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Diabetes associates with mortality in critically ill patients with SARS-CoV-2 pneumonia: No diabetes paradox in COVID-19

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ABSTRACT

Background: Diabetes mellitus (DM) is not associated with increased mortality in critically ill patients, a phenomenon known as the "diabetes paradox". However, DM is a risk factor for increased mortality in patients with COVID-19. This study aims to investigate the association of DM and stress-induced hyperglycemia at intensive care unit (ICU) with mortality in this population.

Methods: This is a retrospective study. Electronic medical records from patients admitted from March 2020 to September 2020 were reviewed. Primary outcome was mortality. Secondary outcomes were ICU and hospital mortality and stay, and need for mechanical ventilation and renal replacement therapy.

Results: 187 patients were included. Overall mortality was 43.2%, higher in patients with DM (55.7% vs. 34%; $p = 0.007$), even after adjustment for age, hypertension, and disease severity. When patients were separated into groups, named normoglycemia (without DM and glycemia $\leq$140 mg/dL), stress-induced hyperglycemia (without DM and glycemia >140 mg/dL), and DM (previous diagnosis or HbA1c $\geq$ 6.5%), the mortality rate was 25.8%, 37.3%, and 55.7%, respectively ($p = 0.021$). Mortality was higher in patients with higher glycemic variability. No statistical difference related to secondary outcomes was observed.

Conclusions: DM, hyperglycemia, and glycemic variability associated with increased mortality in critically ill patients with severe COVID-19, but did not increase the rates of other clinical outcomes. More than stress-induced hyperglycemia, DM was associated with mortality.

1. Introduction

During the COVID-19 pandemic, several studies have reported that patients with diabetes mellitus (DM) have a higher risk of severe

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Abbreviation list

DM	diabetes mellitus
ICU	intensive care unit
HbA1c	glycates hemoglobin
MV	mechanical ventilation
ICU-AW	ICU-acquired muscular weakness
LOS	length of stay
SAPS III	Simplified Acute Physiology Score III
ADA	American Diabetes Association
RRT	renal replacement therapy
SD	standard deviation
HR	hazard ratio
BMI	body mass index

SARS-CoV-2 infection [1]. These patients have a greater likelihood of hospitalization, intensive care unit (ICU) admission, and need for mechanical ventilation [1]. Interestingly, prior to the pandemic, DM was not associated with increased mortality in ICU patients [2], contrary to what might be anticipated based on the known complications and risks associated with DM in other settings. In general, DM is recognized as a chronic condition that predisposes individuals to various health complications, including cardiovascular disease, renal dysfunction, infections, retinopathy, and neuropathy [3]. These complications can contribute to higher morbidity and mortality rates in the general population [4]. However, within the ICU, the impact of DM on mortality appears to be different. This phenomenon is known as the "diabetes paradox". It suggests that in the ICU setting other factors such as the severity of the acute illness may overshadow the direct impact of DM on mortality.

While stress-induced hyperglycemia is linked to higher mortality, the literature does not clarify whether hyperglycemia is a marker of disease severity or a determinant of prognosis [5,6]. Furthermore, other altered glycemic parameters like hypoglycemia, glycemic variability, and glycemic gap [7,8] are related to worse outcomes [9]. In a general population of critically ill patients, Bellaver et al. [9] demonstrated that hypoglycemia and hyperglycemia on ICU admission were independently associated with increased mortality, whereas a higher glycemic gap and a higher glycemic variability were associated with other negative clinical outcomes, such as need for renal replacement therapy and shock incidence. In patients with COVID-19, Bhatti et al. [10] found that a more strict metabolic control, with random blood glucose levels lower than 160 mg/dL and fasting blood glucose levels lower than 126 mg/dL, is associated with a considerably lower risk of mortality.

Chronic hyperglycemia may trigger protective mechanisms against cell damage, which may explain the diabetes paradox and why patients with poor chronic glycemic control have worse outcomes when treated with intensive glycemic control in ICU [11]. By measuring the glycemic gap preexisting chronic hyperglycemia can be distinguished from stress-induced hyperglycemia [12]. Although the unfavorable effects of dysglycemia on critically ill patients are well known, the impact of stress-induced hyperglycemia in ICU patients with COVID-19 and the diabetes paradox are still unclear. Therefore, this study aims to explore the association of acute and chronic glycemic parameters with clinical outcomes in critically ill patients with severe acute respiratory failure due to SARS-CoV-2 infection.

2. Material and methods

2.1. Ethical considerations

The study was approved by the Ethics Committee at the Hospital de Clínicas de Porto Alegre (project number 2020-0218) and adhered to the Helsinki Declaration.

2.2. Study population

This is a retrospective study. Informed consent was obtained. The study assessed critically ill adults (aged >18 years) admitted to the ICU from March 2020 to September 2020. The inclusion criterion was patients admitted to ICU with SARS-CoV-2 infection with one HbA1c measurement available at ICU admission or with the possibility to measure it by using blood stored at the COVID-19 Collection in the Biobank. Exclusion criteria were diabetic ketoacidosis, hyperosmolar hyperglycemic state, hemoglobinopathies, and ICU length of stay (LOS) less than 24 h. Clinical and laboratory data were recorded for all patients. The Simplified Acute Physiology Score 3 (SAPS 3) was used to score disease severity [13]. Data referring to demographic characteristics of the study population, as well as coexisting medical conditions, reasons for ICU admission, origin before ICU admission, nutrition and insulin therapy were extracted from the review of the electronic medical record. SAPS 3 and other variables related to disease severity, such as use of vasopressor, need for MV and RRT, were also extracted from medical records. Routine laboratory tests provided data related to biochemical measurements. Especially regarding HbA1c, it could be available at ICU admission or measured from blood sample stored ate the Biobank. All data extracted from electronic medical records were independently reviewed by two researchers. Outcomes were adjudicated by two

researchers independently.

Diabetes was defined based on previous diagnosis or whenever HbA1c was ≥6.5%. Hyperglycemia was defined according to the American Diabetes Association (ADA) proposed threshold for in-hospital hyperglycemia, and severe hyperglycemia as any blood glucose measurement >200 mg/dL. Patients without previous history of DM, HbA1c <6.5%, and glycemia ≤140 mg/dL were classified as the normoglycemia group. Those without previous history of DM, HbA1c <6.5%, and glycemia >140 mg/dL were classified as stress-induced hyperglycemia group [14]. Hypoglycemia was defined as any glycemic level <70 mg/dL [11,14], and serious hypoglycemia was defined as <54 mg/dL during the first day in the ICU [14]. Glucose variability was calculated as the absolute difference in capillary blood glucose during the first ICU day [15,16]. The glycemic gap was calculated as the difference between the ICU admission serum blood glucose and the estimated mean blood glucose, estimated by the HbA1c [12,17]. Patients were separated by a cutoff value of 80 mg/dL for glycemic gap and 40 mg/dL for glycemic variability based on Bellaver et al. [9] and Liao et al. [18].

The outcomes of interest were mortality (primary endpoint) and ICU and hospital mortality, need for mechanical ventilation (VM), need for renal replacement therapy (RRT), length of stay at the ICU and at the hospital, and ICU readmission (secondary endpoints).

2.3. Statistical analysis

Statistical analysis included the use of the Student's t-test, Mann–Whitney *U* test, or chi-square test, as appropriate. Univariate linear regression or logistic regression models were constructed depending on the characteristics of the outcomes of interest. Kaplan-Meier method was used to perform time-to-event analyses. Time-to-event effect size (hazard ratios, HR) was estimated by Cox proportional hazard analyses with mortality as outcome and variables adjusted for age, presence of hypertension, and disease severity using SAPS 3 score and need of vasopressors. A sample size of 182 patients was calculated for this study. Values were considered statistically significant if $p < 0.05$. Statistical analyses were conducted in the software program SPSS 20.0 (Chicago, IL, USA).

3. Results

Fig. 1 shows the summary of the study.

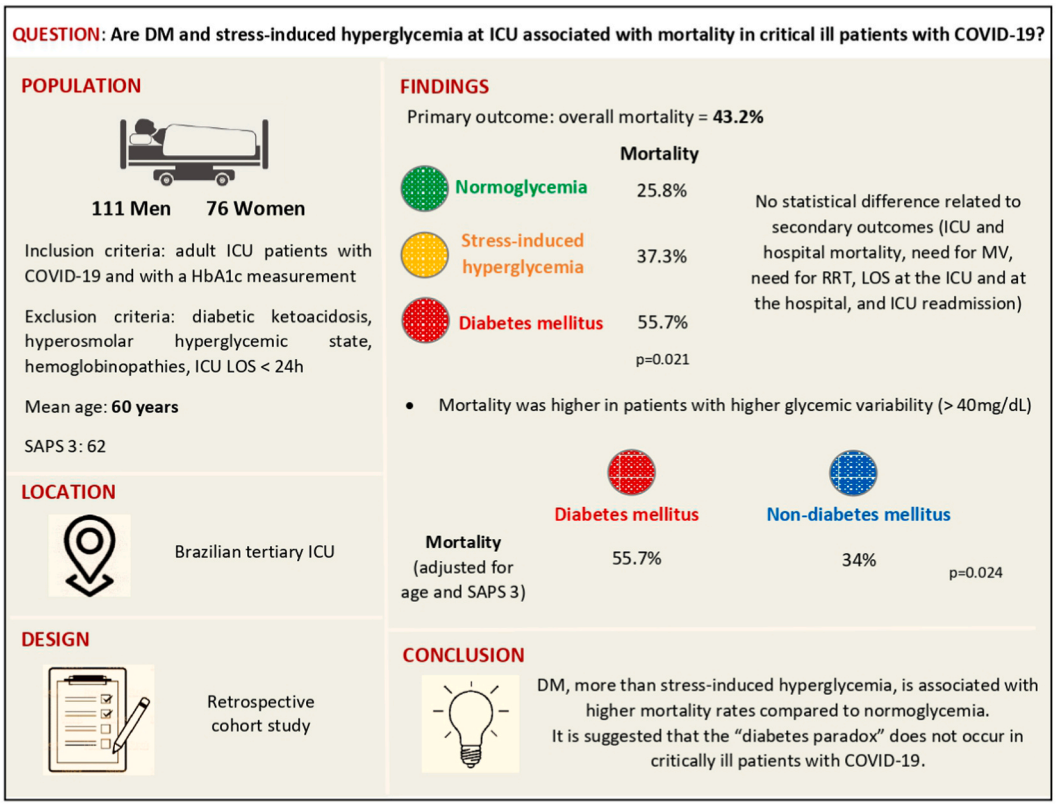

Fig. 1. Flow chart of the study. DM: diabetes mellitus; ICU: intensive care unit; LOS: lenght of stay; MV: mechanical ventilation; RRT: renal replacement therapy.

Table 1
Baseline characteristics of patients.

Characteristics	All patients	Patients with normoglycemia n = 31	Patients with stress- induced hyperglycemia n = 75	Patients with DM n = 79	p
Demographycs					
Age (years)	60 ± 15	53 ± 16[a]	59 ± 15	63 ± 12[a]	0.03
Men (n, %)	111 (60)	17 (54.8)	48 (64)	46 (58.2)	0.623
BMI (kg/m^2)	30.7 ± 7.2	30.8 ± 7	29.7 ± 6.6	31.7 ± 7.8	0.226
Coexisting conditions					
Hypertension (n, %)	114 (61.6)	13 (41.9)[b,c]	41 (54.7)[b]	60 (76)[b,c]	0.001
Diabetes (n, %)	79 (42.7)	0	0	79 (100)	–
Cancer (n, %)	16 (8.6)	3 (9.7)	6 (8)	7 (8.9)	0.958
Chronic kidney disease (n, %)	16 (8.6)	2 (6.5)	6 (8)	8 (10.1)	0.799
Ischemic heart disease (n, %)	20 (10.8)	1 (3.2)	7 (9.3)	12 (15.2)	0.166
Heart failure (n %)	15 (8.1)	1 (3.2)	7 (9.3)	7 (8.9)	0.548
COPD (n, %)	18 (9.7)	2 (6.5)	6 (8)	10 (12.7)	0.495
Asthma (n, %)	21 (11.4)	4 (12.9)	7 (9.3)	10 (12.7)	0.774
Transplantation (n, %)	6 (3.2)	0	4 (5.3)	2 (2.5)	0.331
Immunosuppresion (n, %)	10 (5.4)	1 (3.2)	6 (8)	3 (3.8)	0.433
Previous use of corticosteroids	51 (28.8)	7 (23.3)	22 (31)	22 (28.9)	0.74
Reasons for ICU admission					0.814
Acute respiratory failure (n, %)	177 (96)	29 (93)	72 (96)	76 (96)	
Other (n, %)	8 (4)	2 (7)	3 (4)	3 (4)	
Place before ICU admission					0.228
Emergency room (n, %)	54 (29)	8 (26)	18 (24)	28 (35)	
Medical unit (n, %)	46 (25)	11 (35)	21 (28)	14 (18)	
External transfer (n, %)	85 (46)	12 (38)	36 (38)	37 (47)	
Disease severity					
SAPS 3 score	62 ± 16	57 ± 16	61 ± 15	64 ± 16	0.15
Presence of sepsis (n, %)	166 (89.7)	28 (90.3)	68 (90.7)	70 (88.6)	0.9
Pulmonary (n, %)	161 (87)	26 (83.4)	65 (86.7)	70 (88.6)	
Other (n, %)	5 (2.7)	2 (7.1)	3 (4.4)	0	
Need for vasopressors (n, %)	99 (53.5)	10 (32.3)[d]	43 (57.3)	46 (58.2)	0.034
Need for renal replacement therapy (n, %)	60 (32.4)	11 (35.5)	21 (28)	28 (35.4)	0.568
Need for invasive mechanic ventilation (n, %)	137 (74.1)	22 (71)	56 (74.7)	59 (74.7)	0.912
Prone position (n, %)	71 (38.4)	13 (41.9)	30 (40)	28 (35.4)	0.764
ECMO (n, %)	2 (1.1)	1 (3.2)	1 (1.3)	0	0.326
Use of corticosteroids (n, %)	126 (71.2)	19 (70.4)	54 (74)	53 (68.8)	0.781
Nutrition					0.876
None (n, %)	30 (16)	5 (16)	11 (37)	14 (47)	
Oral or enteral (n, %)	155 (84)	26 (84)	64 (85)	65 (42)	
Insulin therapy					
Long-acting insulin, first 24 h from admission (n, %)	28 (15.3)	0	2 (2.7)	26 (33.3)	<0.0001
Short-acting insulin, first 24 h from admission (n, %)	89 (51.4)	4 (13.8)	29 (41.4)	56 (75.7)	<0.0001
Biochemical measurements					
Hematocrit (%)	37.1 ± 5.9	36.6 ± 5.7	37.5 ± 6	36.9 ± 6	0.723
Hemoglobin (g/dL)	12.3 ± 2.1	12.2 ± 2	12.4 ± 2.2	12.2 ± 2.1	0.788
Leukocytes (10^3/mm^3)	10.9 ± 5.8	9 ± 3.9	11.4 ± 6.7	11.1 ± 5.4	0.135
Lymphocytes (%)	9.4 ± 7	10.3 ± 6.5	7.9 ± 5.8	10.4 ± 8	0.071
Platelets (10^3/uL)	230 (164–284)	203 (148–250)	233 (167–278)	229 (159–306)	0.315
Creatinine (mg/dL)	1.1 (0.8–1.7)	0.9 (0.7–1.9)	1.1 (0.8–1.8)	1.1 (0.8–1.6)	0.715
Potassium (mEq/L)	4.4 ± 0.6	4.3 ± 0.5	4.4 ± 0.7	4.4 ± 0.6	0.668
CRP (mg/dL)	151 (86–220)	142 (77–216)	146 (86–219)	152 (95–225)	0.316
Lactate (mmol/L)	1.9 ± 0.4	1.2 ± 0.5	2.3 ± 0.7	1.9 ± 0.3	0.54
Blood glucose (mg/dL)	174 ± 106	104 ± 12[a]	125 ± 44[e]	245 ± 122[a,e]	<0.0001
HbA1C (%)	6.8 ± 2	5.6 ± 0.4[a]	5.7 ± 0.4[e]	8.3 ± 2.2[a,e]	<0.0001

DM: diabetes mellitus; BMI: body mass index; SAPS 3 score: Simplified Acute Physiology 3 score; COPD: chronic obstructive pulmonary disease; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; CRP: C-reactive protein; HbA1c: glycated hemoglobin. Values are mean ± SD or median and interquartile range.

[a,e:] values are statistically different between groups, ANOVA with Bonferroni post-hoc test.

[b,c,:] values are statistically different between groups, chi-square test.

[d:] values are statistically different from other groups, chi-square test.

3.1. Patient characteristics

A total of 556 patients admitted to the ICU with SARS-CoV-2 infection were evaluated for eligibility. Then, 187 patients had HbA1c results available and were included in this study. Table 1 shows their main characteristics. Briefly, 60% were male, mean age was 60 ± 15 years, and SAPS 3 score was 62 ± 16. The most common primary coexisting condition was hypertension (61.6%), which was more frequent in non-survivors than in survivors (70.4% vs. 50.4%, p = 0.029). Presence of DM was based on previous diagnosis in 62 patients (33.2%) and on HbA1c quantification in additional 17 patients (9%), totalizing 79 patients with DM (42,7%). Acute respiratory failure was the main reason for ICU admission (96%), with 74.1% of patients requiring invasive MV. Most patients received antibiotics for presumed sepsis from pulmonary origin (87%) and 71.2% received corticosteroids.

3.2. Metabolic parameters and mortality

Table 2 shows that the overall mortality rate was 43.2% (n = 80), which was higher in critically ill patients with severe COVID-19 pneumonia with DM than in those without DM (55.7% vs. 34%; p = 0.007). This association persists even after adjustment for age, hypertension, and disease severity estimated by the need for vasopressors (p = 0.033). Fig. 2 shows the probability of survival according to the presence or absence of DM, after adjusting for age, hypertension, SAPS 3 score, and vasopressors use. When patients were separated into the normoglycemia, stress-induced hyperglycemia, and DM groups mortality rate was 25.8%, 37.3%, and 55.7%, respectively, with significant difference of mortality between patients with DM and those with normoglycemia (p = 0.021). Fig. 3 shows the individuals' time until death in the three groups. The mean HbA1c was 6.8 ± 2% and the mean blood glucose was 174 ± 106 mg/dL, different among patients with normoglycemia, stress-induced hyperglycemia, or DM, as expected (Table 1), but no difference was found between survivors and non-survivors (Supplementary Table 1). Hyperglycemia (glucose >140 mg/dL) was present in 80% (n = 149) of patients and severe hyperglycemia (glucose >200 mg/dL) in 43% (n = 81) within the first 24 h of ICU admission. Patients who had hyperglycemia >140 mg/dL and hyperglycemia >200 mg/dL in the first 24 h of ICU admission had higher mortality rates compared to those who presented lower glycemic parameters (47% vs. 26%, p = 0.048) and (56% vs. 34%, p = 0.003), respectively.

The median glycemic variability was 67 mg/dL (38 to 149 mg/dL) and the glycemic gap varied from −16 to 65 mg/dL, with a median of 14 mg/dL. In critically ill patients with severe COVID-19 pneumonia, mortality rate was higher in those with glycemic variability >40 mg/dL compared to those with <40 mg/dL (48.4% vs. 26.7%, p = 0.011). No differences in mortality rates were detected between patients with a glycemic gap below or above >80 mg/dL (42.3% vs. 48.6%, p = 0.484) (Table 3).

Hypoglycemia was a rare event. Glycemic values < 70 mg/dL occurred in five patients (2.7%) and severe hypoglycemia <54 mg/dL occurred in one patient (0.5%), not affecting mortality (p = 0.45 and p = 0.38, respectively).

Mean body mass index (BMI) was 30.7 ± 7.2 kg/m^2, similar between patients with normoglycemia, stress-induced hyperglycemia, or DM (Table 1), but higher in survivors than in non-survivors (31.8 ± 7.6 vs. 29.2 ± 6.4, p = 0.012).

3.3. Glycemic parameters and other outcomes

Table 2 shows that the need for MV, need for RRT, ICU and hospital length of stay, and ICU readmission rate were similar between patients with normoglycemia, stress-induced hyperglycemia, or DM. Table 3 shows the impact of glycemic gap, glycemic variability, and hypoglycemia <70 mg/dL on secondary outcomes. All these glycemic parameters were not different for secondary outcomes. Mean glycated hemoglobin was not different between survivors and non-survivors (6.2 ± 1.9 vs. 7 ± 2, p = 0.131), between patients who need RRT or not (6.7 ± 1.5 vs. 6.8 ± 2.1, p = 0.736), and between patients who need MV or not (6.7 ± 1.8 vs. 7.1 ± 2.5, p = 0.275).

4. Discussion

In this retrospective cohort study of 187 critically ill patients with severe COVID-19 pneumonia, DM and hyperglycemia at ICU admission were independently associated with increased mortality, but not with increased need for supportive therapies, ICU and

Table 2
Effects of hyperglycemia on clinical outcomes in critically ill patients with severe Covid-19.

Outcomes	All patients	Patients with normoglycemia	Patients with stress-induced hyperglycemia	Patients with DM	p
Mortality (n, %)	80 (43.2)	8 (25.8)[a,b]	28 (37.3)[b]	44 (55.7)[a,b]	**0.021**
Need for RRT (n, %)	60 (32.4)	11 (35.5)	21 (28)	28 (35.4)	0.568
Need for VM (n, %)	137 (74.1)	22 (71)	56 (74.7)	59 (74.7)	0.912
ICU readmission (n, %)	4 (2.2)	0	2 (2.7)	2 (2.5)	0.662
Time on VM (days)	16 (9–26)	17.5 (8.3–26.3)	15 (6.5–23.8)	17 (10.3–28)	0.685
LOS, hospital (days)	19 (10–36)	22 (10–35)	21 (9–37)	17 (10–29)	0.708
LOS, ICU (days)	14 (6–26)	19 (8–27)	14 (6–26)	14 (6–23)	0.839

RRT: renal replacement therapy; MV: mechanical ventilation; LOS: length of stay; ICU: intensive care unit. Values are mean ± SD or median and interquartile range.
[a, b:] values are statistically different between groups, chi-square test.

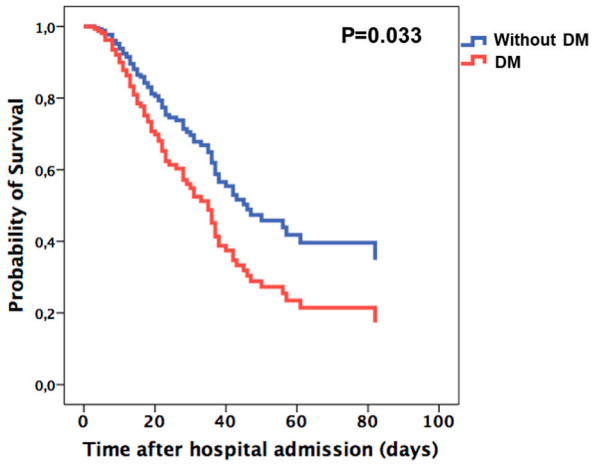

Fig. 2. Probability of survival according to the presence or absence of DM after adjusting for age, presence of hypertension, and disease severity using SAPS 3 score and need of vasopressors. DM: diabetes mellitus.

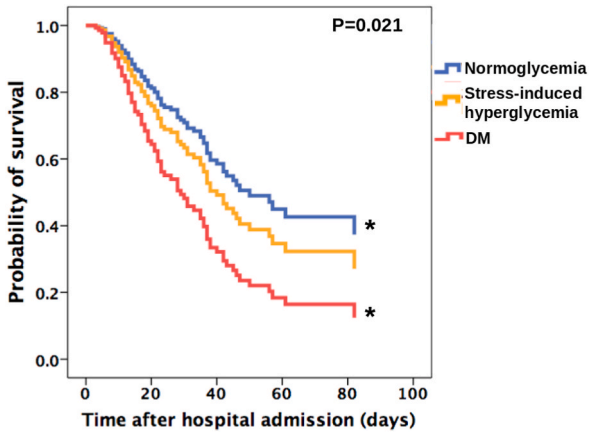

Fig. 3. Probability of survival according to glycemic status. DM: diabetes mellitus. *: difference between groups.

Table 3
Effects of glycemic gap and glycemic variability on clinical outcomes in critically ill patients with severe COVID-19 pneumonia.

Outcomes	Glycemic gap		p	Glycemic variability		p
	<80 mg/dL n = 149	>80 mg/dL n = 37		<40 mg/dL n = 45	>40 mg/dL n = 128	
Mortality (n, %)	63 (42.3)	18 (48.6)	0.484	12 (26.7)	62 (48.4)	**0.011**
Need for RRT (n, %)	47 (31.5)	13 (35.1)	0.676	13 (28.9)	43 (33.6)	0.562
Need for MV (n, %)	109 (73.2)	30 (81.1)	0.321	32 (71.1)	95 (74.2)	0.685
ICU readmission (n, %)	4 (2.7)	0	0.314	0	4 (3.1)	0.23
Time on MV (days)	16 (9–26)	17 (8–27.3)	0.969	16.5 (9.3–26.8)	15 (8–26)	0.594
LOS, hospital (days)	24 (14–39.5)	19.5 (12.5–37)	0.757	28.5 (16–39.8)	21 (13–37)	0.415
LOS, ICU (days)	20 (20–31.5)	18 (9–28)	0.613	21 (11.2–35)	17 (9–29)	0.406

RRT: renal replacement therapy; MV: mechanical ventilation; LOS: length of stay; ICU: intensive care unit. Hypoglycemia was defined as any blood or capillary glucose <70 mg/dL during the first ICU day. Hyperglycemia was defined as any blood glucose >140 mg/dL at ICU admission. Values are mean ± SD or median and interquartile range.

hospital length of stay, and ICU readmission. Most interestingly, more than stress-induced hyperglycemia, DM was associated with mortality, contrary to the "diabetes paradox" in ICU patients.

Throughout the SARS-CoV-2 pandemic, people with chronic diseases, including DM and hypertension, have been disproportionately affected, with an increased risk of hospitalization and mortality [19,20]. The prevalence of DM in our sample was 42.7%, 1.5-fold higher than the general population of critically ill patients [9] and the prevalence of hypertension was 61.6%. This high prevalence confirms DM and hypertension as risks factor for ICU admission during COVID-19 [21], in agreement with a systematic review of 18

studies that reported a high risk of severe COVID-19 in patients with DM compared with those without DM [22]. The mortality rate in our study was significantly higher in patients with hyperglycemia >140 mg/dL and severe hyperglycemia (>200 mg/dL), as expected. However, and most importantly, the mortality was higher in patients with DM than in those without DM, even after adjustment for age, hypertension, and disease severity, a new aspect for ICU patients, specifically associated with COVID-19. Accordingly, a meta-analysis of 33 studies conducted by Kumar et al. demonstrated that patients with DM faced increased odds of developing a composite endpoint of severe COVID-19 or death (2.49 [95% CI: 1.98–3.14], $p < 0.01$) [23]. DM associates with increased risk of developing complications during critical illnesses, but the presence of DM was not independently associated with increased risk of death in critically ill patients before the COVID-19 pandemic [2]. The "diabetes paradox" [2] suggests that chronic hyperglycemia before the acute insult may be associated with favorable outcomes in critical illnesses [24,25]. Cellular adaptations to chronic hyperglycemia of DM would "prepare" the cellular antioxidant apparatus to deal with a subsequent hyperglycemia during an acute illness [26]. Thus, acute hyperglycemia would be more deleterious in critically ill patients without DM, who have no previous cellular conditioning against glucose toxicity. Additionally, patients with DM receive more insulin than those without DM, but with in-hospital hyperglycemia. Insulin has many beneficial non-glycemic effects, including modulation of inflammation, reduction of circulating free fatty acids, regulation of apoptosis, prevention of endothelial dysfunction and hypercoagulation, decrease in neutrophil chemotaxis and leukocyte adhesion, attenuation of the catabolic state of critical illness, and prevention of excessive nitric oxide generation, reducing oxidative stress [27]. In our sample, DM chronic hyperglycemia, rather than stress-induced hyperglycemia, was associated with higher mortality. We demonstrated this phenomenon by two separate analyses. First, by Cox-regression, in which we separated the sample into three groups (normoglycemia, stress-induced hyperglycemia, and DM), and second by the glycemic gap analysis. Thus, our results were consistent, robust, and presented a new aspect of critically ill patients with COVID-19, in which the diabetes paradox cannot be identified.

This population of critically ill patients with SARS-CoV-2 infection clearly presents particularities compared to other ICU patients, especially regarding metabolic pathways of glycemic control and inflammatory mechanisms. In SARS-CoV-2 infection, excessive production of inflammatory mediators leads to a condition known as "cytokine storm [28]". DM is also a chronic pro-inflammatory state characterized by an exaggerated cytokine response, where patients with DM had significantly higher levels of interleukin-6 (IL-6), ferritin, and C-reactive protein compared to individuals without DM [29]. The "cytokine storm" condition results in an increase of oxidative stress and cellular damage, including muscle and liver tissue, which play a central role in the regulation of glucose metabolism, leading to insulin resistance [30]. This suggests that individuals with uncontrolled blood glucose levels may be more vulnerable to cytokine production outbursts, which consequently may lead to rapid exacerbation of COVID-19, with the development of ARDS and shock [31]. Furthermore, previous research found that COVID-19 subjects with DM had higher D-dimer levels than those without DM, probably indicating hemostatic system over-activation [29]. This preexisting pro-thrombotic hypercoagulable state of COVID-19 [32] exacerbated by the presence of DM may result in severe thromboembolic outcomes and eventually higher mortality.

Our sample of critically ill patients with severe COVID-19 pneumonia showed an extremely high rate of hyperglycemia (80%). Hyperglycemia is deleterious to the microvasculature, which may facilitate the mechanisms by which viral replication damages the cells, leading to a vicious circle of inflammation and hyperglycemia [33]. In addition to the severity of the pulmonary disease and inflammation, resulting in stress hyperglycemia as an adaptive response, high doses of corticosteroids used in many patients at the time of ICU admission may have contributed to high glucose levels. In our sample, 28.8% of patients were using corticosteroids before hospital admission. Besides, the high incidence of sepsis (89.7% on admission) probably had a role in inducing hyperglycemia [6].

Glycemic parameters that distinguish the effect of stress-induced hyperglycemia from chronic hyperglycemia did not affect clinical outcomes of these patients. In our sample, glycemic gap and glycated hemoglobin levels were not associated with the outcomes, whereas high glycemic variability was associated with a higher mortality rate. Interestingly, a low rate of severe hypoglycemia was evidenced, despite the high use of short-acting insulin therapy to control acute hyperglycemia on admission. Two main interpretations can be explored: 1) the severity of the disease evolving with stress-induced hyperglycemia, and 2) the high number of patients already using corticosteroids at admission. We believe both explanations are complementary, although corticosteroids were used more frequently and at higher doses than they usually are in ICU patients.

DM is strongly associated with obesity and hypertension. According to the diabetes paradox, obesity is also protective during critical illnesses, with reports of better outcomes in patients with obesity with ARDS [34] and sepsis [35–38]. The chronic low-grade inflammation status observed in patients with obesity could modulate the sepsis host response, resulting in an attenuated cytokine response, thus leading to lower mortality rates compared to individuals with normal weight [39]. In our sample, the mean BMI was 30.7 ± 7.2 kg/m^2, which was higher in survivors than in non-survivors ($p = 0.012$), corroborating the protective effect of moderate obesity in critically ill patients. Besides, hypertension has also been associated with poorer outcomes in patients with COVID-19 [40]. Our results align with this observation, as we observed a higher prevalence of hypertension in non-survivors.

The findings of our study provide new insights regarding the concept of the "diabetes paradox". Traditionally, DM is not associated with increased mortality rates in critically ill patients. However, our results reveal that in the context of COVID-19, DM emerges as a significant risk factor for mortality. This observation introduces a new hypothesis-generating concept, suggesting that the impact of DM on mortality may vary in different population of critically ill patients.

This study has limitations. First, due to the retrospective design, some information may have been overlooked. However, the outcomes of interest were decided by two researchers. Second, our analysis revealed no significant differences in the secondary outcomes among the different glycemic groups under investigation. These findings suggest that factors other than glycemic control might influence these outcomes, or that the sample size might have been insufficient to detect subtle differences, as the sample size calculations was estimated for the primary outcome (mortality). Third, glucose monitoring was not continuous, increasing the possibility that some extreme glucose values may have gone unrecorded. Fourth, the assessment of glycemic variability was performed based on capillary measurements, which is a less reliable method in hemodynamic unstable patients. However, this is the most

common method for glucose measurement worldwide. Lastly, the glycemic control during all ICU length of stay was not evaluated.

In summary, this retrospective cohort study showed that DM – more than stress-induced hyperglycemia – was associated with higher mortality rates compared to normoglycemia. Although patients with DM have more comorbidities, they do not have higher mortality rates than patients without DM when admitted to the ICU before the COVID-19 pandemic. However, our results suggest that the "diabetes paradox" is not present in critically ill patients with COVID-19. DM seems to be "unprotective" in this population, presenting a new aspect of COVID-19.

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Author contribution statement

Priscila Bellaver: Cristiane B Leitão: Tatiana H Rech: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Larissa Schneider: Ariell F. Schaeffer: Conceived and designed the experiments; Performed the experiments.

Lilian Rodrigues Henrique: Performed the experiments.

Joíza Lins Camargo: Contributed reagents, materials, analysis tools or data.

Fernando Gerchman: Analyzed and interpreted the data.

Data availability statement

Data will be made available on request.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18554.

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