in COVID-19 patients without diabetes.

Most cases of COVID-19 are mildly symptomatic or even asymptomatic. As such, these cases may not be detected or are managed by a general practitioner or in an outpatient setting. However, pneumonia and severe symptoms occur in about 15% of cases of COVID-19.<sup>15</sup> Patients with severe COVID-19 are usually admitted to hospital



**FIGURE 1** Factors significantly associated with the composite endpoint (death or admission to the ICU) in a multivariable logistic regression analysis. Diabetes (yes, no); age (years); sex (female vs male); obesity (yes if BMI  $\geq 30$  kg/m<sup>2</sup>, no); cardiac disease (coronary heart disease, arrhythmia or heart failure); and serum C-reactive protein (CRP) on admission (per 10 mg/L). The ORs [95%CI] were obtained in multivariable logistic regressions



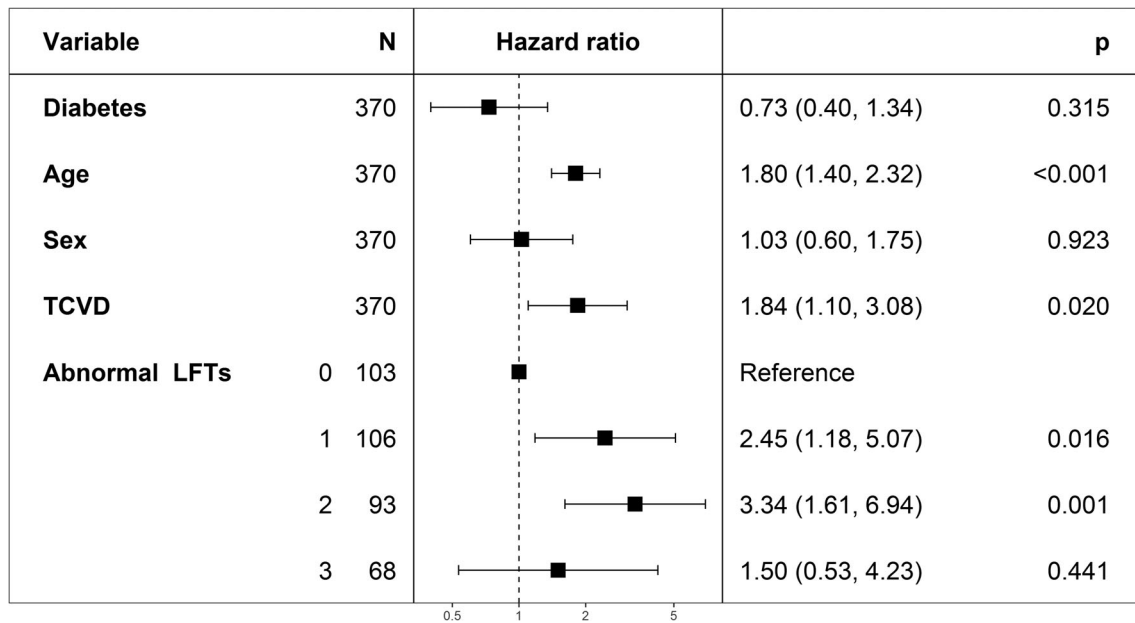
**FIGURE 2** Factors significantly associated with admission to the ICU in a multivariable logistic regression analysis. Diabetes (yes, no); age (per 10 years); sex (female vs male); BMI, body mass index as a numerical variable (per 5 kg/m<sup>2</sup>); and serum C-reactive protein (CRP) on admission (per 10 mg/L). The ORs [95%CI] were obtained in multivariable logistic regressions

for monitoring and treatment. Diabetes is one of the most common comorbidities in patients hospitalized with COVID-19, since most large studies have reported that diabetes is present in 19% to 34% of this patient population.<sup>4,6</sup> Our results are in line with the literature data because the proportion of hospitalized COVID-19 patients with diabetes in our cohort was significantly greater than the prevalence of diabetes in the local population. Another 5% of COVID-19 patients develop critical disease with respiratory failure and/or multiple organ dysfunction. These patients typically require admission to the ICU. Our results confirm that diabetes is a common comorbidity among COVID-19 patients admitted to the ICU (a third of all ICU admissions in our cohort). In a large study in the Lombardy region of Italy, diabetes was present in 17% of patients admitted to the ICU.<sup>7</sup> Interestingly,

data on 7162 COVID-19 patients from the United States showed that diabetes was present in 6% of non-hospitalized patients, 24% of hospitalized patients, and 32% of those admitted to the ICU.<sup>8</sup>

Our results show that diabetes is significantly associated with ICU admission and the development of ARDS and acute renal injury. At the time of ICU admission, diabetic and non-diabetic patients had a similar Simplified Acute Physiology Score II; this suggests that the COVID-19 was not more severe in the diabetic group and does not support the application of a lower threshold for ICU referral among diabetic patients. Indeed, type 2 diabetes is associated with obesity, insulin resistance, and low grade inflammation; these factors may result in immune dysregulation and more severe COVID-19. In one study, mice were made susceptible to Middle East respiratory syndrome





**FIGURE 3** Factors significantly associated with death in a multivariable Cox proportional hazards analysis. Age (per 10 years); sex (female vs male); total cardiovascular disease (TCVD: yes, no); abnormal liver function tests (Abnormal LFTs: no abnormal tests, one abnormal test, two abnormal tests, or three abnormal tests). The HRs [95%CI] were obtained in multivariable Cox's proportional hazards analyses

coronavirus (via the expression of human dipeptidyl peptidase-4) and given a high fat diet to induce diabetes. The mice showed delayed but prolonged, severe inflammation of the lungs upon infection.<sup>16</sup> It remains to be seen whether these observations are of relevance to COVID-19. Interestingly, people with diabetes have elevated urine levels of ACE 2, the SARS-CoV-2's co-receptor for cell entry.<sup>17</sup>

The relationship between diabetes and our present study endpoints was independent of obesity (as a categorical variable) and BMI (as a continuous variable). Indeed, obesity is one of the main underlying conditions in patients with COVID-19, and is associated with an elevated risk of hospital admission<sup>18</sup> and with worse inpatient outcomes<sup>19</sup> (eg, invasive mechanical ventilation<sup>9</sup> and mortality<sup>20</sup>). The mechanisms responsible for the poor prognosis in obese people with COVID-19 include obesity-related respiratory dysfunction, low-grade systemic inflammation, and complement system hyperactivation. Moreover, it has been suggested that adipose tissue accumulation within the lungs has a detrimental local effect.<sup>21</sup>

Our most striking finding is that diabetes was not associated with greater risk of in-patient death, despite a longer hospital stay. In a small study from China, diabetes was associated with an increased risk of death in a univariable analysis (OR [95%CI]: 2.85 [1.35-6.05];  $P = .0062$ ) but was not selected for multivariable analysis.<sup>6</sup> Notably, the patients' median age was 56 years in the Chinese study and 72 in the present study. Furthermore, a recent meta-analysis and systematic review found that diabetes was associated with an elevated relative risk (RR) [95%CI] of death (2.12 [1.44-3.11]). The review's authors suggested that the RR was lower in studies with a median age  $\geq 55$  years than in studies with a median age  $< 55$ .<sup>22</sup> It is therefore possible that the RR of death in patients with COVID-19 and diabetes falls with age - a phenomenon that is also encountered for diabetes-related cardiovascular disease,

cardiovascular death,<sup>23</sup> and overall mortality.<sup>24</sup> In our cohort, patients who died were considerably older than those admitted to the ICU; this suggests that younger patients with co-existing diseases (including diabetes) were more frequently referred to the ICU, whereas elder patients were not. This is supported by the fact that more than 75% of deaths in our study (regardless of diabetes status) occurred outside the ICU. In our multivariable analyses, age was positively associated with death but negatively associated with ICU admission.

The main strength of our study relates to its inclusive nature: the inclusion of consecutive patients gave us a true, precise picture of COVID-19 in our region. The fact that the study was undertaken in only one tertiary hospital is also a strength because the criteria for admission to the hospital in general and to the ICU in particular were relatively homogenous. Furthermore, the diabetic group was relatively homogenous, as almost all of the patients had type 2 diabetes.

Our study had the limitations inherently associated with observational studies. Firstly, causality cannot be inferred from an association between variables, and the absence of a statistically significant association does not rule out clinical relevance. Secondly, there were some missing data for important variables, such as BMI and smoking status. Other measures of adiposity (such as waist circumference and neck circumference) were not available. In a recent multicentre study performed in Italy, neck circumference was significantly associated with the need for invasive mechanical ventilation in COVID-19 patients.<sup>25</sup> Thirdly, and despite our adjustment for a large number of variables, residual confounding cannot be ruled out. Lastly, the observational design prevented us from prespecifying the statistical power, and so our results should be considered as being indicative only.

In conclusion, our observational study of all consecutive patients hospitalized with COVID-19 in a tertiary referral centre found that

diabetes was present in a quarter of admissions and was associated with a greater risk of ICU admission and a longer length of stay but not with mortality (relative to non-diabetic patients). Further investigations of the relationship between COVID-19 and diabetes are now warranted, with a focus on (i) the RR of death in COVID-19 patients with vs without diabetes and (ii) the interaction between age and/or diabetes duration on one hand and COVID-19 mortality and other outcomes on the other.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## AUTHOR CONTRIBUTIONS

Abdallah Al-Salameh and Jean-Daniel Lalau designed the study and drafted the manuscript which was revised and then approved by all authors; Abdallah Al-Salameh and Jean-Daniel Lalau had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Analysis and interpretation of data: Abdallah Al-Salameh, Benoit Vaysse, Rachel Desailoud, Olivier Ganry, Jean-Daniel Lalau. Patient recruitment: Jean-Philippe Lanoix, Youssef Bennis, Claire Andrejak, Etienne Brochot, Guillaume Deschasse, Hervé Dupont, Vincent Goeb, Maité Jaureguy, Sylvie Lion, Julien Maizel, Julien Moyet, Benoit Vaysse, Rachel Desailoud, Olivier Ganry, and Jean-Luc Schmit.

## ORCID

Abdallah Al-Salameh  <https://orcid.org/0000-0002-7951-9926>

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## SUPPORTING INFORMATION

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

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