ORIGINAL ARTICLE

Effects of Glycemic Variability in Critically Ill Patients with Coronavirus Disease 2019: A Retrospective Observational Study

Emerson Boschi[1], Gilberto Friedman[2], Rafael B Moraes[3]

Received on: 01 January 2024; *Accepted on:* 05 March 2024; *Published on:* 30 March 2024

Abstract

Aim and background: Hyperglycemia is considered an adaptive metabolic manifestation of stress and is associated with poor outcomes. Herein, we analyzed the association between glycemic variability (GV) and hospital mortality in patients with coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU), and the association between GV and mechanical ventilation (MV), ICU stay, length of hospital stays, renal replacement therapy (RRT), hypoglycemia, nosocomial infections, insulin use, and corticosteroid class.

Materials and methods: In this retrospective observational study, we collected information on blood glucose levels during the first 10 days of hospitalization in a cohort of ICU patients with COVID-19 and its association with outcomes.

Results: In 239 patients, an association was observed between GV and hospital mortality between the first and last quartiles among patients without diabetes [odds ratio (OR), 3.78; confidence interval, 1.24–11.5]. A higher GV was associated with a greater need for RRT ($p = 0.002$), regular insulin ($p < 0.001$), and episodes of hypoglycemia ($p < 0.001$). Nosocomial infections were associated with intermediate GV quartiles ($p = 0.02$). The corticosteroid class had no association with GV ($p = 0.21$).

Conclusion: Glycemic variability was associated with high mortality in patients with COVID-19 and observed in the subgroup of patients without diabetes.

Clinical significance: Glycemic control in critically ill patients remains controversial and hyperglycemia is associated with worse outcomes. Diabetes mellitus (DM) is one of the most prevalent comorbidities in patients with COVID-19. In addition, they require corticosteroids due to pulmonary involvement, representing a challenge and an opportunity to better understand how glycemic changes can influence the outcome of these patients.

Keywords: Coronavirus 2019, Critical care, Diabetes mellitus, Glycemic variability, Hyperglycemia, Respiratory distress syndrome.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24688

Highlights

- Glycemic variability (GV) was associated with high mortality in patients with COVID-19.
- This association was particularly observed in patients without diabetes.
- Higher GV was associated with a greater need for regular insulin.

Introduction

Hyperglycemia in critically ill patients is considered an adaptive metabolic manifestation of stress and is associated with poor outcomes.[1,2] Guidelines recommend maintaining glycemic levels between 140 and 180 mg/dL in patients without diabetes.[3,4] However, it remains unclear whether this recommendation should be used in all patients, especially under premorbid conditions.[5–7] Besides hyperglycemia, glycemic variability (GV) is defined by the measurement of fluctuations of glucose over a given interval of time and is associated with morbidity and mortality, especially in patients without diabetes who seem to benefit from maintaining a glycemic level that varies less.[5–10]

A severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) epidemic started in December 2019.[11] Comorbidities, age, and obesity are the conditions associated with an unfavorable evolution of the disease, mainly represented by acute respiratory distress syndrome (ARDS).[12,13] Fasting plasma glucose and glycated hemoglobin (HbA1c) levels upon admission are also predictors of mortality in patients with coronavirus disease 2019 (COVID-19) or ARDS.[14,15] Glycemic variability has rarely been studied in this group of patients, but it seems to be an independent factor associated with worse outcomes, although there is still no consensus regarding its magnitude.[16–18]

[1]Hospital Geral de Caxias do Sul, Postgraduate Program in Pneumological Sciences of Universidade Federal do Rio Grande do Sul (UFRGS); (RS, Brazil)

[2]Programa de Pos-graduacao em Ciencias Pneumologicas, Universidade Federal do Rio Grande do Sul – School of Medicine, Porto Alegre, Rio Grande do Sul, Brazil

[3]Intensive Care Unit, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil

Corresponding Author: Emerson Boschi, Hospital Geral de Caxias do Sul, Postgraduate Program in Pneumological Sciences of Universidade Federal do Rio Grande do Sul (UFRGS); (RS, Brazil), Phone: +55 54 999680563, e-mail: boschimd@gmail.com

How to cite this article: Boschi E, Friedman G, Moraes RB. Effects of Glycemic Variability in Critically Ill Patients with Coronavirus Disease 2019: A Retrospective Observational Study. Indian J Crit Care Med 2024;28(4):381–386.

Source of support: Nil

Conflict of interest: None

© The Author(s). 2024 Open Access. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

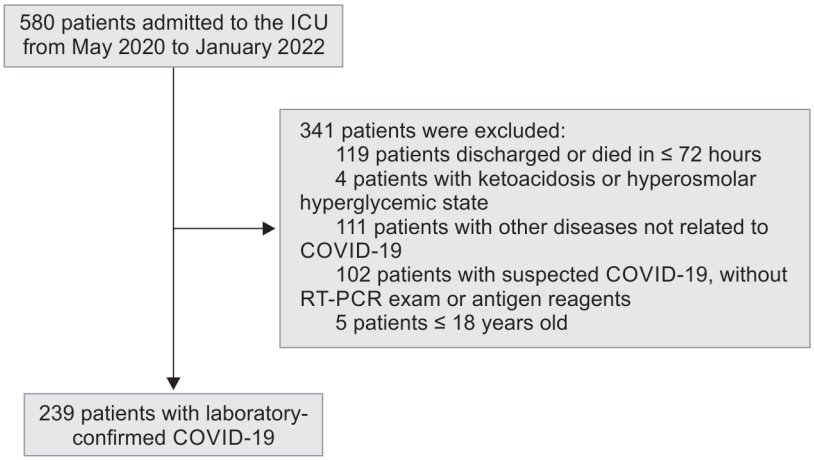


Fig. 1: Flowchart of patients

Diabetes mellitus (DM) is one of the main factors associated with an unfavorable prognosis.[19,20] Studies have shown that COVID-19 can amplify hyperglycemia in patients with type-2 diabetes.[21,22] Moreover, epidemiological observations have shown that the risk of fatal outcomes increases by 50% for these patients.[23] Elevated glycemia levels can increase the concentration of glucose secreted in the airway, thereby reducing the defense capacity of the epithelium and worsening pulmonary inflammation.[24]

Corticosteroids are routinely used in patients requiring oxygen who are admitted to hospitals and in need of critical care, further exacerbating hyperglycemia and increasing insulin use to control these oscillations.[18,25,26]

In this study, we investigated the association between GV and mortality and other relevant clinical outcomes in critically ill patients affected by SARS-CoV-2.

Materials and Methods

Between 1 May 2020 and 31 January 2022, a total of 580 patients were admitted to the intensive care unit (ICU) with a diagnosis of SARS-CoV-2 infection, confirmed by reverse transcription polymerase chain reaction (RT-PCR) or antigen, associated with severe pulmonary infiltrate and oxygen need. The analysis excluded 119 patients who died or were discharged within 72 hours, four patients diagnosed with diabetic ketoacidosis or hyperosmolar hyperglycemic state, 111 patients who were hospitalized for other reasons unrelated to COVID-19, five patients aged below 18 years, 102 patients with acute respiratory failure with negative PCR or negative antigen test results. Finally, 239 patients were included (Fig. 1). The study was analyzed and approved by the Ethics Committee of the University of Caxias do Sul Foundation under the Certificate of Ethical Presentation and Appreciation 39177320.6.0000.5341.

Data related to severity scores were collected and represented using the simplified acute physiology score 3 (SAPS-3) and sequential organ failure assessment (SOFA).[27,28] Epidemiological data, including age, body mass index (BMI), and comorbidities, were also recorded. Obesity was defined by a BMI ≥ 30. The comorbidities analyzed included systemic arterial hypertension, cancer, acquired immunodeficiency syndrome, DM, congestive heart failure, chronic renal failure, chronic obstructive pulmonary disease, alcoholism, and other comorbidities that represented pathologies that were not previously listed. Each comorbidity was added and separated into the following three categories: Absence of comorbidities (0), one to two comorbidities (1, 2), and three or more comorbidities (≥3).

The blood glucose levels available in the electronic medical records for the first 10 days of ICU hospitalization were analyzed. The coefficient of variability (CV) was calculated as the ratio of the standard deviation (SD) to the glycemic mean of each patient, which was multiplied by 100 (CV = SD/glycemic mean × 100).[9] Patients were divided into variability quartiles that were calculated from the total number of the samples obtained, which were represented as ≤19, 20–27, 28–34, and ≥35%.

Blood glucose levels were determined using a specific glucometer for measuring capillary blood glucose (Accu-Check®, Roche). Values above 180 mg/dL were considered hyperglycemia.[4] A glycemic control protocol aimed at maintaining levels between 140 and 180 mg/dL was applied, as assessed by the medical team.

The main outcomes were death or hospital discharge related to different CV quartiles. The need for renal replacement therapy (RRT) in the ICU, use and duration of mechanical ventilation (MV), length of stay in the ICU and hospital, episodes of hypoglycemia (blood glucose <60 mg/dL) at any time during the 10 days of glycemic analysis, number of nosocomial infections during ICU stay, and use of corticosteroids and insulin class were related to different quartiles of variability; all of these were considered as secondary outcomes. Insulin and corticosteroids were considered the predominant class during the first 10 days of evaluation. In addition, the outcomes of the subgroups of patients with and without diabetes and their associations with variability quartiles were analyzed.

Statistical Analysis

Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as percentages. The normality of the tests was analyzed using the Shapiro–Wilk test. An independent *t*-test was used for the analysis of parametric variables, and the Mann–Whitney *U* test was used for continuous non-parametric variables. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Binomial logistic regression was used to verify independent causal relationships with patient deaths. The Kruskal–Wallis test was used to compare three or more independent groups evaluated using a quantitative variable without a normal distribution. Kaplan–Meier survival curve with log-rank test was used for each group for the 28-day outcome. For all tests, a *p*-value below 0.05 was considered significant. Statistical tests were performed using statistical package for the

Table 1: Baseline patient characteristics by glycemic variability quartiles

	Quartile 1 ≤19%	*Quartile 2* 20–27%	*Quartile 3* 28–34%	*Quartile 4* ≥35%	*p*
Number of patients, *n* (%)	56 (23)	63 (26)	59 (25)	61 (26)	–
Age, median (IQR)	48 (37–65)[a]	62 (48–74)[a]	59 (53–68)[a]	64 (56–67)[a]	<0.001*
Gender					0.69
Female, *n* (%)	28 (50)	27 (42)	23 (39)	27 (44)	
Male, *n* (%)	28 (50)	36 (58)	36 (61)	34 (56)	
DM, *n* (%)	3 (5)[a]	9 (14)[b]	24 (41)[ab]	30 (49)[ab]	<0.001*
Number of comorbidities					<0.001*
0, *n* (%)	26 (46)	21 (33)	7 (12)	10 (10)	
1–3, *n* (%)	28 (50)	33 (52)	45 (76)	31 (51)	
≥3, *n* (%)	2 (4)	9 (15)	7 (12)	20 (39)	
BMI, median (IQR)[†]	30 (26–38)	29 (25–35)	33 (27–34)	31 (25–37)	0.69
Obesity, *n* (%)[†]	28 (50)	30 (48)	29 (49)	32 (52)	0.86
SAPS-3, median (IQR)	52 (43–62)[a]	59 (50–68)	57 (48–67)	63 (52–70)[a]	0.007*
SOFA, median (IQR)	3 (3–6)[a]	5 (3–6)	6 (3–7)[a]	4 (4–8)[a]	0.002*
MV, *n* (%)	36 (64)[a]	55 (87)[a]	50 (84)	55 (90)[a]	0.001*

BMI, body mass index; DM, diabetes mellitus; IQR, interquartile range; MV, mechanical ventilation; SAPS-3, simplified acute physiology score 3; SOFA, sequential organ failure assessment. *$p < 0.05$ is considered statistically significant. Continuous and ordinal variables were compared using the Kruskal–Wallis test, with Dwass–Steel–Critchlow–Fligner multiple comparisons test. Categorical variables compared using the Chi-square test. [a]Statistically significant difference between quartile 1 compared to other quartiles. [b]Statistically significant difference between quartile 2 compared to other quartiles. [†]BMI information was not obtained for 6 patients in quartile 1, 2 patients in quartile 2, 4 patients in quartile 3, and 4 patients in quartile 4

social sciences (SPSS) (IBM Corp.; Released 2015. IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp.) and JAMOVI (The jamovi project (2022). jamovi (version 2.0) (Computer software). Retrieved from https://www.jamovi.org.

Results

The median age of the patients was 60 years (IQR, 48–68). Most patients had one or two comorbidities (57%). During ICU stay, 82% of the patients required MV, with a median MV time of 15 days (IQR, 8–23). The maximum CV was 61%. The preferred class of corticosteroids was dexamethasone, and only 11% of the patients did not use any class of corticosteroids.

Patients with a higher CV were also associated with a greater need for MV and higher values of SAPS-3 and SOFA, mainly between the first and last quartiles. Obesity and BMI were similar across all the quartiles (Table 1).

As we progressed to the quartiles of variability, the number of deaths increased (25 vs 65% in the first and last quartiles, $p < 0.01$) (Fig. 2). When RRT among patients in the first and last quartiles was analyzed, 9 and 34% required hemodialysis, respectively ($p = 0.002$). Hypoglycemia was also observed in the higher quartiles of variability, affecting 39% of patients in the highest quartile. The number of nosocomial infections was also higher in the second and third quartiles, in which more than half of the patients had nosocomial infections (Table 2).

The use of dexamethasone was predominant over the other classes of corticosteroids according to the variability quartiles; however, there were no significant differences between the use of a given corticosteroid and its respective CV (Table 3). The use of corticosteroid classes, compared to each other, was not associated with different CVs, even when not grouped by quartiles.

The analysis of the relationship between insulin and GV showed a greater frequency of regular insulin use in the upper quartile, representing 76.7% of the patients in this quartile, contrasting

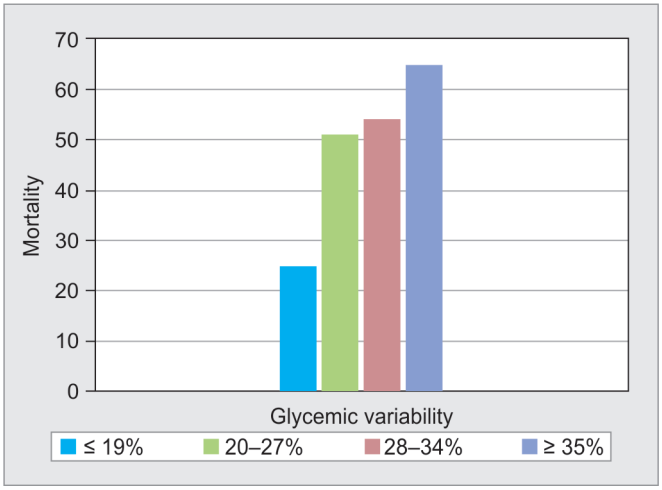


Fig. 2: Glycemic variability and death

with hypoglycemia at some point, 0.4% in the group that used only neutral protamine Hagedorn (NPH) insulin, and 3.4% when no insulin scheme was used.

We performed an a priori model of binomial logistic regression with the SAPS-3 score, SOFA score, age, obesity, number of comorbidities, and DM, with CV [odds ratio (OR), 1.03; $p = 0.04$, confidence interval (CI), 1.00–1.06), and age (OR, 1.03; $p = 0.007$; CI, 1.009–1.06)] as independent mortality factors. When we performed an analysis comparing variability quartiles in the same model, an independent mortality relationship between the first and fourth quartiles was evident (OR, 3.34; $p = 0.01$; CI, 1.27–8.74) (Table 4). CV was not associated with mortality among patients with diabetes, even when different quartiles of variability were analyzed. However, patients without diabetes showed a tendency toward increased mortality ($p = 0.06$; CI, 0.99–1.07), and between the first and last

Table 2: Patient outcomes by GV quartiles

	Quartile 1 ≤19%	*Quartile 2 20–27%*	*Quartile 3 28–34%*	*Quartile 4 ≥35%*	*p-value*
Death, *n* (%)	14 (25)[a]	32 (51)[a]	32 (54)[a]	40 (65)[a]	<0.01*
Days on MV, median (IQR)	10 (4–18)	16 (8–26)	16 (11–26)	15 (8–22)	0.19
RRT, *n* (%)	5 (9)[a]	8 (12)[b]	14 (24)	21 (34)[ab]	0.002*
Length of stay in ICU, Median (IQR)	10 (4–18)	16 (8–26)	16 (11–26)	15 (9–22)	0.054
Length of stay in hospital median (IQR)	16 (9–32)	20 (12–34)	21 (13–30)	18 (11–28)	0.47
Hypoglycemia, *n* (%)	0[a]	3 (5)[b]	6 (10)[c]	24 (39)[abc]	<0.001*
Nosocomial infections, *n* (%)	17 (30)[a]	33 (52)[a]	31 (52)[a]	26 (43)	0.02*

ICU, intensive treatment unit; IQR, interquartile range; MV, mechanical ventilation; RRT, renal replacement therapy. *$p < 0.05$ was considered statistically significant. Continuous and ordinal variables were compared using the Kruskal–Wallis test, with Dwass–Steel–Critchlow–Fligner multiple comparisons test. Categorical variables were compared using the Chi-square test. [a]Statistically significant difference between quartile 1 compared to other quartiles. [b]Statistically significant difference between quartile 2 compared to other quartiles. [c]Statistically significant difference between quartile 3 and quartile 4

Table 3: Corticosteroid and insulin use according to GV quartiles

	Quartile 1 ≤19%	*Quartile 2 20–27%*	*Quartile 3 28–34%*	*Quartile 4 ≥35%*	*p-value*
Insulin use					<0.001*
None, *n* (%)	49 (20.9)	37 (15.9)	19 (8.1)	13 (5.6)	
IR IB, *n* (%)	6 (2.6)	19 (8.1)	34 (14.5)	46 (19.7)	
NPH, *n* (%)	1 (0.4)	4 (1.7)	5 (2.1)	1 (0.4)	
Corticosteroid					0.21
None, *n* (%)	10 (4.2)	9 (3.8)	1 (0.4)	6 (2.5)	
Dexamethasone, *n* (%)	39 (16.4)	49 (20.6)	50 (21)	50 (21)	
Methylprednisolone, *n* (%)	5 (2.1)	3 (1.3)	3 (1.3)	4 (1.7)	
Hydrocortisone, *n* (%)	2 (0.8)	2 (0.8)	4 (1.7)	1 (0.4)	

IR IB, regular insulin in infusion pump; NPH, neutral protamine hagedorn. Variables were compared using the Chi-square test. *$p < 0.05$ considered statistically significant. One piece of data was lost on the corticosteroid class in the 28–34% quartile

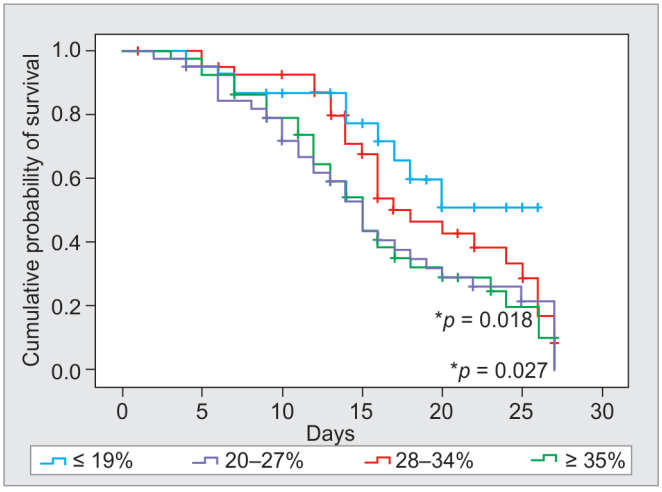
Table 4: Prognostic factors compared by quartile of variability

			Confidence Interval 95%	
Variable	*OR*	*p-value*	*Inferior limit*	*Superior limit*
CV				
Quartile 1–2	2.04	0.11	0.83	4.98
Quartile 1–3	2.10	0.12	0.82	5.41
Quartile 1–4	3.34	0.01*	1.27	8.74
SAPS-3	1.02	0.18	0.98	1.05
Obesity	0.72	0.31	0.39	1.34
SOFA	1.09	0.24	0.94	1.27
Age	1.03	0.01*	1.00	1.06
Comorbidities	1.21	0.53	0.66	2.20
Diabetes	1.37	0.45	0.59	3.17

Bivariate logistic regression with calculation of risk factors for hospital mortality predefined model with prognostic factors previously analyzed in observational studies. *$p < 0.05$ considered statistically significant; VC, coefficient of variability; Quartile 1, ≤19%; Quartile 2, 20–27%; Quartile 3, 28–34%; Quartile 4, ≥35%

quartiles, there was an independent association with mortality (OR, 3.78; $p = 0.01$; CI, 1.24–11.5).

The 28-day mortality survival curve showed a statistically significant difference between the first and second quartiles and the first and fourth quartiles of variability (Fig. 3).



*$p = 0.018$ between the first and second quartiles
*$p = 0.027$ between the first and fourth quartiles

Fig. 3: The 28-day survival analysis for quartiles of coefficients of variability with log–rank test

Discussion

This cohort study found an independent association between mortality and GV, especially when analyzed in the highest quartile.

Our findings are similar to those of the previous studies that demonstrated GV as a factor associated with worse outcomes in patients with COVID-19. Chen et al. analyzed four levels of GV adjusted for other confounding factors during the first week of hospitalization and demonstrated that a higher level of variability was associated with mortality and progression to ARDS.[17] Hartmann et al. studied patients with ARDS caused by COVID-19 and found an association between GV and mortality.[16] Oscillations in glycemic levels may correlate more with inflammatory damage than isolated or constant hyperglycemic episodes, making CV an amplifying factor for these alterations.[5,29] This was evident when we compared the variability quartiles, where higher quartiles, which represented greater glycemic fluctuations, demonstrated greater complications in addition to an independent relationship with mortality. Similar to other studies,[30–32] our analysis demonstrated the influence of greater GV on acute renal failure and the need for RRT. The number of infections was higher in the intermediate GV values, which may be associated with lower survival in the highest quartile, leading to fewer episodes of infection. Other studies have shown this association of quartiles with increased mortality, but related to different variations.[9]

Our study showed a prevalence of 28% in patients with diabetes, similar to that in other epidemiological studies related to COVID-19.[33] When we separately evaluated the CV of the subgroup of patients with diabetes, there was no relationship with mortality, even in higher quartiles, represented in our study by a CV of ≥35%. In the subgroup of patients without diabetes, we found an association between the highest quartile and mortality, which demonstrates the importance of previous diagnoses in the management of hyperglycemia in these patients. Several studies have revealed the importance of the premorbid state as a fundamental factor in glycemic control, as patients with diabetes may have a greater tolerance to hyperglycemia and greater oscillations.[7,9,34–36]

The main corticosteroid used in this cohort was dexamethasone, which has been used in the main clinical trials in patients with severe COVID-19; however, other corticosteroids are also used according to the particularity of each patient and may also have benefits.[25,37,38] The class of corticosteroids was not relevant for glycemic alterations; however, it cannot be inferred whether the use of corticosteroids influenced the variability owing to the small number of patients who did not use steroids during the analyzed period.

Insulin plays a fundamental role in the glycemic control of these patients; however, its use poses some risks, such as hypoglycemia and pro-inflammatory effects.[39,40] This study showed an association between the different quartiles and an increasing prevalence of the use of continuous regular insulin for higher glycemic levels, which may be associated with greater episodes of hypoglycemia and consequent worse outcomes. Patients with diabetes presented with episodes of hypoglycemia in this study compared with other patients (27.2 vs 8.7%), even without using insulin (4.5%), which may be correlated with their high mortality. Work overload caused by the pandemic, associated with inadequate monitoring, could explain the high rates of hypoglycemia.

This study had some limitations. Besides its retrospective character, there was a large variation in the number of blood glucose levels measured in each patient; the measurements were performed using capillary blood glucose, which could influence the reliability of the values obtained.[41] Many of these patients had prolonged hospitalization after a period in which the management of the pathology studied was modified, owing to a better understanding of its pathophysiology and greater experience. We could not rule out DM diagnosis before hospitalization, as it was measured based only on previous history or information from family members. HbA1c levels were not evaluated in critically ill patients, and this information may be useful for analyzing patients' previous glycemic control. Corticosteroid dose could not be measured in the study, showing high variability. Nutritional intake and insulin administration were not quantified, and their relationship with episodes of hypoglycemia could not be ruled out.

Conclusion

Glycemic variability is an independent risk factor for mortality in critically ill patients with COVID-19; the higher the blood glucose level, the greater the mortality. However, GV does not seem to have the same effect in patients with diabetes. New studies that correlate different levels of GV with outcomes in patients with SARS-CoV-2 infection and their relationship with the premorbid state are required.

Clinical Significance

Glycemic control in critically ill patients remains controversial and hyperglycemia is associated with worse outcomes. Diabetes mellitus is one of the most prevalent comorbidities in patients with COVID-19. In addition, they require corticosteroids due to pulmonary involvement, representing a challenge and an opportunity to better understand how glycemic changes can influence the outcome of these patients.

Orcid

Emerson Boschi https://orcid.org/0000-0002-0273-4759
Gilberto Friedman https://orcid.org/0000-0001-9369-2488
Rafael B Moraes https://orcid.org/0000-0001-6631-7260

References

1. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet 2009;373(9677):1798–1807. DOI: 10.1016/S0140-6736 (09)60553-5.
2. Mifsud S, Schembri EL, Gruppetta M. Stress-induced hyperglycaemia. Br J Hosp Med (Lond) 2018;79(11):634–639. DOI: 10.12968/hmed.2018.79.11.634.
3. Kavanagh BP, McCowen KC. Clinical practice. Glycemic control in the ICU. N Engl J Med 2010;363(26):2540–2546. DOI: 10.1056/NEJMcp1001115.
4. American Diabetes Association Professional Practice Committee. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes-2022. Diabetes Care 2022;45(Suppl. 1):S46–S59. DOI: 10.2337/dc22-S004.
5. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology 2006;105:244–252. DOI: 10.1097/00000542-200608000-00006.
6. Todi S, Bhattacharya M. Glycemic variability and outcome in critically ill. Indian J Crit Care Med 2014;18(5):285–290. DOI: 10.4103/0972-5229.132484.
7 Krinsley JS, Egi M, Kiss A, Devendra AN, Schuetz P, Maurer PM, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. Crit Care 2013;17(2):R37. DOI: 10.1186/cc12547.
8. Zhou Z, Sun B, Huang S, Zhu C, Bian M. Glycemic variability: Adverse clinical outcomes and how to improve it? Cardiovasc Diabetol 2020;19(1):102. DOI: 10.1186/s12933-020-01085-6.

9. Krinsley JS. Glycemic variability and mortality in critically ill patients: The impact of diabetes. J Diabetes Sci Technol 2009;3(6):1292–1301. DOI: 10.1177/193229680900300609.
10. Todi S. Glycemic control in critically ill: A moving target. Indian J Crit Care Med 2014;18(4):229–233. DOI: 10.4103/0972-5229.130574.
11. World Health Organization. COVID-19 timeline. Pan-American Health Organization/World Health Organization. 2023. Available from: https://www.paho.org/en/topics/coronavirus-infections/coronavirus-disease-covid-19-pandemic.
12. Reyes LF, Bastidas A, Narváez PO, Parra–Tanoux D, Fuentes YV, Serrano–Mayorga CC, et al. Clinical characteristics, systemic complications, and in-hospital outcomes for patients with COVID-19 in Latin America. LIVEN-COVID-19 study: A prospective, multicenter, multinational, cohort study. PLoS One 2022;17(3):e0265529. DOI: 10.1371/journal.pone.0265529.
13. Motiaa Y, Rachidi SA, Labib S, Sbai H, Mohammed TB, Adil Z, et al. Comparison of ICU patients' characteristics across two waves of COVID-19: A monocentric cohort study. Indian J Respir Care 202312(2):139–145. DOI: 10.5005/jp-journals-11010-1047.
14. Coppelli A, Giannarelli R, Aragona M, Penno G, Falcone M, Tiseo G, et al. Hyperglycemia at hospital admission is associated with severity of the prognosis in patients hospitalized for COVID-19: The Pisa COVID-19 study. Diabetes Care 2020;43(10):2345–2348. DOI: 10.2337/dc20-1380.
15. 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(8):1500–1515. DOI: 10.1007/s00125-020-05180-x.
16. Hartmann B, Verket M, Balfanz P, Hartmann NU, Jacobsen M, Brandts J, et al. Glycaemic variability is associated with all-cause mortality in COVID-19 patients with ARDS: A retrospective subcohort study. Sci Rep 2022;12(1):9862. DOI: 10.1038/s41598-022-13816-8.
17. Chen L, Sun W, Liu Y, Zhang L, Lv Y, Wang Q, et al. Association of early-phase in-hospital glycemic fluctuation with mortality in adult patients with coronavirus disease 2019. Diabetes Care 2021;44(4):865–873. DOI: 10.2337/dc20-0780.
18. Becker CD, Sabang RL, Cordeiro MFN, Hassan IF, Goldberg MD, Scurlock CS. Hyperglycemia in medically critically ill patients: Risk factors and clinical outcomes. Am J Med 2020;33(10):e568–e574. DOI: 10.1016/j.amjmed.2020.03.012.
19. Hespanhol V, Bárbara C. Pneumonia mortality, comorbidities matter? Pulmonology 2020;26(3):123–129. DOI: 10.1016/j.pulmoe.2019.10.003.
20. Zou Q, Zheng S, Wang X, Liu S, Bao J, Yu F, et al. Influenza A-associated severe pneumonia in hospitalized patients: Risk factors and NAI treatments. Int J Infect Dis 2020;92:208–213. DOI: 10.1016/j.ijid.2020.01.017.
21. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013;495(7440):251–254. DOI: 10.1038/nature12005.
22. Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? Diabetes Res Clin Pract 2020;162:108125. DOI: 10.1016/j.diabres.2020.108125.
23. Remuzzi A, Remuzzi G. COVID-19 and Italy: What next? Lancet 2020;395(10231):1225–1228. DOI: 10.1016/S0140-6736 (20)30627-9.
24. Brufsky A. Hyperglycemia, hydroxychloroquine, and the COVID-19 pandemic. J Med Virol 2020;92(7):770–775. DOI: 10.1002/jmv.25887.
25. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384(8):693–704. DOI: 10.1056/NEJMoa2021436.
26. Pretty C, Chase JG, Lin J, Shaw GM, Le Compte A, Razak N, et al. Impact of glucocorticoids on insulin resistance in the critically ill. Comput Methods Programs Biomed 2011;102(2):172–180. DOI: 10.1016/j.cmpb.2010.08.004.
27. Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3: From evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med 2005;31(10):1345–1355. DOI: 10.1007/s00134-005-2763-5.
28. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22(7):707–710. DOI: 10.1007/BF01709751.
29. Xie W, Wu N, Wang B, Xu Y, Zhang Y, Xiang Y, et al. Fasting plasma glucose and glucose fluctuation are associated with COVID-19 prognosis regardless of pre-existing diabetes. Diabetes Res Clin Pract 2021;180:109041. DOI: 10.1016/j.diabres.2021.109041.
30. Meersch M, Schmidt C, Zarbock A. Perioperative acute kidney injury: An under-recognized problem. Anesth Analg 2017;125(4):1223–1232. DOI: 10.1213/ANE.0000000000002369.
31. Gorelik Y, Bloch–Isenberg N, Hashoul S, Heyman SN, Khamaisi M. Hyperglycemia on admission predicts acute kidney failure and renal functional recovery among inpatients. J Clin Med 2021;11(1):54. DOI: 10.3390/jcm11010054.
32. Moriyama N, Ishihara M, Noguchi T, Nakanishi M, Arakawa T, Asaumi Y, et al. Admission hyperglycemia is an independent predictor of acute kidney injury in patients with acute myocardial infarction. Circ J 2014;78(6):1475–1480.DOI: 10.1253/circj.cj-14-0117.
33. Ranzani OT, Bastos LSL, Gelli JGM, Marchesi JF, Baião F, Hamacher S, et al. Characterisation of the first 250 000 hospital admissions for COVID-19 in Brazil: A retrospective analysis of nationwide data. Lancet Respir Med 2021;9(4):407–418. DOI: 10.1016/S2213-2600(20)30560-9.
34. Plummer MP, Bellomo R, Cousins CE, Annink CE, Sundararajan K, Reddi BA, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. Intensive Care Med 2014;40(7):973–980. DOI: 10.1007/s00134-014-3287-7.
35. Krinsley JS. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: Six and one-half years experience at a university-affiliated community hospital. Semin Thorac Cardiovasc Surg 2006;18(4):317–325. DOI: 10.1053/j.semtcvs.2006.12.003.
36. Morse J, Gay W, Korwek KM, McLean LE, Poland RE, Guy J, et al. Hyperglycaemia increases mortality risk in non-diabetic patients with COVID-19 even more than in diabetic patients. Endocrinol Diabetes Metab 2021;4(4):e00291. DOI: 10.1002/edm2.291.
37. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA 2020;324(13):1330–1341. DOI: 10.1001/jama.2020.17023.
38. Ranjbar K, Moghadami M, Mirahmadizadeh A, Fallahi MJ, Khaloo V, Shahriarirad R, et al. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: A triple-blinded randomized controlled trial. BMC Infect Dis 2021;21(1):337. DOI: 10.1186/s12879-021-06045-3.
39. Yu B, Li C, Sun Y, Wang DW. Insulin treatment is associated with increased mortality in patients with COVID-19 and type 2 diabetes. Cell Metab 2021;33(1):65.e2–77.e2. DOI: 10.1016/j.cmet.2020.11.014.
40. Soop M, Duxbury H, Agwunobi AO, Gibson JM, Hopkins SJ, Childs C, et al. Euglycemic hyperinsulinemia augments the cytokine and endocrine responses to endotoxin in humans. Am J Physiol Endocrinol Metab 2002;282(6):E1276–E1285. DOI: 10.1152/ajpendo.00535.2001.
41. Corstjens AM, Ligtenberg JJ, van der Horst IC, Spanjersberg R, Lind JS, Tulleken JE, et al. Accuracy and feasibility of point-of-care and continuous blood glucose analysis in critically ill ICU patients. Crit Care 2006;10(5):R135. DOI: 10.1186/cc5048.