

MORTALITY-RELATED RISK FACTORS OF INPATIENTS WITH DIABETES AND COVID-19: A MULTICENTER RETROSPECTIVE STUDY IN BELGIUM

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Original article

Mortality-related risk factors of inpatients with diabetes and COVID-19: A multicenter retrospective study in Belgium

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ABSTRACT

Background and aims. – We describe mortality-related risk factors of inpatients with diabetes and coronavirus disease 2019 (COVID-19) in Belgium.

Methods. – We conducted a multicenter retrospective study from March to May, 2020, in 8 Belgian centers. Data on admission of patients with diabetes and COVID-19 were collected. Survivors were compared to non-survivors to identify prognostic risk factors for in-hospital death using multivariate analysis in both the total population and in the subgroup of patients admitted in the intensive care unit (ICU).

Results. – The study included 375 patients. The mortality rate was 26.4% (99/375) in the total population and 40% (27/67) in the ICU. Multivariate analysis identified older age (HR 1.05 [CI 1.03–1.07], $P < 0.0001$) and male gender (HR 2.01 [1.31–3.07], $P = 0.0013$) as main independent risk factors for in-hospital death in the total population. Metformin (HR 0.51 [0.34–0.78], $P = 0.0018$) and renin-angiotensin-aldosterone system blockers (HR 0.56 [0.36–0.86], $P = 0.0088$) use before admission were independent protective factors. In the ICU, chronic kidney disease (CKD) was identified as an independent risk factor for death (HR 4.96 [2.14–11.5], $P < 0.001$).

Conclusion. – In-hospital mortality due to the first wave of COVID-19 pandemic in Belgium was high in patients with diabetes. We found that advanced age and male gender were independent risk factors for in-hospital death. We also showed that metformin use before admission was associated with a significant reduction of COVID-19-related in-hospital mortality. Finally, we showed that CKD is a COVID-19-related mortality risk factor in patients with diabetes admitted in the ICU.

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1. Introduction

Since the onset of the pandemic in Wuhan, China, at the end of 2019 [1], almost 500 million people have been infected by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 6 million people died from coronavirus disease 2019 (COVID-19) worldwide [2].

Diabetes mellitus was identified early on as a risk factor for adverse outcomes due to COVID-19. According to the first-published Chinese data, diabetes prevalence reached 5% to 19% among individuals with COVID-19, a higher prevalence being found among inpatients [3]. The rate of critical COVID-19 requiring intensive care unit (ICU) admission or causing death rose to 25–30% in patients with diabetes during the first wave of the pandemic, when the SARS-CoV-2 wild-type (Wuhan-Hu-1) was predominant [4–7]. The case fatality rate of individuals with diabetes was up to 8 times higher than that of those without diabetes [3]. A recent meta-analysis including more than 400,000 patients showed that relative mortality due to COVID-19 was increased by 17 to 52% among inpatients with diabetes compared to those without diabetes [8].

Obesity, hypertension, cardiovascular disease, older age and male gender were also identified as independent risk factors for poor outcomes due to COVID-19, independently of diabetes [8,9]. These factors as well as cognitive impairment, chronic kidney disease (CKD), and chronic obstructive pulmonary disease were pointed out by several observational studies as factors of poor prognosis in patients with diabetes [10–18].

Diabetes is a heterogeneous disease. However, whether diabetes type and/or diabetes-related clinical (e.g. macrovascular and microvascular complications, and body mass index (BMI)) or biological characteristics (e.g. glycated hemoglobin A1c (HbA1c) level) affect COVID-19 outcome remains debated. From large cohort studies and meta-analyses, the odds for COVID-19-related hospitalization and mortality seem increased in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [8,19–24]. Furthermore, poor glycemic control on admission (elevated HbA1c and/or plasma glucose), microvascular complications, and treatment with insulin were associated with higher risk of COVID-19-related hospitalization, disease severity and/or death [9,19–22,25–34].

In Belgium, pre-existing diabetes was reported in 21.5% of patients hospitalized with COVID-19 by the Belgian Public Health Institute (Sciensano) [35]. This figure is higher than that reported in the general population (6% and 14% in people older than 15 years and 65 years, respectively) [36]. Nevertheless, the phenotype and prognostic factors for in-hospital mortality of patients with diabetes in Belgium are poorly described [14]. In this multicenter retrospective study, we aimed to describe the characteristics and prognostic factors for in-hospital mortality in patients with diabetes and COVID-19 during the first months of the pandemic.

2. Patients and methods

2.1. Study design and population

This multicenter retrospective cross-sectional study was carried out in 8 Belgian centers (Table 1), including two academic tertiary care centers, from March 1, 2020 to May 6, 2020. During this period, referred as the first wave of the pandemic, the SARS-CoV-2 wild-type (Wuhan-Hu-1) was predominant [7,37]. Inpatients with both diabetes and confirmed COVID-19 were identified based on institutional registries. Clinical and biological data were extracted from medical records of the participating centers. The institutional review board approved the present study (N.CEHF 2020/22MAI/290).

Table 1

Number of patients recruited from participating centers.

Center	Number of patients	Number/total population (%)
CHR de Huy	23	6%
CH de Mouscron	29	8%
Clinique Saint-Luc Bouge	31	8%
Hôpital Universitaire Erasme	36	10%
Cliniques Saint-Jean	49	13%
Hôpital de Jolimont	49	13%
Cliniques Universitaires Saint-Luc	73	19%
CHU Ambroise-Paré	85	23%
Total	375	100%

CHR: Centre Hospitalier Régional; CH: Centre Hospitalier; CHU: Centre Hospitalier Universitaire.

Patients included in the study had known or newly diagnosed preexisting diabetes ($\text{HbA1c} \geq 6.5\%$ on admission). These patients were hospitalized with COVID-19, diagnosed on the basis of a positive SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) test on nasopharyngeal swab and/or on a chest computed tomography (CT) scan consistent with SARS-CoV-2 pneumonia (bilateral ground-glass opacities) [38]. The hospital stay ended with an unequivocal outcome (discharged alive from hospital or in-hospital death). Pregnant women, children (aged ≤ 18 years) and patients with glucocorticoid-induced hyperglycemia during the hospital stay were excluded. Glucocorticoid-induced hyperglycemia was considered in patients with no history of diabetes, $\text{HbA1c} < 6.5\%$ on admission, and occurrence of hyperglycemia after glucocorticoid administration during the hospital stay as well as in patients with a diagnosis of glucocorticoid-induced hyperglycemia at the end of the hospital stay by the attending physician.

2.2. Study aims

The primary aims were to describe the clinical, biological, and radiological characteristics on admission of patients with diabetes and COVID-19 as well as their prognostic factors for in-hospital death by comparing survivors to non-survivors. The secondary aims were to describe the characteristics on admission and the prognostic factors for in-hospital death in the subgroup of patients admitted in the ICU.

2.3. Data abstraction

Physicians from each participating center extracted data from electronic medical records. Demographic and clinical data included age, gender, place of residence (living at home or institutionalized), type and duration of diabetes, BMI, microvascular (retinopathy, nephropathy, neuropathy, and foot ulcer) and macrovascular (ischemic heart disease, peripheral arterial disease, ischemic cerebrovascular disease (transient ischemic attack and/or stroke)) disease, and other pre-existing comorbidities such as hypertension, dyslipidemia (hypercholesterolemia and/or hypertriglyceridemia), current tobacco use, chronic pulmonary disease, CKD (related or not to diabetes), solid cancer and/or hemopathy, chronic liver disease, cardiovascular disease (CVD) and cognitive impairment. CKD was considered in patients with glomerular filtration rate $\leq 60 \text{ mL/min/1.73m}^2$ and a history of chronic kidney disease based on the electronic medical records. We also considered patients with a diagnosis of CKD at the end of the hospital stay by the attending physician. Medications taken regularly before admission were also recorded. Regarding SARS-CoV2 infection, duration and type of symptoms were recorded, with influenza-like symptoms including headache, myalgia, arthralgia, and fatigue. The severity of COVID-19 was defined as mild with symptoms of upper respiratory tract infection, moderate with clinical or radiographic lower

respiratory tract disease without hypoxemia (oxygen saturation (SpO_2) $\geq 94\%$), severe with clinical or radiological pneumonia with hypoxemia ($\text{SpO}_2 < 94\%$, respiratory rate ≥ 30 breaths per minute, and/or infiltrates $> 50\%$ of lung fields), and critical when requiring ICU admission [39]. Patients deemed not suitable for ICU admission and invasive procedures including cardiopulmonary resuscitation owing to older age and/or comorbidities were identified.

Biological data on admission included HbA1c (on admission or last value available within six months), plasma glucose, hemoglobin, white blood cells count, lymphocytes count, platelets count, C-reactive protein (CRP), glomerular filtration rate (GFR, calculated by the CKD-EPI formula), lactate dehydrogenase, creatine phosphokinase, aspartate-aminotransferase, and alanine-aminotransferase.

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 was defined as severe when infiltrates involved $> 50\%$ of lung fields [40].

In-hospital treatments for COVID-19 (oxygen therapy, antibiotics, hydroxychloroquine, corticosteroids), and requirement for non-invasive ventilation were recorded, as well as ICU admission and requirement for invasive mechanical ventilation (IMV). The outcome of COVID-19 (discharged alive from hospital or in-hospital death) was recorded as well as the total length of stay in survivors.

2.4. Statistical analysis

Continuous data are reported as medians and interquartile range [IQR: P25–P75]. Categorical variables are reported as numbers, frequencies, or percentages of participants, based on available data. Differences between groups were assessed by Mann-Whitney U test for continuous variables and by Chi² or Fisher's exact test for categorical variables, as appropriate. A univariate logistic regression analysis was performed for each demographic, clinical, radiological, and biological characteristic, except for the type of diabetes. A multivariable logistic regression model, namely a frailty model, was used to identify prognostic factors for in-hospital death, after adjustment for age and sex. This multivariable logistic regression model takes into account the effects of unobserved heterogeneity between groups (center effect) [41]. We used four distinct models to analyze the total population. Each model was adjusted for age, sex, and center effect. Models 2, 3, and 4 were also adjusted for HbA1c and BMI; long-term diabetes complications and metformin; CKD, renin-angiotensin-aldosterone system (RAAS) blockers (angiotensin-converting-enzyme inhibitors and/or angiotensin II receptor blockers) and CRP, respectively. One model was applied to the UCI population. This model was adjusted for age, sex, center effect, and CKD. The variables selected for the multivariate models were either different to the statistical significance level in univariate analysis (P value < 0.10) or shown to be significant in the existing literature and deemed clinically pertinent. A P value < 0.05 was considered statistically significant in the multivariate analysis. Statistical analysis was performed with JMP Pro 16.0.0 and SPSS version 27.

3. Results

3.1. Patients' characteristics

A total of 375 patients were included in the study (Table 2). The diagnosis of COVID-19 was based on a positive SARS-CoV-2 RT-PCR test in 97% of cases. The median age was 73 [IQR: 64–81] years. Women represented 43% of the cohort. Most patients had T2DM (91%) while T1DM accounted for less than 1% of the patients. Newly diagnosed diabetes and secondary diabetes (due to

kidney transplantation, chronic pancreatic disease, or pancreatectomy) accounted for 4% each, while the type of diabetes remained unknown in the remainder (data not shown). Median HbA1c was 7.1 [6.3–8.0] %. Median duration of diabetes was 11 [6–19] years. Obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) was reported in 49% and class 3 obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) in 9% (22/257) of the patients. Hypertension and dyslipidemia were found in 79% and 74% of the patients, respectively. History of either CVD or CKD was present in 54% and 37% of patients, respectively. Microvascular and macrovascular complications were highly prevalent. Fifty-three percent of patients suffered from at least one of them and 33% had microvascular disease (data not shown). Metformin was the most frequently used glucose-lowering medication (61%), while 38% of the patients were on insulin therapy and 21% on sulfonylureas. RAAS blockers (angiotensin-converting-enzyme inhibitors and/or angiotensin II receptor blockers) and statins were taken before admission by 51% and 53% of patients, respectively.

The median duration of COVID-19 symptoms before hospital admission was 4 [2–7] days. The commonest symptoms were dyspnea (64%), cough (63%), fever (62%) and influenza-like symptoms (52%). When performed, chest-CT scans showed severe COVID-19 pneumonia in 51% (96/189) of cases, while ground-glass opacities were present in 86% (data not shown). Biological findings on admission showed an inflammatory syndrome with elevated CRP in 94% of patients. Lymphopenia was found in 61% of patients. A $\text{GFR} < 60 \text{ mL/min/1.73m}^2$ was found in 54% of patients. Median plasma glucose on admission was 153 [119–210] mg/dL. Four patients had hypoglycemia on admission ($< 70 \text{ mg/dL}$) (data not shown).

3.2. Outcome and treatments of COVID-19

In the total population, 99 patients (26%) died from COVID-19 and 67 (18%) were admitted to the ICU. Among the latter, 37 (55%) patients required IMV, and 27 (40%) died. Patients deemed unfit for ICU admission and invasive procedures represented 39% (145/374) of the total population. COVID-19-related medical treatments consisted of oxygen (81%), hydroxychloroquine (59%) and corticoids (12%). There was no effect of hydroxychloroquine on mortality in the univariate analysis. Half of the patients (50%) received antibiotics.

3.3. Risk factors for in-hospital death in the total population

In the univariate analysis, non-survivors were older ($P < 0.0001$) and were more often men ($P = 0.019$) than survivors (Table 2). Comorbidities such as cancer/hemopathy ($P = 0.007$), CKD ($P = 0.020$) and/or cognitive impairment ($P < 0.001$) were more prevalent in non-survivors. Survivors were more frequently treated with metformin ($P < 0.001$) and/or RAAS blockers ($P = 0.045$) before admission than non-survivors. Severe pneumonia on chest-CT was found more often in non-survivors ($P = 0.018$). Non-survivors had more frequently hyperleukocytosis ($P = 0.001$), elevated CRP ($P = 0.034$), and a $\text{GFR} < 60 \text{ mL/min/1.73m}^2$ ($P < 0.01$) on admission.

Multivariate analyses are shown in Table 3. No center effect was found. Advanced age and male gender were found as independent risk factors for in-hospital death across all models, except model 2. Metformin use before admission was associated with decreased mortality risk (HR 0.51 [0.34–0.78], $P = 0.0018$) in model 3. RAAS blockers use before admission were associated with decreased mortality risk (HR 0.56 [0.36–0.86], $P = 0.0088$) in model 4. CRP level on admission was a mortality risk factor in model 4 (HR 1.00031 [1.001–1.005] per one milligram per liter increase, $P = 0.0081$).

Table 2
Characteristics before admission of patients with diabetes hospitalized with COVID-19.

Variables	Total population (n=375)	Survivors (n=276)	Non-survivors (n=99)	p value
Age (years)	73 [64–81]	72 [61–79]	78 [72–85]	<0.001
Gender (female/male)	163/375 (43%)	130/276 (47%)	33/99 (33%)	0.019
Types of diabetes				
Type 1	3/375 (0.8%)	N/A	N/A	N/A
Type 2	342/375 (91%)	N/A	N/A	N/A
BMI (kg/m ²)	29 [26–33]	29 [26–33]	28 [24–34]	0.791
BMI class				
≥30 kg/m ²	142/289 (49%)	110/223 (49%)	32/66 (49%)	1.000
≥40 kg/m ²	22/257 (9%)	14/200 (7%)	8/57 (14%)	0.104
HbA1c (%)	7.1 [6.3–8.0]	7.1 [6.3–8.1]	6.7 [6.2–7.8]	0.091
Diabetes duration (years)	11 [6–19]	10 [5–19]	12 [9–20]	0.069
Microvascular and/or macrovascular complications	189/358 (53%)	130/262 (50%)	59/96 (62%)	0.056
Glucose-lowering agents				
Metformin	217/357 (61%)	174/261 (67%)	46/96 (45%)	<0.001
DPP4-inhibitors	19/357 (5%)	14/261 (5%)	5/96 (5%)	1.000
Sulfonylurea/glinides	75/357 (21%)	58/261 (22%)	17/96 (18%)	0.973
SGLT2-inhibitors	20/357 (6%)	14/261 (5%)	6/96 (6%)	0.796
GLP1-RA	11/357 (3%)	10/261 (4%)	1/96 (1%)	0.301
Insulin	137/357 (38%)	97/261 (37%)	40/96 (42%)	0.465
Comorbidities				
Hypertension	293/371 (79%)	214/271 (78%)	79/98 (81%)	0.773
Dyslipidemia	268/363 (74%)	193/266 (73%)	75/97 (77%)	0.419
Current tobacco use	26/358 (7%)	15/267 (6%)	11/91 (12%)	0.058
Cardiovascular disease	189/352 (54%)	134/257 (52%)	55/95 (58%)	0.399
Chronic pulmonary disease	98/352 (28%)	65/257 (25%)	33/95 (35%)	0.083
Chronic kidney disease	131/352 (37%)	85/257 (33%)	46/95 (48%)	0.020
Cognitive impairment	81/352 (23%)	47/257 (18%)	34/95 (36%)	<0.001
Chronic liver disease	35/352 (10%)	28/257 (11%)	7/95 (7%)	0.423
Cancer/hemopathy	53/352 (15%)	30/257 (12%)	23/95 (24%)	0.007
Routine medication				
RAAS blockers ^a	190/373 (51%)	149/275 (54%)	41/98 (42%)	0.045
Beta-blockers	174/373 (46%)	127/275 (46%)	47/98 (48%)	0.814
Diuretics	138/373 (37%)	101/275 (37%)	37/98 (38%)	0.903
Statins	199/373 (53%)	145/275 (53%)	54/98 (55%)	0.724
Positive SARS-CoV-2 RT-PCR	365/375 (97%)	269/276 (98%)	69/99 (70%)	0.728
Time before hospital admission (days)	4 [2–7]	5 [2–8]	3 [1–6]	0.005
Clinical signs				
Fever	232/374 (62%)	163/276 (59%)	69/98 (70%)	0.053
Dyspnea	240/373 (64%)	175/276 (63%)	65/98 (67%)	0.541
Cough	234/373 (63%)	181/276 (66%)	53/98 (55%)	0.067
Influenza-like illness ^b	195/373 (52%)	158/276 (57%)	37/97 (38%)	0.001
Pneumonia	324/353 (92%)	238/263 (91%)	86/90 (96%)	0.181
Infiltrates >50% of lung fields (chest-CT)	96/189 (51%)	65/142 (46%)	31/47 (66%)	0.018
Biological findings				
CRP (mg/L)	76 [38–138]	69 [31–130]	106 [53–170]	<0.001
GFR (mL/min/1.73m ²) ^c	58 [42–82]	62 [44–84]	53 [32–75]	0.011
LDH (%ULN)	136 [102–181]	132 [99–178]	153 [119–187]	0.007
ALT (%ULN)	71 [42–108]	70 [42–107]	71 [42–113]	0.135
AST (%ULN)	103 [71–153]	95 [64–146]	125 [88–335]	0.383
White blood cells (/mm ³)	6555 [5471–8815]	6400 [4710–8420]	7210 [5000–10350]	0.012
Lymphocytes (/mm ³)	940 [670–1280]	960 [680–1290]	890 [640–1230]	0.130
Hemoglobin (g/dL)	12.9 [11.5–14.4]	13.1 [11.5–14.4]	12.5 [10.2–14.2]	0.118
Plasma glucose (mg/dL)	153 [119–210]	150 [122–206]	163 [121–206]	0.373

Data are expressed as medians [IQR], or % (n/N), where *n* is the available total number of cases per group. *P* value < 0.05 is considered as statistically significant. N/A: not applicable; BMI: body mass index; HbA1c: glycated hemoglobin A1c; DPP4: dipeptidyl peptidase-4; SGLT2: sodium/glucose co-transporter type 2; GLP1-RA: glucagon-like peptide-1 receptor agonist; RAAS: renin-angiotensin-aldosterone system; RT-PCR: real-time polymerase chain reaction; CT: computed tomography; CRP: C-reactive protein; ULN: upper limit of normal; GFR: glomerular filtration rate; LDH: lactate dehydrogenase; ALT: alanine-aminotransferase; AST: aspartate-aminotransferase.

^a RAAS blockers include angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers.

^b Included headaches, myalgia, arthralgia, and fatigue.

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

3.4. Characteristics of patients admitted to ICU

ICU patients' characteristics are shown in [ESM Table 1](#). The median age was 70 [63–77] years. Men represented 73% of the cohort. The median symptoms duration before admission was 5 [3–7] days. Ninety percent of patients had T2DM (data not shown), and median HbA1c was 7.0 [6.3–8.0] %. The commonest comorbidities were hypertension (82%), dyslipidemia (70%), CVD (50%), and chronic pulmonary disease (39%). Microvascular and/or macrovascular complications were found in 42% of patients. Most patients were on metformin before admission (66%) while 27% of

patients were on insulin and 18% on sulfonylureas. RAAS blockers and statins were taken by 62% and 46% of patients, respectively. Compared to patients not admitted to ICU, those patients in ICU were more frequently men (*P* = 0.003), younger (*P* = 0.016), more often obese (*P* = 0.047), and had more chronic pulmonary disease (*P* = 0.031) in the univariate analysis. However, they had less often CKD and cognitive impairment (*P* = 0.003 and 0.032, respectively). ICU patients required more often oxygen therapy (*P* < 0.017), antibiotics (*P* < 0.0001), and glucocorticoids (*P* = 0.001), whereas the use of hydroxychloroquine was not statistically different between ICU and no ICU groups (*P* = 0.412).

Table 3
Risk factors for in-hospital death from COVID-19 in the total population.

Variables	Multivariate Model 1			Multivariate Model 2			Multivariate Model 3			Multivariate Model 4		
	HR	CI	p value	HR	CI	p value	HR	CI	p value	HR	CI	p value
Age (years)	1.05	1.03–1.07	<0.001	1.02	0.99–1.05	0.170	1.04	1.02–1.07	<0.001	1.05	1.02–1.07	<0.001
Gender (male)	2.01	1.31–3.07	0.001	1.64	0.89–3.03	0.120	2.22	1.41–3.49	<0.001	2.26	1.40–3.66	<0.001
Center effect	N/A	N/A	0.220	N/A	N/A	0.250	N/A	N/A	0.170	N/A	N/A	0.280
HbA1c > 7%	–	–	–	0.95	0.52–1.72	0.860	–	–	–	–	–	–
BMI ≥ 30 kg/m ²	–	–	–	1.27	0.68–2.36	0.450	–	–	–	–	–	–
Hypertension	–	–	–	–	–	–	–	–	–	–	–	–
Dyslipidemia	–	–	–	–	–	–	–	–	–	–	–	–
Chronic kidney disease	–	–	–	–	–	–	–	–	–	1.24	0.79–1.93	0.350
Cognitive impairment	–	–	–	–	–	–	–	–	–	–	–	–
Cancer/hemopathy	–	–	–	–	–	–	–	–	–	–	–	–
Microvascular and/or macrovascular complications	–	–	–	–	–	–	0.93	0.59–1.45	0.730	–	–	–
Metformin	–	–	–	–	–	–	0.51	0.34–0.78	0.001	–	–	–
RAAS blockers ^a	–	–	–	–	–	–	–	–	–	0.56	0.36–0.86	0.008
Infiltrates > 50% of lung fields	–	–	–	–	–	–	–	–	–	–	–	–
Hyperleukocytosis	–	–	–	–	–	–	–	–	–	–	–	–
CRP (mg/L)	–	–	–	–	–	–	–	–	–	1.0031	1.001–1.005	0.008

All models are adjusted for age, gender, and center effect. Model 1 was applied to 375 patients of whom 99 died, yielding a case fatality rate of 26.4%. Model 2 also adjusted for HbA1c and BMI, was applied to 224 patients, of whom 45 died, yielding a case fatality rate of 20.1%. Model 3 also adjusted for long-term diabetes complications and metformin, was applied to 346 patients of whom 94 died, yielding a case fatality rate of 21.2%. Model 4 also adjusted for chronic kidney disease, RAAS blockers and CRP, was applied to 340 patients, of whom 87 died, yielding a case fatality rate of 25.6%. HR: hazard ratio; CI: confidence interval; BMI: body mass index; HbA1c: glycated hemoglobin A1c; RAAS: renin-angiotensin-aldosterone system; CRP: C-reactive protein; N/A: not applicable.

^a RAAS blockers include angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers.

Table 4
Multivariate analysis of risk factors for in-hospital death from COVID-19 in the ICU population.

Variables	HR	CI	P value
Age (years)	1.09	1.04–1.15	<0.001
Gender (male)	1.58	0.58–4.34	0.270
Center effect	N/A	N/A	0.650
Chronic kidney disease	4.96	2.14–11.5	<0.001

The model was applied to 64 patients of whom 26 died, yielding a case fatality rate of 41%. Three patients were excluded due to missing data. ICU: intensive care unit; HR: hazard ratio; CI: confidence interval; N/A: not applicable.

3.5. Risk factors for in-hospital death in the ICU population

In the univariate analysis, non-survivors were older ($P=0.02$), had more often dyslipidemia ($P=0.030$), CKD ($P<0.001$) and/or cancer/hemopathy ($P=0.039$) than survivors. Regarding glucose-lowering therapies, insulin use prior to admission was more frequent in non-survivors ($P=0.011$). Severe pneumonia on chest-CT ($P=0.028$), and anemia ($P<0.0001$) on admission were more prevalent in non-survivors.

The multivariate analysis is shown in Table 4. No center effect was found. Advanced age (HR 1.09 [1.04–1.15], $P<0.001$) and CKD (HR 4.96 [2.14–11.5], $P<0.001$) were found as independent risk factor for in-hospital death.

4. Discussion

This is the first multicenter retrospective study describing the clinical characteristics and prognosis of inpatients with diabetes and COVID-19 during the first two months of the pandemic in Belgium, when the SARS-CoV-2 wild-type (Wuhan-Hu-1) was predominant.

Included patients were mainly men over 65 years. Their characteristics were quite similar to those of inpatients with diabetes and COVID-19 from other European studies [15,16,33,34]. In our study, patients with T1DM represented less than 1% of the total population. This figure is lower than those of the European ACCREDIT (5%) and CORONADO (3%) studies [33,34]. However, the high prevalence

of T2DM in our cohort is consistent with other studies [12,33,34,42].

The prevalence of obesity, microvascular and/or macrovascular complications and other comorbidities including hypertension, CVD and CKD was high. As a result, RAAS blockers and statins were frequently taken before admission in included patients. In our cohort, glycemic control was deemed acceptable (median HbA1c 7.1%). In the French CORONADO study, 38% of patients were obese and the median HbA1c was higher (8.1%) [33]. In the UK multicenter ACCREDIT study, obesity was found in 38% of patients and the median HbA1c was 7.3% [34]. Thus, compared to our cohort, median HbA1c was higher while obesity was less prevalent.

The overall mortality rate of COVID-19 in our cohort was 26.4%. This figure is slightly higher than the in-hospital mortality rate of 21.3% reported by Kaminska et al. in a meta-analysis including publications from the start of the pandemic to December 2020 [43]. Diabetes was identified early in the current pandemic as an independent risk factor for ICU admission (OR 2.79 ($P<0.0001$)) [44]. In our cohort, ICU admission rate was 18% and mortality in ICU reached 40%. Likewise, Roncon et al. showed in a meta-analysis that overall ICU admission rate and ICU case fatality rate were 21% and 39% in patients with diabetes, respectively [44].

In the total population, we showed that both advanced age and male gender were independent risk factors increasing COVID-19-related mortality while metformin and/or RAAS blockers use prior admission were associated with a decreased risk of mortality. On admission, we found a positive relationship between CRP levels and in-hospital death from COVID-19. Finally, HbA1c, BMI, microvascular and/or macrovascular diabetes-related complications, or CKD were not independently associated with COVID-19 mortality. However, older age and CKD were independent risk factors for death in patients admitted to the ICU in our study.

Most of the patients of our cohort were elderly. Advanced age may explain the higher COVID-19-related mortality in patients with diabetes. Moreover, age and comorbidities are often criteria that reduce admission to ICU. However, Cariou et al. with the CORONADO initiative [45], have recently showed that diabetes was associated with poorer COVID-19 prognosis independently of age. In our cohort, metformin use was associated with decreased probability of death. Several studies reporting similar findings

showed an even greater beneficial effect of metformin by reducing in-hospital admissions, ICU admissions and length of hospital stay [31,33,46]. Han et al. confirmed the decreased mortality risk linked to metformin use in a recent meta-analysis [47]. They calculated an overall OR of 0.62 [0.5–0.76], which is close to ours. The underlying mechanisms remains unknown. Metformin may have an anti-inflammatory effect [48]. Beyond mechanistic explanations, metformin could be a mere bystander as it is contraindicated in patients with severe CKD, liver failure or chronic hypoxemic conditions. Furthermore, metformin use is higher in patients with a shorter duration of diabetes, who are often younger. Therefore, the positive impact of metformin use on COVID-19 prognosis may be related to patients' characteristics rather than a pharmacological effect of its own. Furthermore, a recent randomized controlled trial involving patients with overweight and obesity reported that metformin did not prevent hypoxemia, emergency department visit, hospitalization, or death related to COVID-19 [49].

HbA1c level was not associated with death in our cohort, as previously reported in the CORONADO and ACCREDIT studies. The excess mortality associated with poor glycemic control (i.e. higher HbA1c) was only reported in large Anglo-Saxon registry-based studies [20–22,25,29]. Nevertheless, other studies reported a positive relationship between HbA1c and the risk for COVID-19-related hospitalization [26–29]. Thus, elevated HbA1c seems to be a risk factor of poor prognosis of COVID-19.

The CORONADO study showed that a higher BMI was associated with poor prognosis including IMV and death [33]. Ruan et al. showed that a higher BMI was associated with increased in-hospital mortality and/or ICU admission related to COVID-19 in patients with T1DM. Irrespective of diabetes, the adverse impact of higher BMI on COVID-19 prognosis in the general English population was demonstrated when BMI is higher than 23 kg/m² [32]. However, compared to the general population, the impact of weight on the prognosis of COVID-19 may be somewhat mitigated in patients with diabetes [9]. Finally, only two UK studies have shown that increasing BMI proportionally increases mortality from COVID-19 in patients with diabetes [19,28].

In our study, microvascular disease was not associated with in-hospital mortality. The ACCREDIT study did not associate microvascular and/or macrovascular complications with higher risk of COVID-19-related death either [34]. The CORONADO study showed that having microvascular disease increased in-hospital mortality with COVID-19 despite of a lower proportion of T1DM, less patients with microangiopathy and an equivalent duration of diabetes than the ACCREDIT study [31,33]. In comparison with these studies, T1DM and microvascular disease were less prevalent in our population, but median duration of diabetes was similar (11 years). Regarding patients with T1DM, Ruan et al. associated the presence of one or more microvascular complications with increased in-hospital mortality and/or ICU admission [32]. Two large population-based studies from the UK, including T1DM and T2DM, showed that microangiopathy was associated with an increased risk of death or ICU admission [20,22]. Thus, the impact of microvascular complications on the prognosis of COVID-19 is still debated.

We showed no effect of hydroxychloroquine treatment on the prognosis of inpatients with diabetes. The ineffectiveness of hydroxychloroquine in treating hospitalized people with COVID-19 was confirmed later, at the end of 2020 [50].

Our study has some obvious limitations. Due to the retrospective design, data were missing for some variables, in particular diabetes duration, HbA1c, and BMI. Hyperglycemia-related complications were not systematically assessed. The cohort, although multicenter, was small compared to other studies but not in relation with the Belgian population. The strengths of our study include its multicenter design as well as a multivariate analysis.

In conclusion, this is the first study describing the clinical characteristics and prognosis of inpatients with diabetes and COVID-19 during the first two months of the pandemic in Belgium. Older age, male gender and elevated CRP on admission were independent risk factors for in-hospital death from COVID-19. In contrast, prior metformin and RAAS blockers use were independent protective factors. In our study, neither HbA1c, diabetes type and duration, nor prevalent microvascular complications were associated with poor prognosis. Finally, we showed that CKD is a COVID-19-related mortality risk factor in patients with diabetes admitted in the ICU.

Disclosure of interest

The authors declare that they have no competing interest.

Human and animal rights

Not applicable.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Credit Author Statement

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Thomas Roland: resources.

Camelia Rossi: resources.

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Laura Orioli: conceptualization, methodology, validation, formal analysis, investigation, data curation, writing – review and editing, supervision, project administration.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ando.2023.08.002>.

References

- [1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33, <http://dx.doi.org/10.1056/NEJMoa2001017>.
- [2] COVID-19 United States Cases by County. Johns Hopkins Coronavirus Resource Center n.d. <https://coronavirus.jhu.edu/us-map>. (accessed April 19, 2022).
- [3] The novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) – China, 2020. *China CDC Weekly* 2020;2:113–22, <http://dx.doi.org/10.46234/ccdcw2020.032>.
- [4] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62, [http://dx.doi.org/10.1016/S0140-6736\(20\)30566-3](http://dx.doi.org/10.1016/S0140-6736(20)30566-3).
- [5] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20, <http://dx.doi.org/10.1056/NEJMoa2002032>.
- [6] Guan W-J, Liang W-H, Zhao Y, Liang H-R, Chen Z-S, Li Y-M, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020;55:2000547, <http://dx.doi.org/10.1183/13993003.00547-2020>.
- [7] Akkiz H. The biological functions and clinical significance of SARS-CoV-2 variants of Concern. *Front Med (Lausanne)* 2022;9:849217, <http://dx.doi.org/10.3389/fmed.2022.849217>.
- [8] Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis* 2021;21:855, <http://dx.doi.org/10.1186/s12879-021-06536-3>.
- [9] Longmore DK, Miller JE, Bekkering S, Saner C, Mifsud E, Zhu Y, et al. Diabetes and overweight/obesity are independent, nonadditive risk factors for in-hospital severity of COVID-19: An international, multicenter retrospective meta-analysis. *Diabetes Care* 2021;44:1281–90, <http://dx.doi.org/10.2337/dc20-2676>.
- [10] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020:e3319, <http://dx.doi.org/10.1002/dmrr.3319>.
- [11] Alkundi A, Mahmoud I, Musa A, Naveed S, Alshawwaf M. Clinical characteristics and outcomes of COVID-19 hospitalized patients with diabetes in the United Kingdom: a retrospective single centre study. *Diabetes Res Clin Pract* 2020;165:108263, <http://dx.doi.org/10.1016/j.diabres.2020.108263>.
- [12] Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. *Diabetes Care* 2020;43:1382–91, <http://dx.doi.org/10.2337/dc20-0598>.
- [13] Moon SJ, Rhee E-J, Jung J-H, Han K-D, Kim S-R, Lee W-Y, et al. Independent impact of diabetes on the severity of coronavirus disease 2019 in 5,307 patients in South Korea: a nationwide cohort study. *Diabetes Metab J* 2020;44:737–46, <http://dx.doi.org/10.4093/dmj.2020.0141>.
- [14] Orioli L, Servais T, Belkhir L, Laterre P-F, Thissen J-P, Vandeleene B, et al. Clinical characteristics and short-term prognosis of in-patients with diabetes and COVID-19: a retrospective study from an academic center in Belgium. *Diabetes Metab Syndr* 2021;15:149–57, <http://dx.doi.org/10.1016/j.dsx.2020.12.0200>.
- [15] Ciardullo S, Zerbini F, Perra S, Muraca E, Cannistraci R, Lauriola M, et al. Impact of diabetes on COVID-19-related in-hospital mortality: a retrospective study from Northern Italy. *J Endocrinol Invest* 2021;44:843–50, <http://dx.doi.org/10.1007/s40618-020-01382-7>.
- [16] Aziz F, Aberer F, Bräuer A, Ciardi C, Clodi M, Fasching P, et al. COVID-19 in-hospital mortality in people with diabetes is driven by comorbidities and age-propensity score-matched analysis of Austrian national public health institute data. *Viruses* 2021;13:2401, <http://dx.doi.org/10.3390/v13122401>.
- [17] Bailly L, Fabre R, Courjon J, Carles M, Dellamonica J, Pradier C. Obesity, diabetes, hypertension and severe outcomes among inpatients with coronavirus disease 2019: a nationwide study. *Clin Microbiol Infect* 2022;28:114–23, <http://dx.doi.org/10.1016/j.cmi.2021.09.010>.
- [18] Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – A systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr* 2020;14:395–403, <http://dx.doi.org/10.1016/j.dsx.2020.04.018>.
- [19] Barron E, Bakhtai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020;8:813–22, [http://dx.doi.org/10.1016/S2213-8587\(20\)30272-2](http://dx.doi.org/10.1016/S2213-8587(20)30272-2).
- [20] Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020;8:823–33, [http://dx.doi.org/10.1016/S2213-8587\(20\)30271-0](http://dx.doi.org/10.1016/S2213-8587(20)30271-0).
- [21] Gregory JM, Slaughtter JC, Duffus SH, Smith TJ, LeSturgeon LM, Jaser SS, et al. COVID-19 severity is tripled in the diabetes community: a prospective analysis of the pandemic's impact in type 1 and type 2 diabetes. *Diabetes Care* 2021;44:526–32, <http://dx.doi.org/10.2337/dc20-2260>.
- [22] McGurnaghan SJ, Weir A, Bishop J, Kennedy S, Blackburn LAK, McAllister DA, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. *Lancet Diabetes Endocrinol* 2021;9:82–93, [http://dx.doi.org/10.1016/S2213-8587\(20\)30405-8](http://dx.doi.org/10.1016/S2213-8587(20)30405-8).
- [23] Figliozzi S, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, et al. Predictors of adverse prognosis in COVID-19: a systematic review and meta-analysis. *Eur J Clin Invest* 2020;50:e13362, <http://dx.doi.org/10.1111/eci.13362>.
- [24] Li Y, Ashcroft T, Chung A, Dighero I, Dozier M, Horne M, et al. Risk factors for poor outcomes in hospitalised COVID-19 patients: a systematic review and meta-analysis. *J Glob Health* 2021;11:10001, <http://dx.doi.org/10.7189/jogh.11.10001>.
- [25] Hamer M, Gale CR, Batty GD. Diabetes, glycaemic control, and risk of COVID-19 hospitalisation: population-based, prospective cohort study. *Metabolism* 2020;112:154344, <http://dx.doi.org/10.1016/j.metabol.2020.154344>.
- [26] O'Malley G, Ebekozien O, Desimone M, Pinnaro CT, Roberts A, Polsky S, et al. COVID-19 hospitalization in adults with type 1 diabetes: results from the T1D exchange multicenter surveillance study. *J Clin Endocrinol Metab* 2021;106:e936–42, <http://dx.doi.org/10.1210/clinem/dgaa825>.
- [27] Merzon E, Green I, Shpigelman M, Vinker S, Raz I, Golan-Cohen A, et al. Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes. *Diabetes Metab Res Rev* 2021;37:e3398, <http://dx.doi.org/10.1002/dmrr.3398>.
- [28] Kristan MM, Kim YK, Nelson T, Moxley MC, Yip TC-F, Munir K, et al. Predictors of severe COVID-19 in patients with diabetes: a multicenter review. *Endocr Pract* 2021;27:842–9, <http://dx.doi.org/10.1016/j.eprac.2021.05.011>.
- [29] Min JY, Williams N, Simmons W, Banerjee S, Wang F, Zhang Y, et al. Baseline haemoglobin A1c and the risk of COVID-19 hospitalization among patients with diabetes in the INSIGHT Clinical Research Network. *Diabet Med* 2020;39:e14815, <http://dx.doi.org/10.1111/dme.14815>.
- [30] Schlesinger S, Neuenschwander M, Lang A, Pafili K, Kuss O, Herder C, et al. Risk phenotypes of diabetes and association with COVID-19 severity and death: a living systematic review and meta-analysis. *Diabetologia* 2021;64:1480–91, <http://dx.doi.org/10.1007/s00125-021-05458-8>.
- [31] Wargny M, Potier L, Gourdy P, Pichelin M, Amadou C, Benhamou P-Y, et al. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. *Diabetologia* 2021;64:778–94, <http://dx.doi.org/10.1007/s00125-020-05351-w>.
- [32] Ruan Y, Ryder REJ, De P, Field BCT, Narendran P, Iqbal A, et al. A UK nationwide study of people with type 1 diabetes admitted to hospital with COVID-19 infection. *Diabetologia* 2021;64:1717–24, <http://dx.doi.org/10.1007/s00125-021-05463-x>.
- [33] Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* 2020;63:1500–15, <http://dx.doi.org/10.1007/s00125-020-05180-x>.
- [34] Llanera DK, Wilmington R, Shoo H, Lisboa P, Jarman I, Wong S, et al. Clinical characteristics of COVID-19 patients in a regional population with diabetes Mellitus: the ACCREDIT study. *Front Endocrinol (Lausanne)* 2021;12:777130, <http://dx.doi.org/10.3389/fendo.2021.777130>.
- [35] Sciensano. Surveillance de la sante et des maladies – Diabète – Chiffres. Sciensano.be n.d. <https://www.sciensano.be/fr/sujets-sante/diabete/chiffres>. (accessed April 25, 2022).
- [36] Van der Heyden J, Charafeddine R. Enquête de santé 2018 : Maladies et affections chroniques. SciensanoBe; 2019 [accessed September 19, 2022, https://www.sciensano.be/sites/default/files/ma_fr_2018.pdf].
- [37] Sciensano. COVID-19 Bulletin Épidémiologique Hebdomadaire – 30 septembre 2022. Info-CoronavirusBe 2022. <https://covid-19.sciensano.be/sites/default/files/Covid19/Derni%C3%A8re%20mise%20%C3%A0%20jour%20de%20la%20situation%20%C3%A9pid%C3%A9miologique.pdf>. (accessed October 3, 2022).
- [38] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020;324:782–93, <http://dx.doi.org/10.1001/jama.2020.12839>.
- [39] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for disease control and prevention. *JAMA* 2020;323:1239–42, <http://dx.doi.org/10.1001/jama.2020.2648>.
- [40] Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med* 2020;383:2451–60, <http://dx.doi.org/10.1056/NEJMcp2009575>.
- [41] Balan TA, Putter H. A tutorial on frailty models. *Stat Methods Med Res* 2020;29:3424–54, <http://dx.doi.org/10.1177/0962280220921889>.
- [42] Izzi-Engbeaya C, Distaso W, Amin A, Yang W, Idowu O, Kenkre JS, et al. Adverse outcomes in COVID-19 and diabetes: a retrospective cohort study from three London teaching hospitals. *BMJ Open Diabetes Res Care* 2021;9:e001858, <http://dx.doi.org/10.1136/bmjdc-2020-001858>.
- [43] Kaminska H, Szarpak L, Kosior D, Wiecek W, Szarpak A, Al-Jeabory M, et al. Impact of diabetes mellitus on in-hospital mortality in adult

- patients with COVID-19: a systematic review and meta-analysis. *Acta Diabetol* 2021;58:1101–10, <http://dx.doi.org/10.1007/s00592-021-01701-1>.
- [44] Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. *J Clin Virol* 2020;127:104354, <http://dx.doi.org/10.1016/j.jcv.2020.104354>.
- [45] Cariou B, Wargny M, Boureau A-S, Smati S, Tramunt B, Desailoud R, et al. Impact of diabetes on COVID-19 prognosis beyond comorbidity burden: the CORONADO initiative. *Diabetologia* 2022;65:1436–49, <http://dx.doi.org/10.1007/s00125-022-05734-1>.
- [46] Ojeda-Fernández L, Foresta A, Macaluso G, Colacioppo P, Tettamanti M, Zambon A, et al. Metformin use is associated with a decrease in the risk of hospitalization and mortality in COVID-19 patients with diabetes: a population-based study in Lombardy. *Diabetes Obes Metab* 2022;24:891–8, <http://dx.doi.org/10.1111/dom.14648>.
- [47] Han T, Ma S, Sun C, Zhang H, Qu G, Chen Y, et al. Association between anti-diabetic agents and clinical outcomes of COVID-19 in patients with diabetes: a systematic review and meta-analysis. *Arch Med Res* 2022;53, <http://dx.doi.org/10.1016/j.arcmed.2021.08.002>.
- [48] Cameron AR, Morrison VL, Levin D, Mohan M, Forteach C, Beall C, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. *Circ Res* 2016;119:652–65, <http://dx.doi.org/10.1161/CIRCRESAHA.116.308445>.
- [49] Bramante CT, Huling JD, Tignanelli CJ, Buse JB, Liebovitz DM, Nicklas JM, et al. Randomized trial of metformin, ivermectin, and fluvoxamine for covid-19. *N Engl J Med* 2022;387:599–610, <http://dx.doi.org/10.1056/NEJMoa2201662>.
- [50] Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate covid-19. *N Engl J Med* 2020;383:2041–52, <http://dx.doi.org/10.1056/NEJMoa2019014>.