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Clinical characteristics and short-term prognosis of in-patients with diabetes and COVID-19: A retrospective study from an academic center in Belgium

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STRUCTURED ABSTRACT

Background and aims: We describe the characteristics and short-term prognosis of in-patients with diabetes and COVID-19 admitted to a Belgian academic care center.

Methods: We retrospectively reviewed the data on admission from patients with known or newly-diagnosed diabetes and confirmed COVID-19. First, survivors were compared to non-survivors to study the predictive factors of in-hospital death in patients with diabetes. Secondly, diabetic patients with SARS-CoV-2 pneumonia were matched for age and sex with non-diabetic patients with SARS-CoV-2 pneumonia, to study the prognosis and predictive factors of in-hospital death related to diabetes.

Results: Seventy-three diabetic patients were included. Mean age was 69 (± 14) years. Women accounted for 52%. Most patients had type 2 diabetes (89.0%), long-term complications of hyperglycemia (59.1%), and hypertension (80.8%). The case-fatality rate (CFR) was 15%. Non-survivors had more severe pneumonia based on imaging ($p = 0.029$) and were less often treated with metformin ($p = 0.036$). In patients with SARS-CoV-2 pneumonia, CFR was 15.6% in diabetic ($n = 64$) and 25.0% in non-diabetic patients ($n = 128$), the difference being non-significant ($p = 0.194$). Predictive factors of in-hospital death were elevated white blood cells count (HR 9.4, CI 1.50–58.8, $p = 0.016$) and severe pneumonia on imaging (HR 25.0, CI 1.34–466, $p = 0.031$) in diabetic patients, and cognitive impairment (HR 5.80, CI 1.61–20.9, $p = 0.007$) and cardiovascular disease (HR 5.63, CI 1.54–20.6, $p = 0.009$) in non-diabetic patients.

Conclusion: In this monocentric cohort from Belgium, diabetic in-patients with COVID-19 had mostly type 2 diabetes, prevalent hyperglycemia-related vascular complications and comorbidities including hypertension. In this cohort, the CFR was not statistically different between patients with and without diabetes.

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1. Introduction

The novel “coronavirus disease 2019” (COVID-19) has caused more than 38 million cases and 1 million deaths worldwide, as of

October 9, 2020 [1]. Since the onset of the pandemic in Wuhan, China, risks factors for severe and fatal forms of COVID-19 have been identified and include age, male sex, archaic genetic variants (in Eurasians) [2], anomalies of interferon immunity [3,4], and chronic underlying conditions [5,6]. Among the latter, hypertension, cardiovascular disease (CVD), and diabetes are the most frequently reported in both Caucasian and non-Caucasian populations [5,6]. Diabetes in hospitalized patients with COVID-19 was reported in 3–25% of non-critical [7–9], and in 15–58% of critical cases [8–11], respectively. Poorer outcomes, including the onset of

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Abbreviations

ACEI	angiotensin-converting-enzyme inhibitors
ALT	alanine-aminotransferase
ARBs	angiotensin II receptor blockers
AST	aspartate-aminotransferase
BMI	body mass index
CFR	case fatality rate
CI	confidence interval
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CT	computed tomography
CVD	cardiovascular disease
DDP4	dipeptidylpeptidase-4
HbA1c	glycated hemoglobin A1c

HR	hazard ratio
GFR	glomerular filtration rate
GLP1	glucagon-like peptide-1
ICU	intensive care unit
IQR	interquartile range
IVM	invasive mechanical ventilation
LDH	lactate dehydrogenase
NLR	neutrophils-to-lymphocytes ratio
OR	odds ratio
OSA	obstructive sleep apnea
SARS	severe acute respiratory syndrome
SD	standard deviation
SGLT2	sodium/glucose co-transporter type 2
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
WBC	white blood cells count

complications such as ARDS (Acute Respiratory Distress Syndrome), shock, multi-organ failure, and death were reported more frequently in patients with diabetes [8,9]. The case fatality rate (CFR) of COVID-19 in the general population varies from 2 to 15% in severe cases [7–9], to more than 20% and even 50% in critical cases [8–11]. Diabetes increases the odds of in-hospital death by 2 to 3-fold [8,9,12,13].

The respective impacts of diabetes *per se*, chronic hyperglycemia, insulin deficiency and/or resistance, obesity, chronic low-grade inflammation, immune dysfunction, and other preexisting comorbidities in driving poorer outcomes in patients with diabetes are still unclear [8]. Most diabetic patients with severe or critical COVID-19 have type 2 diabetes (T2DM) [14,15]. However, a nationwide study in England showed that both type 1 diabetes (T1DM) and T2DM were independently associated with increased odds of in-hospital death from COVID-19 [37]. Obesity was reported as a risk factor for severe COVID-19 and intensive care unit (ICU) admission in the general population [17,18]. Body mass index (BMI) was the sole preadmission factor positively associated with an adverse composite endpoint of tracheal intubation and death in patients with diabetes in a multicenter study from France [15]. Hypertension and CVD, frequent in patients with diabetes, are also commonly associated with severe and critical forms of COVID-19 [9]. Finally, age, micro- and macrovascular complications of diabetes, as well as obstructive sleep apnea (OSA), were identified as predictive factors of early in-hospital death in patients with diabetes [15].

In Belgium, more than 140,000 cases including 10,000 deaths and 21,000 hospitalizations had been reported as of October 9, 2020 [1,19]. Comorbidities were reported only for in-patients with COVID-19 in whom the mean prevalence of preexisting diabetes reached 21.5% [19]. This figure is more than 3-fold higher than the 6% prevalence found in the adult general population, and the 14% prevalence reported in people older than 65 years according to both a National Health Survey carried out in 2018 [20] and another from the International Diabetes Federation in 2016 [21]. The overall mortality ascribed to COVID-19 in Belgium has been reported jointly for in- and out-patients. At the time of writing this article, mortality in Belgium reached 7% of confirmed cases, with 50% of deaths occurring in nursing homes [19]. However, the characteristics and prognosis of in-patients with diabetes and COVID-19 were not reported so far in Belgium. In this retrospective study, we report the characteristics and short-term prognosis of diabetic in-patients with COVID-19 admitted to one academic center during the first 3 months of the pandemic.

2. Patients and methods

2.1. Design and aims of the study

This monocentric retrospective study was performed at the Cliniques Universitaires Saint-Luc in Brussels, Belgium, a tertiary care academic center. The Ethics Committee approved the systematic registration of data from in-patients with confirmed COVID-19 in an institutional registry (N° CEHF 2020/06AVR/201) in order to provide epidemiological data to the Belgian Public Health Institute (Sciensano). COVID-19 was confirmed on the basis of a positive SARS-CoV-2 RT-PCR test on nasopharyngeal swab and/or a chest computed tomography (CT) consistent with SARS-CoV-2 pneumonia. The Ethics Committee approved the present study and waived informed consent due to its retrospective design (N° CEHF 2020/22MAI/290).

In the first part of this study, patients with known or newly-diagnosed diabetes (HbA1c $\geq$ 6.5% on admission) who were admitted from March 1, 2020 to May 6, 2020 were identified within the institutional registry. Seventy-three patients with diabetes (21.2%) were identified among 345 patients hospitalized with COVID-19. All had an unequivocal issue related to COVID-19 (discharge or death) and were included in the study. Seventy patients (95.9%) had a positive SARS-CoV-2 RT-PCR and 64 patients (87.7%) had SARS-CoV-2 pneumonia on admission (infiltrates on either chest x-ray or chest-CT). Our primary aim was to describe the clinical, biological, and radiological characteristics on admission and the short-term prognosis of these patients with diabetes and COVID-19 admitted in a Belgian academic care center.

In the second part of this study, the 64 diabetic patients with SARS-CoV-2 pneumonia were compared to 128 non-diabetic patients with SARS-CoV-2 pneumonia matched for age (± 2 –3 years) and sex. Our secondary aim was to describe the similarities or differences in clinical, biological, and radiological characteristics on admission, short-term prognosis and risk factors for in-hospital death between diabetic patients and age- and sex-matched non-diabetic patients with SARS-CoV-2 pneumonia.

Pregnant women or patients with preexisting glucocorticoid-induced abnormal glucose homeostasis were excluded from the study.

2.2. Data abstraction

Demographics, clinical, biological, and radiological data on admission of patients with and without diabetes were extracted

from the institutional registry and systematically cross-checked with the electronic medical records. Demographic and clinical data included age, sex, type and duration of diabetes, micro- and macrovascular complications related to diabetes (retinopathy, nephropathy, neuropathy, foot ulcer, and ischemic heart disease, peripheral arterial disease, ischemic cerebrovascular disease, respectively), comorbidities such as hypertension, CVD, OSA, chronic kidney disease (CKD), chronic liver disease, and cognitive impairment, duration and type of COVID-19 symptoms, as well as current medications. The severity of COVID-19 was defined as follows: mild: symptoms of upper respiratory infection (fever, headache, myalgia, cough, sore throat) and/or digestive symptoms (nausea, vomiting, abdominal pain, diarrhea); moderate: clinical and radiological pneumonia (infiltrates) without hypoxemia; and severe: clinical and radiological pneumonia with hypoxemia (oxygen saturation < 93%); critical: admission to the ICU required [22]. Patients deemed not suitable for ICU admission and invasive procedures including cardiopulmonary resuscitation owing to older age and/or comorbidities were identified. Levels of care in our hospital are adapted from the INESSS from Québec [23].

Biological data on admission included glycated hemoglobin A1c (HbA1c) level (on admission or in the previous 6 months), plasma glucose level, white blood cells count (WBC), lymphocytes count, neutrophils-to-lymphocytes ratio (NLR), platelets count, C-reactive protein (CRP), glomerular filtration rate (GFR) calculated by the CKD-EPI formula, lactate dehydrogenase (LDH), aspartate-aminotransferase (AST), and alanine-aminotransferase (ALT).

The radiological severity of SARS-CoV-2 pneumonia on admission was based on the extent of lung surface area showing lesions on chest-CT, and defined as follows: mild-to moderate ($\leq 25\%$ of the lung area) or extended to critical ($> 25\%$ of the lung area) [24]. SARS-CoV-2 RT-PCR was performed on nasopharyngeal swabs with genegig® Real-Time RT-PCR assay (Primerdesign Ltd, Chandler's Ford, United Kingdom), which allows for the detection of viral RNA by targeting the RNA-dependent RNA polymerase gene. The amplification was performed on a LightCycle 480 instrument (Roche Diagnostics, Mannheim, Germany). A cycle threshold < 40 was considered as positive.

Treatments for COVID-19 (oxygenotherapy, antibiotics, hydroxychloroquine with or without azithromycin, corticosteroids), and requirement for non-invasive ventilation were recorded as well as ICU admission, requirement for invasive mechanical ventilation (IMV), and complications such as suspected or proven secondary lower respiratory tract infection (proven if positive sputum, tracheal aspirate, urinary pneumococcal antigen and/or FilmArray multiplex PCR). The short-term outcome of COVID-19 (discharge or in-hospital death) and the total length of hospitalization were registered, the latter in survivors only.

2.3. Statistical analysis

Continuous variables are reported as means and standard deviation (SD) or medians and interquartile range (IQR). Discrete variables are described as frequencies and percentages based on the available data. Differences between groups were assessed by Student's T-test or Mann-Whitney test according to the distribution of continuous variables, and by Chi² or Fisher's exact test for discrete variables, as appropriate. Risks factors associated with in-hospital death were assessed in the 192 patients with SARS-CoV-2 pneumonia using a multivariable Cox proportional hazards regression model. Age and sex were not included in the model since patients with and without diabetes were matched for these variables. Before conducting the multivariate analysis, a univariate analysis was performed to select the variables to be introduced into the model ($p < 0.200$). The variables considered for univariate

analysis were selected on the basis of clinical understanding and previous findings from the literature. A backward elimination procedure was used for the multivariate analysis. We also performed Cox regression analyses to identify risk factors for in-hospital death in patients with diabetes and in matched patients without diabetes using the same methodology. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics software version 25.0.

3. Results

3.1. Clinical, biological, and radiological characteristics on admission of patients with diabetes and COVID-19

Patients' characteristics on admission are summarized in Table 1. The mean age was 69 (± 14) years. Women accounted for 52.0% of patients. The mean BMI was 30.5 (± 5.3) kg/m². Ethnicity was Caucasian, Sub-Saharan African or Asian in 79.5%, 16.4%, and 4.1%, respectively (data not shown). Clinical severity was mild to moderate, severe, or critical in 23.3%, 65.8%, and 11.0% of patients, respectively (data not shown). Most patients had T2DM (89.0%), none had T1DM. Secondary diabetes was reported in 3 patients on immunosuppressive therapy for kidney transplantation. Diabetes was newly-diagnosed on admission in 5 patients. Median duration of preexisting diabetes was 11 [5–18] years. The median HbA1c was 7.1 [6.6–8.3] %. Current smoking and dyslipidemia were reported in 2.9% and 80.0% of the patients, respectively (data not shown). Complications of diabetes were reported in 59.1% of the patients. Among these, 43.6% had microvascular complications, 28.2% macrovascular complications, and 28.2% both. Most patients had chronic comorbidities (94.5%), half of them having ≥ 3 . Hypertension (80.8%), CVD (43.8%) and CKD (34.2%) were the most frequent comorbidities. The most frequently-used glucose-lowering and blood pressure-lowering agents were: metformin (66.2%), insulin (45.6%), sulfonylureas/glinides (27.9%), angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin II receptor blockers (ARBs) (61.6%), and diuretics (47.9%). Dipeptidylpeptidase-4 (DPP4) inhibitors were used in 5.9% of the patients. Median duration of symptoms before admission was 7 [4–9] days. Cough (80.6%), fever (65.8%), and dyspnea (63.9%) were the commonest symptoms on admission (data not shown). Chest-CT was performed in 82.2% of the patients of whom 93.3% had ground glass opacity/crazy paving and 47.3% had extended to critical pneumonia based on the surface area of lung injury ($> 25\%$). Treatments consisted of azithromycin (11.0%) and/or other antibiotics (31.5%) and/or hydroxychloroquine (75.3%), and/or glucocorticoids (17.8%) and/or non-invasive ventilation (27.4%).

3.2. Short-term prognosis of in-patients with diabetes and COVID-19

Thirteen patients (17.8%) were admitted to an ICU, 7 (53.8%) of them requiring IMV. The overall CFR was 15%, as 11 patients died. Compared to survivors, non-survivors had more severe pneumonia on the basis of lung surface area involvement on chest-CT ($p = 0.029$), and they were less often treated with metformin prior to admission ($p = 0.036$) and/or with Beta-blockers ($p = 0.046$). No statistically significant difference was found regarding ethnicity, HbA1c, diabetes duration, BMI, current smoking, dyslipidemia, complications of diabetes, duration and type of COVID-19-related symptoms, clinical severity, biological values, rate of positive SARS-CoV-2 RT-PCR, current therapies, and ICU admissions. Comorbidities were as frequent in non-survivors as in survivors, except for cognitive impairment which was more frequent in non-survivors ($p = 0.041$). Non-survivors were older and developed more secondary lower

Table 1

Clinical characteristics and COVID-19-related biological values, radiological data, treatments, and outcomes in patients with diabetes according to vital outcomes.

Variables	All (N = 73)	Survivors (N = 62)	Non-survivors (N = 11)	p value
Age (years)	69 ± 14	67 ± 13	76 ± 16	0.061
Sex female/male	52.0/48.0 (38/35)	55.0/45.0 (34/28)	36.0/64.0 (4/7)	0.334
BMI (kg/m²)	30.5 ± 5.3	30.1 ± 4.9	32.5 ± 7.9	0.236
Diabetes				0.451
Type 2	89.0 (65/73)	87.1 (54/62)	100.0 (11/11)	
Secondary	4.1 (3/73)	4.8 (3/62)	0.0 (0/11)	
Newly-diagnosed	6.9 (5/73)	8.1 (5/62)	0.0 (0/11)	
Diabetes duration (years)	11 [5–18]	12 [5–18.5]	9 [3.6–13.5]	0.449
HbA1c (%)	7.1 [6.6–8.3]	7.1 [6.7–8.3]	6.7 [5.3–8.3]	0.322
Complications of diabetes^a	59.1 (39/66)	58.9 (33/56)	60.0 (6/10)	1.000
Comorbidities	94.5 (69/73)	93.5 (58/62)	100.0 (11/11)	1.000
CVD	43.8 (32/73)	45.2 (28/62)	36.4 (4/11)	0.746
Hypertension	80.8 (59/73)	82.3 (51/62)	72.7 (8/11)	0.431
OSA	19.2 (14/73)	19.4 (12/62)	18.2 (2/11)	1.000
CKD	34.2 (25/73)	33.9 (21/62)	36.4 (4/11)	1.000
Cognitive impairment	20.5 (15/73)	16.1 (10/62)	45.5 (5/11)	0.041
Chronic liver disease	13.7 (10/73)	14.5 (9/62)	9.1 (1/11)	1.000
Glucose-lowering agents				
Metformin	66.2 (45/68)	71.9 (41/57)	36.4 (4/11)	0.036
Sulfonylureas/glinides	27.9 (19/68)	31.6 (18/57)	9.1 (1/11)	0.163
DPP4 inhibitors	5.9 (4/68)	7.0 (4/57)	0.0 (0/11)	1.000
SGLT2-inhibitors	5.9 (4/68)	7.0 (4/57)	0.0 (0/11)	1.000
GLP-1 receptor agonists	7.4 (5/68)	8.8 (5/57)	0.0 (0/11)	0.583
Insulin	45.6 (31/68)	45.6 (26/57)	45.5 (5/11)	1.000
Current medications				
ACEI/ARBs	61.6 (45/73)	64.5 (40/62)	45.5 (5/11)	0.315
Beta-blockers	37.0 (27/73)	41.9 (26/62)	9.1 (1/11)	0.046
Diuretics	47.9 (35/73)	50.0 (31/62)	36.4 (4/11)	0.519
Statins	35.6 (26/73)	33.9 (21/62)	45.5 (5/11)	0.506
Antiplatelet drugs	30.1 (22/73)	32.3 (20/62)	18.2 (2/11)	0.486
COVID-19 symptoms				
Duration before admission (days)	7 [4–9]	7 [4–9]	4 [2–7]	0.093
Area of lung injury				0.044
<25% (mild to moderate)	52.7 (29/55)	58.3 (28/48)	14.3 (1/7)	
>25% (extended to critical)	47.3 (26/55)	41.7 (20/48)	85.7 (6/7)	
Laboratory values	Normal values			
Plasma glucose (mmol/L)	3.8–5.5	9.4 [6.8–13.1]	7.0 [6.2–11.8]	0.227
WBC (10 ³ /μL)	4.0–10.0	6.4 [4.1–8.3]	6.5 [3.6–10.6]	0.725
Lymphocytes (10 ³ /μL)	0.8–5.0	0.9 [0.6–1.2]	0.9 [0.7–1.3]	0.234
Laboratory values	Normal values			
NLR (%)	0.78–3.53	5.4 [3.2–8.8]	3.5 [2.0–6.1]	0.186
Platelets (x10 ³ /μL)	150–450	207 [162–269]	140 [124–250]	0.186
ALT (units/L)	13–35	31 [22–46]	39 [31–54]	0.135
AST (units/L)	7–35	21 [13–40]	24 [14–38]	0.669
LDH (units/L)	<250	323 [239–429]	374 [271–418]	0.542
GFR (ml/min/1.73 m ²) ^b	>60	71 [49–85]	57 [49–78]	0.358
CRP (mg/L)	<5	73 [40–130]	72 [34–193]	0.775
COVID-19-related treatments				
Oxygen therapy	83.6 (61/73)	82.3 (51/62)	90.9 (10/11)	0.678
Hydroxychloroquine	75.3 (55/73)	75.8 (47/62)	72.7 (8/11)	1.000
Azithromycin	11.0 (8/73)	12.9 (8/62)	0.0 (0/11)	0.598
Other antibiotics	31.5 (23/73)	27.4 (17/62)	54.5 (6/11)	0.089
Glucocorticoids	17.8 (13/73)	19.4 (12/62)	9.1 (1/11)	0.676
Non-invasive ventilation	27.4 (20/73)	27.4 (17/62)	27.3 (3/11)	1.000
COVID-19-related complications				
Secondary lung infection	27.4 (20/73)	22.6 (14/62)	54.5 (6/11)	0.060
COVID-19-related outcomes				
Not suitable for ICU admission	30.1 (22/73)	22.6 (14/62)	72.7 (8/11)	0.002
ICU admission	17.8 (13/73)	16.1 (10/62)	27.3 (3/11)	0.401

Data are expressed as means ± SD, medians [IQR], % (n/N), where N is available total number of cases per group. P values < 0.05 are considered as statistically significant. Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin A1c; CVD, cardiovascular disease; OSA, obstructive sleep apnea; CKD, chronic kidney disease; CRP, C-Reactive Protein; DPP4, dipeptidylpeptidase-4; SGLT2, sodium/glucose co-transporter type 2; GLP1, glucagon-like peptide-1; ACEI, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers; WBC, white blood cells; NLR, neutrophils-to-lymphocytes ratio; ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; LDH, lactate dehydrogenase; GFR, glomerular filtration rate; ICU, intensive care unit.

^a Included retinopathy (p 0.655), nephropathy (p.661), neuropathy (p 0.674), peripheral arterial disease (p 0.564), ischemic heart disease (p 0.370), stroke/transient ischemic attack (p 0.123).

^b GFR was calculated by the CKD-EPI formula.

respiratory tract infections during the hospital stay than survivors, but these differences did not reach statistical significance. Patients deemed not suitable for ICU admission and/or invasive procedures accounted for 22.6% of survivors and 72.7% of non-survivors ($p = 0.002$). Consequently, most deaths (72.7%) occurred outside the ICU department (data not shown).

3.3. Clinical, biological, and radiological characteristics on admission of patients with SARS-CoV-2 pneumonia, with and without diabetes

Patients' characteristics on admission are summarized in Table 2. Mean age was 67 (± 14) years, and women accounted for 50.0% of the patients in both groups. We found no difference in ethnicity (patients with diabetes compared to those without diabetes: Caucasians 76.6% vs. 80.8%, Sub-Saharan Africans 18.7% vs. 17.6%, and Asians 4.7% vs. 1.6%, $p = 0.438$, data not shown). Clinical severity on admission was similar in both groups (patients with diabetes compared to those without diabetes: moderate 21.9% vs. 18%, severe 65.6% vs. 68.8%, and critical 12.5% vs. 13.3%, $p = 0.811$, data not shown). Compared to patients without diabetes, patients with diabetes had a higher mean BMI (30.6 ± 5.1 kg/m² vs. 26.8 ± 4.9 kg/m², $p < 0.0001$) and were more often obese (54.1% vs. 21.1%, $p < 0.0001$). Dyslipidemia was more frequent in patients with diabetes than in those without diabetes (80.6% vs. 35.2%, $p < 0.0001$), as were comorbidities such as hypertension (79.6% vs. 51.6%, $p < 0.0001$), OSA (18.7% vs. 7.8%, $p = 0.031$) and CKD (32.8% vs. 13.3%, $p = 0.002$). As a consequence, patients with diabetes took more often ACEI/ARBs (60.9% vs. 24.4%, $p < 0.0001$), diuretics (45.3% vs. 23.4%, $p = 0.003$), and/or statins (34.4% vs. 18%, $p = 0.018$) prior to admission. We found no difference in median duration of COVID-19 symptoms before admission between groups (7 [4–10] days vs. 7 [4–9] days, $p = 0.345$). The prevalence of specific symptoms was comparable between groups, except for cough which was more frequent in patients with diabetes (85.7% vs. 71.1%, $p = 0.031$). Radiological severity of SARS-CoV-2 pneumonia was comparable between groups (patients with diabetes compared to patient without diabetes, extended to critical 47.2% vs. 55.1%, $p = 0.401$). COVID-19 related treatments were also similar in both groups (Table 2). We found no statistically significant difference in current smoking, or in the rate of positive SARS-CoV2-PCR (data not shown).

3.4. Short-term prognosis and risk factors for death in patients with SARS-CoV-2 pneumonia a, with and without diabetes

ICU admission was required in 18.8% of patients in both groups, while 26.6% of the patients from both groups were deemed not suitable for ICU. IMV was required in 58.3% of patients with diabetes and 60.9% of patients without diabetes ($p = 1.000$). Ten patients with diabetes and 32 patients without diabetes died from COVID-19, yielding comparable in-hospital CFRs in both groups (15.6% versus 25.0%, $p = 0.194$) (Table 2). The median length of hospital stay in survivors was longer in patients with diabetes than in patients without diabetes (13 [8–17] days vs. 9 [6–14] days, $p = 0.007$). In the overall cohort, multivariate analysis found that cognitive impairment (HR 3.84, CI 1.50–9.86, $p = 0.005$), CVD (HR 3.54, CI 1.60–7.82, $p = 0.002$) and extended to critical pneumonia ($>25\%$ lung surface) on admission (HR 9.39, CI 2.89–30.4, $p < 0.0001$) were risk factors/markers associated with in-hospital death (Table 3). Diabetes was not associated with increased risk of death (HR 0.43, CI 0.16–1.17, $p = 0.100$). In patients with diabetes, multivariate analysis identified extended to critical pneumonia ($>25\%$ lung surface) (HR 26.0, CI 1.35–501, $p = 0.031$) and WBC (HR 9.52, CI 1.50–59.7, $p = 0.016$) on admission as risk factors/markers for in-hospital death (Table 4). In

patients without diabetes, multivariate analysis identified cognitive impairment (HR 5.80, CI 1.61–20.9, $p = 0.007$) and CVD (HR 5.63, CI 1.54–20.6, $p = 0.009$) as independent predictors of in-hospital death (Table 4).

4. Discussion

This is the first study to provide comprehensive data on the clinical, biological, and radiological characteristics at admission and on hospitalization outcomes of in-patients with diabetes and COVID-19 in Belgium. Moreover, information regarding diabetes such as type, duration, HbA1c and complications was inconsistently reported so far. In our monocentric cohort, in-patients with diabetes and COVID-19 were mostly middle-aged or elderly, overweight or obese, and most suffered from T2DM. Median diabetes duration and HbA1c were 11 years and 7.1%, respectively. Most patients had complications of diabetes and chronic comorbidities, the most frequent being hypertension, CVD, and CKD. Cough, fever, and dyspnea were the commonest symptoms on admission. Pneumonia was found in 88% of the patients, and those who underwent a chest-CT had mostly ground glass/crazy paving, compatible with SARS-CoV-2 pneumonia [24]. The most prominent biological abnormalities on admission were markedly elevated CRP and raised LDH levels, both suggestive of severe COVID-19 [25]. Overall, these characteristics are rather similar to those reported in the multicenter French CORONADO study, which like ours analyzed a mostly Caucasian population [15]. The overrepresentation of patients with T2DM among in-patients with COVID-19 is consistent with other studies [15,32,26,27]. A retrospective study from Belgium showed no evidence of increased hospitalization rate for COVID-19 in community-dwelling people with T1DM, at least in the first 3 months of the pandemic [14]. Of note, the prevalence of chronic diabetes-related complications and/or comorbidities such as hypertension and CKD was surprisingly low in Chinese studies [26,28].

The prevalence of obesity was higher in our cohort than that reported in the CORONADO study, as it reached 52% compared to 38% [15]. Yet, these results are by far higher than the prevalence of obesity reported in both Belgian and French in-patients with COVID-19, in whom it reaches 9.8%, and 25%, respectively, according to available data [18,19]. Conversely, HbA1c was lower in our cohort than in the CORONADO study. On the one hand, the mean HbA1c (8.1%) reported in the CORONADO study was higher than that reported by a nationwide survey in patients older than 64 years whose mean HbA1c was 7.1% [15], despite other clinical characteristics being rather similar. On the other hand, results from a Belgian nationwide survey performed in 2017–2018 in diabetic patients treated with at least 3 daily injections of insulin, showed that 38% of patients with T2DM older than 75 years, and 34% of those between 50 and 75 years had an HbA1c below 7% [29]. Further studies should precise the characteristics of in-patients with diabetes and severe/critical COVID-19 and those of out-patients with diabetes and mild/moderate COVID-19, to explore the potential effects of differences in chronic glycemic control.

Our study also provides insights on the short-term prognosis of diabetic patients with COVID-19. The CFR in our cohort was 15%, a figure two-fold higher than that reported in the general Belgian population affected by COVID-19 as of October 9, 2020 [19]. However, this comparison is limited as the rules governing SARS-CoV-2 RT-PCR testing in Belgium evolved over time. Testing was restricted to symptomatic patients requiring a hospitalization in the first months of the pandemic because of limited availability of testing reagents. Since then, testing has been extended to milder cases, departing or returning foreign travelers, and contact-tracing in particular [19]. On the other hand, the CFR in patients with diabetes

Table 2

Clinical characteristics and COVID-19-related biological values, radiological data, treatments, and outcomes in patients with diabetes and in sex- and age-matched patients without diabetes.

Variables	Patients without diabetes (N = 128)	Patients with diabetes (N = 64)	p value
Age (years)	67 ± 14	67 ± 14	
Sex female/male	50.0/50.0 (64/64)	50.0/50.0 (32/32)	
BMI (kg/m²)	26.8 ± 4.9	30.6 ± 5.1	< 0.0001
Stratification of BMI			< 0.0001
<25 kg/m ²	36.6 (41/112)	14.8 (9/61)	
25–29 kg/m ²	42.9 (48/112)	32.8 (20/61)	
≥30 kg/m ²	20.5 (23/112)	52.5 (32/61)	
Dyslipidemia	35.2 (45/128)	80.6 (50/62)	< 0.0001
Current Smoking	6.3 (7/111)	3.2 (2/62)	0.492
Comorbidities	78.9 (101/128)	93.8 (60/64)	0.007
CVD	28.1 (36/128)	39.1 (25/64)	0.141
Hypertension	51.6 (66/128)	79.6 (51/64)	< 0.0001
OSA	7.8 (10/128)	18.7 (12/64)	0.031
CKD	13.3 (17/128)	32.8 (21/64)	0.002
Cognitive impairment	14.8 (19/128)	18.8 (12/64)	0.535
Chronic liver disease	7.0 (9/128)	15.6 (10/64)	0.074
Current medications			
ACEI/ARBs	34.4 (44/128)	60.9 (39/64)	< 0.0001
Beta-blockers	25.0 (32/128)	31.3 (20/64)	0.391
Diuretics	23.4 (29/128)	45.3 (29/64)	0.003
Statins	18.0 (23/128)	34.4 (22/64)	0.018
Antiplatelet drugs	22.7 (29/128)	25.0 (16/64)	0.721
Symptoms			
Duration before admission (days)	7 [4–10]	7 [4–9]	0.345
Fever	81.3 (104/128)	70.3 (45/64)	0.100
Dyspnea	69.5 (89/128)	69.8 (44/63)	1.000
Cough	71.1 (91/128)	85.7 (54/63)	0.031
Flu-like symptoms ^a	66.4 (85/128)	66.7 (42/63)	0.328
Digestive disorders	30.5 (39/128)	38.1 (24/63)	0.328
Confusion	19.5 (25/128)	22.2 (14/63)	0.704
Area of lung injury			0.401
<25% (mild to moderate)	44.9 (48/107)	52.8 (28/53)	
>25–50% (extended to critical)	55.1 (59/107)	47.2 (25/53)	
Laboratory values	Normal values		
Plasma glucose (mmol/L)	3.8–5.5	6.4 [5.7–7.1]	< 0.0001
WBC (×10 ³ /μL)	4.0–10.0	6.1 [5.0–8.1]	0.507
Lymphocytes (×10 ³ /μL)	0.8–5.0	0.8 [0.5–1.0]	0.188
NLR (%)	0.78–3.53	6.4 [4.3–10.4]	0.197
Laboratory values	Normal values		
Platelets (×10 ³ /μL)	150–450	200 [144–250]	0.805
ALT (units/L)	13–35	36 [27–64]	0.058
AST (units/L)	7–35	27 [17–49]	0.059
LDH (units/L)	<250	354 [267–456]	0.245
GFR (ml/min/1.73 m ²) ^b	>60	67 [50–84]	0.989
C-reactive protein (mg/L)	<5	85 [54–147]	0.614
COVID-19-related treatments			
Oxygen therapy	89.8 (115/128)	87.5 (56/64)	0.630
Other antibiotics	42.2 (54/128)	31.2 (20/64)	0.159
Hydroxychloroquine	85.2 (109/128)	81.3 (52/64)	0.535
Azithromycin	9.4 (12/128)	12.5 (8/64)	0.617
Glucocorticoids	19.5 (25/128)	18.8 (12/64)	1.000
Non-invasive ventilation	19.5 (25/128)	29.7 (19/64)	0.145
COVID-19-related complications			
Secondary lung infection	29.7 (38/128)	28.1 (18/64)	0.868
COVID-19-related outcomes			
Not suitable for ICU admission	26.6 (34/128)	26.6 (17/64)	1.000
ICU admission	18.8 (24/128)	18.8 (12/64)	1.000
Death	25.0 (32/128)	15.6 (10/64)	0.194
Total hospital stay in survivors (days)	9 [6–14]	13 [8–17]	0.007

Data are expressed as means ± SD, medians [IQR], % (n/N), where N is available total number of cases per group. P values < 0.05 are considered as statistically significant. Abbreviations: BMI, body mass index; CVD, cardiovascular disease; OSA, obstructive sleep apnea; CKD, chronic kidney disease; CRP, C-Reactive Protein; ACEI, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers; WBC, white blood cells; NLR, neutrophils-to-lymphocytes ratio; ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; LDH, lactate dehydrogenase; GFR, glomerular filtration rate; ICU, intensive care unit.

^a Included headaches, myalgia, arthralgia, fatigue.

^b GFR was calculated by the CKD-EPI formula.

in our cohort was lower than the overall CFR observed in patients with COVID-19 in our center during the same period, the latter being 23.5%. CFRs in patients with diabetes and COVID-19 ranged from 6 to 24% in China [26,28,30–32], 27 to 33% in the United

States [27,33], 11 to 17% in France [15,34], and amounted to 28% in Italy [35]. Of note, death within 7 days after hospital admission was only evaluated in the CORONADO study [15] while 55% of deaths occurred >7 days after admission in our study. We found that non-

Table 3

Risk factors for in-hospital death in patients with SARS-CoV-2 pneumonia, with or without diabetes.

Variables	Patients with SARS-CoV-2 pneumonia					
	Univariate			Multivariate		
	HR	CI	p value	HR	CI	p value
BMI	0.95	0.89–1.02	0.131	—	—	—
Diabetes	0.53	0.26–1.08	0.081	0.43	0.16–1.17	0.100
CVD	2.19	1.19–4.04	0.012	3.54	1.60–7.82	0.002
Hypertension	1.02	0.54–1.94	0.955	—	—	—
OSA	0.69	0.27–1.78	0.439	—	—	—
CKD	0.98	0.47–2.05	0.956	—	—	—
Cognitive impairment	2.74	1.44–5.20	0.002	3.84	1.50–9.86	0.005
ACEI/ARBs	1.02	0.55–1.02	0.215	—	—	—
Beta-blockers	0.67	0.32–1.38	0.270	—	—	—
Diuretics	0.69	0.35–1.35	0.282	—	—	—
Statins	0.87	0.42–1.83	0.713	—	—	—
Antiplatelet drugs	1.12	0.62–2.32	0.597	—	—	—
Clinically severe/critical	1.55	0.19–12.7	0.683	—	—	—
Area of lung injury >50%	5.98	2.30–15.55	< 0.0001	9.39	2.89–30.4	< 0.0001
WBC > ULN	1.57	0.71–3.48	0.261	—	—	—
Lymphocytes < LLN	0.97	0.52–1.79	0.915	—	—	—
NLR (log, + 1SD) ^a	1.48	0.63–3.46	0.368	—	—	—
Platelets > > ULN	2.34	0.55–9.92	0.249	—	—	—
ALT > ULN	1.38	0.71–2.68	0.338	—	—	—
AST > ULN	0.88	0.43–1.80	0.729	—	—	—
LDH > ULN	1.76	0.62–5.01	0.290	—	—	—
CRP (log, + 1SD) ^a	1.61	0.66–3.94	0.299	—	—	—
GFR (log, + 1SD) ^{a,b}	0.48	0.17–1.37	0.169	—	—	—

Model applied to 192 patients of whom 42 died, yielding a case fatality rate of 21.9%. Sixty-four patients had diabetes.

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; CVD, cardiovascular disease; OSA, obstructive sleep apnea; CKD, chronic kidney disease; ACEI, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers; WBC, white blood cells; NLR, neutrophils-to-lymphocytes ratio; ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; LDH, lactate dehydrogenase; GFR, glomerular filtration rate; CRP, C-reactive protein; LLN, lower limit of normal; ULN, upper limit of normal.

See ranges of normal values in Tables 1 and 2.

^a Log transformed, HR corresponds to an increase of 1 SD.^b Calculated with the CDK-EPI formula.

survivors had more often a history of preexisting cognitive impairment (e.g. Alzheimer's disease) and extended to critical pneumonia (>25% lung surface area) (p 0.029). They were also less often treated with metformin (p 0.036) and/or Beta-blockers (p 0.046). Moreover, most non-survivors lived in nursing homes before admission (63.6% in non-survivors vs. 14.5% in survivors, p 0.001, data not shown). They were more often deemed not suitable for ICU admission compared to survivors owing to advanced age, comorbidities, and/or a life expectancy considered reduced irrespective of COVID-19. Despite being older in non-survivors (by an average of 9 years) did not reach statistical significance compared to survivors and most comorbidities were as frequent in survivors as in non-survivors, except for cognitive impairment, it may be that death in our cohort was probably and at least partly driven by age and frailty.

In patients with diabetes and SARS-CoV-2 pneumonia, we found that extended to critical pneumonia (>25% lung surface area) and increased WBC were independently associated with increased mortality risk, while age and sex were not. Age has been identified as the major risk factor for death from COVID-19 in both patients with and without diabetes [15,26,27,32,34]. Interestingly, a recent study from England showed that the additional mortality risk associated with T2DM was attenuated by age [36]. BMI was related to ICU admission and requirement for IMV in patients with COVID-19, independently of their metabolic status in 2 studies from France [17,18]. In patients with diabetes, BMI was positively associated with death and/or intubation [15,27]. Interestingly, most studies failed to show an association between death and HbA1c on admission, diabetes duration, type of diabetes, hypertension, and ACEI/ARBs [15,26,27]. On the other hand, CVD and CKD were associated with increased mortality in patients with diabetes

[27,31]. One study from England showed that death in patients with diabetes (either T1DM or T2DM) was associated with cardiovascular and renal complications of diabetes, but also with BMI and glycemic control, with HbA1c on admission as a proxy [16]. The CORONADO study found the same relationship between odds of death and complications of diabetes [15]. Among glucose-lowering medications, metformin and sitagliptin were associated with reduced mortality [15,35,38]. Conversely, insulin was associated with poorer outcome [27,31] as it would reflect longer diabetes duration in T2DM, older age and comorbidities precluding use of oral medications. Beyond simply improving glycemic control, DDP4 inhibitors might have beneficial effects on COVID-19 by modulating the immune response to SARS-CoV-2 and by reducing its virulence, its entry receptor within human cells (ACE2) having high homology with DDP4 [35]. The putative beneficial effects of metformin in patients with diabetes and/or obesity and COVID-19 could be mediated by decreased cytokines release [39].

As expected, patients with (mostly type 2) diabetes had higher BMI and had more often comorbidities including hypertension, OSA, and CKD as well as prevalent dyslipidemia compared to age- and sex-matched patients without diabetes. Consequently, their current medications included more often ACEI/ARBs, diuretics, and statins. In survivors, total hospitalization length was twice as long in diabetic patients as in non-diabetic ones. Nevertheless, in-hospital CFRs were similar between patients with and without diabetes. Indeed, diabetes was not associated with increased risk of death in the multivariate analysis. Cognitive impairment and CVD, both correlated to age, were independently associated with increased risk of death in the overall cohort as well as in patients without diabetes. Extended to critical pneumonia (>25% lung surface area) was also independently associated with increased

Table 4
Risk factors for in-hospital death in patients with SARS-CoV-2 pneumonia.

Variables	Patients with diabetes						Patients without diabetes					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	CI	p value	HR	CI	p value	HR	CI	p value	HR	CI	p value
Age	1.04	0.99–1.08	0.102	—	—	—	1.08	1.04–1.10	< 0.0001	1.05	0.99–1.12	0.072
Male sex	1.83	0.46–7.39	0.392	—	—	—	0.91	0.45–1.84	0.794	—	—	—
BMI	0.64	0.17–2.40	0.348	—	—	—	0.94	0.87–1.02	0.157	—	—	—
CVD	0.86	0.24–3.10	0.816	—	—	—	3.17	1.56–6.44	0.001	5.63	1.54–20.6	0.009
Hypertension	0.65	0.17–2.54	0.536	—	—	—	1.34	0.64–2.78	0.440	—	—	—
OSA	0.97	0.21–4.68	0.985	—	—	—	0.75	0.23–2.49	0.638	—	—	—
CKD	1.03	0.26–4.02	0.965	—	—	—	1.06	0.43–2.60	0.903	—	—	—
Cognitive impairment	2.18	0.61–7.87	0.233	—	—	—	3.35	1.59–7.07	0.001	5.80	1.61–20.9	0.007
ACEI/ARBs	0.49	0.14–1.74	0.270	—	—	—	1.57	0.79–3.16	0.201	—	—	—
B-blockers	0.25	0.03–1.97	0.187	—	—	—	0.84	0.38–1.88	0.674	—	—	—
Diuretics	0.42	0.11–1.65	0.215	—	—	—	1.02	0.47–2.21	0.958	—	—	—
Statins	1.40	0.39–4.97	0.605	—	—	—	0.76	0.29–1.99	0.583	—	—	—
Antiplatelet drugs	0.25	0.03–2.04	0.198	—	—	—	1.71	0.83–3.53	0.145	—	—	—
Clinically severe/critical	1.60	0.13–19.0	0.712	—	—	—	1.40	0.44–4.43	0.563	—	—	—
Area of lung injury > 50%	9.68	1.07–88.0	0.044	26.0	1.35–501	0.031	4.95	1.71–14.3	0.003	3.61	0.87–15.0	0.078
WBC > ULN	3.78	1.06–13.5	0.041	9.52	1.50–59.7	0.016	1.01	0.35–2.91	0.990	—	—	—
Lymphocytes < LLN	0.35	0.07–1.65	0.184	—	—	—	1.27	0.63–2.58	0.506	—	—	—
NLR (log, + 1SD) ^a	0.45	0.06–3.46	0.440	—	—	—	1.67	0.66–4.23	0.280	—	—	—
Platelets > ULN	2.73	0.79–9.44	0.989	—	—	—	2.20	0.51–9.47	0.289	—	—	—
ALT > ULN	1.24	0.33–4.71	0.754	—	—	—	1.28	0.59–2.78	0.527	—	—	—
AST > ULN	0.71	0.15–3.46	0.672	—	—	—	0.87	0.39–1.97	0.743	—	—	—
LDH > ULN	0.69	0.14–3.44	0.651	—	—	—	2.95	0.69–12.5	0.144	—	—	—
CRP (log, + 1SD) ^a	2.51	0.43–14.6	0.308	—	—	—	1.21	0.42–3.48	0.726	—	—	—
GFR (log, + 1SD) ^{a,b}	0.12	0.01–1.70	0.118	—	—	—	0.67	0.20–2.26	0.513	—	—	—

Model applied to 64 patients with diabetes of whom 10 died and to 128 patients without diabetes of whom patients of whom 32 died, yielding a case fatality rate of 15.6% and 25.0%, respectively.

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; CVD, cardiovascular disease; OSA, obstructive sleep apnea; CKD, chronic kidney disease; angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers; WBC, white blood cells; NLR, neutrophils-to-lymphocytes ratio; ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; LDH, lactate dehydrogenase; GFR, glomerular filtration rate; CRP, C-reactive protein; LLN, lower limit of normal; ULN, upper limit of normal.

See ranges of normal values in Table 1 and Table 2.

^a Log transformed, HR corresponds to an increase of 1 SD.

^b Calculated with the CDK-EPI formula.

mortality risk in the whole cohort. In the study of Guo et al., patients with diabetes died more often than patients without diabetes (17% vs. 0%) but they were twice as old [28]. Studies from China [30], the United States [33], France [34] and Africa [40] did not report increased mortality risk in diabetic patients compared to non-diabetic ones. In the study of Chen et al., mortality was not significantly different in patients with diabetes compared to those without diabetes when COVID-19 was confirmed on the basis of a positive SARS-CoV-2 PCR, whereas patients with diabetes died more often when the infection was diagnosed on clinical grounds [31]. Yet, patients with diabetes were 16 years older than those without diabetes. Finally, Shi et al. reported a 2-fold higher mortality in patients with diabetes compared to those without diabetes matched for age and sex [26]. However, diabetes was not independently associated with death in multivariate analysis.

We acknowledge that this study has limitations, including a single-center retrospective design, small and heterogeneous population of diabetic patients, and some missing data regarding diabetes duration, HbA1c, complications of diabetes, and BMI, which were more often missing in older patients. Given the retrospective design, diabetes was not systematically screened at admission. Globally, comparisons between studies and countries might be limited for several reasons including difference in demographics, ethnicity, treatment regimens for both diabetes and COVID-19, healthcare levels, health insurance coverage, and prevalent COVID-19 strains. More specifically, the CFR of diabetic patients in our cohort could have been attenuated by a relatively good pre-admission glycemic control (median HbA1c 7.1%) and/or by other

unidentified determinants underlying it, that may in turn have mitigated the adverse outcomes. Indeed, the bulk of published evidence suggests that diabetes increases both severity and mortality in patients with COVID-19.

In conclusion, this is the first report describing the characteristics and outcomes of in-patients with diabetes and confirmed COVID-19 from Belgium. In accordance with the CORONADO study, most diabetic patients suffered from T2DM, and half of them had chronic vascular complications. Moreover, half of them were obese. Neither BMI, nor chronic glycemic control with HbA1c as proxy, adversely influenced mortality in our cohort. Among patients with SARS-CoV-2 pneumonia, those with diabetes had more comorbidities such as hypertension, OSA and CKD, but their CFR was similar to that of sex- and age-matched patients without diabetes. These data need confirmation in larger series from other European centers.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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